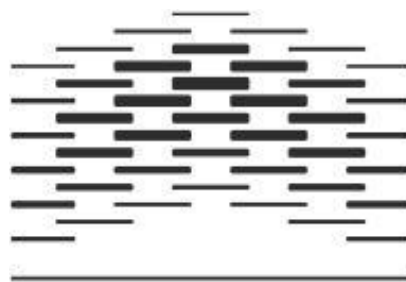# MASTER THESIS
PUBLIC HEALTH NUTRITION
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IODINE STATUS

IN PREGNANT WOMEN IN NORWAY

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Abstract

Background: Iodine deficiency is one of the most widespread nutritional disorders worldwide and has multiple adverse effects on growth and development in humans. Inadequate iodine intake during pregnancy may lead to irreversible foetal brain damage.

Objective: The overall objective of this study was to assess iodine status in pregnant women in Oslo and Akershus by evaluating urinary iodine concentration (UIC), urinary iodine excretion (UIE), and iodine intake from food and supplements.

Methods: A cross-sectional study was performed during 2016 by convenient sampling in 804 pregnant women (18-44 years) in eight Mother and Health Centres in Oslo and Akershus. Spot urine samples were collected from 728 women for assessment of UIC and 804 participants provided information about 24-h iodine intake and supplement use. In addition, 49 participants in a sub-study collected a 24-hour urine sample for assessment of UIC and UIE, and answered a 24-hour dietary recall and a food frequency questionnaire comprising 31 food items.

Results: The median UIC was 92 μg/L (n=777), which according to WHO reflects insufficient iodine intake. The median UIE was 120 μg/24h (n=49). In the large study, median 24-hour iodine intake from food and total iodine intake was 110 μg/day and 148 μg/day. In 24-hour recall, the median iodine intake from food and total intake was 114 μg/day and 143 μg/day. The median habitual iodine intake from food and total was 117 μg/day and 149 μg/day. Milk/dairy was the main dietary iodine source (contributing ~50%), followed by seafood (contributing 25%). The median iodine intake estimated from UIC and UIE was 157 μg/day and 133 μg/day (n=49). The predictors for UIC were smoking, low metabolism, maternal age, and iodine from supplements. Together they explain 11% of the variance in UIC.

Conclusions: The findings from the present study indicate suboptimal iodine status due to insufficient iodine intake in pregnant women in Norway, shown through UIC and estimated iodine intake.

Key words: Iodine status, pregnancy, iodine deficiency, iodine intake, urinary iodine concentration, urinary iodine excretion

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Abbreviations

ADHD	Attention Deficit/Hyperactivity Disorder
BMI	Body Mass Index
DIT	Diiodotyrosine
EAR	Estimated Average Requirement
EFSA	European Food Safety Authority
FCT	The Norwegian Food Composition Table
FFQ	Food Frequency Questionnaire
FHI	Norwegian Institute of Public Health
fT_4	Free thyroxine
H_2O_2	Hydrogen peroxide
HiOA	Oslo and Akershus University College
HDI	Human Development Index
I	Iodine
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
ID	Iodine deficiency
IDD	Iodine-deficiency disorders
IGN	Iodine Global Network
IOM	Food and Nutrition Board, Institute of Medicine, Academies
IQ	Intelligence quotient
IQR	Interquartile range
LOD	Limit of detection
LOQ	Limit of quantification
M	Missing
MIT	Monoiodotyrosine
MoBa	The Norwegian Mother and Child Cohort Study
NaCl	Sodium chloride
NHMRC	National Health and Medical Research Council
NNR	Nordic Nutrition Recommendations
RDI	Recommended daily intake
RNI	Recommended nutrient intake
REK	Regional Commitees for Medical and Heath Research Ethics, Norway
SPSS	Statistical Package for the Social Sciences

T3	Triiodothyronine
T4	Thyroxine
Tg	Thyroglobulin
TH(s)	Thyroid Hormone(s)
TPO	Thyroid peroxidase
TSH	Thyroid stimulating hormone
UI	Urinary Iodine
UIC	Urinary iodine concentration
UIE	Urinary iodine excretion
UNICEF	United Nations Children's Fund
WHO	World Health Organization
24 h	24 hours

1 Introduction

World Health Organization (WHO) considers iodine deficiency (ID) to be the single most important preventable cause of brain damage worldwide (WHO *et al.* 2007). Although iodine deficiency is often thought to be a problem in developing countries, industrialised countries are not immune (Andersson *et al.* 2012). Indeed, concern is emerging that suboptimal iodine intake might be prevalent in Norway, even though Norway has been considered iodine replete for six decades (National Nutrition Council, 2016). Recent studies have revealed insufficient status in vulnerable groups, and pregnant women in particular (Brantsæter *et al.* 2013; Sanchez, 2015; Seldal, 2012). Insufficient iodine intake is also shown in other Scandinavian countries (Bath *et al.* 2013; Granfors *et al.* 2015; Andersen *et al.* 2014; Nyström *et al.* 2016).

Iodine is an essential micronutrient for the synthesis of thyroid hormones that are critical for brain development and growth during pregnancy and infancy. Thyroid hormones, and therefore iodine, are essential for mammalian life. The thyroid hormones participate in metabolic regulation in every single cell, and major target organs are the developing brain, muscle, heart, pituitary, and kidney. Iodine deficiency (ID) has many adverse effects on growth and development, and these effects are due to inadequate production of thyroid hormone and are termed iodine deficiency disorder. It occurs when iodine intake is insufficient for the body to produce adequate amounts of thyroid hormones (Zimmermann & Andersson, 2012a). ID in utero and early childhood leads to the loss of millions of IQ points globally, making it one of the most important preventable cause of brain damage worldwide (WHO, 2007).

In Norway, the most important iodine sources are milk and dairy products, and fish and seafood (Dahl *et al.* 2003b; The Norwegian Directorate of Health, 2016). For pregnant women, The Nordic Nutrition Recommendation recommends an intake of 175 micrograms (Nordic Council of Ministers , 2004), while WHO recommends 250 microgram (WHO, 2008). Both too low and too high iodine intake may be negative for the health (Laurberg *et al.* 2003; Zimmermann *et al.* 2016a; Lee & Pearce, 2015).

Recently there has been increased attention on possible inadequate iodine status in Norway. Results from the Norwegian Mother and Child Cohort study (MoBa) have shown that a high

proportion of pregnant women had suboptimal iodine intake (Brantsæter *et al.* 2013). Similar results were shown in Sweden in a cross-sectional study in pregnant healthy women (Granfors *et al.* 2015). ID during pregnancy may affect cognitive function of the offspring and lead to mental impairment (Bath *et al.* 2013; Hynes *et al.* 2015; Taylor *et al.* 2014). Because of the above-mentioned results, WHO now categorize Norway in the group of countries with iodine deficiency amongst pregnant women (Zimmermann & Galetti, 2015). A National report on iodine status in Norway was released in June 2016 (National Nutrition Council, 2016), pointing to the need for action to secure iodine nutrition in Norway. The report also highlighted the need for more studies on iodine status in pregnant women in Norway (National Nutrition Council, 2016).

During 2016, Associate Professor Sigrun Henjum at Oslo and Akershus University College initiated a study in pregnant and lactating women to evaluate iodine status. Two master students participated in the research; I was given the opportunity to be a part of the study on iodine among pregnant women. From March to December 2016 I participated both in the data collection which included recruitment of participants at Mother and Child Health Centres, sample collection and interviewing participants. Fellow student Anna Dudareva presents the study on iodine status among lactating women.

The overall objective of my master thesis was to assess iodine status through evaluation of urinary iodine concentration (UIC) and calculated iodine intake from iodine-containing food items and supplements. In addition, in a sub-sample, urinary iodine excretion (UIE) from 24-hour urine samples was analysed in order to compare the agreement between UIC and UIE. In this master thesis the status study is referred to as the large study and with the highest study population, where participants donated a spot urine sample for UIC analysis and answered a questionnaire assessing 24-hour iodine intake and use of supplement. The other study is referred to as the sub-study, where participants collected a 24-hour urine sample and answered a more in-depth questionnaire (31 food frequency questions) assessing habitual intake, and answered a 24-hour recall for calculating a detailed short-time iodine intake and use of supplement. We also collected data on knowledge on iodine among the pregnant women. However, this master thesis does not include data on iodine knowledge.

2 Theoretic background

During history iodine has mainly been associated with iodine deficiency diseases endemic goitre and cretinism (Laurberg, 2014). Iodine discovery is credited to Bernard Courtois in 1811 and was named iodine from the Greek *ioedes*, meaning violet coloured, the colour of iodine vapour. Iodine is not naturally found in pure form, but act as iodine salts (I⁻), especially in seawater containing about 50 µg/L (National Nutrition Council, 2016; Zimmermann et al., 2008a). Iodide ions in seawater oxidise to form elemental iodine, which is volatile and evaporates into the atmosphere and returns to the soil by rain, completing the cycle.

The first use of iodine for treatment of goitre was published in 1820 in Geneva (Hetzel, 1989). In the early nineteenth century, the use of high doses of iodine for medical purposes led to the first reports of clinical thyrotoxicosis in relation to iodine intake (Stanbury *et al.* 1998). Between 1917 and 1922 results of a trial performed in Ohio showed profound effects of iodine supplements on goitre frequencies (Carpenter, 2005). During the same period, Hunziker observed in an iodine-deficient population in Switzerland, that as little as 100 µg iodine per day was effective in preventing goitre (Bürgi *et al.* 1990), and in 1922, voluntary iodine prophylaxis was introduced in parts of Switzerland. Despite considerable knowledge on the prevention of iodine deficiency, developmental brain damage caused by iodine deficiency occurred in many parts of the world until recent decades. The formation in 1985 of the International Council for the Control of Iodine Deficiency Disorders (ICCIDD now known as Iodine Global Network, IGN) and its subsequent activities in collaboration with the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) improved the situation, but further efforts are necessary (Laurberg, 2014).

In the following section I will give an outline of the role of iodine in human nutrition: iodine function and metabolism, recommendations, deficiency, how iodine status is evaluated, and various factors affecting iodine status. Furthermore, I will give a description of the importance of iodine for pregnant women, which is a vulnerable group for iodine deficiency.

2.1 Iodine in human nutrition

For humans, iodine is an essential micronutrient, and a daily intake of about 0.1 milligrams of iodide is needed. The only known physiological role of iodine in humans is to contribute in a series of reactions in the creation of the thyroid hormones thyroxine (T4) and the biologically

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active form triiodothyronine (T3) (Zimmermann, 2011; WHO, 2004). All vertebrates have developed a thyroid gland to cater for synthesis, storage and secretion of the iodine-containing hormones. Our bodies contain up to 20 milligrams of iodine, mainly stored in the thyroid gland. The thyroid hormones regulate metabolism in body cells. The proposed mechanism of action includes increased synthesis of enzymes involved in a metabolic activity and increased size and number of mitochondria in response to the hormones (Nordic Council of Ministers , 2004). In addition, they regulate and control embryonic development and coordinate physiology within and between cells and tissues via dose-dependent regulatory effect on essential genes (Younes-Rapozo *et al.* 2006; Salvatore, 2011; Crockford, 2009). A certain level of thyroid hormones is therefore needed for optimal metabolic rate, mental and physical development, and to sustain a normal function of the central nervous system.

Bioavailability, defined as a substance's ability to reach its target, is essential for the understanding of iodine's incorporation into the thyroid and then in T4 and T3. Although iodine absorption from the gut is high, a wide range of bioactive substances in food, called goitrogenic substances, inhibits the incorporation of iodine into the thyroid gland (National Nutrition Council, 2016). Goitrogenic substances appear naturally in some food items, like soybeans (isoflavonoids), cabbage, broccoli, kohlrabi, brussel-sprouts and cauliflower (thiocyanate). In addition, smoke, pesticides and many pollutants also have goitrogenic properties; more than sixty percent of all herbicides, PCBs, dioxins and lead have documented goitrogenic properties (Roman, 2007; Wiersinga, 2013). Most goitrogenic substances do not have a major clinical effect unless there is coexisting iodine deficiency, but can aggravate the effect of low iodine intake (Vanderpas, 2006).

2.1.1 Thyroid physiology and metabolism

Iodine in food occurs in various forms. Most iodine-containing compounds are broken down in the gut, and rapidly absorbed (>90%) in the stomach and duodenum as iodide (Jahreis *et al.* 2001; Nath *et al.* 1992). Certain seaweed and protein-bound iodine may be absorbed less efficiently (Hurrell, 1997). The absorbed iodide enters the bloodstream, together with iodide released by metabolism of thyroid hormones. By the bloodstream, iodine enters the thyroid, where an iodine-transporter, denoted sodium iodide symporter (NIS) effectively provides an iodine concentration 20-50 times higher than the iodine levels in the blood (Eskandari *et al.* 1997).

Most iodide is either excreted by the kidney (clearance of 30 to 50 mL/minute, independent of iodine status) or concentrated in the thyroid gland (Zimmermann and Andersson, 2012a). Thyroid clearance of circulation iodine varies with iodine intake and the functional status of the thyroid. In situations with adequate iodine supply, the thyroid takes up ten percent or less of absorbed iodine, while in chronic iodine deficiency, this percentage can exceed eighty percent (Rousset & Dunn, 2008). In people with a recommended iodine intake of approximately 150 μg/day, thyroid clearance of iodine is approximately half that of renal clearance of iodine. Under normal circumstances, plasma iodine has a half-life of about 10h but this time is reduced in iodine deficiency.

The body saves its stock of iodine. T4 and T3 excreted from tissues are absorbed again in the thyroid to be reused. Low concentrations of T4 and T3 is converted by the liver and excreted in the bile. Most iodine is reabsorbed, and there is little iodine excreted with feces. Iodine is mainly excreted in the urine, and within one or two days, more than 90% of the dietary iodine intake is excreted (Jahreis *et al.* 2001; Zimmermann and Andersson, 2012a). In lactating women, a considerable fraction of the circulating iodide is taken up by the mammary glands and is excreted into the breast milk to supply iodine to the infant (Pearce *et al.* 2007). This has implications for the recommendations for iodine to lactating mothers and higher iodine intake is recommended both during pregnancy and lactation (elaborated in chapter 2.1.3).

The iodine taken up by the thyroid is built into tyrosine groups to create monoiodotyrosine (MIT) and diiodotyrosine (DIT) in the thyroglobulin present in the colloid of thyroid follicles. This process is catalysed by the membrane-bound enzyme thyroid perioxidase (TPO) in the presence of hydrogen peroxide (H_2O_2). TPO is a heme-containing protein, and interaction exists between the effects of iodine and iron deficiency (Zimmermann, 2006). TPO catalyses the coupling of iodinated tyrosine residues in Tg to form the double-ring iodothyrosines L-thyroxine (tetraiodothyronine, T4) and L-triiodothyronine (T3). Figure 2-1 illustrates the pathway of iodine in the synthesis of thyroid hormone.
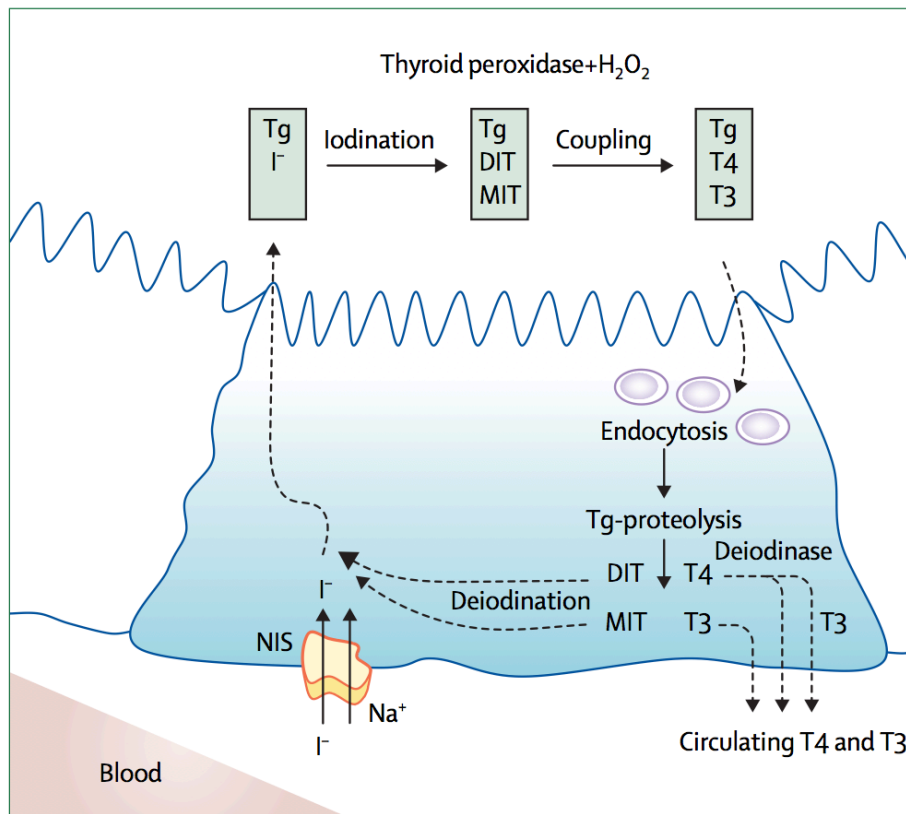
Figure 2-1 Iodine pathway in the thyroid cell: Iodine (I⁻) is transported into the thyrocyte by the sodium iodide symporter (NIS) at the basal membrane and migrates to the apical membrane. I⁻ is oxidised by the enzymes thyroperoxidase (TPO) and hydrogen peroxidase (H_2O_2), and attached to tyrosol residues in thyroglobulin (Tg) to produce the hormone precursors monoiodotyrosine (MIT) and diiodotyrosine (DIT). Residues then couple to form thyroxine (T4) and tri-iodothyronine (T3) within the Tg molecule in the follicular lumen. Tg enters the cell by endocytosis and is digested. T4 and T3 are released into the circulation, and iodine on MIT and DIT is recycled within the thyrocyte.
Source: Zimmermann et al. 2008

The thyroid gland produces the pro-hormone T4, and only about twenty percent of the active hormone T3. T4 is largely inactive until it is deiodinated to T3 by deiodinase. Secretion of thyroid hormones is initiated by uptake into the follicular cells of Tg and liberated by hydrolysis of Tg catalysed by lysosomal enzymes. The cellular processes leading to thyroid hormone action require selenoproteins, the deiodinases, in order to convert the pro-hormone T4 to the active form T3 (Salvatore, 2011). This reaction produces about eighty percent of the T3 present in the circulation in healthy subjects.

The blood level of T4 and T3 is relatively stable regulated by the two most important regulators of thyroid activity; the thyroid-stimulating hormone (TSH) and iodide by auto regulation. At low levels of T4 and T3 in the blood the anterior lobe of the pituitary stimulates excretion of TSH, which increases the excretion of T4 and T3 from the thyroid gland. At high levels of T4 and T3 the pituitary inhibits secretion (National Nutrition Council, 2016). T4 and T3 is transported in the blood bound to one of three transport proteins: thyroxine-binding globuline (TBG), transthyretin (TTR) or albumin. In addition, there are low levels of free-T4 and free-T3 in the blood. The sodium-iodide symporter (NIS) is central in the transport of iodine in the body, that couples the translocations of sodium (Na+) from high to low, and iodine (I-) from low to high concentration into the cells. The most important sites NIS is located is in the follicular cells of the thyroid and in the lactotrophs of the lactating mammary gland, but NIS is also present in salivary glands, in the gut mucosae, in sweat glands, and in the choroid plexus of the cerebral lateral ventricles (Laurberg, 2014).

2.1.2 Dietary sources of iodine

The dietary sources of iodine vary with country, culture and demography. In western countries, iodine is concentrated in milk and the iodine content of dairy products is often relatively high because of iodine fortification of fodder for dairy cows. Before the Danish iodization of salt, iodine in dairy products contributed 44% of iodine intake, whereas iodine in fish products contributed 15% (Rasmussen *et al.* 2002). Countries, like Japan and Korea, where iodine-rich kelp products constitute a significant part of the diet, have a generally high iodine intake (Nagataki, 2008; Kim *et al.* 1998), much higher than the internationally recommended levels. Groundwater iodine content is low in most places, but high levels may be caused by leaching of iodine-containing humic substances into aquifers, presumably from old sea bottom deposits (Andersen *et al.* 2009). Multivitamins that contain iodine, often 150 μg per tablet, is an important source of iodine intake.

Worldwide, iodized salt is a major source of iodine used to prevent iodine deficiency disorders (Andersson, Benoist & Rogers, 2010). Fortification differ among countries; e.g. in the United States, the iodine content of iodized salt is relatively high (45 mg of iodine/kg salt [45 ppm]), while Switzerland use lower amounts of iodine in salt (22 ppm), but the frequency of use is high. In Denmark, iodide (13 ppm) has been added to table salt and to salt used in bread production for the past 15 years. Mandatory use of iodized salt in bread was introduced to secure and improve iodine status in the whole population, and bread was chosen as the

vehicle to obtain a more uniform distribution of iodine intake in the population (Rasmussen *et al.* 2007; Rasmussen *et al.* 2008; Nyström *et al.* 2016; Zimmermann *et al.* 2005).

