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Iodine intake and status in a group of pregnant women in Norway

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ABSTRACT

BACKGROUND: Iodine deficiency is a worldwide problem known to have adverse effects on growth and development in humans. Pregnant women are exceptionally vulnerable to iodine deficiency as the need of iodine is increased during pregnancy. The Mother and Child Cohort Study showed that pregnant women in Norway could be at risk of suboptimal iodine intake.

OBJECTIVE: The main objective was to describe iodine status in a group of pregnant women in Norway.

METHOD: A cross-sectional study was performed among 40 pregnant women (22-47 years) from Norway. Two samples of morning spot urine were collected from each participant for assessment of urinary iodine concentrations and urinary creatinine concentrations. Two-day food diary was recorded to calculate iodine intake from food, including iodine from supplement (total iodine intake). A control group of 26 non-pregnant women in childbearing age (22-48 years) was included in the study.

RESULTS: The median iodine intake from food was 124 μg/day and the median total iodine intake (food and supplement) was 170 μg/day in the pregnant women. Intake of iodine-containing supplements was reported by 25% of the women. The median urinary iodine concentration was 80 μg/L. After adjusting for creatinine the iodine/creatinine ratio was 80 μg/g creatinine and the adjusted age- and sex iodine/creatinine ratio was 87 μg/day. Total iodine intake (food and supplement) correlated well with urinary iodine concentration (r_s = 0.54, p< 0.001). There was a significant difference in total iodine intake (food and supplement) between the pregnant women and the control group (p=0.014).

CONCLUSION: The findings from the present study indicate mild-to-moderate iodine deficiency in the group of pregnant women in Norway, shown through low intake of iodine from food and a low median urinary iodine concentration. A nationally representative study on iodine status in pregnant women in Norway is needed to confirm the findings.

KEYWORDS: Iodine status, pregnancy, mild-to-moderate iodine deficiency, iodine intake, urinary iodine concentration

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ADHD	Attention Deficit/Hyperactivity Disorder
BMI	Body Mass Index
DIT	Diiodotyrosine
Donexpo	Experimental study of deoxynivalenol biomarkers in urine
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
g	Gram
HiOA	Oslo and Akershus University College
I	Iodine
ID	Iodine deficiency
IDD	Iodine-deficiency disorders
IGN	Iodine Global Network
IQ	Intelligence quotient
IQR	Interquartile range
kg	Kilogram
kJ	Kilojoules
L	Liter
M	Missing
MIT	Monoiodotyrosine
MoBa	The Norwegian Mother and Child Cohort Study
n	number
NaCI	Sodium chloride
NHMRC	National Health and Medical Research Council
NNR5	Nordic Nutrition Recommendations
NVI	Norwegian Veterinary Institute
RDI	Recommended daily intake
REK	Regional Committees for Medical and Health Research Ethics, Norway
SAC	School-age children
SPSS	Statistical Package for the Social Sciences

T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid stimulating hormone
UIC	Urinary iodine concentration
UIE	Urinary iodine excretion
UK	United Kingdom
UL	Tolerable Upper Intake Level
UNICEF	United Nations Children's Fund
US	United States
USI	Universal salt iodization
WHO	World Health Organization
Yr	Year
μg	Microgram

1 INTRODUCTION

Iodine deficiency (ID) is one of the most common nutritional disorders in the world, with 1.88 billion people estimated to have inadequate iodine intakes (Andersson, Karumbunathan & Zimmermann, 2012). ID is also the world's greatest single cause of preventable brain damage (World Health Organization [WHO], 2007a). Iodine is an essential trace element required for production of thyroid hormones thyroxine and triiodothyronine (Zimmermann, 2011). The thyroid hormones helps to regulate a wide range of physiological processes, and are crucial for normal growth and development of the central nervous system and the brain (Zoeller & Rovet, 2004). ID occurs when iodine intake is insufficient for the body to produce adequate amounts of thyroid hormones (Zimmermann, 2012). Pregnant women and infants are exceptionally vulnerable to ID and severe ID during pregnancy can result in hypothyroidism[1], goiter[2] and irreversible mental retardation in the child (Skeaff, 2011; Zimmermann, 2012). The effect of mild-to-moderate ID is unclear but it may affect cognitive function of the offspring (Bath, Steer, Golding, Emmett & Rayman, 2013; Hynes, Otahal, Hay & Burgess, 2013; Zimmermann, 2007). In order for pregnant women to meet both her own and the fetus requirement of thyroid hormones, up to a 50% increase in iodine intake is recommended during pregnancy (Glinoer, 2007; Zimmermann, 2007). This is partly due to increased thyroid hormone production, increased renal iodine losses and fetal iodine requirements (Glinoer, 1997).

The Norwegian population has been considered iodine replete for decades but the Norwegian Mother and Child Cohort Study (MoBa) showed that pregnant women can be at risk of suboptimal iodine intake, defined as intake below 150 μg/day (Brantsaeter, Abel, Haugen & Meltzer, 2013). WHO advises each country to assess the iodine status in the population every five-year. If suboptimal iodine status is detected, iodine-containing supplement is recommended for vulnerable groups, such as pregnant women (Andersson, de Benoist, Delange & Zupan, 2007). In the United States (US) and Canada, supplement with 150 μg iodine daily are recommended for use in pregnancy planning and for pregnant and breastfeeding women (Stagnaro-Green, Sullivan & Pearce, 2012). The health authority in Norway does not follow the WHO recommendations, and there are no public recommendations for taking iodine supplements for people at risk of ID, such as pregnant

[1] Insufficient thyroid hormone production (Zimmermann, 2012)

[2] Enlargement of the thyroid gland (Lazarus, 2015)

women. It is therefore essential to increase the public awareness of iodine status in pregnant women and there is an urgent need for studies on iodine intake and iodine status of pregnant women in Norway (Brantsaeter et al., 2013; Zimmermann, 2012).