2.1.3 Dietary iodine sources in Norway

The only natural source rich in iodine is seawater fish and other marine products (Julshamn *et al.* 2001). Although Norwegians traditionally have had a high average intake of fish, this did not secure the iodine intake of inland population groups without access to the sea. Thus goitre used to be widespread wherever fish intake was low (Frey, 1986). In the last 50 decades, fish and fish products have been easily accessible to households in all parts of the countries and Norway has been among the European countries with the highest fish consumption (Nyström *et al.* 2016). According to national dietary surveys, lean and semi-lean species comprise nearly two-thirds while oily fish comprised one third of the total fish intake (The Norwegian Directorate of Health, 2012b; The Norwegian Directorate of Health, 2016). Time trends in fish consumption indicate declining intake and a shift towards more oily fish, like salmon (Sanchez, 2015; National Nutrition Council, 2016). The iodine content in salmon (10 µg/100g) is insignificant compared to iodine concentrations in lean fish, e.g. cod (120 µg/100g) (National Nutrition Council, 2016).

Ever since fortification of cattle fodder with iodine was started in Norway in 1950, iodine deficiency has been eradicated (Frey, 1986). Milk and dairy products have since then been considered the primary source of iodine in the Norwegian diet (Dahl *et al.* 2003a; Frey *et al.* 1993). This is due to a relatively high daily intake of milk and milk product compared to other iodine sources. Even though the main iodine sources in the Norwegian diet today are milk and milk products, and secondly fish and fish products, iodine-containing supplements are also considered to be an important source (Dahl *et al.* 2003b). The iodized salt contains small amounts of iodine that it is not an important source in the Norwegian diet. Food regulations permit the addition of 5 µg I/g NaCl to salt (National Nutrition Council, 2016). This is because only one brand of table salt is fortified with iodine, and this salt is not allowed in industrial food production (Nyström *et al.* 2016; Nordic Council of Ministers , 2014). With an estimated average intake of 3 g table salt per day, iodine-fortified salt only contributes with 15 µg I, which is a small contribution to the recommended intake which ranges from 175-250 µg/day in pregnant women (see chapter 2.1.3).

The iodine content of animal feed is controlled by legislation in Norway. The fortification of cow fodder with 2 mg I/kg as calcium iodiate, $Ca(IO_3)_2$ to protect animal health resulted in milk being an important source of iodine in human diets (Frey, 1986). In 1996, a new regulation in Norway was passed ensuring that cattle should spend at least 8 weeks each summer out of doors, grazing naturally (Minister of Agriculture, 2004). The regulation improves animal welfare, but also makes the animals' feed more vulnerable to local soil-mineral conditions. Because of the seasonal differences in the cattle diet (grazing during the summer and iodine fortified fodder during the winter), there is a seasonally variation in the iodine content in milk. The labelled iodine content on milk cartons is a weighted average over the year. Currently, 20 μg I/100 g milk is the declared content, but recent analytical results from producers indicate a substantially lower content (based on Trøan *et al.* 2016 and personal communication from producers).

Today, there is no recommendation for use of iodine supplementation during pregnancy in Norway (Brantsæter *et al.* 2013). This is different in other countries; The American Thyroid Association, the Developmental Neurotoxicology Society recommend that all women who are pregnant, lactating, or planning a pregnancy should ingest dietary supplements containing 150 μg of potassium iodide per day (Stagnaro-Green, Sullivan & Pearce, 2012).

In Norway, a typical amount of iodine in multi- and mineral supplements for pregnant women is 175 μg. Women with a low intake of iodine-rich food like white fish, eggs and milk products are particularly vulnerable for low iodine intake, and might benefit from using and iodine-containing supplement (Brantsæter *et al.* 2013). Although use of iodine-containing supplements result in increased urinary iodine excretion, there are still unanswered questions related to the impact of supplements on thyroid function and safety related to use of these supplements in pregnancy (Rebagliato *et al.* 2013). Iodine intake both below and above the recommended reference is associated with thyroid disease (Laurberg *et al.* 2010; Zimmermann, 2016). Results from the Norwegian Mother and Child Cohort Study showed that women who used iodine-containing supplements had higher UIE than those who did not use such supplements and that inclusion of milk and seafood in the diet is important to secure optimal iodine nutrition (Brantsæter *et al.* 2007; Brantsæter *et al.* 2009). Because pregnant women in the Nordic countries are generally well nourished and have easy access to milk, seafood and dietary supplements, and because lack of new data supporting changes in intake, the Nordic recommendations from are kept unchanged (Nordic Council of Ministers, 2014).

There is a need for better surveillance and more data on the level of iodine intake that ensures normal thyroid function in both maternal and newborn in the Nordic Countries (Gunnarsdottir & Dahl, 2012).

2.1.4 Recommendations

Due to the limited storing capability of iodine, a regular supply is required. The optimal range of iodine intake is relatively narrow and both low and high iodine intake may interfere with thyroid function (WHO, 2007; Bulow Pedersen *et al.* 2002). According to the Nordic Nutrition Recommendations (NNR), the recommended intake of iodine for non-pregnant adults is 150 μg/day, whereas the recommendation is lower for children and higher for pregnant and lactating women (Nordic Council of Ministers, 2014). Recommendations according to WHO and NNR for different age groups are shown in Table 2-1.

Table 2-1 The recommended daily nutrient intake (RNI) for iodine (μg/day) by age or population group according to WHO (WHO, 2007) and NNR (Nordic Council of Ministers, 2014)

Iodine μg/L Age or population group	WHO*	Age or population group	NNR[b]
Children 0-5 yr	90	Children 2-5 yr	90
Children 6-12 yr	120	Children 6-9 yr	150
		Children 10-13 yr	130
Adults > 12 yr	150	Adults > 13 yr	150
Pregnancy	250	Pregnancy	175
Lactation	250	Lactation	200
*World Health Organization			
[b] Nordic Nutrition Recommendations			

The recommended iodine intakes during pregnancy and lactation in the Nordic countries are 175 μg/day and 200 μg/day, respectively (Nordic Council of Ministers, 2014). The WHO recommends 250 μg/day during pregnancy and lactation (WHO, 2007). The WHO recommendation was increased from 200 μg/day to 250 μg/day in 2007, in consultation with the United Nations Children's Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD, now known as IGN) (WHO, 2007; Andersson *et al.* 2007).

WHO recommends use of iodine-containing supplements in populations with few dietary sources of iodine, and where less than 90 % of households use iodised salt, and the median UIC is less than 100 μg/L (Table 2-2). The Nordic recommendation does currently not have any recommendations for use of supplements.

Table 2-2 Recommendations for iodine supplementation in pregnancy and infancy in areas where less than 90% of households use iodised salt and the median urinary iodine concentration is less than 100 μg/L in schoolchildren.

Population group	Daily dose of iodine supplement (μg/day)	Single annual dose of iodized oil supplement (mg/y)
Pregnant women	250	400
Lactating women	250	400
Women of reproductive age (15-49y)	150	400
Children < 2 years [a,b]	90	200

[a] For children 0-6 months of age, iodine supplementation should be given through breast milk. This implies that the child is exclusively breastfed and that the lactating mother received iodine supplementation as indicated above.

[b] These figures for iodine supplements are given in situations where complementary food fortified with iodine is not available, in which case iodine supplementation is required for children of 7-24 months of age.

It is important to be aware that the recommended daily intake is the amount considered to be sufficient to meet the requirements of 97-98 % of healthy individuals, and intake lower than the recommendation do not necessarily imply deficiency. The WHO recommends monitoring of iodine status in populations by measuring urinary iodine concentrations (UIC) in spot samples and deriving the median UIC. Median urinary iodine concentration is the most commonly used measure for assessing iodine status because >90% of all dietary iodine eventually appears in the urine. Median UIC in the range 100-199 μg /L define an adequate iodine intake in school-aged children and adults (Table 2-3). An median UIC <100 μg /L define an insufficient iodine intake (WHO, 2013). During pregnancy a median UIC in the range, 150-249 μg /L define an adequate iodine intake and a median UIC <150 μg /L define an insufficient iodine intake (WHO, 2013).

Table 2-3 Epidemiological criteria for assessment of iodine nutrition in a population based on median or range of urinary iodine concentration (µg/L) (UIC) in school children/adults and pregnant women (WHO, 2007)

Median UIC, µg/L	Iodine intake	Iodine nutrition
School-aged children[a]		
<20	Insufficient	Severe iodine deficiency
20 - 49	Insufficient	Moderate iodine deficiency
50 - 99	Insufficient	Mild iodine deficiency
100 - 199	Adequate	Optimum
200 - 299	Above requirements	Risk of iodine-included hyperthyroidism in susceptible groups
≥300	Excessive	Risk of adverse health consequences (iodine-included hyperthyroidism, autoimmune thyroid disease)
Pregnant women		
<150	Insufficient	-
150-249	Adequate	-
250-499	Above requirements	-
≥500	Excessive	-
Lactating women[†]		
<100	Insufficient	-
≥100	Adequate	-
Children <2 years of age		
<100	Insufficient	-
≥100	Adequate	-

[a]Applies to adults but not to pregnant and lactating women

[†]In lactating women, the numbers for median UIC are lower than the iodine requirements, because of the iodine excreted in breast milk.

2.1.5 Iodine requirements during pregnancy

Iodine is required throughout the life cycle, but pregnant women and infants are exceptionally vulnerable to iodine deficiency (Laurberg *et al.* 2004; Brantsæter *et al.* 2013; Skeaff, 2011). The iodine requirement during pregnancy is increased because of a rise in maternal T4 production to maintain maternal euthyroidism and transfer of thyroid hormones to the foetus, iodine-transfer to the foetus, especially in late gestation, and a likely increase in renal iodine clearance (Glinoer, 2006; Pearce, 2012; Stagnaro-Green, Sullivan & Pearce, 2012).

The estimated average requirement (EAR) for pregnant women is set to 160 µg/day (Institute of Medicine (IOM), 2001). Iodine balance studies by Delange and coworkers showed that the average iodine retention of full-term infants was 6.7 µg/kg/day (IOM, 2001). With an average foetal weight of 3 kg, the mean retention of a fully developed foetus would be approximately

22 µg/day. Based on balance studies that demonstrated pregnant women to be at balance when consuming iodine in the range from 117 µg/day (22 + 95) to 160 µg/day, the EAR was set at 160 µg/day (IOM, 2001). The proportion of subjects in a population group having iodine intakes below EAR is a better indicator of inadequate iodine intake than the proportion with iodine intakes below the recommended intake (Zimmermann, 2016b). EAR is also used to predict probability of iodine adequacy when more data include iodine intake (or UIC) on at least two days per individual (IOM, 2001).

Adverse effects of iodine deficiency in pregnancy include maternal and foetal goitre, cretinism, intellectual impairments, neonatal hypothyroidism, and increased pregnancy loss and infant mortality. After polycystic ovary syndrome (PCOS), thyroid disease is the second common endocrine-disorder worldwide affecting women of reproductive age, and when untreated during pregnancy is associated with increased risk of miscarriage, placental abruption, hypertensive disorder, and growth restriction (Carmina & Lobo, 1999; Carney *et al.* 2014). Postpartum thyroiditis is the most common form of postpartum thyroid dysfunction and may present as hyper- or hypothyroidism.

Iodine is a nutrient with a narrow window of optimal intake. Excess iodine ingestion in pregnancy may have adverse foetal effects (Laurberg *et al.* 2010; Rebagliato *et al.* 2013). However, the safe upper limit for iodine intake in pregnancy and lactation is not currently well defined. Following exposure to high levels, the synthesis of T4 and T3 is normally acutely inhibited by a process known as the acute Wolff-Chaikoff effect (Wolff & Chaikoff. 1949). The mechanism, although not fully understood, appears to rely on newly formed iodolipids or iodolactones temporarily inhibiting thyroid peroxidase synthesis. If high iodine exposure persists, the thyroid is normally able to escape the acute Wolff-Chaikoff effect within a few days by lowering the expression of sodium iodide-symporter (Figure 2-1) (Eng *et al.* 1999). While most pregnant women can maintain normal thyroid function in the setting of high iodine exposure, women with subtle defects in thyroid hormone synthesis, such as those with Hashimoto's thyroiditis, may be unable to escape from the acute Wolff-Chaikoff effect. Such women can develop iodine-induced hypothyroidism. In addition, the foetal thyroid's ability to escape from the acute Wolff-Chaikoff effect does not fully mature until approximately 36 weeks gestation. Therefore, a large maternal iodine load could selectively cause foetal hypothyroidism. The U.S. Institute of Medicine recommends an upper limit of

1100 μg iodine daily in pregnancy, while World Health Organization (WHO) more conservatively recommends an upper limit of 500 μg per day (WHO, 2007; Institute of Medicine Food and Nutrition Board, 2006). The benefits of correcting iodine deficiency far outweigh the risks of supplementation as long as supplementation is not excessive (Braverman *et al.* 1998).

2.2 The iodine deficiency disorders

Iodine deficiency (ID) is considered to be one of the most important and common nutritional disorders in the world, and has multiple adverse effects on growth and development in mammalians (Nordic Council of Ministers, 2014; WHO, 2007). ID occurs when iodine intake over time is lower than the recommended intake, and it is a natural ecological phenomenon that occurs in many parts of the world. Loss of vegetation from clearing for agricultural production leads to erosion of soil in riverine areas. Tree cutting for firewood results in a continued and increasing loss of iodine in the soil. Combined this leads to low levels of iodine in groundwater locally grown foods in these areas.

When iodine intake falls below recommended levels, the thyroid may no longer be able to synthesize sufficient amounts of thyroid hormone (Delange, 1994). The resulting low level of thyroid hormones in the blood (hypothyroidism) is the principal factor responsible for damage to the developing brain and other harmful effects known collectively as "iodine deficiency disorders" (IDD) (Table 2-5). The adoption of this term emphasizes that the problem extends far beyond simply goitre and cretinism. The classic sign of iodine deficiency (ID) is thyroid enlargement (goitre) and it can occur at any age (Zimmermann, Joste & Pandav, 2008; Zimmermann, 2016). Goitre is a physiologic adaption to chronic ID; as iodine intake falls, secretion of TSH increases in an effort to maximize uptake of available iodine, and TSH stimulates thyroid hypertrophy and hyperplasia (Zimmermann, 2008). In adults, hypothyroidism (myxoedema) can occur (Nordic Council of Ministers, 2014; Zimmermann, 2016).

2.2.1 Iodine deficiency in pregnancy

Normal levels of thyroid hormones are required for optimal development of the brain, and the most critical period is from the second trimester of pregnancy to the third year after birth (Chen & Hetzel, 2010). Consequences include goitre, cretinism, intellectual impairment,

14

growth, retardation, neonatal hypothyroidism, and increased pregnancy loss and infant mortality (Pearce, 2012; Zimmermann, 2013).

Mild-to-moderate iodine deficiency can lead to maternal and foetal hyperthyroidism and impair neurological development of the foetus. The consequences depend upon the timing and severity of the hypothyroidism. The effects of mild to moderate iodine deficiency on foetal neurodevelopment are less clear than those of severe iodine deficiency, but there is concern that even mildly decreased maternal thyroid function in pregnancy may result in cognitive delays in offspring (Zoeller & Rovet, 2004). More studies are needed to confirm this (Skeaff, 2011; Nordic Council of Ministers, 2008; Zimmermann, 2016).

Table 2-4 The spectrum of iodine deficiency disorders (IDD) [a]

Physiological groups	Health consequences of iodine deficiency
All ages	Goitre Hypothyroidism Increased susceptibility to nuclear radiation
Foetus	Spontaneous abortion Stillbirth Congenital anomalies Perinatal mortality
Neonate	Endemic cretinism including mental deficiency with a mixture of mutism, spastic diplegia, squint, hypothyroidism and short stature Infant mortality
Child and adolescent	Impaired mental function Delayed physical development Iodine-induced hyperthyroidism (IIH)
Adults	Impaired mental function Iodine-induced hyperthyroidism

[a] Adapted from WHO, UNICEF & ICCIDD, 2007.

The foetal thyroid does not produce thyroid hormone until approximately 20 weeks of gestation. Prior to this, the foetus is reliant on maternal T4 that crosses the placenta in very small quantities (de Escobar *et al.* 2004). Low maternal levels of thyroid hormones up to mid-gestation, when the foetus is completely reliant on maternal thyroid hormone production, may impair radial migration of neurons to the cortex and hippocampus, and thereby result in

behavioural changes (de Escobar *et al.* 2007). If adequate iodine is not available to produce thyroid hormone in pregnancy, TSH rises and consequently maternal and foetal goitre may develop (Smyth *et al.* 1997).

Severe iodine deficiency is associated with adverse foetal effects including congenital anomalies, decreased intelligence, and cretinism (UNICEF, WHO & IGN, 2007). In areas of iodine deficiency, where thyroid hormone levels are low, brain development is impaired (Zimmermann, 2012). In its extreme form, this results in cretinism, but of much greater public health importance are the more subtle degrees of brain damage and reduced cognitive capacity, which affects the entire population. The mental ability of ostensibly normal children and adults living in areas of iodine deficiency is reduced compared to what it would be otherwise (WHO, 2001).
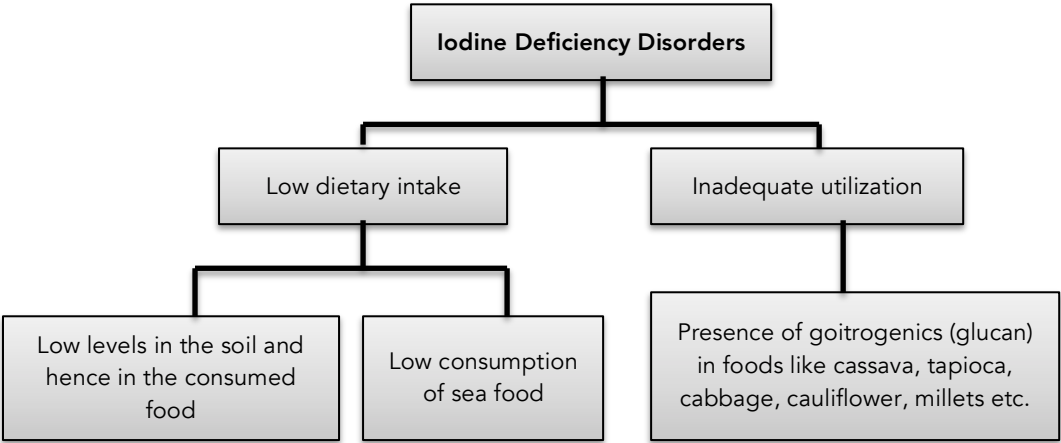
Figure 2-2 Causes of iodine deficiency disorders

2.2.2 Iodine status in the World

It has been estimated that iodine deficiency affects 1.88 billion people worldwide (WHO, 2014), and constitutes the most common cause of brain damage worldwide although it is easy preventable (Andersson, Benoist & Rogers, 2009). An estimated 35% of the world's population has insufficient iodine intake (WHO, 2004). In Figure 2-3, the countries are classified into six different degrees of public health significance with respect to their iodine nutrition estimated from median UIC (Zimmermann & Andersson, 2012b). In 54 countries the population has insufficient iodine intake as indicated by a median UI below 100 μg/L. These countries are classified as iodine deficient: one country is severely deficient, 13 are

moderately deficient and 40 mildly deficient. In 43 countries, the population have adequate iodine intake with a median UI between 100 and 199 μg/L, and iodine nutrition is considered as optimal. In 24 countries, median UI is between 200 and 299 μg/L indicating that the population has more than adequate iodine intake. In these countries, there is a risk of iodine-induced hyperthyroidism in susceptible groups. In five countries, there is excessive iodine intake as shown by a median UI above 300 μg/L. In these countries, there is a risk of iodine-induced hyperthyroidism and other adverse health consequences.

The country estimates in the cross-hatched countries are based on subnational data. The national coverage of iodized salt in these countries is incomplete, there are large variations in the iodine intake and some regions likely remain deficient.
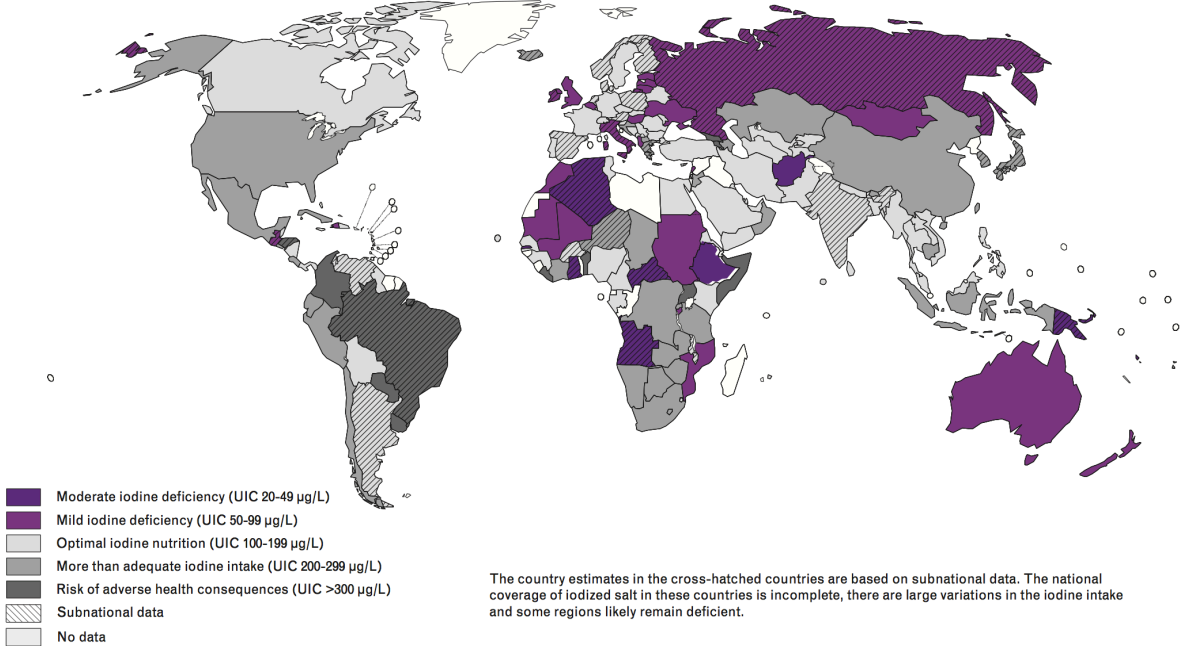
Figure 2-3 Global iodine map Degree of public health significance of iodine nutrition based on nationally representative UIC surveys in 97.4 % of the world's populations of school-age children. Elaborated by Zimmermann & Andersson, 2012b.

Globally, the prevalence of goitre in the general population is estimated to be 15.8%, varying between 4.7% in America to 28.3% in Africa. When comparing the estimates from 2003 with the 1993 estimates, the prevalence of goitre has increased by 31.7% worldwide. The worldwide prevalence of goitre of sixteen percent is above the five percent cut-off used to signal a public health problem (WHO, 2001). An update on iodine status in Europe from 2014 showed that iodine status in pregnancy was adequate in only 38 % of the countries included (Lazarus, 2014). This result is alarming because even mild-to-moderate iodine deficiency

during pregnancy can have harmful consequences for the developing infant (Skeaff, 2011; Zimmermann, 2016).

2.2.3 Iodine status in Scandinavian countries

Iodine deficiency goitre was common in Sweden and Finland during the first decades of the 1900s, but the introduction of iodine fortification of salt resulted in a sharp decrease in the prevalence (Sjöberg, 1980). As recommended by WHO and IGN iodization of salt has been- and still is the preferred strategy to control iodine deficiency (Skeaff, 2011; Zimmermann, 2008; Zimmermann, 2016). In Denmark, mandatory iodization of table salt and bread salt was introduced in 2000 which resulted in a significantly increase in urinary iodine excretion in the population (Rasmussen *et al.* 2014). Severe iodine deficiency and goitre was widespread, particularly in inland areas of Norway during the 1930s and 1940s. However, when iodine fortification of cow's fodder was initiated in the 1950s, milk became a major dietary source of iodine in Norway. The Norwegian population has since then been considered iodine-replete (Nyström *et al.* 2016; Dahl *et al.* 2003a; National Nutrition Council, 2016).

However, recent studies have shown different findings. The MoBa study showed that a relatively high proportion of pregnant women had suboptimal iodine intakes (Brantsæter *et al.* 2013). The Little in Norway Study (LiN), a prospective cohort study, revealed a median UIC lower than 150 µg/L in a pregnant population (Sanchez, 2015). Similar results are demonstrated in the other Scandinavian countries (Nyström *et al.* 2016). A cross-sectional study in Sweden reported a median UIC lower than 150 µg/L (insufficient iodine status) in the pregnant population (Granfors *et al.* 2015).

2.3 Prevention of iodine deficiency

On the grounds of effectiveness and cost the preferred approach according to WHO is that of universal salt iodization. This means that all salt for human and animal consumption should be iodized (Hetzel, 2002). The recommended iodine level is 20-40 mg as potassium iodate per kg of salt (WHO, 1997).

The World Health Organization guideline issued in 2014 recommended iodine fortification of salt as best and most effective strategy for prevention and control of iodine deficiency in

populations living in stable and emergency settings (WHO, 2014). The WHO
recommendation states that mandatory legislation should exist in each country to support salt
iodization. The amount of iodine to be added to the salt depends on availability of other
sources and should be evaluated for all countries individually to avoid insufficient or
excessive consumption of either sodium (salt) or iodine. In normal circumstances, iodine lost
from salt at production site to household is 20%, and another 20% during cooking before
consumption. With an average salt intake of 10 gram per person per day, iodine concentration
in salt at the point of production should be within the range of 20-40 mg of iodine per kg of
salt (i.e., 20-40 ppm of iodine) in order to provide 150 μg of iodine per person per day (Allen
et al. 2006). The iodine should preferably be added as potassium iodate. Under these
circumstances, median urinary iodine levels are expected to vary from 100-199 μg/L.
Women's need of iodine during pregnancy is so substantial that the amount of iodine supplied
by a common model of iodine prophylaxis is likely to be insufficient. Given the increased
daily iodine requirement during pregnancy, additional interventions such as iodine
supplementation should be considered if iodine inadequacy is found.

2.4 Methods to assess iodine status

Several methods are used to assess iodine status in populations. Iodine status was traditionally
evaluated by palpation of the thyroid gland and reported as prevalence of goitre
(Zimmermann & Andersson, 2012). Already in the 1980s, expert groups working to control
ID had recognized the limitations of focusing only on goitre. It was Basil Hetzel that proposed
the term "iodine deficiency disorders (IDD)" to replace "endemic goitre" to describe the
broad spectrum of adverse health effects of ID (Hetzel, 1983), and the emphasis of iodine
monitoring began to shift toward measurement of urinary iodine concentration (UIC).

In addition to UIC, measures of thyroid function are also important when evaluating iodine
status and iodine intervention in a population. The thyroid hormones (TSH, T4, T3) are not
good indicators of mild to moderate iodine sufficiency (WHO, 2008). However,
thyroglobulin, the major protein component of normal thyroid glands, has been shown to be a
sensitive indicator of iodine deficiency (Rohner *et al.* 2014; Vejbjerg *et al.* 2009a).
Calculating iodine intake from dietary assessment is useful for assessing iodine status,
especially in populations where the contribution of iodine from salt is limited, as in Norway
(Rohner *et al.* 2014). However, there is no dietary assessment that is without error (Shim *et al.*
2014; Baranowski, 2013).

2.4.1 Urinary iodine concentration and excretion

The currently recommended method for assessing dietary iodine intake of populations is to measure the concentration of iodine in urine and compare the median UIC to UIC cut-offs established by WHO in order to categorize the iodine status of the population (Andersson, Benoist & Rogers, 2009; Vejbjerg, 2009b). The body has low storage capacity of iodine and the amount excreted in urine reflects the ingested intake. Therefore, urinary iodine is a good indicator of recent iodine intake because ≥ 92 % of dietary iodine is absorbed, and, in healthy iodine-replete adults, > 90 % is excreted in the urine within 24-48 h (Nath *et al.* 1992; Jahreis *et al.* 2001; Zimmermann, 2009).

Urinary iodine can be expressed as a 24-h excretion (UIE; μg/24h), as a concentration (UIC; μg/L) or in relationship to creatinine excretion (μg iodine/g creatinine). Because it is impractical to collect 24-h samples in field studies, UIC are usually measured in spot urine collections (Zimmermann & Andersson, 2012). In healthy well-nourished adults, daily creatinine excretion is fairly constant at about one gram, so expressing the UIE from spot samples in adults as μg iodine/g creatinine approximates the value in a 24-h collection and reduces variations due to hydration status (Vejbjerg *et al*. 2009; König *et al.* 2011).

Nevertheless, in malnourished populations with poor protein intakes, daily creatinine excretion is more variable and often lower than 1 g (Bourdoux, 1998). In these settings, expressing the UIE as μg iodine/g creatinine may introduce greater variation. Due to these limitations and the additional expense of measuring creatinine, the routine co-measurement of creatinine fell out of favour and was replaced by the expression of UIC in μg/L. If a large number of samples are collected, variations in hydration among individuals and day-to-day variations in iodine intake generally even out, so that the median UIC in spot samples correlates well with the median from 24-h samples and with the estimated UIE from creatinine-corrected UICs (König *et al.* 2011). In individual assessment of iodine status, UIE is more precise (Laurberg, 2014; König, *et al.* 2011). Figure 2-4 illustrates the relationship between iodine intake and risk of disease.
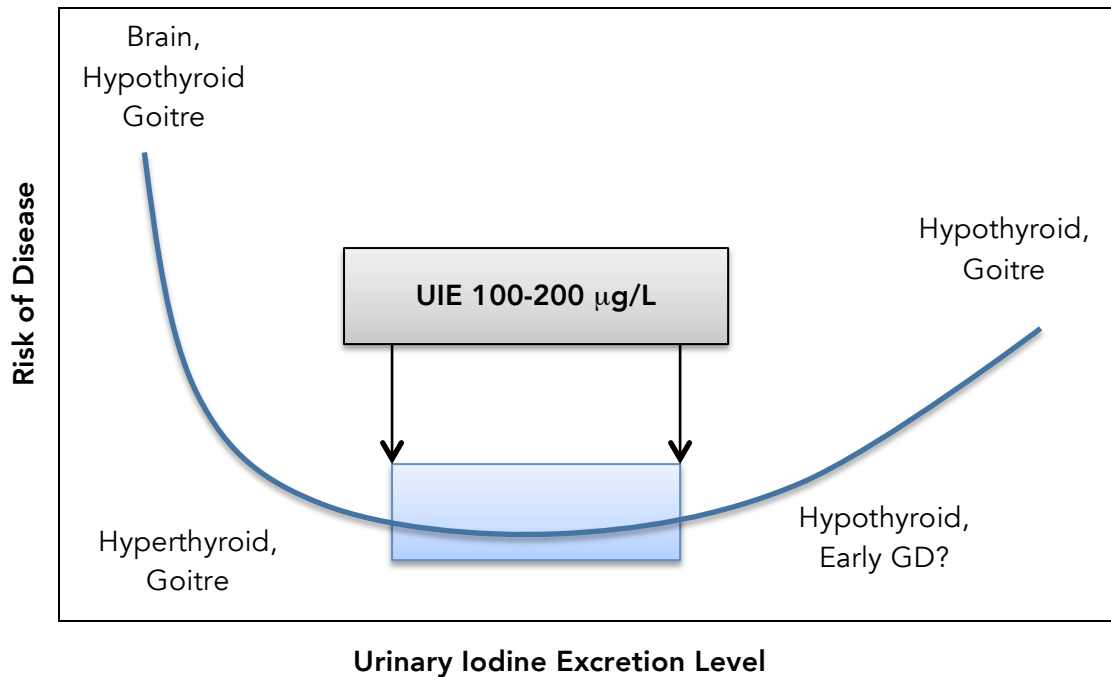
Figure 2-4 Illustration of the theoretical relationship between exposure to a certain iodine intake level over a long period and the risk of developing a thyroid disease. The box indicates the recommended level with a median urinary iodine excretion (UIE) of 100 to 200 µg/L. GD = Graves' disease.
Source: Laurberg, 2014.

WHO, UNICEF and IGN recommends median UIC as the primary tool for assessment of iodine status in pregnancy (WHO, 2007). For the general population, national population-based UI monitoring is recommended in school-age children (SAC) (6-12 years) every 5 years (WHO, 2007). Iodine status in SAC serves as proxy for the general population, as schools are relatively easy to access for large-scale studies in countries at all developmental stages. The recommended study design is a cross-sectional 30-cluster survey design with at least 30 children per cluster (WHO, 2007). A minimum of 100-5000 spot urine samples are required for each group or sub-group, depending on the variation of iodine intake within the population and the precision of the estimates. Classification of iodine nutritional status is based on the population median UIC (WHO, 2007).

However, whether schoolchildren are good proxy for the population groups most vulnerable to ID, such as young children and pregnant women, needs further investigation (Andersson *et al.* 2010). The focus on SAC simplified iodine monitoring, but is too narrow, because the groups most vulnerable to irreversible damage from ID are developing foetuses (via pregnant women) and infants (Zimmermann, 2009). Iodine status in pregnant women or in women of

reproductive age is not necessarily represented by the iodine status of schoolchildren. Women can have low intakes even when SAC have optimal intakes. This may be particularly true in populations eating Western diets since a substantial proportion of total iodine intake in such diets comes from milk, and milk consumption is typically highest in children (Caldwell *et al.* 2011). Because there are insufficient data to estimate the regional or global prevalence of low iodine intake in these important target groups (pregnant women), the median UIC in SAC continues to be used as a proxy for the general population in most surveys (Zimmermann & Andersson, 2012).

Iodine status according to NNR and WHO criteria for iodine intake in pregnancy is described in Table 2-1 (Nordic Council of Ministers, 2014; WHO, 2007). Comparison between the median UIC with WHO cut-off values, where UIC >150 μg/L indicates adequate iodine intake in pregnancy (WHO, 2007). It is possible to estimate daily iodine intake by using UIC. The US Institute of Medicine (Institute of Medicine (US), 2001) has suggested the following equation:

Urinary iodine concentration (μg/L) x 0.0235 x weight (kg) = estimated daily iodine intake

2.4.2 Dietary assessment of iodine intake

The goal of dietary iodine assessment is to quantify the relative contribution of habitual intake from iodine-containing foods in terms of amounts and frequency. The three primary tools to accomplish this include FFQs (Meltzer *et al.* 2008), food diaries/weighed food records (Bath *et al.* 2014a), or 24-hour recall (Mao *et al.* 2015). However, all dietary assessment tools used to measure iodine exposure are imprecise (Zimmermann, Joste & Pandav, 2008; Shim *et al.* 2014). The FFQ method captures iodine rich sources that are irregularly consumed and accounts, to some extent, for day-to-day variation in the overall consumption patterns. Food diaries or 24-hour recalls measure short-term intakes. To capture the day-to-day variation in dietary iodine intake, at least 10 repeated assessment days and/or a large sample size is needed. Dietary assessment can identify the most important food sources of iodine, which can be useful to design or adopt iodine intervention strategies (Rohner *et al.* 2014). The disadvantage by these methods is time-consuming data collection, and only a few food composition databases containing information on iodine rich foods, additionally due to wide variations in iodine content in the specific food item. Dietary recall in general is often

inaccurate with regard to generally underestimates or overestimates of consumption. The quality of iodine data in food composition tables is often poor and depends on whether the food iodine analysis is up-to-date and to what extent natural variability in iodine content is taken into account. Food composition databases generally contain information on the salt content of foods, but they rarely specify if the salt used in processed foods is iodized or not (Rohner *et al*. 2014).

2.4.3 Other measurement of iodine status

Evaluation of thyroid size by thyroid ultrasonography and testing for abnormal levels of TSH, T3, T4 and thyroglobulin, can reflect iodine deficiency (Rhoner *et al*. 2014; Vejbjerg *et al*. 2009a).

TSH

TSH is secreted by the anterior pituary gland and regulates thyroid hormone synthesis and secretion. TSH is the principal screening test for thyroid dysfunction. Serum TSH concentrations are increased when thyroid hormone concentrations are low (hypothyroidism) and decreased when thyroid hormone concentrations are high (hyperthyroidism or thyrotoxicosis).

T4 and T3

T4 and T3 are the hormones secreted by the thyroid gland. As thyroid function diminishes, serum TSH concentrations begin to increase. The presentation with elevated TSH concentrations and normal T4 and T3 concentrations is termed subclinical hypothyroidism. As hypothyroidism progresses, serum T4 concentrations decrease, and the combination of elevated TSH and low T4 concentrations is termed hypothyroidism.

Thyroglobulin

Thyroglobulin is the scaffold protein within which T3 and T4 are synthesized, and small amounts may be secreted into the blood along with T4 and T3 secretion (Rohner *et al*. 2014). Serum thyroglobulin increases due to greater thyroid cell mass and TSH stimulation in areas of iodine deficiency and endemic goitre. Measurement of thyroglobulin by dried blood spot technology to categorize iodine status of populations of school-aged children (WHO, 2008; Zimmermann *et al*. 2013).

Goitre

The diagnosis of goitre is traditionally made when palpation-revealed thyroid lobes are bigger than the terminal phalanx of the patient's thumbs, but a grading system is now recommended (WHO, 2008). Thyroid palpation in areas of mild IDD lacks specificity and sensitivity, necessitating the use of ultrasound to improve diagnostic precision. Although iodine deficiency is the primary cause of goitre, sometimes it is the result of a combination of low intake with high goitrogenic intake.

2.5 Summary

In this chapter I have given a description of the importance of iodine nutrition in pregnancy. In short, iodine is an essential trace element for the synthesis of thyroid hormones. These hormones are involved in growth, development and control of the metabolic processes in the body. Women of reproductive age comprise the most susceptible group for inadequate iodine intake, due to the crucial importance for foetal development. Norway was considered iodine replete for decades, but recent studies in Norway and other affluent countries have indicated that is no longer the case. Hence, the current study was initiated to provide data on iodine status in a large population of pregnant women.

3 Objectives

The overall objective of this study was to assess iodine status in pregnant women in Oslo and Akershus by evaluating urinary iodine concentration (UIC), urinary iodine excretion (UIE), and iodine intake from food and supplements.

The specific objectives were to†:

A. In the large study, assess urinary iodine concentration (UIC) and evaluate status against the WHO recommendation for sufficient iodine status in pregnancy
B. In the sub study, assess both UIC and 24-hour urinary iodine excretion (UIE)
C. For all participants, describe and evaluate 24-hour iodine intake from food and supplements in relation to WHO and Nordic recommendations. Evaluate the agreement between estimated iodine intake and UIC
D. In the sub study, describe 24-hour iodine intake and habitual iodine intake (food frequencies) and the main iodine sources
E. In the sub study, compare the calculated 24-hour and habitual iodine intake (food frequencies). To assess the associations between UIC, UIE and iodine intake
F. For all participants, assess predictors for UIC

In this master thesis the study are divided in two studies; the status study is referred to as the large study and with the highest study population, collecting of spot urine samples for UIC analyse and a questionnaire with short-term iodine intake mapping. The other study is referred to as the sub-study, where 24-hour urine samples are collected, and a more in-depth questionnaire (31 food frequency questions in seven frequencies) for habitual intake, and iodine intake interview from 24-hour recall. The participants were assigned an ID number and data treated anonymously.

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†The specific aims are linked with a letter A, B, C, D, E & F through out this thesis.

4 Materials and methods

4.1 Population and study design

The current master thesis is based on data from a cross-sectional study on iodine status in pregnant women in Oslo and Akershus. The pregnant women were recruited from Mother and Child Health Centres in Oslo, in the southern-east of Norway (about 650 000 inhabitants) and Akershus (about 585 000 inhabitants). In Oslo, 18 healthcare centres are divided in 15 districts, and in Akershus, 19 healthcare centres are divided in 17 districts. For the present study, eight healthcare centres in Oslo and Akershus were selected through convenience sampling and invited to participate (Table 4-1). The sample size was calculated based on the WHO reference ranges (Table 2-2) defining optimal iodine status based on UIC for population groups of at least 500 participants (Vejbjerg, 2009b).

Table 4-1 The included Mother and Child Health Centres in Oslo and Akershus, and distribution of all participants, both for spot urine samples in the large study and 24-hour urine samples in a sub-study

Mother and Child Health Centres	N
Sandvika	148
Asker/Bærum	70
Grünerløkka	148[w]
Kolbotn	100
Lillestrøm	96
Lørenskog	100
Skedsmo	43
Alnabru	99
N	**804**

[w] Included the sub-study participants (n=49)

4.2 Data collection

The data collection for the large study was conducted between February and August 2016, and during November and December 2016 for the sub-study. Participants for the large study were recruited at prenatal care at their Mother and Child Health Centres in eight districts.

The pregnant women were first given information on the study purpose and informed that they have the opportunity to refuse to participate. All pregnant women who can read and write Norwegian were invited to participate. The women who agreed to participate filled in an informed consent and a questionnaire covering background information and data on intake of iodine-rich food and dietary supplements. Midwifes collected the spot urine sample from each women and the questionnaire. Around 50-150 women from each of the eight Mother and Child Health centres participated.

To further analyse the daily iodine variation and to assess the urinary iodine excretion, a sub sample of pregnant women were recruited in a sub-study and asked to collect 24-h urine samples and answer a semi-structured 24-h recall conducted by the project worker. Out of 54 recruited women, 49 pregnant women were included in the study. The six women, who withdrew, fell off due to labour, lack of time or withdrew without giving an explanation. One of the eight Mother and Child Health Centres was asked to recruit women in the sub-study (Table 4-1). All participants were recruited in the waiting room at prenatal care at the Mother and Child Health Centre. As in the large study, the pregnant women recruited to the sub-study were informed about the study, including the study purpose, what participation in the study entailed and description of the different methods used. The women were informed that they had the opportunity to withdraw from the study at any time. All participants received a bag with sterile containers with double lid, a pair of gloves, procedure on how to collect urine, contact information to study leaders, consent form and a six pages questionnaire, including food frequency questions covering 31 food items for habitual iodine intake. The women could choose a day they saw fit to perform the collection. The first morning urine should not be included, but from the second time they urinated and until midnight they had to collect all urine in the containers. The morning after they had to collect the morning urine in a seperate container marked *morning*. The urine samples was stored at <4 degrees Celsius. Time for delivery of the urine was agreed upon at the day of recruitment, and the collecting point of 24-h urine samples from the 49 participants was performed both at the Mother and Child Health Centres and for most pregnant women at the participant's home. In addition to report their habitual food intake, the pregnant women had to answer a 24-hour recall interview covering the day of 24-h urine collecting urine. The women were asked to continue with their normal food intake. After delivery of urine samples, completing all the questions, participants received an information sheet about iodine and recommendations for iodine intake.