1.1 Context and delimitation

The work of this master thesis includes collaboration with The Norwegian Institute of Public Health (FHI). Together with another master student we got the opportunity to use data from a study conducted by FHI called "Experimental study of deoxynivalenol biomarkers in urine" (Donexpo), where the main aim was to analyze mycotoxins in urine. In addition, we recruited participants exclusively to the master thesis. The focus for my master thesis is iodine status during pregnancy, while the other master student evaluated iodine status in vegetarians. In the present master thesis, pregnant women in all trimesters were included, and two-day food diaries and morning spot urine samples were collected from the participants, as well as a background form with maternal characteristics. Urinary iodine concentration, urinary creatinine levels, and calculated iodine intake from food and supplement were analyzed. This master thesis did not include infants or measurement of thyroid hormones.

1.2 Aim of the study

The main purpose of the present study was to assess iodine intake in a group of pregnant women in Norway. The main objective was to describe iodine status through iodine intake and urinary iodine concentration. Relatively few studies have been conducted on iodine status in pregnant Norwegian women, and this master thesis can raise further awareness of iodine status among pregnant women in Norway.

2 THEORETICAL BACKGROUND

Iodine is a halogen element in the periodic table and is distributed in the earth's environment as iodide. Today most iodide is found in the ocean, with small amounts in the soil due to leaching from glaciations, flooding and erosion (Zimmermann, 2009).

2.1 Iodine in human nutrition

Iodine is an essential trace element required for the production of thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) (Zimmermann, 2011). Iodine, as in iodide, is found in relatively few food groups, and irrigation, soil and fertilizers affect the iodine content in food (Ghirri, Lunardi & Boldrini, 2014). Goitrogens[3] which is found in cruciferous vegetables, including kale, broccoli, cabbage, rapeseed and cauliflower can affect the uptake of iodine (Zimmermann, 2009). Fish and seafood is the most important source of iodine around the world because marine plants and animals concentrate iodine from seawater (Zimmermann, 2009). However, the iodine content varies greatly between lean and fatty fish with the highest content in lean fish like cod, haddock and saithe (Rasmussen, Andersen, Ovesen & Laurberg, 2009). The fortification of cow fodder with 2mg I/kg NaCI as calcium iodate has been controlled by legislation in Norway since the 1950s, which have resulted in higher iodine content in milk and dairy products (Dahl, Johansson, Julshamn & Meltzer, 2004). The main source of iodine in Norway today is therefore milk and dairy products, contributing with almost 60% of iodine in the diet (Brantsaeter, Haugen, Julshamn, Alexander & Meltzer, 2009; Dahl, Opsahl, Meltzer & Julshamn, 2003a). In 2003, a Norwegian study found a seasonal variation in iodine content in milk and dairy products. Dahl et al. (2003a) found that low-fat milk from the summer season had significant lower median iodine concentration (88 µg/L, range 63-122 µg/L) than low-fat milk from the winter season (232 µg/L, range 103-272 µg/L). In organic summer milk the median iodine concentration was 60 µg/L, which was significant lower than organic winter milk with a median iodine concentration of 127 µg/L. The difference was explained by the eight weeks in the summer season where the cattle's are grazing outdoors and did not have the same access to fortified cow fodder as in the winter season (Dahl et al., 2003a). Today, the seasonal variation in milk and dairy products is probably not that significant because the cattle's are getting the same amount of fortified cow

[3] Dietary substances that interfere with thyroid metabolism (Zimmermann, 2009)

fodder and mineral salt in both summer and winter season (L, Nordang, personal communication, April 20, 2016). Seafood and eggs are also important sources of iodine in the Norwegian diet (Brantsaeter et al., 2009; Dahl et al., 2004). The mean iodine concentration in other food items, e.g., meat and meat products, bread and cereals, vegetables, potatoes, fruits and berries, and fats and oils is assumed to be 2-3 μg/100g and their contribution of iodine to the diet are therefore limited (Dahl et al., 2004).

The iodine content in soil is highly dependent on its geological origin, and European inland soils are often depleted in iodine relative to soils from costal areas (Haldimann, Alt, Blanc & Blondeau, 2005; Rasmussen et al., 2009). In Norway, the iodine concentrations in drinking water differ with locations with the highest concentration in the coast areas (2.0 μg L^{-1}) and the lowest in the inland areas (0.8 μg L^{-1}), and the contribution of iodine from Norwegian drinking water is insignificant (Dahl et al., 2004). Norway has never had mandatory iodization of salt, but some brands of salt are fortified with iodine and regulations permit the addition of 5 μg of iodine per gram of NaCI (Andersson et al., 2007; Dahl et al., 2004).