Table 4-2 The number of participants included in the current study

Participated	Large study	Sub-study	Total
Questionnaire	755	49	**804**
UIC	728	49	**777**
UIC + questionnaire	728	49	**777**

Spot urine samples were collected from 728 of 755 (96.4%) participating women in the large study for UIC (Figure 4-1, Table 4-2). Twenty-seven women who had filled out the questionnaire and consent form, but did not provide a urine sample. Spot urine samples from women who did not return the questionnaires (n=8) were excluded from the study. In total, including the morning urine samples from the participants in the sub-study, spot urine samples were delivered from 777 of 804 (96.6%) participating women in this study.
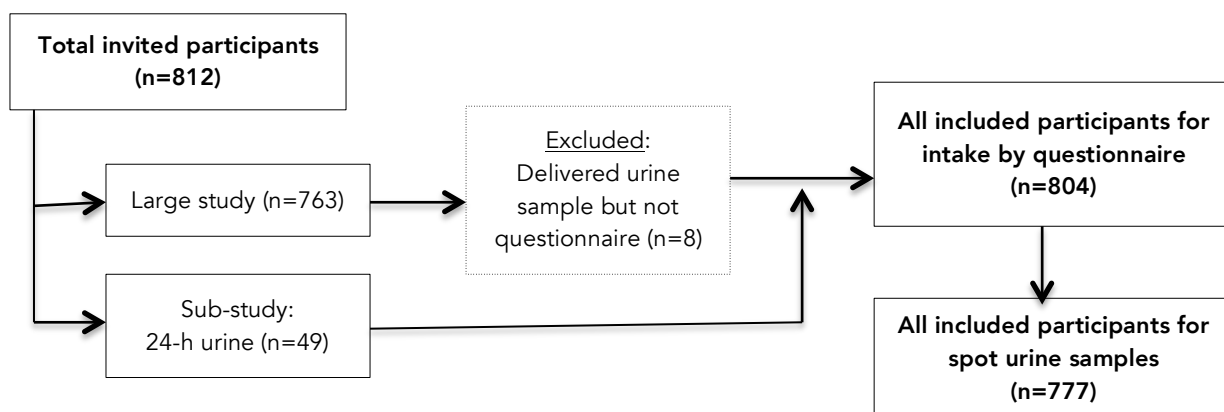
Figure 4-1 Overview of recruited study participants in the current study

4.2.1 Determination of urinary iodine concentration

Urine spot samples were stored in refrigerator (4°C) at each Mother and Child Health Centre, until they were brought to HiOA for storage at -80° C until analysis. Measurement of the iodine concentration was performed by Norwegian University of Life Sciences in Aas (Faculty of Environmental Sciences and Natural Resource Management). After defrosting from -80 Celsius degrees, 1.5 ml urine was pipetted out from all urine samples to analyse. The samples were diluted ten times with an alkaline reagent of 2% (w/v) NH_4OH, 4% (w/v) 1-Butanol, 0.1% (w/v) H_4EDTA and 0.1% (w/v) Triton X-100. The samples were analysed with use of Agilent 8800 ICP-QQQ-MS. Certified reference materials (CRM) used for quality control was Trace Elements Urine L-1 (78 µg/L) and Trace Elements Urine L-2 (280 µg/L)

from Seronorm. All the measured values of CRM were within the certified range. The same procedure was followed for blank samples as other samples, and all had values under the limit of detection (LOD, 0.4 µg/L) or limit of quantification (LOQ, 1.2 µg/L). The detection and quantification limits were calculated at three and ten times the SD of blank samples, respectively.

4.2.2 Assessment of urinary iodine excretion

Participants were given one 0.5 L and two 1 L plastic bottles with wide opening and screw capped double lids for collecting morning urine and 24-h urine. The 24-h urine samples were stored at <4 degrees Celsius in the time period prior to handling. During handling, the 24-h urine volume was determined on electronic scales, assuming 1 g equal to 1 ml. Aliquots of 1 ml were transferred by pipetting to 50 ml vials for determination of UIC as described above. A laboratory at STAMI (Statens Arbeidsmiljøinstitutt) was used for weighing and pipetting. Participants had been asked to record an approximate volume if some urine unintendedly had been omitted from the 24-h sample. The volume of their morning spot urines as well as reported omissions (n=15, mean volume 650 ml). Given the UIC of the 24-hour urine samples, UIE was calculated in SPSS by multiplying UIC and the total urinary volume;

$$Urinary\ iodine\ excretion\ (µg/24h) =$$
$$Urinary\ iodine\ concentration\ (µg/L) * Total\ urinary\ volume\ (L/24h)$$

4.2.3 Assessment of iodine from food and supplements

In order to assess iodine status in the group of pregnant women, Nordic and WHO criteria for iodine intake in pregnancy was used, as described in Table 2-2 (Nordic Council of Ministers, 2012; WHO, 2007). For the large study, the questionnaire included three questions on iodine intake of iodine rich foods during the last 24-hours, based on a food frequency questionnaire developed and validated to measure diet of pregnant women (Meltzer et al, 2008; Brantsæter et al, 2008). The first question asked for number of glasses of cow's milk and milk based drinks including milk in coffee and tea, the second question asked for portions of lean and/or fatty fish for dinner and/or bread, and the third question asked about number of eggs or dishes with egg. The reported amount was multiplied with the iodine concentration in the specified food/dishes to obtain iodine amount. For fish and egg dishes, a weighted estimate of commonly consumed items was applied.

For calculating habitual iodine intake, participants in the sub-study reported their average intake of thirty-one different food types with seven alternative answer options (food frequencies ranging from rarely/never to 5 times daily or more). Of the 31 food questions, three questions assessed intake milk and dairy products, four assessed intake of fish and fish dishes, and one assessed intake of egg and egg-dishes. The frequency answers were converted to daily amounts and multiplied with iodine concentrations in the same manner as for questions about food intake over the last 24 h in the large study. For the intake calculations that only relied on milk, fish and eggs, an additional amount of 30 μg was added to account for iodine contributed by other foods and dishes. A similar approach was used in the iodine report from the National nutrition council (National Nutrition Council, 2016) when iodine intake was estimated from the amounts of fish, milk and eggs reported in the National dietary survey Norkost-3.

The Norwegian Food Composition Table provides information about the nutrients- and energy content of food and beverages in Norway, both raw and prepared foods and dishes, and including the description of the food, a food code and the nutrient composition per 100 grams of edible food (The Norwegian Food Safety Authority, The Norwegian Directorate of Health & University of Oslo, 2015). Iodine concentrations in Norwegian Food Composition Table (Matvaretabellen) were used except for milk and egg. Because recent analytical results for iodine concentration in milk and eggs has been lower than the values in the food composition table, for milk, 13 μg/100g were used instead of 20 μg/100g (information from producers), and for eggs 30 μg/100g were used instead of 49 μg/100g (National Food Authorities, 2017).

In the sub-study, the 24-hour recall interview was performed as a semi-structured with a interview guide. The 24-hour recall comprised all food and drinks consumed, not only iodine rich foods as in the 24-h questions in the large study. The participants were asked to recall everything they ate and drank from they woke up, and the next 24 hours, even night snack. If they ate meals outside that they did not prepare them selves, or if they prepared meals them selves, they had to list up the ingredients and approximate measurements, to make a most thorough calculation. A food number for food items in the Norwegian Food Composition table was assigned to each food and beverage items reported by each participants. To code the 24-h recall interviews, Excel version 14.2.0 (2010) was used. The amounts of all food items and beverages were coded as grams. For items that were described in household units (e.g.,

ml, tablespoons, pieces or a handful) the diet planner (web-based programme) "Kostholdsplanleggeren" was used to calculate food items or beverages into gram. The diet planner contains an overview of what different food weighs per item, how much a portion weighs and how much a decilitre of a certain food or beverage weighs. The diet planner is based on The Norwegian Food Composition Table and is developed by The Norwegian Directorate of Health and The Norwegian Food Safety Authority, 2015. For items and dishes that were not in the Food Composition Table, every ingredient was manually coded. This applied either when the participant described the single ingredients for a dish, or named the dish with unknown content. A Google search with the name of the item was conducted to find the content (e.g., pumpkin soup, homemade summer rolls, Thai-curry courses). The name of the course was typed in Google, which often resulted in thousands of recipes. For simplicity, the first or second option was chosen based on relevance.

Not all foods and beverages in the Norwegian Food Composition Table had a value for iodine. For composite dishes, a dietitian in the project used recipes to estimate iodine content i.e. dishes including milk, fish and eggs. For other items without a value for iodine, the value was sat to 0. This was true for foods and beverages that are probably not significant for iodine intake in the Norwegian diet, like soda. Not all the food items and beverages with a natural content of iodine was given a value and in those cases the items got the same value from similar products.

FoodCalc is a programme developed to calculate intake of nutrients. The FoodCalc programme was written by Jesper Lauritsen and funded by the Diet, Cancer and Health project at the Danish Cancer Society (Lauritsen, 2005). The programme requires a list with amounts of different foods and beverages consumed and a food composition table. FoodCalc was used to calculate the amount of iodine in the diet. A protocol was developed along with the coding process to act as a standardized approach for foods and beverages that were not found in The Norwegian Food Composition Table, and for items that was not specified. For items that were not found in The Norwegian Food Composition Table, a similar product was used instead. In cases were the participants remembered the name of the food or beverage consumed, like cheese, the same type or brand was always used (in this example; *Norvegia cheese*). The type or brand chosen as reference value in the protocol was based on the most common product in Norway. Because of small differences in iodine value within the different

food and beverage groups listed in the protocol, the iodine values used probably does not differ significantly from the true values.

4.2.4 Assessment of iodine from dietary supplements

In the large study, the questionnaire filled in by the participants included a question about habitual use of all dietary supplements. Participants were asked to report each supplement by name and how many times weekly each supplement was taken. For the participants in the sub-study, use of iodine containing supplements were reported in the 24-h recall interview. Most of the participants only listed the name of the supplements used, so the process of finding the iodine content in the supplements, the pharmacy and health shops were approached. All supplements were coded and the amount of iodine provided by iodine containing supplements was calculated separately before the data on iodine from supplements were added as a variable in SPSS.

4.2.5 Other variables

Self-reported pre-pregnancy and current weight and height were collected via the background form and used to calculate body mass index (BMI) (kg/m^2), which was divided into WHO categories (<18.5, 18-5-24.9, 25-29.9, ≥30 kg/m^2). Parity was divided into three categories (0 = nulliparous, 1 = primiparous, ≥2 = multiparous) and was measured as the number of previous pregnancies. The other countries of origin were categorized in rich, medium rich and poor based on Human Development Index (HDI). Gestational age at participation was both divided into three trimesters (1 = 0-12 weeks, 2 = 13-28 weeks, 3 = 29-42 weeks), and in nine categories (5-8 weeks, 9-12 weeks, 13-16 weeks, 17-20 weeks, 15-28 weeks, 29-32 weeks, 33-36 weeks, 37+ weeks) (Figure 5-2). In statistical linear regression analysis, length of education was divided into two categories (no higher education, and higher education in college/university).

4.3 Statistical methods

All analyses were performed using the statistical software IBM SPSS 23 (SPSS Inc., Chicago, III., USA), IBM SPSS Statistics version 24 (SPSS Inc., Chicago, III., USA). Figures and tables were made using SPSS 23, Microsoft Excel version 14.2.0 (2010), and Microsoft Word Version 14.2.0 (2010). Normally distributed data were presented as mean ± SD. Non-

normally distributed data were presented as median (25th-75th percentiles) values. UIC, UIE, short-term iodine intake from food and supplements, and habitual iodine intake were checked for normality using Q-Q plots and the Shapiro-Wilk test. Due to the skewed distribution, non-parametric tests were used. Independent group differences were examined using Mann-Whitney U-test and dependent group differences were examined using Wilcoxon's signed rank test. Spearman's rank correlation was used to evaluate the linear relationship between continuous variables.

The UIC was used as dependent variable in multiple linear regression analyses. Because of skewed distribution, this dependent variable was log-transformed (lnUIC). All socioeconomic variables and iodine intake were selected to find candidate variables inclusion in the model. After linear association ($p < 0.10$), the following variables were included in the initial model: maternal age, gestational age, smoking, low metabolism and mean daily use of iodine-containing supplement. Further, these variables were included in a multivariate logistic regression model ($p < 0.10$) and presented in the final model. P-values < 0.05 was considered statistical significant. All covariates showing a linear association ($p < 0.10$) in the crude regression models were included in a preliminary multiple regression model. Excluded variables were reintroduced and those who were still significantly associated in this model ($p < 0.10$) were retained in the final model. Analysis of the residuals was performed in order to examine the fit of the model.

4.4 Ethical considerations

The present study was conducted according to the guidelines in the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Norway (2015/1845). All information was treated confidentially.

5 Results

5.1 Study population

Background characteristics of all study participants are presented in Table 5-1. The participants in this study varied with regard to age (mean: 31 years, range 18-44 years) and pre-body mass index (mean: 23.7 kg/m^2, range 15.2-47.1 kg/m^2). At time of participation the women were approximately 29 weeks pregnant (range 4-41 weeks), and 53% and 37% were expecting their first or second child, respectively. Only one percent of the pregnant women were breastfeeding. Ninety-seven percent of the women were married or cohabiting.

Twenty-three percent of the study population were born outside of Norway. Top countries of non-Norwegian origin represented were Sweden (15%), Poland (6%), Pakistan (6%), Germany (5%), Denmark (4%) and Philippines (4%). Thirty-three percent of the participants reported use of iodine-containing dietary supplements during pregnancy. Ten of ninety women who reported smoking before pregnancy were still smoking in pregnancy. Approximately five percent of the participating women reported having thyroid disease diagnosis, with most (4%) having low metabolism. Approximately three percent reported use of Levaxin, a thyroid hormone replacement medication, at the time of participation.

Table 5-1 Socio-economic, behavioural characteristics and anthropometric measurements of 804 study participants

Characteristics	n (%)
Age[w]	31.05 ± 4.42
Prior BMI, kg/m²[w]	23.68 ± 4.12
Current BMI, kg/m²[w]	27.37 ± 4.49
Gestational age[a]	
1 trimester	28 (3.5)
2 trimester	344 (43.1)
3 trimester	426 (53.4)
Parity	
Nulliparous	426 (53.0)
Primiparous	296 (36.8)
Multiparous	82 (10.2)
Born in Norway	**620 (77.1)**
Not born in Norway	**184 (22.9)**
Rich country	71 (8.8)
Medium rich country	52 (6.5)
Poor country	61 (7.6)
Marital Status	
Cohabiting	429 (53.4)
Married	347 (43.2)
Single	19 (2.4)
Other	9 (1.1)
Education	
Lower secondary school	25 (3.1)
Higher secondary school	137 (17.0)
< 4 years of University[b]	334 (41.5)
≥ 4 years of University[b]	308 (38.3)
Employment status	
Employed	696 (87.7)
Stay at home/Unemployed	30 (3.8)
Student	38 (4.8)
Other	30 (3.8)
Use iodine supplement	**263 (32.7)**
Smoking during pregnancy	**10 (1.3)**[c]
Self-reported use of dry snuff	**10 (1.3)**[c]
Thyroid disease	**38 (4.7)**
Low metabolism	32 (4.0)
High metabolism	6 (0.7)

[w]Mean ± Standard deviation
[a]1 trimester = 0-12 weeks, 2 trimester = 13-28 weeks, 3 trimester = 29 weeks-birth
[b]University or University College
[c]Daily amounts ranged from 1-10 cigarettes, both occasionally and daily use

The specific aims are linked with a letter A, B, C, D, E & F throughout this chapter.

5.2 Urinary iodine concentration and status evaluation (A)

The median urinary iodine concentration in this pregnant study population was 92 μg/L. UIC status according to trimesters is presented in Table 5-2, and the frequency distribution of UIC is shown in Figure 5-1.

Table 5-2 Descriptive of iodine status by urinary iodine concentration (UIC, μg/L) in 777 pregnant women for all and by trimester

UIC, μg/L

	Median	25th and 75th percentile	Mean	SD	Min, max
All participants	92.0	59.0, 140.0	113.6	86.0	11, 860
1st Trimester	91.5	42.5, 172.5	114.9	75.1	23, 280
2nd Trimester	95.5	64.0, 140.0	118.5	95.1	14, 860
3rd Trimester	91.0	58.0, 130.0	109.7	79.8	11, 660

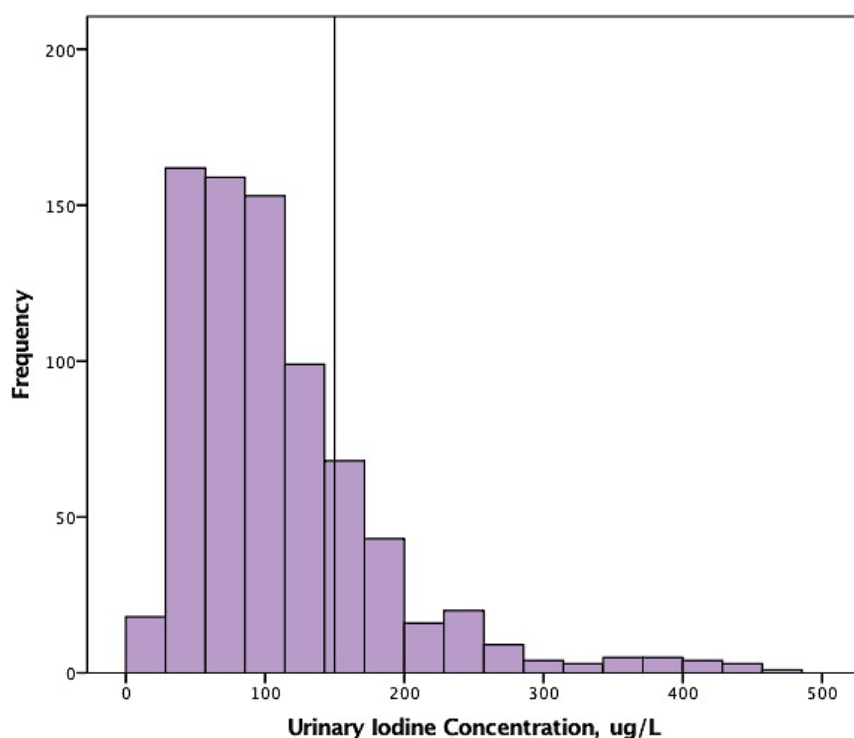**Figure 5-1** Histogram illustrating the urinary iodine concentration in pregnant women (n=772) after exclusion of 5 subjects with UIC>500 μg/L. The vertical line marks sufficient UIC from ≥150μg/L according to WHO, 2007.

With regard to the characteristics shown in Table 5-1, there was a borderline significant negative correlation between UIC and gestational age (the only infant characteristic), showing a trend towards lower UIC with increasing gestational age (r=-0.7, *p*=0.06). Associations between UIC and maternal characteristics, iodine intake and supplement use, will be presented later in the result chapter.

Table 5-3 Frequency distribution of urinary iodine concentration in 777 pregnant women in Oslo and Akershus, categorized according to WHOs criteria for assessing iodine nutrition (WHO, 2007)

UIC, μg/L	N	%	Cum%
<150	595	76.6	76.6
150-249	137	17.6	94.2
250-499	40	5.1	99.4
≥ 500	5	0.6	100
Total	*777*	*100*	

According to WHOs criteria for assessing iodine nutrition for pregnant women based on median UIC, iodine nutrition in pregnant women was insufficient. Seventy-seven percent of the participants had UIC below 150 μg/L (Table 5-3). Only 17.6 % of the pregnant women had UIC in the range of 150-249 μg/L, which is considered as desirable, while approximately 6% had a concentration above 250 μg/L, which according to WHO is above requirements (250-499 μg/L) or excessive (≥500 μg/L). Figure 5-2 shows the percentage distribution of median UIC among the women.
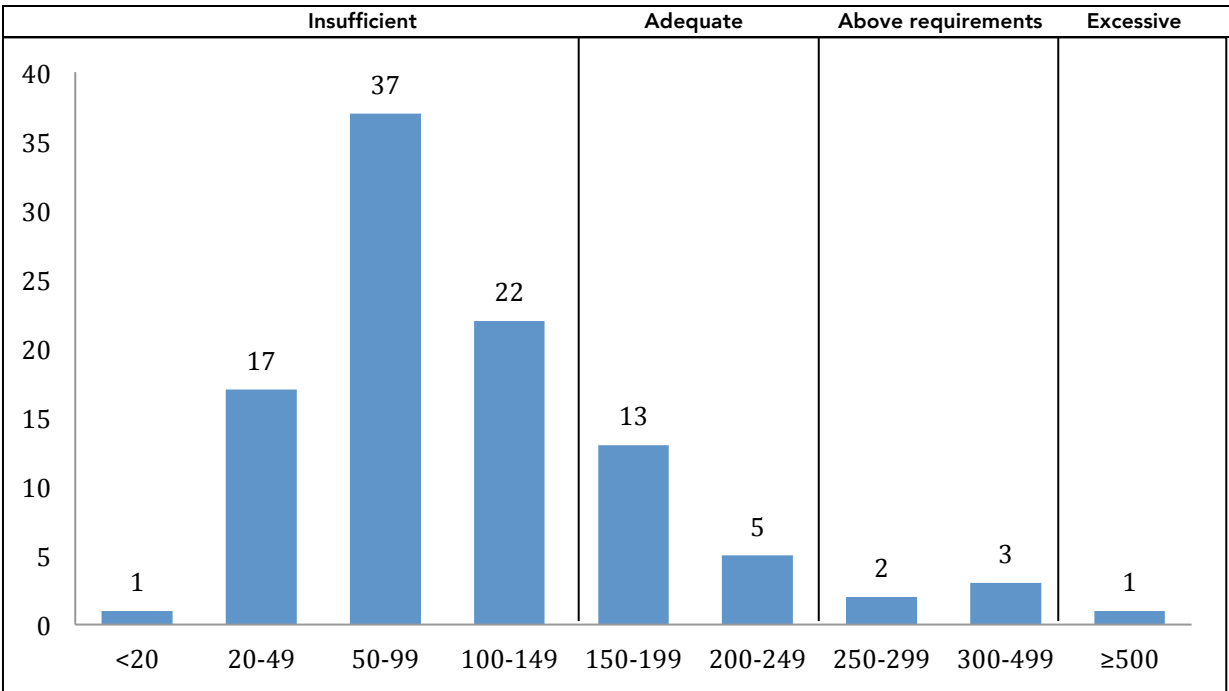
Figure 5-2 Frequency distribution of urinary iodine concentration (UIC, µg/L) in pregnant women (n=777) and prevalence in iodine deficiency categorized according to WHOs criteria for assessing iodine nutrition shown in percent (WHO, 2007)