2.1.1 Iodine requirements

The human body needs a daily supply of iodine to maintain an adequate production of thyroid hormones (Vanderpas, 2006). The Nordic Nutrition Recommendations (NNR5), and WHO, the United Nations Children's Fund (UNICEF) and the Iodine Global Network[4] (IGN) recommendations for iodine are shown in Table 2-1. The recommendation by NNR5 is meant for the general population and not for people with diseases or other conditions that can affect their nutrient requirements (Nordic Council of Ministers, 2014). For adolescents and adults the recommended daily intake of iodine is 150 μg/day. 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). This is partly due to an increased production of thyroid hormones, fetal iodine needs and increased renal iodine losses (Glinoer, 2007; Zimmermann, 2007). WHO, UNICEF and IGN recommends 250 μg/day during pregnancy and lactation (WHO, 2007a).

[4] Formerly International Council for the Control of Iodine Deficiency Disorders

Table 2-1 Recommended daily intake (RDI) of iodine (µg/day) by age or population group.

WHO		NNR5	
Age or population group	RDI (µg/day)	Age or population group	RDI (µg/day)
Children 0-50 months	90	Infants 0-24 months	50-70
Children 6-12 yr	120	Children 2-5 yr	90
Adults > 12 yr	150	Children 6-9 yr	150
		Children 10-13 yr	120
		Adults > 13 yr	150
Pregnancy	250	Pregnancy	175
Lactation	250	Lactation	200

Sources: (Nordic Council of Ministers, 2014; WHO, 2007a).

Lower intake level

An intake of iodine below the recommended level can have several harmful consequences (Zimmermann, Jooste & Pandav, 2008). For adolescents and adults the lower intake level of iodine is sat to 70 µg/day to avoid the development of goiter (Nordic Council of Ministers, 2014). Insufficient intake of iodine during pregnancy becomes potential dangerous for the fetus when maternal iodine intake falls below 100 µg/day, and can in more severe cases cause mental retardation or cretinism (Glinoer, 2007).

Upper intake level

According to the Institute of Medicine US Food and Nutrition Board (Institute of Medicine), the Tolerable Upper Intake Level (UL) of iodine for adults, including pregnant and lactating women is 1100 µg/day (Institute of Medicine (US), 2001). The European Food Safety Authority (EFSA) recommends an UL of iodine of 600 µg/day for pregnant and lactating women (European Food Safety Authority, 2006), and WHO has sat the UL of iodine to 500 µg/day for pregnant women (WHO, 2007a). An intake of iodine above the recommendation can lead to iodine excess, which during pregnancy may cause maternal thyroid dysfunction, especially subclinical hypothyroidism (Sang et al., 2012).

2.2 Pregnancy

During the nine months of pregnancy the body goes through the most intense period of growth and development in human life, and there are several factors involved in the processes from fetus to infant. One factor that is of great importance and is within our control to change

is optimal nutritional status. Deficits or excesses of certain nutrients during critical periods of development can cause irreversible damage to the fetus, and maternal nutritional status is therefore a key element of successful reproduction (Brown, 2014). A pregnancy is divided into three trimesters, where all represent a new area for the developing fetus. First trimester represents the 12 first weeks of pregnancy, second trimester represents the weeks 13-28, and third trimester is week 29 to birth (Brown, 2014). During the two first months after conception, a majority of organs and tissues begin to form. If damage in growth or development should occur during this critical period, there is no possibility to correct the damage. Consequently, adverse effects of nutritional and other insults occurring during critical periods of growth and development persist throughout life (Brown, 2014). Because the fetus grows and develops organs and tissues rapidly through pregnancy, good nutritional status is an important determinant during all the trimesters (Brown, 2014; Williamson, 2006).

The Norwegian Directorate of Health provides dietary advice for women planning a pregnancy. The general dietary recommendations are similar to the advice given to non-pregnant women in terms of following a healthy, varied and balanced diet to ensure an adequate intake of energy and nutrients. Women who are planning a pregnancy are advised to take a folic acid supplement of 400 μg per day and continue with the supplement the three first months of pregnancy (The Norwegian Directorate of Health, 2012a). Folic acid is of critical importance in protecting against neural tube defects in the developing fetus (Williamson, 2006). In addition, an optimal intake of vitamin D, iron, calcium and essential fatty acid are recommended (The Norwegian Directorate of Health, 2012a). A Norwegian study from 2008 using data from the MoBa study found that the use of supplement during pregnancy improved the intake of folate, iron and vitamin D, but it was not enough to reach the recommended amounts. The same was true for iodine where 28% and 80% did not reach the recommended intake among iodine supplements user and nonuser, respectively (Haugen, Brantsaeter, Alexander & Meltzer, 2008).

As of today, there is no recommendation concerning adequate intake of iodine during pregnancy in Norway (Brantsaeter et al., 2013).

2.3 Thyroid metabolism

2.3.1 Absorption and transportation

Iodine is consumed in different chemical forms whereas dietary iodide is rapidly and nearly completely absorbed (>90%) in the stomach and duodenum as iodide before concentrated by the thyroid gland (Hurrell, 1997; Zimmermann, 2009). A sodium-iodide transporter transfers iodide into the thyroid gland and the thyroid in conditions of adequate iodine supply takes up only about 10% of absorbed iodine. The body of a healthy adult is able to maintain a store of iodine ranging from 15-20 mg, of which 70-80% is in the thyroid (Glinoer, 2007; Zimmermann, 2009). Renal iodine clearance is fairly constant but thyroid clearance varies with iodine intake. In chronic iodine deficiency (ID) the uptake of iodine by the thyroid can exceed 80% and the iodine content of the thyroid may fall below 20 μg (Zimmermann, 2009). During lactation, the mammary gland concentrates iodine and secrets it into breast milk in order to provide enough iodine for the infants (Zimmermann, 2009). Around 10-15% of the daily iodine intake is excreted into breast milk (Institute of Medicine (US), 2001; Scientific Committee on Food, 2002). Other tissues that may concentrate iodine are the salivary glands and choroid plexus, but they are considered to be minor pathways for uptake of iodide (Institute of Medicine (US), 2001; Sharp, 2011). To balance for losses and maintain thyroid hormone synthesis, the thyroid of euthyroid[5] adults traps 60-80 μg of iodine per day. In adults, about 90% of iodine is excreted in the urine and a very small amount is excreted through feces or sweat, making urinary iodine a good indicator for iodine status (Yarrington & Pearce, 2011; Zimmermann, 2009).

2.3.2 Thyroid hormone synthesis

The thyroid secretes two thyroid hormones, T_4 and T_3. The release of thyrotropin-releasing hormone from hypothalamus stimulates the pituitary gland to secrete thyroid-stimulating hormone (TSH) (Ghirri et al., 2014). TSH regulates the active transport where iodine from the blood goes into the thyroid, and also the secretion of T_4 and T_3 (Zimmermann, 2009). When iodine is entering the thyroid it oxidize and produce monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are the precursors of thyroid hormones. The coupling of MIT and DIT results in the formation of thyroid hormones. In order to produce T_4 there has to be a linkage of two DIT molecules, and the linkage of a MIT and DIT molecule produces T_3. The

[5] The state of having normal thyroid gland function (Morreale de Escobar, Obregon & Escobar del Rey, 2004)

whole process of generating the thyroid hormones is stimulated by the enzyme thyroid peroxidase (Yarrington & Pearce, 2011; Zimmermann, 2009). After T_4 and T_3 enter the circulation, the hormones are rapidly attach to binding proteins, including thyroxine-binding globulin, albumin and transthyretin, before transported to peripheral tissues in need of the hormones. In the tissues, T_4 is deiodinated to T_3, which is the active form (Ghirri et al., 2014; Institute of Medicine (US), 2001). The enzyme deiodinase, which is responsible for this process contains selenium and selenium deficiency can result in a decrease in T_3 levels (Institute of Medicine (US), 2001).

2.3.3 Biological functions of iodine

Iodine is a crucial component in the thyroid hormones, which are necessary for physical and mental development, including accelerated myelination and improved differentiation, maturation and cell migration (Zoeller & Rovet, 2004). The hormones, and therefore iodine, are important in biochemical reactions such as enzymatic activity and protein synthesis, making iodine to a very important trace element (Institute of Medicine (US), 2001).

2.4 Iodine deficiency

2.4.1 Iodine-deficiency disorders

ID occurs when iodine intake is insufficient and the body is not able to produce enough thyroid hormones (Zimmermann, 2012). The consequences of ID are called iodine-deficiency disorders (IDD), which have many adverse effects on growth and development in humans (Table 2-2). People living in areas affected by severe ID may have a lower intelligence quotient (IQ) than people from comparable communities with no IDD (Qian et al., 2005; Zimmermann, 2007). The negative consequences of IDD may affect women's health, child learning capacity and economic productively, which further can affect the public health status of a community (WHO, 2007a). When ID is present the thyroid will adjust all of the physiological processes of thyroid hormone production in order to maximize the use of iodine. The result will be an increased thyroidal iodine uptake and the size of the thyroid will increase, which may lead to goiters (Lazarus, 2015; Zimmermann et al., 2008). Goiter can occur at any age and is often the first clinical evidence of ID, and can be characterized by diffuse, homogeneous enlargement that eventually can develop into nodules (Zimmermann,

2009). Goiters is not seen in populations with a median iodine intake of >150 μg/day (WHO, 2007a). In chronic severe ID the synthesis of thyroid hormones is gradually reduced, which results in hypothyroidism. This condition results from inadequate thyroid hormone production and is characterized by elevated TSH levels and low concentration of free T_4 (fT_4) (Zimmermann, 2011). Hypothyroidism is the main reason for the harmful effects of IDD, with the most damaging effect being on the developing brain. The thyroid hormones are crucial for myelination of the central nervous system and ID during critical periods as fetal and perinatal development can therefore cause mental retardation (WHO, 2007a; Zoeller & Rovet, 2004).

Mild-to-moderate ID can increase the risk of diffuse goiter, nontoxic and toxic nodular goiter, and corresponding hyperthyroidism[6] and subclinical hypothyroidism[7], as well as an increased risk of aggressive subtypes of thyroid cancer (Zimmermann, 2009; Zimmermann et al., 2008).

Table 2-2 The spectrum of iodine-deficiency disorders.

All ages	Goiter Hypothyroidism Increased susceptibility to nuclear radiation
Fetus	Spontaneous abortion Stillbirth Congenital anomalies Perinatal mortality
Neonate	Infant mortality Endemic cretinism
Child and adolescent	Impaired mental function Delayed physical development Iodine-induced hyperthyroidism
Adults	Impaired mental function Iodine-induced hyperthyroidism

Source: Adopted from WHO (WHO, 2007a).