5.3 Urinary iodine concentration and 24-hour urinary iodine excretion in sub-study participants (B)

The median UIC for participants in the sub-study group was 91 μg/L (range: 24-250 μg/L) in the 24-hour urine sample, and 110 μg/L (range 35-340 μg/L) in the morning urine sample (Figure 5-3 and Table 5-4), the difference was not statistically significant (p=0.082).
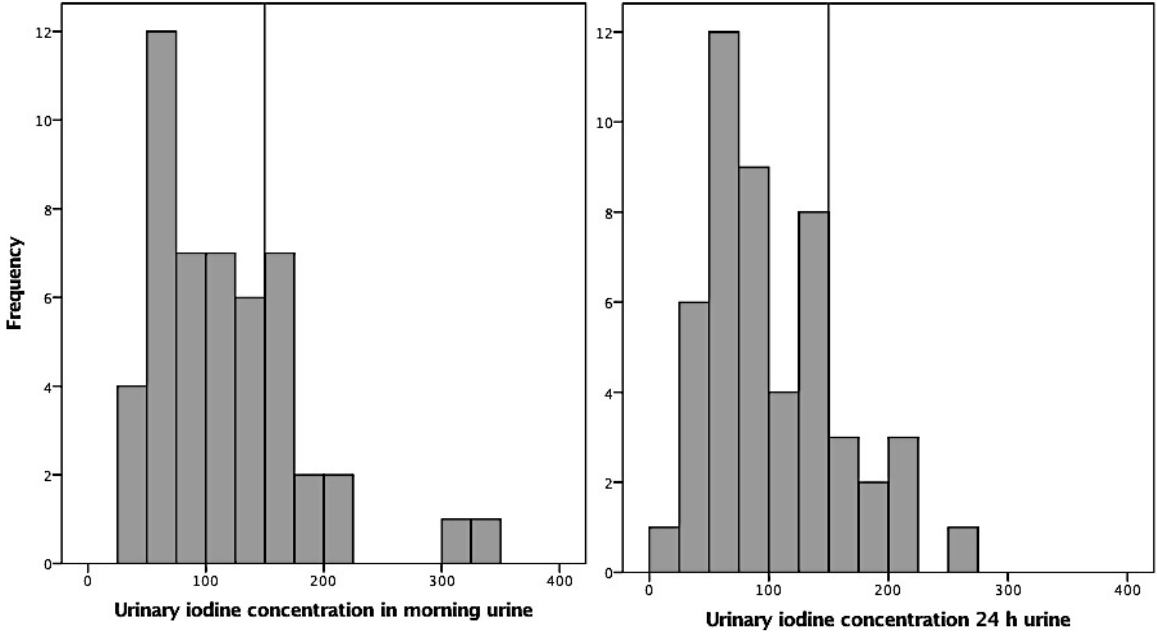
Figure 5-3 Frequency distribution of urinary iodine concentration (μg/L) in morning sample and total urine sample for pregnant women in a sub-study (n=49). The vertical reference line is set at 150 μg/L

The total excreted 24-hour urine volume was normally distributed, with a mean (median) volume of 1.43 L (1.39 L), ranging from 0.45 L to 3.1 L. Using information about 24-hour volume, the urinary iodine excretion (UIE) was computed. The median UIE in this group was 120 μg/24h (range 43-309 μg/24h) (Table 5-4). Both UIC and UIE were skewed.

Table 5-4 Distribution of urinary iodine concentration (UIC) in morning spot and 24-hour sample, and urinary iodine excretion (UIE) in 49 pregnant women

		Percentiles			
	Median	5	25	75	95
UIC (µg/L)					
Morning spot	110	41	66	150	265
Total 24 h UIC	91	32	61	140	220
UIE (µg/24h)	120	69	83	181	272

There was a strong positive correlation between UIC and UIE (r=0.75, *p*<0.001) (Figure 5-4). However, the UIC differed with increasing 24-hour urine volume (hydration status) as illustrated in Figure 5-5.
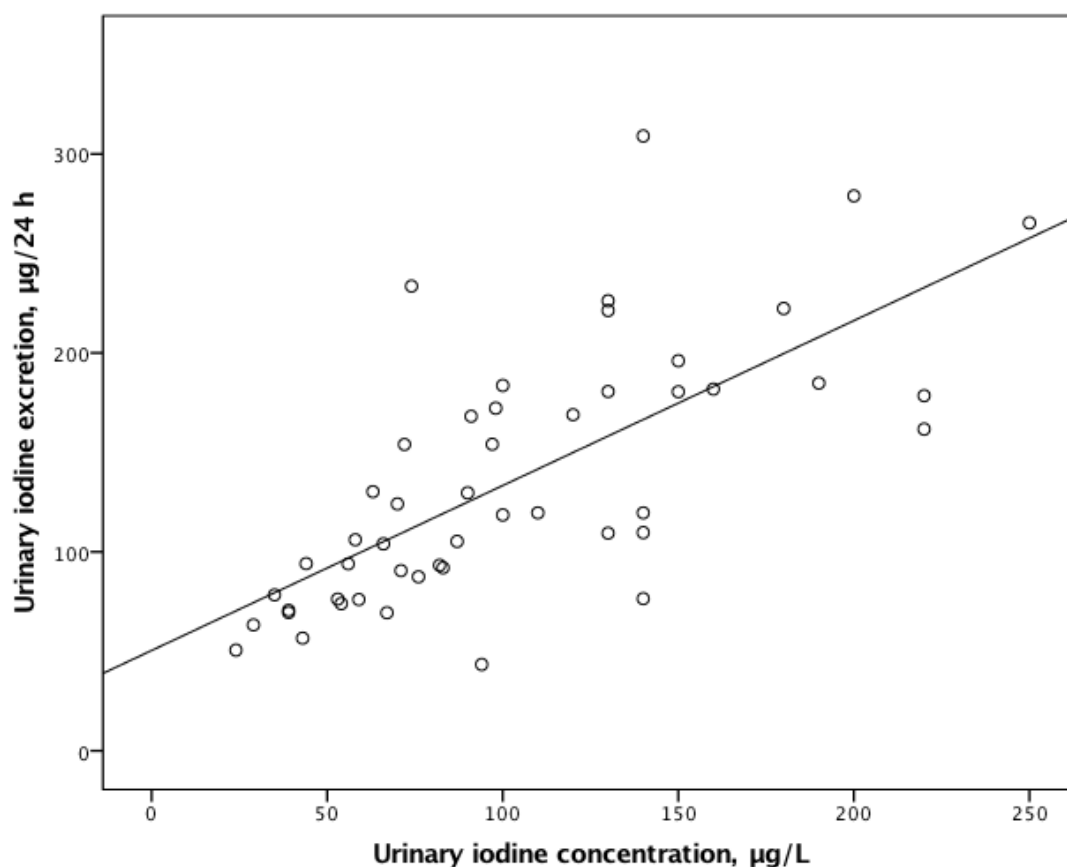
Figure 5-4 Scatterplot illustrating the correlation between urinary iodine concentration (µg/L) in X-axsis, and urinary iodine excretion (µg/L) in Y-axis, in pregnant women in a sub-study (n=49), R^2 = 0.496

When evaluating the UIC by the total excreted urine volume, the urinary iodine concentration correlated significantly negative with volume of urine (*p*=0.002) (Figure 5-5). Higher volume urine was correlated with lower UIC.
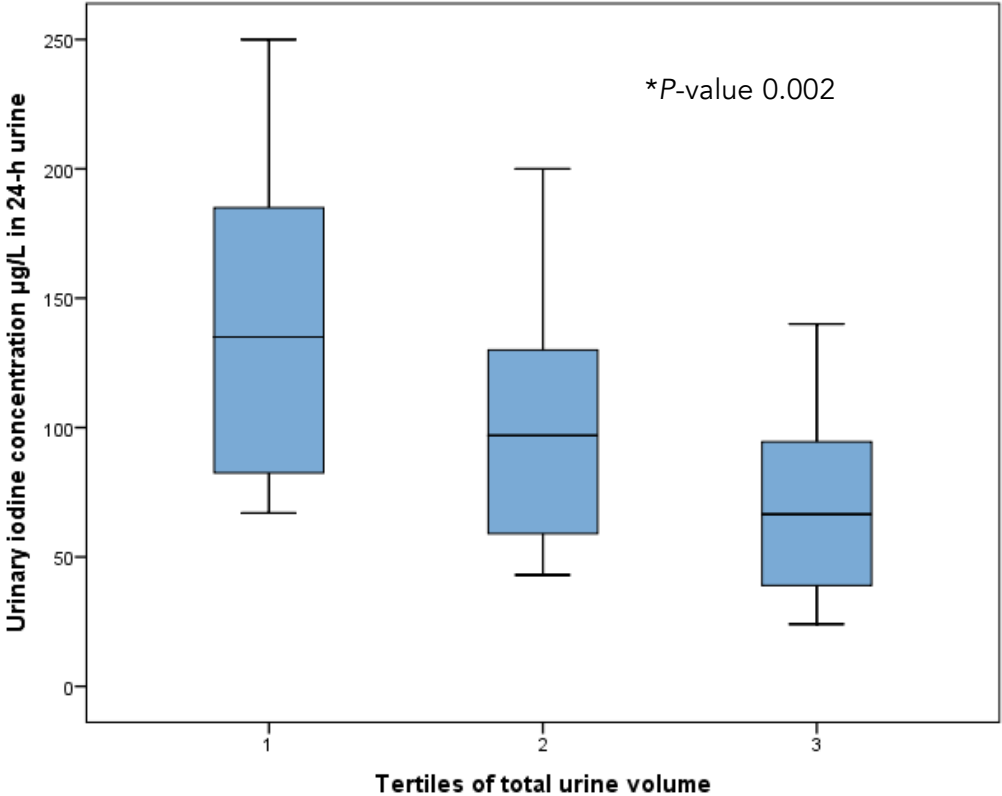
Figure 5-5 Urinary iodine concentration in 24-hour urine samples by tertiles of total urine volume in 49 pregnant women in a sub-study. The horizontal line illustrates the median UIC for the three tertiles of urine volume; the boxes indicates the interquartile range (IQR) (IQR: 25th percentile to 75th percentile); and the whiskers represent observations within 1.5-times the IQR.

5.4 The 24-h iodine intake from food and supplements in all participants (C)

The median iodine intake from iodine-containing food items the last 24 hours was 110 µg/day (range 18-667 µg/day). From food only, eighty percent had an intake below estimated average requirement (EAR), eighty-one percent below the Nordic recommendations, and ninety-six percent below the WHO recommendations.

The median iodine intake from both food and supplement was 148 µg/day (range 18-689 µg/day). Evaluation of median total iodine intake in relation to recommendations showed that a large proportion of pregnant women had inadequate iodine intake, with 25.1 % having iodine intake below 100 µg/day (Table 5-5). A total of 45.1 % reached the Nordic recommendation (175 µg/day) and 26 % reached the WHO recommendation. More than half of the women (54.4%) had total iodine intake below the IOM estimated average requirement (EAR) of 160 µg/day for pregnant women. Eighty percent had an iodine intake below the IOM EAR, from food only.

Table 5-5 Prevalence of the calculated 24-hour iodine intake from food and supplements in µg/day given as percent in each category (n=804)

Iodine intake	N	%
< 100 µg/day	202	25.1
100-174 µg/day	240	29.9
175-249 µg/day	154	19.2
≥ 250 µg/day	208	25.9

Under one percent (n = 5) had an iodine intake over 500 µ/day, which is excessive according to WHO. When excluding these participants, 25.2 % had a total iodine intake of 250-499 µg/day, which is in the desired range according to WHO. Forty-four percent of the pregnant women had an iodine intake within the Nordic recommendation (175-499 µg/day).

5.4.1 Use of iodine-containing supplements

Iodine was obtained from supplements in 263 (32.7%) of the women, and the median iodine intake contributed by supplements in this group was 175 µg/day. The participants who reported use of iodine containing supplements had a significant higher UIC than non-iodine

supplement users (Figure 5-6). The median UIC and median iodine intake for non-supplement users was 83 μg/L and 110 μg/day (n =541), while median UIC and total iodine intake for supplement users were 120 μg/L and 285 μg (n = 263).

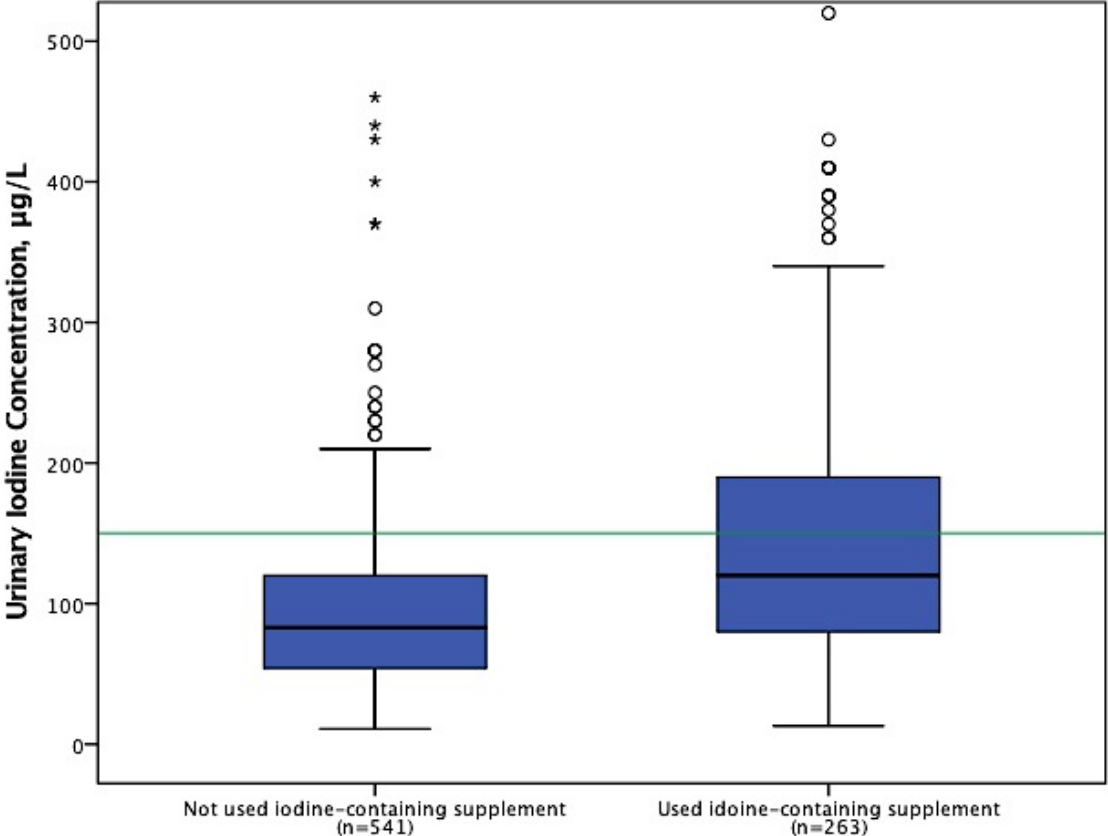**Figure 5-6** Urinary iodine concentration for pregnant women distributed by use of iodine containing supplements. The horizontal green line marks (UIC=150) the cut-off value for UIC from WHO (n=777) The horizontal line in the boxes illustrates the median UIC; the boxes indicates the interquartile range (IQR) (IQR: 25th percentile to 75th percentile); and the whiskers represent observations within 1.5-times the IQR.

5.4.2 The agreement between dietary iodine intake and UIC

There was a significant, but weak positive correlation between calculated 24-hour iodine intake from food and urinary iodine concentration (r = 0.07, *p* = 0.038), but only borderline significant in the group of non-supplement users (r = 0.09, *p* = 0.051) (Table 5-6). When taking iodine from supplements into account, the correlation between the total calculated 24-hour iodine intake (food and supplements) and UIC was strong (r = 0.26, *p* < 0.001). However, the strongest correlation with UIC was seen for iodine from iodine-containing supplements alone (r = 0.30, *p* < 0.001).

Table 5-6 Correlation between 24-hour iodine intake from food, supplements and total iodine intake (food and supplements) and urinary iodine concentration in 777 pregnant women

Correlations for UIC, μg/L Spearman's rho	r	*p*
24h iodine intake from food	0.074*	0.038
24h iodine intake from food non-supp[a]	0.085	0.051
24h iodine supplement	0.289***	<0.001
24h iodine intake from food and supplements	0.257***	<0.001

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed)
***. Correlation is significant at the 0.01 level (2-tailed)
[a] Non-supplement users (n = 541), supplement users excluded

For the iodine containing food items studied, there was a positive significant correlation between intake of milk last 24 hours and UIC (r = 0.074, *p* = 0.047). There was no significant correlation between UIC and the other food items lean fish, fatty fish and eggs).

5.5 Description of 24-hour and habitual iodine intake (food frequencies) in sub-study participants (D)

The distribution of iodine intakes calculated from food intakes during the last 24 hours and habitual iodine intake calculated from food frequency questions are presented in Table 5-7. Based on 24-hour recall, median iodine intake from food only was 114 µg/day in 49 pregnant women. When including intake of iodine from iodine-containing supplements, total median iodine intake was 143 µg/day. Calculated iodine intake based on the 31 food frequency questions was 117 µg/day, and 149 µg/day when including iodine from supplements. The intake range was larger for the 24-h recall (18-403 µg/day) than for the food frequency estimate (50-206 µg/day). However, although the estimates differed both with regard to method and time frame, there was no statistical difference between iodine intake from food, only (p=0.99), or the total iodine intake (p=0.99) by the 24-hour recall and the habitual food intake questions.

Table 5-7 Calculated intake of iodine from food and total iodine (food and supplements) by food intakes reported in the 24-hour recall and habitual (frequency questions) in 49 pregnant women

Iodine, µg/day	Median	25th-75th percentile	Min, Max	Mean ± SD
24-h intake from food[a]	114	78, 149	18, 403	128 ± 75
24-h total intake[a]	143	101, 289	18, 403	188 ± 106
Habitual intake from food[b]	117	95, 147	50, 206	122 ± 37
Habitual total intake[b]	149	109, 268	56, 361	182 ± 90

5.5.1 Main dietary iodine sources

The distribution of food groups as sources of iodine for the pregnant women showed that the group 'milk and dairy products' was the major contributor to iodine intake according to intake calculations for the 24-hour recall (55%) and for habitual intake (45%) (Figure 5-7 and 5-8). The second most important source was 'fish and seafood' which contributed with 18% (24-hour recall) and 25% (habitual intake). It should be noted that the categorisation of food intakes into food groups differed for the 24-hour recall where food groups were defined based on the food numbers in food composition table, while in the frequency questions, the food

groups were defined based on each question. Still, the overall picture showed a comparable ranking of sources.

When taking into account the amount of iodine contributed by iodine-containing dietary supplements, the mean contribution of the food groups were smaller and dietary supplements contributed with an average of 32% of the total iodine intake from food and supplements.