2.4.2 Iodine status in the World

According to WHO, ID is the number one cause of preventable brain damage in the world (WHO, 2007a). Globally, 1.88 billion people were estimated to have inadequate iodine intakes in 2011, including 44% of European school-age children (SAC) (Andersson et al.,

[6] Excessive thyroid hormone production (De Leo, Lee & Braverman, 2016)

[7] Mildly elevated TSH levels (Zimmermann, 2009)

2012). In Europe, ID has been recognized as a problem for more than a decade (Delange, 2002). During these years, a remarkable progress has been done to eradicate the problem. Nevertheless, an update on iodine status in Europe from 2014 showed that 11 countries (30%) were iodine-deficient which is the largest number from any continent (Lazarus, 2014). This indicates that ID in Europe has re-emerged (Figure 2-1) (Lazarus, 2014). Data on the prevalence of iodine status in pregnant women has been insufficient, and was available for 21 countries when measured in 2014 whereas 8 countries (38%) reported adequate iodine intake in pregnant women (Lazarus, 2014). In 2015, Zimmermann et al. (2015) again reviewed ID in pregnant women in Europe and they reported that in ten countries the iodine intake was adequate for pregnant women and in 21 countries the intake was deficient. In addition, two-thirds of European countries that had assessed iodine status in pregnant women reported inadequate iodine intakes (Zimmermann, Gizak, Abbott, Andersson & Lazarus, 2015). In most countries the ID is mild or moderate, however, it can still have negative impact on the affected population (Lazarus, 2014; Zimmermann, 2007). In Belgium, a comprehensive evaluation of iodine status in pregnancy found that the iodine intake was suboptimal according to the median urinary iodine concentration (UIC) of 117 μg/L and 131 μg/L in pregnant women in first trimester and third trimester, respectively (Moreno-Reyes, Glinoer, Van Oyen & Vandevijvere, 2013), despite the fact that around 60% of pregnant women were consuming iodine-containing supplements (Vandevijvere, Amsalkhir, Mourri, Van Oyen & Moreno-Reyes, 2013). Pregnant women in Denmark not consuming iodine-containing supplements had a median UIC (68 μg/L) indicating inadequate iodine intake (Andersen, Sorensen, Krejbjerg, Moller & Laurberg, 2013). Other European countries with suboptimal iodine status in pregnant women according to Lazarus (2014) are Albania, Greece, Portugal and Romania, as well as Norway (Lazarus, 2014).

Areas with endemic goiter existed in Norway before World War II but since the iodization of cow fodder in the 1950s the Norwegian population has been considered iodine-replete (Dahl et al., 2004). Some groups in the population can, however, be at risk of ID, including pregnant women (Brantsaeter et al., 2013; Dahl, Opsahl, Julshamn & Meltzer, 2003b; Sanchez, 2015).

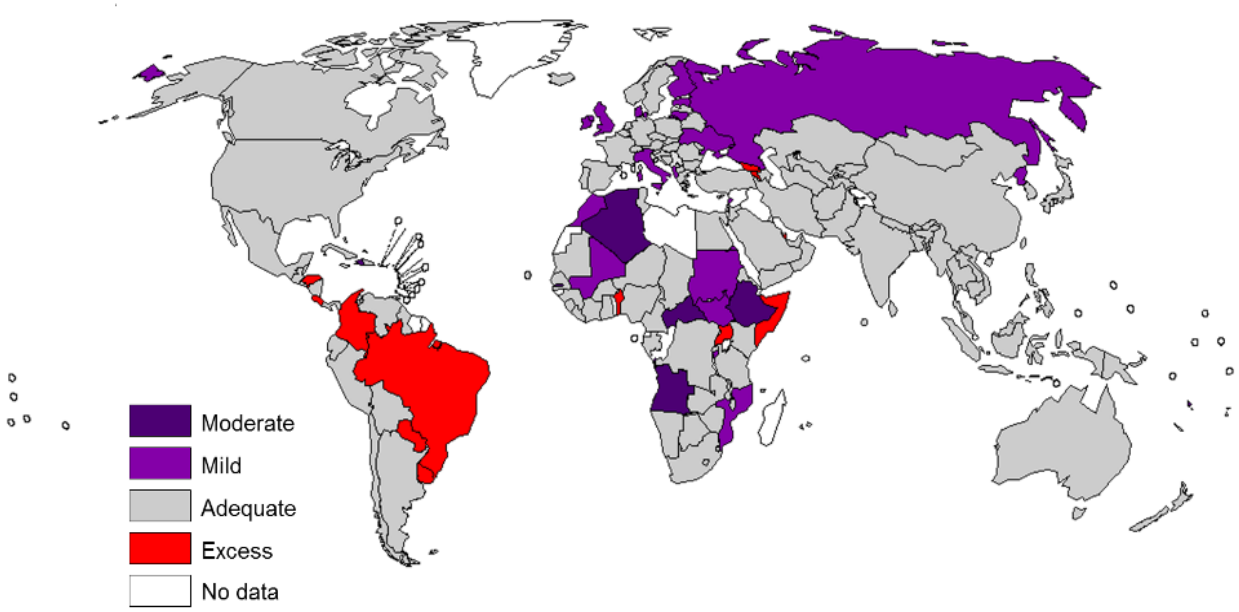

Figure 2-1 Global iodine map[8] 2014-15 elaborated by Iodine Global Network.

2.4.3 Iodine deficiency in pregnancy

Pregnant women, infants and children up to two years of age are exceptionally vulnerable to ID (Skeaff, 2011). The requirement of iodine during pregnancy is increased with around 50% to ensure an adequate production of thyroid hormones to meet fetal requirements (Glinoer, 2007). There are several events leading to the increased requirement. Firstly, the thyroid gland is stimulated to increase the maternal T_4 production to maintain maternal euthyroidism because of the rise in the concentration of estrogen during pregnancy. This increase starts during early gestation, which reaches a plateau at mid-gestation and is maintained thereafter (Glinoer, 2007; Zimmermann, 2007). Secondly, the transfer of thyroid hormones and iodine to the fetus requires an increase in iodine intake during pregnancy (Zimmermann, 2007). Thirdly, there is an increase in renal iodine clearance due to a greater glomerular filtration rate, which begins in early gestation because of an increase in renal blood flow (Glinoer, 2007; Zimmermann, 2007). All of these events represent metabolic changes that lead to the transition from the preconception thyroidal steady state to the pregnancy steady state (Figure 2-2) (Glinoer, 2004).

[8] Figure based on median urinary iodine concentration in school-age children

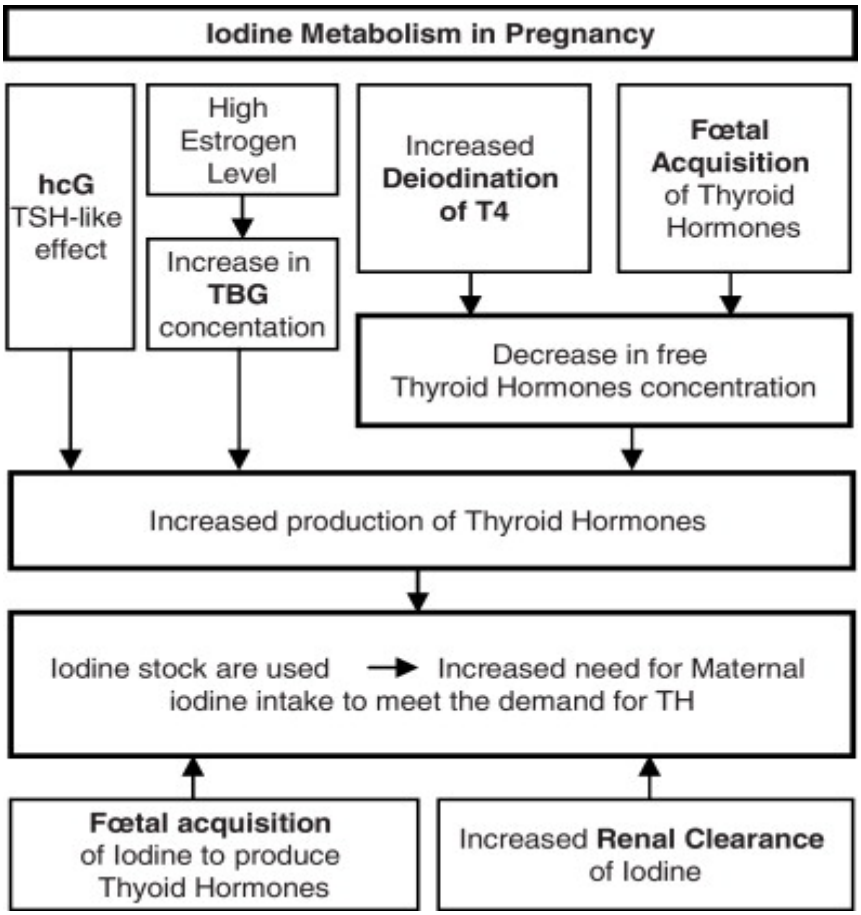

Figure 2-2 Iodine metabolism in pregnancy (Trumpff et al., 2013).

How all of the metabolic changes and the regulation mechanisms during pregnancy work, is not completely understood. However, we know that thyroid hormones are necessary in the development of hearing and vision and maturation of most organs including the brain and muscles (Zimmermann, 2009). From the second half of the first trimester in pregnancy the fetus depends on maternal fT_4, which is converted to cerebral T_3 in the fetal brain, for development of the central nervous system (Calvo et al., 2002). The placenta has an important role in the transportation of T_4 but details are still unclear (Lazarus, 2011). In this stage, neuronal proliferation and the onset of neuronal migration in the cerebral cortex and hippocampus takes place (Williams, 2008). The fetal thyroid begins to produce hormones in the second trimester but because the reserves of the fetal gland are low and the gland itself does not fully mature until birth, maternal thyroid hormones will continue to be an important source of fT_4 until birth (Brown et al., 2000; Skeaff, 2011). As such, the developing fetus depends heavily upon adequate maternal iodine status and thyroid hormone levels, particularly during early gestation (Katz et al., 2013). To assure for normal neuronal