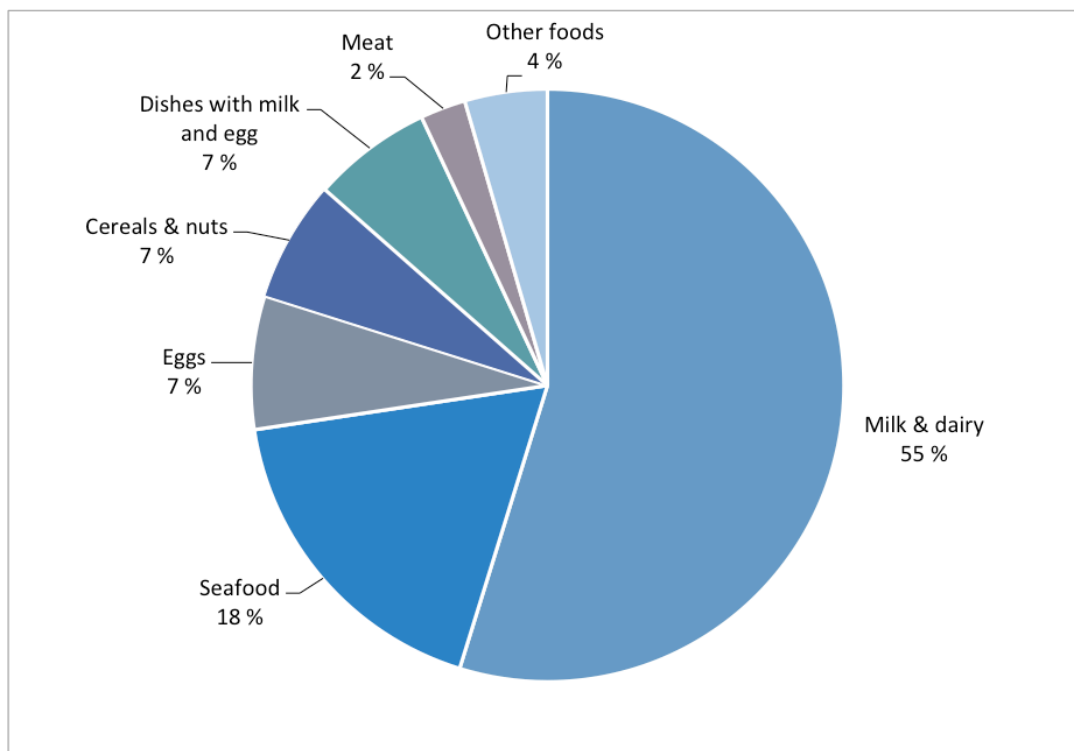**Figure 5-7** Dietary sources in 24-h recall
Mean contribution (%) to the calculated iodine intake from different food groups from 24-hour recall in a group of pregnant women (n=49)
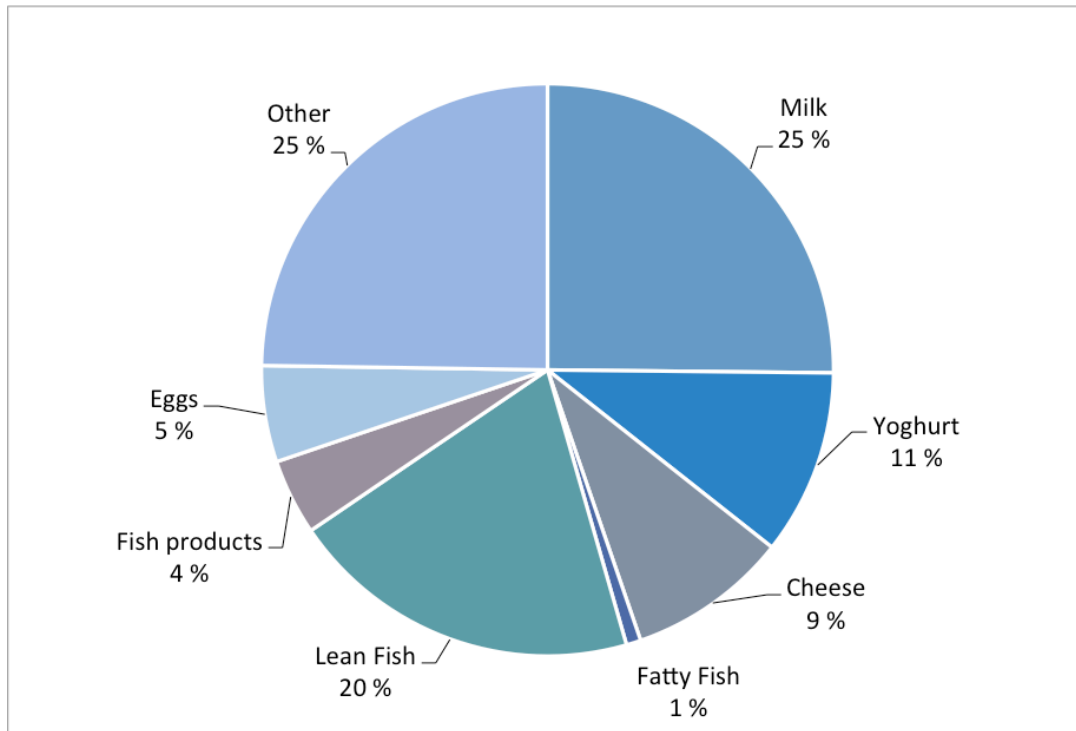
Figure 5-8 Dietary sources in habitual intake from food frequency questions
Mean contribution (%) to the calculated iodine intake from different food groups from 24-hour recall in a group of pregnant women (n=49)

5.6 Comparison of iodine intake by 24-hour recall and food frequencies, and intake estimated from UIC and UIE in sub-study participants (E)

The calculated 24-hour (short term) iodine intake correlated with habitual iodine intake (longer term intake), both for iodine from food (r=0.35, *p*=0.013), and for the total iodine intake (r=0.70, *p* <0.001). Figure 5-9 shows the scatterplot for total iodine intake by the two methods.
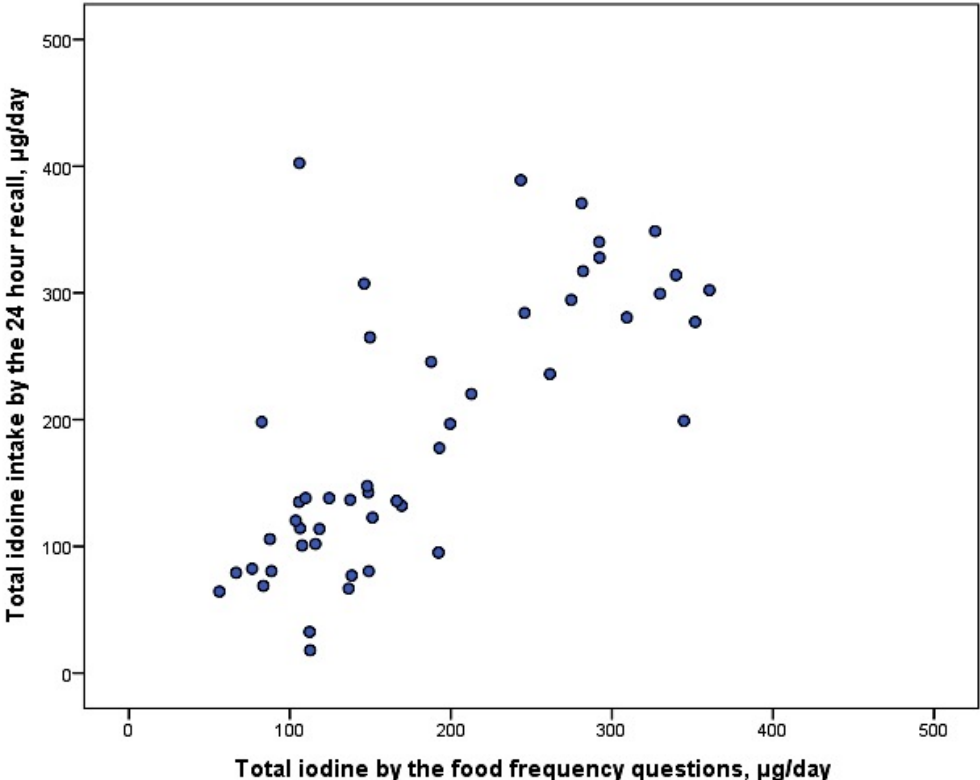
Figure 5-9 Scatterplot showing total iodine intake (µg/day) calculated from the 24-hour recall (y-axis) and the food frequency questions (x-axis) (n=49). Each point represents a survey pair.

The mean habitual intake of milk and yoghurt was 3.3 dl/day and the mean intake of cheese was 10 g/day. The mean 24-hour intake of main food groups were: milk/dairy 390 g, seafood 40 g, eggs 28 g, and dishes with egg and milk: 130 g.

5.6.1 Iodine intake estimated from UIC and UIE

In the sub-study, it was also possible to estimate the short-time iodine intake from UIC and UIE. Median iodine intake estimated from UIC according to the US Institute of Medicine equation (iodine intake = UIC x 0.0253 x bodyweight) was 157 µg/day, and median iodine intake estimated from UIE (assuming that 90% of ingested iodine is excreted in urine) was 133 µg/day. Iodine intake estimated from UIE was significantly lower than iodine intake estimated from UIC (p=0.009). The calculated 24-hour iodine intake was also significantly lower than intake estimated from UIC (p=0.017), but not different from iodine intake estimated from UIE (p=0.99).

5.6.2 Associations between urinary iodine concentration, excretion and iodine intake

The correlations between the different methods for assessing iodine status were all statistically significant (Table 5-8).

Table 5-8 Spearman's correlations rho (r) of UIC and UIE with 24-hour total iodine intake (24-h recall), total habitual iodine intake (Food frequency), estimated intake by UIE, and estimated intake by UIC in a group of pregnant women (n=49)

Iodine, µg/day	Median, µg/day	UIC r	UIE r
24-h recall	143	0.37*	0.43**
Habitual intake	149	0.39**	0.38*
Estimated from UIE[a]	133	0.75***	
Estimated from UIC[b]	157		0.72***

P-value given as statistical significant <0.05
* p-value ≤0.05
** p-value ≤0.005
*** p-value ≤0.0005
[a] Estimated daily iodine intake by UIE = UIE (µg/24h)x100/90
[b] Estimated daily iodine intake by UIC = UIC (µg/L)x0.0235 x bodyweight (kg)

5.7 Predictors for UIC in all participants (F)

The variables considered as potential predictors for UIC are calculated iodine intake and supplements, and maternal and infant characteristics presented in Table 5-1. In the unadjusted crude analyses of predictors for UIC, four variables were significantly associated with UIC; maternal age ($p = 0.004$, $\beta = 0.015$), suffering from low metabolism ($p = 0.015$, $\beta = 0.291$), smoking during pregnancy ($p = 0.014$, $\beta = -0.529$), and mean daily intake of iodine-containing supplements ($p < 0.001$, $\beta = 0.002$). Gestational age was not have a statistically significant in the crude linear regression ($p = 0.139$, $\beta = -0.004$), but was included in the multiple linear regression analysis because the p-value was <0.150 and because including the variable increased the total variance explained by the model.

In multiple linear regression models (Table 5-9), maternal age (β 0.013, 95% CI (0.003, 0.022)), gestational age (β -0.007, 95% CI (0-0.012, -0.001)), suffering from low metabolism (β 0.313, 95% CI (0.090, 0.536)), mean daily iodine intake from supplements (β 0.002, 95% CI (0.002, 0.003)), and smoking during pregnancy (β -0.442, 95% CI (-0.869, -0.016)) were associated with UIC. The r squared (R^2) of 0.105 means that together, these predictors explain 11% of the variance in UIC.

Table 5-9 Predictors of urinary iodine concentration (UIC) in pregnant women in Oslo (n=777), with UIC[a] (μg/L) as dependent variable

Predictor variables	Unadjusted coefficient (95% CI)		p	Adjusted coefficient (95% CI)		p	Stand Beta
Constant				4.2	(3.8, 4.5)	<0.001	
Maternal age [b]	0.015	(0.005, 0.025)	0.004	0.013	(0.003, 0.022)	0.011	0.088
Gestational age	-0.004	(-0.010, 0.001)	0.139	-0.007	(-0.012, -0.001)	0.019	-0.081
Low metabolism [c]	0.291	(0.057, 0.525)	0.015	0.313	(0.090, 0.536)	<0.001	0.289
24-h iodine Supp [d]	0.002	(0.001, 0.002)	<0.001	0.002	(0.002, 0.003)	0.006	0.094
Smoke [e]	-0.529	(-0.951, -0.108)	0.014	-0.442	(-0.869, -0.016)	0.042	-0.070
R^2						*0.105*	

[a] UIC log transformed
[b] Continues variable of maternal age in years
[c] Dichotomous variable for diagnosed with low metabolism
[d] Continues variable of mean daily intake of iodine containing supplements
[e] Dichotomous variable of smoking during pregnancy

6 Discussion

6.1 Main findings of the present study

The main finding in this large population-based study was a median UIC of 92 μg/L, which according to WHO reflects insufficient iodine intake. Approximately half of the women had a total iodine intake below 160 μg/day, which is the estimated average requirement for pregnant women. This strengthens the findings of insufficient iodine intake shown by UIC and the probability of iodine inadequacy in this population. Results from the sub study participants, for which urinary iodine was measured in 24-h urine collections and who provided a detailed dietary recall, confirmed the findings of insufficient iodine status observed in the large study. Comparison of UIC and UIE confirmed that hydration status influenced UIC, and that UIE is a more reliable biomarker of iodine status at the individual level than UIC. Use of iodine-containing supplements contributed substantially to the total iodine intake, but only one third of the participants reported use of iodine-containing supplements. Women who reported use of iodine-containing supplements had significantly higher UIC than non-supplement users. In multiple regression analysis we found that use of iodine containing supplements was the main contributor to UIC. Food sources alone did not provide the amounts of iodine required during pregnancy to meet maternal and foetal needs during pregnancy.

6.2 Importance of adequate iodine nutrition in pregnancy

Sufficient iodine status in pregnancy is crucial for the neurological development in children. In utero, iodine deficiency causes irreversible damage to the developing brain (Melse-Boonstra & Jaiswal, 2010; Toft, 2004; Bougma *et al.* 2013; Zoeller & Rovet, 2004).

In the years 1991 to 1992, a longitudinal study in the United Kingdom in 1040 mother-child pairs showed that inadequate maternal iodine status was associated with lower IQ in their 8-year-old children (Bath *et al.* 2013). The group of pregnant women in early gestation was classified as having mild-to-moderate iodine deficiency on the basis of median UIC concentration of 91 μg/L. Children of mothers with an iodine-to-creatinine ratio of less than 150 μg/g in early pregnancy (median 12 weeks) was associated with lower verbal IQ, reading accuracy and reading comprehension, than were those of mothers with iodine-to-creatinine ratio of 150 μg/g or more. When the less than 150 μg/g group was subdivided, scores declined

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when going from iodine values of 150 μg/g or more, to 50-150 μg/g, to less than 50 μg/g. In contrast, a prospective cohort study in Greece with 575 mother-child pairs and where mothers had sufficient iodine intake during pregnancy (median UIC: 172 μg/L), found no association between maternal iodine status in pregnancy and their children's general cognitive score at 4 years of age (Kippler *et al.* 2016). In a Dutch case-control study in the years 1997-98, pregnant women (n=108) with low fT4 concentrations at 12 weeks gestation were matched for parity and gravity with pregnant women with fT4 concentrations in the normal range (n=96), and neurobehavioral profile of new-borns was assessed at 3 weeks of age (Kooistra *et al.* 2006). Infants born to case mothers scored significantly lower on orientation, but no significant differences in 'habituation', 'motor', 'range of state', 'regulation of state' or 'autonomic stability'. In a small study at Sicily, it was found that nine children born out of 16 pregnant women living in a moderately iodine-deficient area were diagnosed with attention deficit hyperactivity disorder (ADHD) at 8-10 years of age, as compared with none of the children born out of a group of 11 mothers from an iodine-sufficient area. Moreover, IQ scores of the children were 18 points lower (*p* <0.001) in the deficient area as compared with the iodine-sufficient area (Vermiglio *et al.* 2004). Maternal iodine supplementation in areas of mild-to-moderate iodine deficiency may improve cognitive performance of the offspring, but randomised controlled studies with long-term outcomes are lacking. Zimmermann and co-workers found significant improvements in information processing, fine motor skills and visual problem solving by iodine repletion in moderately iodine-deficient 10-12 year-old schoolchildren (n=310) (Zimmermann *et al*. 2006b).

These studies show the importance of adequate iodine status during early gestation and emphasise the risk that iodine deficiency can pose to the developing infant, even in countries classified as only mildly iodine deficient.

6.3 Comparison with other studies

6.3.1 Comparison of status

Although there is no screening program for iodine deficiency, Norway has been considered iodine replete for six decades (Brantsæter *et al.* 2013; Nyström *et al.* 2016). Recent studies in Norway have shown inadequate iodine intake in the female population, both in childbearing age and during pregnancy (The Norwegian Directorate of Health, 2012b; Brantsæter *et al.*

2013). The median UIC demonstrated in the present study (92 µg/L) support findings of inadequate iodine status in pregnant women.

Low UIC in pregnant women or women in childbearing age is found in four other studies from Norway, with a median UIC between 69-112 µg/L (Sanchez, 2015; Brantsæter *et al.* 2013; Dahl *et al.* 2003c; Seldal, 2012). A Norwegian study "Little in Norway" (LiN) in 1008 pregnant women demonstrated that eighty percent of the pregnant women had UIC below 150 µg/L, with median UIC at 82 µg/L (Sanchez, 2015). The National Mother and Child (MoBa) cohort study collected 24-hour urine samples from 119 participants during 2003-2004 for validating calculated iodine intake (Brantsæter *et al.* 2013). Median UIC was 69 µg/L, and the median UIE was 110 µg/24-h. Only 11 % had adequate UIC levels, while 89 % had UIC <150 µg/L. A Norwegian study in 63 non-pregnant women recruited in Tromsø (n=28) and Bergen (n=35) during years 1999-2001 reported a median UIC of 112 µg/L in Tromsø and of 82 µg/L in Bergen (Dahl *et al.* 2003c). In "The Fjell Study" including pregnant women in a municipality near Bergen recruited in 2010-2011, median UIC was 127 µg/L (n=64) (Seldal, 2012). The current study is the most recent study in Norway and the results add to the evidence that a large proportion of pregnant women have insufficient iodine intake and that iodine nutrition is a health concern in Norway.

Inadequate iodine status has also been reported in other Nordic countries. A cross-sectional study in Denmark reported that the median UIC in 158 pregnant women recruited in 2012 was UIC 119 µg/L (IOR 67-180). In iodine-containing supplement users, the median UIC was 130 µg/L, and 76 µg/L in non-supplement users (Andersen *et al.* 2014). The median UIC in study population in a Swedish cross-sectional study from 2015 in 459 pregnant healthy women was 98 µg/L (Granfors *et al.* 2015). In UK, data of 1040 pregnant women in the years 1991-1992 from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort showed similar results as the present study (Bath *et al.* 2013). The median UIC was 91 µg/L (IQR: 53.8-143), and over two thirds (67%) of the women fell into the category of insufficient according to WHO (less than 150 µg/L). There is a clear trend towards the same results in all these studies, and in agreement with our study all available studies show insufficient iodine status in pregnant women.

The WHO reference ranges defining optimal iodine status based on UIC are for population groups and should be used for population samples of at least 500 participants (WHO, 2007; Vejbjerg, 2009b). Our study sample of n=777 is sufficiently large to evaluate iodine status at the group level and suitable also for evaluating the impact of predictors, particularly use of iodine-containing supplements. When iodine-containing supplement users were excluded (37.7%), median UIC in the remaining group (n=541) was 83 µg/L (Figure 5-6) and therefore suggests that iodine nutrition is an important public health concern. The Norwegian Health Authorities published a report in March this year (2017) acknowledging the need for action to secure better iodine nutrition (Norwegian Health Authorities, 2017).

6.3.2 Comparison of intakes

In the present large study, we based the estimates for 24-hour intake mainly on iodine concentrations measured in Norwegian iodine-rich food items; milk and dairy products, seafood and eggs. The median calculated 24-hour iodine intake from food and total iodine intake was 110 µg/day and 148 µg/day (n=804), respectively. The iodine intake calculations in the sub-study, both the 24-hour recall and the food frequency questions were more detailed than the iodine intake calculated in the whole study. Median total short-term iodine intake from 24-hour recall was 143 µg/day, and median total habitual intake was 149 µg/day (frequency method). These calculations support the findings in the large study.

The 24-hour intake from food in non-supplement users (n=541) was borderline significant correlated with UIC ($r = 0.09$, $p = 0.051$) (Table 5-6). The total 24-hour intake in supplement users (n=263) was positively correlated with UIC ($r = 0.26$, $p < 0.001$), as was iodine from supplements ($r = 0.29$, $p < 0.001$).

Calculated iodine intake in 61 904 pregnant women participating in MoBa in the years 2002-08 showed that over fifty percent had iodine intake lower than the Nordic recommendations of 175 µg/day (Brantsæter *et al.* 2013). Another study in Norwegian pregnant women (LiN) has shown inadequate habitual iodine intake in the period 2010-2011 (Sanchez, 2015). The total median iodine intake from foods and supplements was 153 µg/day in 833 pregnant women. Use of iodine-containing supplements was reported by 14 % of the participants, whereas the median iodine intake estimated was 268 µg/day (Sanchez, 2015). An increasing number of Norwegians take dietary supplements, and today many multivitamin-mineral supplements contain iodine (Nyström *et al.* 2016). In the present study, thirty-three percent of

all participants reported use iodine-containing supplements, which on average contributed with 175 μg/day to these women's diet. The median UIC for supplement users was significantly higher than in non-supplement users; 120 μg/day and 83 μg/day, respectively. As was median iodine intake in supplement users compared to non-supplement users; 285 μg/day and 110 μg/day, respectively. Similarly in the MoBa Study, 32 % of the pregnant women took iodine-containing supplements which on average contributed with 100 μg/day to these women's diet (Brantsæter *et al.* 2013).

A higher iodine intake was demonstrated in the Donexpo study of 40 pregnant Norwegian women conducted in 2016; median total iodine intake 170 μg/day (Nyheim, 2016). However, the median UIC was lower than in the present study (80 μg/L). With such differences between intake and excretion, it is likely that the calculated intake is overestimated, or that there is a systematic bias in the analytical values of UIC, or that a reduced iodine excretion is a physiologic explanation in an iodine deficient pregnant population. Most likely, the iodine intake was overestimated as the iodine concentrations for milk and eggs used were those in the Food Composition Table and higher than the concentrations used in the present study. We applied lower concentrations for these items based on information released in 2017 (see chapter 4.2.3).

Even though majority of the study participants had an insufficient iodine nutrition status based on intake calculations and urinary iodine concentration, the hormone concentrations in these individuals are unknown. A Norwegian study found low iodine intake (<150 μg/day) and UIC status in most participants (median 82 μg/L), but thyroid hormone concentrations in blood did not show signs of iodine deficiency (Dahl *et al.* 2003c). If there is a prolonged period of insufficient iodine intake, there will be an increase in TSH. However, adverse effects of insufficient iodine intake may occur also before changes in thyroid hormone concentrations are seen. This is why it is important to monitor urinary iodine concentration. Compared to non-pregnant women, there is an increase in TBG during pregnancy due to increased oestrogen levels. Especially T4 has a high affinity to TBG. Physiological free T4 decreases in maternity, while free T3 and TSH are normal (Andersen *et al.* 2014; Laurberg *et al.* 2007).

6.4 Comparison with the recommended intakes

Evaluation of the total iodine intake in relation to the recommendations showed that a large proportion of the pregnant women had inadequate iodine intake. One fourth of all participants had iodine intake below 100 μg/day, and more than half of the women had iodine intake below the EAR (160 μg/day for pregnant women). According to the 24-hour recall in sub-study participants, 39 % had total iodine intake below EAR, and 45 % had intake below EAR according to habitual intake (the frequency method). It is increased likelihood of inadequate iodine status with an intake below EAR (IOM, 2001). Even though 45 % of the pregnant women reached the Nordic recommendations for pregnant women (175 μg/day), only one fourth reached the WHO recommendations (250 μg/day). The short-term intake showed that only 1 of 4 in this group had an adequate iodine intake and that iodine intake according to either the Nordic recommendations or the WHO recommendation is difficult to achieve in Norway.