migration and myelination of the fetal brain, which starts in the second half of the first trimester, the mother has to be euthyroid. If not, irreversible damage to the developing brain will occur (Morreale de Escobar et al., 2004; Skeaff, 2011). If the mother becomes iodine deficient, the mother and the fetus will respond differently. The mother will remain euthyroid and the fetus becoming hypothyroid for two reasons. Firstly, the increase in maternal fT_4 that occurs at the end of the first trimester and secondly, because the maternal thyroid gland responds to ID by increasing iodine trapping, preferential synthesis of T_3 over T_4. The women will therefore be seen as euthyroid because the concentration of TSH and T_3 falls within normal reference range (Morreale de Escobar et al., 2004). Insufficient maternal iodine intake during pregnancy will, however, lead to maternal hypothyroxinaemia, which is characterized by low fT_4 concentration (Williams, 2008). Maternal hypothyroxinaemia cause neurological hypothyroidism in the fetus, which result in neurological and psychological deficits in the offspring, as well as poor growth and cognitive impairment depending upon the timing and severity of the hypothyroidism. The first half of pregnancy is the most sensitive period for damaging on the central nervous system and the brain (Williams, 2008). Hypothyroidism in the fetus is characterized by decreased synthesis and secretion of T_4 and T_3 and an increase in the concentration of TSH (de Escobar, Obregon & del Rey, 2007). Cretinism is the most serious consequence of ID and it is an irreversible state of mental retardation, which is seen in combination with deaf-mutism, dwarfism and spasticity. This is characterized by motor, cognitive and auditory defects (Zimmermann, 2009). Spontaneous abortion, increased infant mortality and stillbirth is other consequences of ID during pregnancy (WHO, 2007a).

Mild hypothyroxinaemic pregnant women might not be diagnosed as clinically or subclinically hypothyroid because these diagnoses are sat by measuring TSH levels, as stated above will fall within normal reference range, and they will appear to be euthyroid (Berbel, Obregón, Bernal, Rey & Escobar, 2007; Morreale de Escobar et al., 2004). The amount of fT_4 available for the fetus is not sufficient for normal development when the mother is hypothyroxinaemic, caused by a low intake of iodine. Even mild hypothyroxinaemia can be damaging for the developing fetus, and it is therefore important to optimizing iodine status previous to pregnancy (Zimmermann, 2007).

2.4.4 Mild-to-moderate iodine deficiency in pregnancy

Severe ID is known to cause cretinism and mental retardation but less is known about the effects of mild-to-moderate ID in pregnancy, which is defined as a median UIC of 50-150 µg/L (WHO, 2007a; Zimmermann, 2007). The re-emerged problem of mild-to-moderate ID in several European countries, such as in the UK, has caused concern and multiple studies have been conducted with the goal to assess the effects of mild-to-moderate ID in pregnancy (Trumpff et al., 2013; Vanderpump et al., 2011). Other countries around the world such as New Zealand and the US have also reported mild-to-moderate ID in pregnant women (Caldwell et al., 2013; Pettigrew-Porter, Skeaff, Gray, Thomson & Croxson, 2011). Mild-to-moderate ID in pregnancy can effect the intellectual, psychomotor and cognitive development in children (Trumpff et al., 2013). A study from the UK found an association between maternal UIC and cognitive development in the child. The children of women with urinary iodine to creatinine ratios of less than 150 µg/g creatinine had significantly lower scores for verbal IQ, reading accuracy and reading comprehension than did children of women with ratios of 150 µg/g creatinine or more (Bath et al., 2013). A study from Australia showed similar results with a reduction in spelling, grammar and English-literacy performance in children from mothers who had an UIC <150 µg/L during pregnancy (Hynes et al., 2013). Furthermore, two studies have suggested a connection between maternal ID during pregnancy and the risk of ADHD symptoms in their children (van Mil et al., 2012; Vermiglio et al., 2004).

Iodine excess

In 2011, 11 countries worldwide had excessive iodine intakes based on the median UIC in SAC (>300 µg/L) (Andersson et al., 2012). Few studies have examined the prevalence and consequences of excessive iodine intake during pregnancy but a study conducted by Sang et al. (2012) concluded that excessive iodine intake during pregnancy may cause maternal thyroid dysfunction, especially subclinical hypothyroidism (Sang et al., 2012). Excessive iodine intake among the general population can be due to overconsumption of seaweed, kelp, iodized water or salt, or iodine-containing supplement. The result may be thyroiditis, goiter, hypothyroidism, iodine-induced hyperthyroidism and thyroid papillary cancer (Scientific Committee on Food, 2002; WHO, 2007a; Zimmermann, 2009). It is especially those with present or previous abnormalities of the thyroid, who are vulnerable to iodine excess. The reason being that the damaged thyroid is not able to adjust to the higher iodine intake,

increasing the risk of hyper- or hypothyroidism (Leung & Braverman, 2014; Zimmermann, 2009). In individual without ID or abnormalities of the thyroid, the thyroid in case of an increased intake of iodine will down-regulate thyroid hormone synthesis and secretion in order to avoid hyperthyroidism (Laurberg et al., 2010).

In Japan, where intake of varies seaweed is common, the estimated intake of iodine averages 1000-3000 µg/day, which is characterized as excessive intakes (WHO, 2007a; Zava & Zava, 2011). High intake of iodine is further found in Algeria among Saharawi refugees due to a high iodine concentration in drinking water (Henjum, Barikmo, Strand, Oshaug & Torheim, 2012).