6.4.1 Dietary iodine sources

Even though the participants in the current study had a mean daily intake of milk/yoghurt of 3-4 dl, and the majority reported regular consumption of fish, they had an insufficient total iodine intake. The National Nutrition Council showed in their report that even with an intake according to the food-based recommendations for a healthy diet, iodine intake is insufficient (National Nutrition Council, 2016). In this study, the food groups that contributed the most to the iodine intake were milk and milk products (contributing ~50 %) followed by seafood (contributing 25 %).

There are few dietary sources of iodine in Norway (Dahl *et al.* 2003b), and the individual intake of these food groups vary significantly. The highest iodine content are in foods of marine origin, with lean fish, such as cod (120 μg/100g), having significant higher iodine content than in fatty fish, such as farmed salmon (10 μg/100g) (National Nutrition Council, 2016; Julshamn, Dahl & Eckhoff, 2001). Even though seafood is naturally high in iodine, the Norwegians mainly get iodine from milk and dairy products, and secondly fish and fish products (Nyström *et al.* 2016; Dahl *et al.* 2003b). The consumption of seafood, especially lean fish, is shown to decline, and more so in the female population (Norwegian Scientific Committee for Food Safety, 2007; Brantsæter *et al.* 2013). This is a cause of concern and as a result, the health authorities has decided to evaluate and implement actions to improve iodine

nutrition in Norway, e.g. increase the amount of iodine in iodized salt in Norway (Norwegian Health Authorities, 2017).

The iodine content in milk and eggs was recently found to be lower than the expected and consequently, iodine content used for calculating iodine from milk and eggs in this study was reduced by 35 % in milk/yoghurt (from 20 to 13μg/100g) (Trøan *et al.* 2016; communication with producers), and by 39 % in eggs (from 49 to 30μg/100g) (Food Safety Authority, 2017). This implies that a daily intake of 0.4 litres of milk will only contribute with ~30 % of the Nordic recommended intake of 175 μg/day, and ~21% of the WHO recommended intake of 250 μg/day, for pregnant women (Nordic Council of Ministers, 2014; WHO, 2007).

It is recommended to eat 300-450 gram fish per week, both lean and fatty fish, whereas 200 gram should be fatty fish like salmon, trout, mackerel or herring. Other seafood like shellfish is not included in the national recommendations (Norwegian Directorate of Health, 2016). As opposed to many other countries, The Norwegian Directorate of Health do not give specific recommendations for the amount of dairy products, but recommends a daily use of milk and dairy products, mainly from low-fat products (Norwegian Directorate of Health, 2016). Pregnant women who do not consume or have low intake of dairy and/or seafood, and who do not obtain iodine from supplements are at great risk of having inadequate iodine intake (Brantsæter *et al.* 2013; National Nutrition Council, 216). In the current study, iodine-containing supplements, contributed significantly to UIC. Milk consumption has been shown to decline, resulting in a decline in iodine contributed by milk (Brantsæter *et al.* 2013; Gunnarsdottir *et al.* 2012).

The iodine content in milk in Norway differs with time of the year and demography (Dahl *et al.* 2003). The low-fat milk from the summer season had significantly lower median iodine concentration (88 μg/L, range 63-122 μg/L) compared with low-fat milk from winter season (232 μg/L, range 103-272 μg/L). The median iodine concentration of organic summer milk (60 μg/L) was significantly lower than the iodine concentration of organic winter milk (127 μg/L) (Dahl *et al.* 2003). Changes in farming practices and legislation may have resulted in lower iodine content in milk over the last decade, but no values of iodine content in Norwegian milk have been published since 2003. The seasonal variation in the iodine content of milk vary because of the iodine fortification of cow feed during the winter, and grass feed

during the summer (Pennington, 1990). Two studies from Denmark and Norway showed both geographical and seasonal variations in the iodine content of milk (Rasmussen *et al.* 2000; Dahl *et al.* 2003a). Cow fodder containing iodine is widely used by farmers in Norway, even though cows are fed with different brands of fodder, the fortification of iodine (2 mg/kg) is stable and supplies the cows with a standardised amount of iodine (Dahl *et al.* 2003a).

The low UIC measured in Scandinavian women can be explained by a reduction in milk and seafood consumption (Nyström *et al.* 2016; The Norwegian Department of Health, 2016; Brantsæter *et al.* 2009; Brantsæter *et al.* 2013; Gunnarsdottir *et al.* 2009). Major changes were found in dietary habits in Iceland in the national dietary survey in 2002 (Gunnarsdottir *et al.* 2009), fish consumption had decreased and mostly in young women. Milk consumption was also considerably lower than before. In Norway there is monitored a negative trend in milk consumption in the female population (The Norwegian Directorate of Health, 2016; Brantsæter *et al.* 2009; Brantsæter *et al.* 2013; National Nutrition Council, 2016). Intake of the primary iodine sources in Norway, milk and dairy products along with white fish, is reduced (The Norwegian Directorate of Health, 2016). In addition, the iodine content in these actual sources has declined (National Food Authorities, 2017).

6.5 Predictors for UIC

In the multiple regression analysis, the predictors of UIC were maternal age, gestational age, suffering from low metabolism, mean daily iodine intake from supplements, and smoking during pregnancy, and together they explained approximately 11% of the variance in UIC. The fact that iodine from supplements was a significant predictor of UIC in the regression analysis confirms that iodine-containing supplement use is an important determinant of iodine status and an important iodine source for pregnant women.

One of the predictors for UIC in this present study was maternal age. Similar results were found in a cross-sectional study in one hundred pregnant women conducted in the United Kingdom in 2009. According to analysis, maternal age was positively associated with estimated 24-hour iodine excretion (Bath *et al.* 2014b). A potential explanations for this is older women consume more iodine-rich foods. Data from the 2000/01 Adult National Diet and Nutrition Survey (NDNS) suggests an increased dietary iodine intake with advancing age,

as older women had a significantly higher iodine intake (estimated from food-diaries) than younger women (Henderson *et al.* 2003).

In the present study, a negative borderline significant correlation between gestational age and UIC was found. The explanation could be increased iodine transfer to the foetus. This result is not consistently found in other studies. In a cross-sectional study in 50 pregnant women, UIC increased with gestational age, but the differences between the first, second and third were not statistically significant (Grewal *et al.* 2013). In an Austrian study of 246 pregnant women, either maternal or gestational age influenced UIC (median UIC: 87 µg/L) (Lindorfer *et al.* 2015). Stillwell and colleges reported that median UIC levels in Tasmania declined after elevated excretion seen in early pregnancy (Stilwell *et al.* 2008).

Tobacco smoke contains thiocyanate, a chemical toxin that has goitrogenic properties (Roman, 2007; Wiersinga, 2013). Most goitrogenics do not have a major clinical effect unless there is coexisting iodine deficiency, but can aggravate the effect (Vanderpas, 2006). However, the smoking pregnant women in our study have mild-to-moderate iodine deficiency. In addition, smoking during pregnancy is associated with reduced iodine content in breast milk (smokers 26.0 µg/L vs. non-smokers 53.8 µg/L, $p < 0.001$), and the infant's urine (smokers 33.3 µg/L vs. non-smokers 50.4 µg/L, $p = 0.005$) (Laurberg, *et al.* 2004). Smoking during the period of lactation increases the risk of iodine deficiency-induced brain damage in the child (Laurberg *et al.* 2004). The mammary glands of breastfeeding mother concentrate iodide from blood and excrete it into milk (Semba & Delane, 2001). The transport protein responsible for iodide accumulation in the mammary gland has recently been characterized and is identical with the sodium-iodide symporter of the thyroid gland (Figure 2-1) (De La Vieja *et al.* 2000). A number of chemicals may competitively inhibit the function of this transporter. One such compound is thiocyanate (Leung *et al.* 2011; De La Vieja *et al.* 2000; Brown-Grant, 1957), which accumulates in the blood and tissues of smokers (Butts *et al.* 1974).

Suffering from low metabolism was a strong predictor for increased UIC. Maternal hypothyroidism, as categorized by elevated TSH levels is relatively common in pregnancies (Leung *et al.* 2011). Women who suffer from low metabolism is prescribed a synthetic thyroid hormone (levothyroxine), which is a synthetic derivative of T4 (thyroixine), and it

normalizes blood levels of TSH, T4 and T3. Since T4 contains iodine, this treatment will provide a substantial dose of iodine, which explains the positive association between hypothyroidism and UIC.

6.6 Methodological considerations

6.6.1 Representatively of study participants and sample size

External validity, or generalizability, measure to what extent the study captures accurately phenomenon as it exist in the target population (Gibson, 2005). The sample size based on the WHO reference ranges defining optimal iodine status based on UIC for population groups of at least 500 participants (Vejbjerg, 2009b) were sufficient in the present study (n=777). Considering that the recruitment method was convenience sampling and the participants were not randomly selected, the findings from the present study cannot be generalized to pregnant women in Norway. This is partly due to the risk of systematic bias when using convenience sampling. Bias can de described as a condition causing a result that departs from the true value, which can reduce the accuracy of a measurement (e.g. mean and median value), and it is important to take bias into consideration because it cannot be removed by statistical analysis (Gibson, 2005). A systematic bias that is common in nutritional studies is selection bias, because people who voluntarily take part in a study are more likely to differ from the general population by being more health conscious and/or highly educated (Kirkpatrick *et al.* 2014). On the other hand, the current study support findings from other studies in other parts of Norway and are of importance in spite of not coming from a nationally representative sample.

Nutrition is multidimensional in that different aspects of diet are important for a range of health outcomes of interest. Thus, the most relevant food and nutrition data for monitoring will differ according to purpose and audience (Rutishauser *et al.* 2007). Some demographic characteristics of the population in this present study are not entirely representative for the Norwegian female population. The proportion of higher educated subjects was significantly higher in our study than in the rest of the female Norwegian population. In this present study, approximately 40 % of the total study population were highly educated (≥ 4 years of University/College), and a total of 80 % of the pregnant women had a University/College education (1-4 years). In comparison, in the Norwegian female population, approximately 8

% are highly educated (≥ 4 years of University/College), and 27 % have a University/College education (1-4 years) (Statistics Norway, 2016). On the other hand, longer education is associated with healthier diet and lifestyle, and when insufficient iodine intake is found in the current study population, it is not likely that a population comprising a higher proportion of less educated women would have higher iodine intake.

Statistics from 2012 show that there are approximately 11 % ethnic non-Norwegians in Norway (Statistics Norway, 2013). In our study, the percentage of non-Norwegians was twenty-three percent, and there were no significant association between ethnicity and UIC. A cross-sectional study in Austria in 246 pregnant women found a significantly higher UIE in women of foreign origin than in Austrian women (Lindorfer *et al.* 2015). In the years 1998 and 2002 a prospective study in approximately 8500 pregnant women found significant differences in UIC between three ethnic groups; Caucasian, Vietnamese and Indian/Sri Lankan (Hamrosi, Wallace & Riley, 2005). The distribution of UIC for Caucasians was significantly lower than for both Vietnamese ($p < 0.01$) and the Indian/Sri Lankan ($p = 0.03$) group. The median UIC in each ethnic group was consistent with mild iodine deficiency, but the Caucasian group had almost half of the group under 50 μg/L. The associations of ethnicity with iodine status are most likely due to differences in dietary behaviours.

Before analysing the results, level of education and ethnicity were expected to be predictors of UIC. However, no association were found for these variables. Despite the high level of education among the participants, insufficient iodine status was evident both from UIC and calculated iodine intakes. This implies that iodine insufficiency is present in a larger scale than expected, and it is important the National Health Authorities implement actions immediately.

In this study, ninety women reported to be smokers before pregnancy, but only ten reported to smoke during pregnancy. Whether it is reliable that approximately ninety percent of regular smokers quit when getting pregnant, or if underreporting of smoking in pregnancy is the case, remains unknown (Graham & Owen, 2003; Rebagliato, 2002). However, pregnant women are shown to be more likely to smoke if they were less educated, in unskilled manual or unemployed groups, and single or had a partner who smokes (Rebagliato, 2002).

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6.6.2 Uncertainty in dietary intake

There is no method for assessing dietary intake that is without errors, and it is important to be aware of the pros and cons (or strengths and weaknesses) of the different methods. An outline of different methods or assessing iodine intake was presented in chapter 2.4.2. All methods are prone to recall bias and misreport. Different methods cover different time windows, and in the current study both short time and habitual iodine intake was assessed. The iodine intakes by the different methods were in the same range although they reflected different time windows. This is probably due to the limited number of iodine rich foods and that consumption of milk/yoghurt and fish is easier to recall than most other foods (Brantsæter *et al.* 2013). Self-report in dietary intakes might also be biased by participants being aware of participating in a health study and therefore reporting healthier habits than their true habits. Studies have shown that foods perceived as unhealthy tend to be underreported while foods perceived as healthy tend to be over reported (Shim *et al.* 2014; Olafsdottir *et al.* 2006). Mild and milk products, the main dietary iodine source, is probably less affected by this than food items with a high content of sugar or fat, e.g. sweet drinks or snacks.

The use of food frequency questions to assess iodine intake, as well as assigning iodine concentrations to all food items studied may result in imprecisions in the intake estimates, not only due to over- and underestimating the amount of intake, but also uncertainties to the actual content (Dahl *et al.* 2003). The natural iodine content of food sources differs considerably, which contributes to the fluctuations in daily iodine intake of individuals (IOM, 2000; IOM, 2003). The iodine exposure scenarios vary greatly due to not only differences in inherent content of food (Zimmermann *et al.* 2004; Zimmermann *et al.* 2003; Murphy *et al.* 2006), but also to factors such as seasonality of food intake patterns, sources, and iodine content of milk (Zimmermann *et al.* 2003; Dahl *et al.* 2001). Many food items are not updated in iodine content, and many food items even lack information on iodine content (Matvaretabellen, 2010). A limitation of the present study is therefor that a single average iodine value was applied to all milk and yoghurt (130 µg/L). In addition, there were uncertainties when monitoring the use of supplements the day of collecting urine samples. UIC measurements were lower than the calculated iodine intake, both in 24-hour and habitual intake. This implies that there might be an overestimated iodine-containing supplement intake. In the large study, some of the participants misunderstood the question about use of iodine-containing supplement regarding frequency. This question was therefore changed in the questionnaire answered by participants in the sub-study. In addition, a project worker

interviewed all participants for dietary intake and use of supplement (24-hour recall). One advantage of the 24-hour recall is that a relatively minimal burden is imposed on respondents. However, an inevitable limitation is that all information depends on the respondents' memory and the skill of a well-trained interviewer to minimize recall bias (Shim *et al.* 2014). But strengths by this method include the open-ended questions so that abundant information can be collected and analysed in various aspects. In addition, it can be easily applied to diverse groups with a wide range of eating habits and may be used to estimate the average intake of a certain population.

6.6.3 UIC versus UIE and iodine estimated from UIC

In our study, spot urine samples were collected from 728 pregnant women. In addition, 49 pregnant women provided 24-hour urine samples. We have reported the results as UIC (µg/L), and in the sub-study also as UIE (µg/24h). UIC and UIE are commonly used in the literature but are not interchangeable as one is a concentration and the other an excreted amount (Rasmussen *et al.* 1999). In the following, this is discussed in relation to iodine determination.

In the sub-study, it was also possible to estimate and compare short-time iodine intake from UIC and UIE. The median estimated iodine intake from UIC (157 µg/day) according to the IOM equation was significantly higher than the estimated iodine intake from UIE (133 µg/day) (assuming that 90% of ingested iodine is excreted in urine). This result may indicate that the equation for estimating iodine intake from UIC results in an overestimation of iodine intake in pregnant women.

In cross-sectional surveys, the iodine status of a population is usually assessed through the analysis of casual (or random) spot urine specimens for urinary iodine concentration. A single spot UIC should not be used as an indicator of an individual's iodine status, because the UIC can vary widely within an individual throughout the day and as well as day-to-day (König *et al.* 2011). König *et al.* state that to estimate an individual's iodine status requires ten repeat spot or 24-hour urine collections (König *et al.* 2011). Therefore, while a single spot urine sample is not useful for classifying an individual's iodine status, the median urinary iodine is useful to assess the iodine status of a population (WHO, 2007). Urinary iodine is frequently assessed through school surveys (since this is an efficient way to estimate the household

iodine nutrition situation) or through overall population assessments. While the median value in a representative sample of schoolchildren or the general population provides a reasonable population estimate, it may not reflect the situation in pregnant women, whose iodine requirements are greater. In addition, milk consumption may be lower in pregnant women than in schoolchildren (Gunnarsdottir *et al.* 2013; Bath *et al.* 2016).

A reason why UIC is the recommended method to assess iodine status in populations is the body's low storage capacity of iodine, so the amount excreted in urine reflects the ingested intake (Vejbjerg, 2009b). Urinary iodine is therefore an excellent indicator of recent iodine intake because ≥92 % of dietary iodine is absorbed, and, in healthy iodine-replete adults, >90 % is excreted in the urine within 24-48 h (Nath *et al.* 1992; Jahreis *et al.* 2001; Zimmermann, 2009). However, UIC varies by the women's hydration status (Vejbjerg *et al.* 2009b; König *et al.* 2011), as demonstrated in the present sub-study. Although the median UIC is a good population indicator of iodine status, the distribution of UIC around the median in iodine surveys is often misinterpreted in an attempt to define the number of individuals who are deficient. Therefore, the proportion of participants shown in Table 5-3 and Figure 5-2 must be interpreted with care and the overall result is the result for median UIC in the large study being 92 µg/L indicating insufficient iodine status at the group level.

Dietary iodine intake and therefor UIC are highly variable from day-to-day and throughout a day. In iodine sufficient countries, UIC (both spot and 24-h urine collections) show an individual day-to-day variation of 30-40% (Vejbjerg *et al*. 2009b; König *et al.* 2011). Another aspect is the variation in UIC during the day (Rasmussen *et al.*1999). In particular, UIC in a fasting morning spot sample tend to be lower (Rasmussen *et al.*1999), while in our sub-study, the median UIC in the morning sample was higher than in the total 24-h urine sample (110 µg/L versus 91 µg/L). The explanation of these findings is unclear. The urine is concentrated during night and actually result in higher concentration in the morning compared to the rest of the day, due to the effect of antidiuretic hormone. Measurement of UIC in morning urine for population evaluations may lead to uncertainties in evaluation a population iodine status.

Although the median UIC is a good indicator of iodine status in populations, there is no established biomarker for individual iodine status. The most important information in the determination of the status of iodine nutrition comes from the measurement of the UIE. If the UIC were to be used to assess individuals, it is unclear how many repeat urine collections

would be needed and if the collections should be spot samples or 24-hour samples. However, a prospective study on healthy Swiss women showed that 10 spot urine samples or 24-hour urine samples were needed to assess individual iodine status with 20% precision (König *et al.* 2011). A Danish cross-sectional study in 2012 demonstrated the importance considering time of spot urine sampling and the time span from iodine supplement intake, when evaluating iodine status in pregnancy (Andersen *et al.* 2014). If a large number of samples are collected, variations in hydration among individuals and day-to-day variations in iodine intake generally even out, so that the median UIC in spot samples correlates well with the median from 24-h samples and with the estimated UIE from UICs (König *et al.* 2011). In individual assessment of iodine status, UIE is more precise (Laurberg, 2014; König, *et al.* 2011). Although complete 24-hour samples give a more precise measurement, they have a huge participant-burden, and are subjected to biases introduced by failure to collect total volume (Knudsen *et al.* 2000).

7 Conclusions

This thesis had several aims, and I will first present the conclusion to each of the specific objectives before a summary conclusion, and reflecting on the implication and future perspectives of the findings.

> A. *In the large study, assess urinary iodine concentration (UIC) and evaluate status against WHO recommendations for sufficient iodine status*

The median urinary iodine concentration was 92 μg/L. According to WHOs criteria for assessing iodine nutrition for pregnant women based on median UIC this result indicate insufficient iodine status. Only 18 % of the pregnant women had UIC in the desired range.

> B. *In the sub study, assess both UIC and 24-hour urinary iodine excretion (UIE)*

The median UIC for participants in the sub-study group was 91 μg/L, and the median UIE in this group was 120 μg/24h, confirming the finding of insufficient iodine status in the large study.

> C. *For all participants, describe and evaluate 24-hour iodine intake from food and supplements in relation to WHO and Nordic recommendations. Evaluate the agreement between estimated iodine intake and UIC*

A large proportion of the pregnant women in this large population-based study had insufficient iodine intake. A total of 45.1 % reached the Nordic recommendations (175 μg/day) and 26% reached the WHO recommendation. Approximately half of the women had a total iodine intake below 160 μg/day, which is the estimated average requirement for pregnant women. Thirty-three percent of all participants reported use of iodine-containing supplements. The median UIC was significantly higher in supplement users than non-supplement users. There was a significant positive correlation between calculated 24-hour iodine intake and UIC. The strongest correlation with UIC was with iodine contributed by supplements.

D. In the sub study, describe 24-hour iodine intake and habitual iodine intake (food frequencies) and the main iodine sources

Based on 24-hour recall, median iodine intake from food only was 114 μg/day, and 143 μg/day when including iodine-containing supplements. The habitual iodine intake was 117 μg/day, and 149 μg/day when including mean daily intake of iodine-containing supplements. The distribution of food groups as sources of iodine for the pregnant women showed that the group 'milk and dairy products' was the major contributor to iodine intake according to intake calculations for the 24-hour recall (55%) and for habitual intake (45%). The second most important source was 'fish and seafood' which contributed with 18% (24-hour recall) and 25% (habitual intake). The more detailed dietary assessment methods applied in the sub-study resulted in iodine intakes that were comparable to the iodine intake estimated from in the large study.

E. In the sub study, compare the calculated 24-hour and habitual iodine intake (food frequencies). To assess the associations between UIC, UIE and iodine intake

The calculated 24-hour (short term) iodine intake correlated strongly with habitual iodine intake, both for iodine from food and for the total iodine intake. The strong correlation reflects that few dietary sources contribute to iodine intake. Median iodine intake estimated from UIC was 157 μg/day, and median iodine intake estimated from UIE was 133 μg/day. Iodine intake estimated from UIE was significantly lower than iodine intake estimated from UIC. The calculated 24-hour iodine intake was also significantly lower than intake estimated from UIC, but not different from iodine intake estimated from UIE. The correlations between the different types of methods for assessing iodine nutrition status were statistically significant. Comparison of UIC and UIE showed that hydration status influenced UIC and that UIE is a more reliable biomarker for iodine status at the individual level than UIC.

F. For all participants, assess predictors for UIC

The predictors that were associated with UIC were maternal age, gestational age, low metabolism, use of iodine containing supplements and smoking, and together they explained approximately 11 % of the variance in UIC.

Summary Conclusion

The main finding of the study was that median UIC in this large population-based study was 92 μg/L, which according to WHO reflects insufficient iodine intake. Approximately half of the women had a total iodine intake below 160 μg/day, which is the estimated average requirement for pregnant women. This strengthens the finding of insufficient iodine intake shown by UIC and the probability of iodine inadequacy in this population. Results from the sub study participants, for which urinary iodine was measured in 24-h urine collections and who provided a detailed dietary recall, confirmed the findings of insufficient iodine status observed in the large study. Comparison of UIC and UIE confirmed that hydration status influenced UIC, and that UIE is a more reliable biomarker of iodine status at the individual level than UIC. Use of iodine-containing supplements contributed substantially to the total iodine intake, but only one third of the participants reported use of iodine-containing supplements. Those who reported use of iodine-containing supplements had significantly higher UIC than non-supplement users. In multiple regression analysis we found that use of iodine containing supplements were the main contributor to UIC, and that food sources alone did not provide the amounts of iodine required during pregnancy to meet maternal and infants needs.

7.1 Future perspectives and implications

The Nordic dietary recommendation for iodine intake during pregnancy is difficult to achieve, even when pregnant women follow the Norwegian food based recommendations for a healthy diet (National Nutrition Council, 2016). Insufficient iodine intake in pregnant women in Norway is an important public health issue, and the current study supports the need for actions to improve sufficient iodine nutrition. Even though more studies are needed, it is essential to increase the public awareness of dietary iodine nutrition in pregnant women (Brantsæter *et al*. 2013; Zimmermann, 2012; Zimmermann, 2015).

There are few dietary iodine sources in the Norwegian diet (milk/dairy products, seafood and supplements). Measurements of UIC confirm findings from other studies, but further studies are needed to provide a better surveillance of iodine status in pregnant women in Norway. In the iodine report in June 2016, the National Nutrition Council presented suggestions for action in prevention of iodine deficiency in Norway, which included universal salt iodization, regulation and stabilizing iodine content in milk, supplementation in vulnerable groups, and quantification of recommended intake of milk.

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Appendices

1. REK

Region:	Saksbehandler:	Telefon:		Vår dato:	Vår referanse:
REK sør-øst	Tor Even Svanes	22845521		22.02.2016	2015/1845/REK sør-øst C
				Deres dato:	Deres referanse:
				04.02.2016	

Vår referanse må oppgis ved alle henvendelser

Sigrun Henjum

Høgskolen i Oslo og Akershus

0130 Oslo

2015/1845 Jodstatus blant gravide kvinner i Norge

Forskningsansvarlig: Høgskolen i Oslo og Akershus
Prosjektleder: Sigrun Henjum

Vi viser til tilbakemelding på komiteens vilkår for ovennevnte prosjekt og til prosjektendringssøknad for studien, mottatt henholdsvis 19.01.2016 og 04.02.2016. Henvendelsene er behandlet under ett av leder for REK sør-øst C på fullmakt, med hjemmel i helseforskningsloven § 11.

Ved godkjenning av prosjektet 29.10.2016, satte komiteen følgende vilkår: 1) Deltakerne skal gis informasjon om kosthold og jod i kosten, i etterkant av intervjuene. 2) En plan for å gi denne informasjonen skal sendes komiteen til orientering. 3) Informasjonsskriv skal revideres i tråd med det ovennevnte.

Komiteen mottok tilbakemelding på disse vilkårene 19.01.206, inklusive reviderte informasjonsskriv og en plan for informasjon om kosthold og jodstatus.

Komiteen tar denne informasjonen til orientering, og anser vilkårene som oppfylt.

I endringssøknad av 04.02.2016, angis følgende: *Det er spesielt viktig å se på jod status i første trimester hos gravide kvinner siden det er i denne fasen at store deler av utvikling av hjernen til fosteret foregår. I opprinnelig søknad står det at vi skal sende et samtykkeskjema med kvinnene hjem etter første besøk på Helsestasjonen og deretter starte inkludering ved besøk 2.*

Vi har imidlertid innsett at dette vil være et stort hinder for å rekruttere kvinner i første trimester siden første besøk på helsestasjon for gravide kvinner er ofte ikke før i slutten av 1. trimester. Derfor vil dette resultere i at vi i hovedsak inkluderer kvinner fra 2. og 3. trimester. Vi søker derfor om å få lov til å dele ut samtykkeskjema til de gravide kvinnene på helsestasjonen, samme dagen som vi spør om de vil være med i jod studien.

Komiteen har ingen innvendinger til denne endringen i rekrutteringsprosedyren, som er velbegrunnet i søknaden.

Vedtak

Endringssøknaden godkjennes, jf. helseforskningslovens § 11.

Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og endringsprotokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og

Besøksadresse:	Telefon: 22845511	All post og e-post som inngår i	Kindly address all mail and e-mails to
Gullhaugveien 1-3, 0484 Oslo	E-post: post@helseforskning.etikkom.no	saksbehandlingen, bes adressert til REK	the Regional Ethics Committee, REK
	Web: http://helseforskning.etikkom.no/	sør-øst og ikke til enkelte personer	sør-øst, not to individual staff

Helsedirektoratets veileder for *Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren.*

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK sør-øst. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Britt-Ingjerd Nesheim
professor dr. med.
leder REK sør-øst C

Tor Even Svanes
seniorrådgiver

Kopi til: *fou-hf@hioa.no*

2. Questionnaire large study

SPØRRESKJEMA TIL GRAVIDE – JODSTATUS

ID-nummer i prosjektet |__|__||__|__|

Dagens dato: |__|__|__|__| |__|__|__|__|

Spørsmål om bakgrunnsinformasjon

1. Alder? |___|

2. Svangerskapsuke? |___|

3. Ammer du for øyeblikket ja |___| nei |___|

4. Hvor mange barn har du? |___|

   Hvis du har barn, når fødte du ditt siste barn (dato) |__|__|__|__| |__|__|__|__|

5. Høyde og vekt: Hvor mye veide du før nåværende svangerskap og hvor mye veier du nå?

   Før nåværende svangerskapet |___| kg   Vekt nå |___| kg

   Hvor høy er du? |___| m

6. Hva er din sivilstand

   ☐ Samboer
   ☐ Gift
   ☐ Enslig
   ☐ Annet, forklar …………………………

7. Hvilket land er du født i?

   ☐ Norge
   ☐ Annet land
      Hvilket: ………………….

8. Hva er din høyeste fullførte utdannelse:

   ☐ <12 år (ikke fullført videregående)
   ☐ 12 år videregående/fagbrev
   ☐ 1-4 års utdanning høgskole eller universitet etter videregående
   ☐ Mer enn 4 år høgskole/universitet

9. Er du yrkesaktiv:

☐ Oppgi prosent stilling|___|

☐ Hjemmeværende

☐ Arbeidsledig

☐ Student

☐ Annet, forklar ………………………….

10. Røykevaner

Røkte du før du ble gravid?

☐ Nei, jeg har aldri røyket

☐ Nei, jeg har sluttet å røyke for flere år siden

☐ Ja, av og til

☐ Ja, daglig

Røyker du nå (mens du er gravid)?

☐ Nei

☐ Nei, jeg sluttet å røyke da jeg ble gravid

☐ Ja, av og til

☐ Ja, daglig

Hvor mye i gjennomsnitt røyker du per dag?

Antall sigaretter|___| sigarer/cigarillos |___| pipe |___|

Snuser du? Nei|___| ja, av og til |___| ja, daglig |___|

11. Sykdommer og medisiner av betydning for jodstatus

Har du hatt noen av følgende sykdommer knyttet til skjoldbruskkjertelen?

☐ For høyt stoffskifte, før svangerskapet |___| i svangerskapet |___|

☐ For lavt stoffskifte, før svangerskapet |___| i svangerskapet |___|

Har du hatt brukt medisiner for dette? |___|

Ja, før svangerskapet |___|, Ja, i svangerskapet |___|, Ja, begge tidspunkt |___|

Navn på medisiner:

…………………………………………………………………………………..

Spørsmål om kunnskap om jod i svangerskapet

1. Vet du hva jod er?
   - ☐ Ja
   - ☐ nei
   - ☐ Husker ikke

2. Hva vet du om for lavt og/eller for høyt inntak av jod inntak blant gravide i Norge? Du kan sette flere kryss.
   - ☐ For lavt inntak av jod er et problem i Norge i dag
   - ☐ For høyt inntak av jod er et problem i Norge i dag
   - ☐ For lavt og/eller for høyt inntak er ikke et problem i dag, men var vanlig før
   - ☐ Annet: _____
   - ☐ Vet ikke

3. Hva er de viktigste kilder til jod i kosten? Du kan sette flere kryss.
   - ☐ Kjøtt
   - ☐ Melk- og meieriprodukter
   - ☐ Frukt og grønnsaker
   - ☐ Fisk og sjømat
   - ☐ Brød- og kornprodukter
   - ☐ Vegetabilske oljer
   - ☐ Salt tilsatt jod
   - ☐ Kosttilskudd
   - ☐ Annet: _____
   - ☐ Vet ikke

4. Jod er viktig for? Du kan sette flere kryss.
   - ☐ Normal vekst og utvikling hos barn
   - ☐ Forebygge blindhet
   - ☐ Normal fosterutvikling
   - ☐ Normal styrke i skjelett og tenner
   - ☐ Opprettholde normalt stoffskifte
   - ☐ Unngå ryggmargsbrokk
   - ☐ Vet ikke

5. Jeg tror jeg får nok jod gjennom kosten?
   - ☐ Enig
   - ☐ Uenig
   - ☐ Vet ikke

6. Jeg har fått informasjon om jod fra helsepersonell i løpet av svangerskapet

☐ Ja

☐ Nei

☐ Husker ikke

Spørsmål om kosthold i svangerskapet

1. Jeg spiser sjelden eller aldri:

☐ Brød

☐ Kumelk

☐ Ost

☐ Yoghurt

☐ Fisk

☐ Kjøtt

2. Har du spist/drukket følgende matvarer det siste døgnet:

☐ Kumelk, yoghurt eller annen kumelk basert drikke?

Angi omtrent antall mengde i glass siste 24 timer: |___|

☐ Fisk eller fiskeprodukter?

(Hvis ja, utdyp type) <u>fet fisk (ørret/laks, sild/makrell)</u> |___| eller mager fisk (hvit fisk) |___|

(Hvis ja, utdyp om det var): til middag: |___| og/eller pålegg: |___|

Egg eller produkter med mye egg (e.g. pannekaker, vafler)? (Kryss hvis ja): |___|

3. Tar du et eller flere vitamin og mineraltilskudd, hvilket? _____

Skriv navn på tilskudd:

1._____ 2._____

3._____ 4._____

Hvor mange ganger i uken tar du tilskudd: 1:|___| 2:|___| 3:|___| 4:|___|

Takk for at du deltok i dette forskningsprosjektet om jod.

Skjema leveres til medarbeider i prosjektet «Jodstatus i svangerskapet» eller sendes til:

Sigrun Henjum, Høgskolen i Oslo og Akershus, Postboks 4 St. Olavs plass, 0130 Oslo

3. Questionnaire sub-study

Spørreskjema til gravide – jodstatus

ID-nummer i prosjektet ☐☐☐☐

Dagens dato: ☐☐ ☐☐ ☐☐☐☐

Postnummer: ☐☐☐☐

Bakgrunnsinformasjon

1. Din alder? år ☐☐

2. Hvor mange barn har du fra før? ☐

Hvis du har barn fra før, hvilken dato fødte du ditt forrige barn?

dd mm åååå
☐☐ ☐☐ ☐☐☐☐

3. Ammer du barnet nå?

☐ Ja helt ☐ Ja delvis ☐ Nei

4. Høyde og vekt: Hvor mye veide du før svangerskap og hvor mye veier du nå?

Før svangerskap ☐☐☐ kg

Vekt nå ☐☐☐ kg

Hvor høy er du? ☐☐☐ cm

5. Hva er din sivilstand
☐ Samboer
☐ Gift
☐ Enslig
☐ Annet, forklar …………………………………….

6. Hvilket land er du født i?
☐ Norge
☐ Annet……………………………………..

7. Hvor mange år har du bodd i Norge?
☐☐ År

8. Hvilket språk snakker du mest hjemme?
☐ Norsk
☐ Annet språk, hvilket:………………………..

9. Hva er din høyeste fullførte utdannelse:
☐ <12 år (ikke fullført videregående)
☐ 12 år videregående/fagbrev
☐ 1-4 års høgskole/universitet etter videregående
☐ Mer enn 4 år høgskole/universitet

10. Er du yrkesaktiv:
☐ Oppgi prosent stilling: ………………………..
☐ Hjemmeværende
☐ Arbeidsledig
☐ Student
☐ Annet, forklar …………………………………….

11. Røykevaner: Røyker du nå?
☐ Nei
☐ Nei, men jeg røkte før
☐ Ja, av og til
☐ Ja, daglig

Hvor mye i gjennomsnitt røyker du per dag? Gi antall:
☐ sigaretter …….. stk

☐ sigarer/cigarillos …….. stk

☐ pipe …….. stk

Snuser du?
☐ Nei   ☐ Ja,
☐ Av og til   ☐ Ja, daglig, gi antall: ………stk

7. Har du hatt noen av følgende sykdommer knyttet til skjoldbruskkjertelen?
☐ For høyt stoffskifte
☐ For lavt stoffskifte
Har du hatt brukt medisiner for dette?
☐ Ja   ☐ Nei
Navn på medisiner:………………………

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Kunnskap om jod

1.Vet du hva jod er?

☐ Ja

☐ Nei

☐ Har hørt om det, men husker ikke

2. Hva er de viktigste kilder til jod i kosten? (Du kan sette flere kryss).

☐ Kjøtt

☐ Melk- og meieriprodukter

☐ Frukt og grønnsaker

☐ Fisk og sjømat

☐ Brød- og kornprodukter

☐ Vegetabilske oljer

☐ Salt tilsatt jod

☐ Kosttilskudd

☐ Annet:…………………………………

☐ Vet ikke

3. Jod er viktig for? (Du kan sette flere kryss).

☐ Normal vekst og utvikling hos barn

☐ Forebygge blindhet

☐ Normal fosterutvikling

☐ Normal styrke i skjelett og tenner

☐ Opprettholde normalt stoffskifte

☐ Unngå ryggmargsbrokk

☐ Vet ikke

4. Jeg tror jeg får nok jod gjennom kosten?

☐ Enig   ☐ Uenig   ☐ Vet ikke

5. Jeg har fått informasjon om jod fra helsepersonell

☐ Ja   ☐ Nei   ☐ Husker ikke

6. Hva vet du om lavt og høyt inntak av jod blant gravide/ammende i Norge? (Du kan sette flere kryss):

☐ For lavt inntak av jod er et problem i Norge i dag

☐ For høyt inntak av jod er et problem i Norge i dag

☐ For lavt inntak er ikke et problem i dag, men var vanlig før

☐ Vet ikke

☐ Annet …………………………………………

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Kosthold og kosttilskudd

1. Tar du et eller flere vitamin og mineraltilskudd (for eksempel vitaminer, mineraler, olje, tare-tilskudd)?

☐ Ja   ☐ Nei

Hvis Ja, skriv navn på tilskudd(ene) og hvor mange ganger i uken tar du hvert tilskudd:

1._____: ☐ ganger/uke

2._____: ☐ ganger/uke

3._____: ☐ ganger uke

4._____: ☐ ganger/uke

Kan du lese ut fra innholdsdeklarasjonen om noen av disse tilskuddene inneholder jod?

☐ Ja   ☐ Nei

Hvis ja, skriv hvilket tilskudd det gjelder og hvor mye jod det er per dose:…………………………………

2. Er du vegetarianer? (dvs spiser ikke kjøtt, fisk og fiskeprodukter):

☐ Ja   ☐ Nei

3. Er du veganer? (dvs spiser ikke kjøtt, fisk, fiskeprodukter, melkeprodukter og egg):

☐ Ja   ☐ Nei

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5. Hvor ofte har du i gjennomsnitt drukket eller spist disse matvarene?

		Sjelden/ aldri	Sjeldnere enn ukentlig	1-3 ganger per uke	4-6 ganger per uke	1-2 ganger per dag	3-4 ganger per dag	5 + ganger per dag
1.	Brød/knekkebrød, alle typer (2 skiver)	☐	☐	☐	☐	☐	☐	☐
2.	Frokostblandinger med korn/gryn (usøtet musli, havregrøt) (1 porsjon)	☐	☐	☐	☐	☐	☐	☐
3.	Andre frokostblandinger (corn flakes, honni korn, sjokopuff etc) (1 porsjon)	☐	☐	☐	☐	☐	☐	☐
4.	Ris/pasta kokt (porsjon á 150g)	☐	☐	☐	☐	☐	☐	☐
5.	Kumelk, alle typer gitt i antall glass (ca 2 dl) (og inkludert kaffe latte/cappuccino)	☐	☐	☐	☐	☐	☐	☐
6.	Alternativ melk (havre, ris, mandel, soya) ca 2 dl	☐	☐	☐	☐	☐	☐	☐
7.	Yoghurt/surmelk, all typer gitt i antall beger (ca2dl)	☐	☐	☐	☐	☐	☐	☐
8.	Rød fisk både til middag og som pålegg (laks, makrell, ørret, tunfisk) (Porsjon á ca 100 g)	☐	☐	☐	☐	☐	☐	☐
9.	Hvit fisk både til middag og som pålegg (torsk, sei, hyse, etc) (Porsjon á ca 100 g)	☐	☐	☐	☐	☐	☐	☐
10.	Fiskekaker, fiske- boller, pudding og pinner (1 porsjon)	☐	☐	☐	☐	☐	☐	☐
11.	Sushi med fisk/skalldyr (porsjon á ca 10 biter)	☐	☐	☐	☐	☐	☐	☐
12.	Rent kjøtt av okse, gris og lam (steik, koteletter, filet, biff), (Porsjon á ca 100 g)	☐	☐	☐	☐	☐	☐	☐
13.	Bearbeidede kjøttprodukter (pølser, hamburger, kjøttkaker o.l.) (Porsjon á ca 100 g)	☐	☐	☐	☐	☐	☐	☐
14.	Vilt (elg, hjort, rådyr, villfugl, hære o.l.) (Porsjon á ca 100 g)	☐	☐	☐	☐	☐	☐	☐
15.	Kylling og kalkun, (Porsjon á ca 100 g)	☐	☐	☐	☐	☐	☐	☐
16.	Innmat (lever, nyrer, innmatpudding o.l.), (Porsjon á ca 100 g)	☐	☐	☐	☐	☐	☐	☐
17.	Linser, bønner, kikerter	☐	☐	☐	☐	☐	☐	☐
18.	Olivenolje/rapsolje (til salat og matlaging)	☐	☐	☐	☐	☐	☐	☐
19.	Ost, alle typer, (2 skiver)	☐	☐	☐	☐	☐	☐	☐
20.	Egg hele (kokt, stekt) og i matlaging (pannekaker/vafler)	☐	☐	☐	☐	☐	☐	☐
21.	Kaker, sjokolade, iskrem, smågodt	☐	☐	☐	☐	☐	☐	☐
22.	Saltet snacks (f.eks. potetchips, peanøtter)	☐	☐	☐	☐	☐	☐	☐
23.	Søte drikker (som saft, Cola, Fanta, nektar, juice, smoothie)	☐	☐	☐	☐	☐	☐	☐
24.	Kunstig søte drikker (Cola Zero, Pepsi Zero osv)	☐	☐	☐	☐	☐	☐	☐
25.	Vann som drikke	☐	☐	☐	☐	☐	☐	☐
26.	Kaffe	☐	☐	☐	☐	☐	☐	☐
27.	Te	☐	☐	☐	☐	☐	☐	☐
28.	Grønnsaker alle typer (f.eks. gulrot, kål, brokkoli, løk, erter, tomat, salat, agurk)	☐	☐	☐	☐	☐	☐	☐
29.	Frukt og bær alle typer (f.eks. epler, pærer, banan, jordbær, druer, appelsin)	☐	☐	☐	☐	☐	☐	☐
30.	Poteter (porsjon á 1 middels stor eller 2 små)	☐	☐	☐	☐	☐	☐	☐
31.	Nøtter (valnøtter, hasselnøtter, mandler o.l.)	☐	☐	☐	☐	☐	☐	☐

Takk for at du deltok i dette forskningsprosjektet om jod!

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