2.5 Prevention of iodine deficiency

The global estimate on the prevalence of goiter was first reported in 1980, when WHO estimated that 20-60% of the worlds population was iodine deficient and/or goitrous. The highest prevalence was seen in developing countries but little political attention or action was taken until the 1990s when controlled studies showed that iodine supplementation eliminated the incidence of cretinism, reduced infant mortality and improved cognitive function (Zimmermann, 2008b). In 1990, the United Nations and UNICEF held the World Summit for Children, and together they developed a goal to eliminate ID within the year 2000 (UNICEF, 2007). Previous to this goal, iodized salt had been used in treatment of goiter and cretinism in many places in the world since the 18th century with great success (Zimmermann, 2008b), and universal salt iodization (USI) has become the most effective vehicle for eradicating ID around the world (WHO, 2007a, 2014a). According to WHO, ID is still a worldwide problem affecting millions of people, indicating that the goal has not yet been reached, and ID has even re-emerged in some European countries (Lazarus, 2014; WHO, 2007a). Some progress have, however, been made, especially trough iodization of salt (WHO, 2007a; Zimmermann, 2008b).

2.5.1 Universal salt iodization

USI involves the iodization of all human and livestock salt, including salt used in the food industry, and WHO recommends that all food grade salt should be fortified with iodine (WHO, 2007a, 2014a). USI has been successfully implemented in many countries, and in 2010 it was estimated that 71% of the global population had access to iodized salt (UNICEF,

2012). In Denmark, iodization of salt was implemented in the year 2000 and an update from 2007 indicated that there had been an increase in iodine intake in the general population (Rasmussen et al., 2007). For some vulnerable groups in the population the salt iodization are unable to meet the need for iodine. This applies especially to the increased requirement of iodine during pregnancy, and iodine supplementation may be considered for both pregnant women and children less than two years of age as a daily oral dose of iodine or a single oral dose of iodized oil every six to 12 months (WHO, 2007a, 2014a). Other strategies to cope with ID include drinking or irrigation water supplementation or animal-fodder fortification (Ghirri et al., 2014; Rasmussen et al., 2007). The main strategy is, however, USI since salt is consumed year around and by everyone, and iodization technology is effective (WHO, 2007a, 2014a).

In Europe in 2013, salt iodization was mandatory in 13 countries and not mandatory in 21 countries, leaving about 400 million people in countries without mandatory legislation for iodized salt. The coverage of salt iodization varies between countries, whereas Switzerland has a high coverage with 80% and the coverage in UK is low at about 5% (Lazarus, 2014). As mention earlier, Norway has never had mandatory iodization of salt, but some brands of salt are fortified with iodine (Andersson et al., 2007; Dahl et al., 2004). Industrial salt used in food production is not supplemented with iodine and the contribution from iodized salt is considered to be insignificant in the Norwegian diet (Dahl et al., 2004).

2.5.2 Iodine supplementation

Systematic iodine supplementation during pregnancy has become a normal practice in several developed countries during the last years. One reason for this increasing trend is the small risk of excessive iodine intake compared to the serious consequences of ID, especially during pregnancy (Rebagliato et al., 2013; Zimmermann, 2007). To make sure that women at risk of ID have an adequate intake of iodine before and/or during pregnancy, the WHO recommend each country to assess the iodine status in the population every five-year. Iodine-containing supplement is recommended if suboptimal iodine status is detected (Andersson et al., 2007; WHO, 2007a). Guidelines used in pregnancy planning and for pregnant and breastfeeding women has been implemented in the US and Canada with the recommendation of supplement containing 150 μg iodine daily (Stagnaro-Green et al., 2012). The safety of using iodine-containing supplements during pregnancy has, however, been questioned because the fetal thyroid is vulnerable to iodine excess (Pearce, 2013). Furthermore, there are no clear UL for

iodine intake during pregnancy as WHO has proposed an iodine intake of 500 μg/day as safe, while EFSA and the Institute of Medicine recommends 600 μg/day and 1100 μg/day, respectively, as the UL for iodine per day for pregnant women (European Food Safety Authority, 2006; Institute of Medicine (US), 2001; WHO, 2007a). The effectiveness of the use of iodine-containing supplement for mildly to moderately iodine deficient pregnant women can also be questioned because of the lack of good quality studies, and the ambiguous findings (Pearce, 2013; Zhou, Anderson, Gibson & Makrides, 2013). In Europe, several randomized controlled trials of iodine supplementation in mild-to-moderately iodine-deficient pregnant women have been performed (Antonangeli et al., 2002; Glinoer et al., 1995; Liesenkotter, Gopel, Bogner, Stach & Gruters, 1996; Pedersen et al., 1993). In all studies, the maternal UIC increased after receiving supplementation. However, none of the studies showed effect on maternal and newborn total or free thyroid hormone concentrations, nor did they measured long-term clinical outcomes, such as child development or maternal goiter (Zimmermann & Delange, 2004).

Recent studies have measured the effect of iodine supplementation during pregnancy with various results. In 2009 a study conducted by Velasco et al found that children of mothers receiving iodine supplementation of 300 μg/day had better psychometric assessment than children from mothers not receiving supplement (Velasco et al., 2009). In contrast, a newly published study assessing the effect of iodine supplementation during pregnancy on childhood neurodevelopment found no difference in neurodevelopment in children of women receiving iodine supplementation (150 μg/day) and the placebo group (Zhou et al., 2015). Some studies have even found adverse effects on child development where mothers have received iodine supplementation (150 μg/day or more) during pregnancy, or an increased risk of maternal thyroid dysfunction (Moleti et al., 2011; Rebagliato et al., 2013). These conflicting results have caused different approaches to address the public health issue of ID (Zhou et al., 2015). It should therefore be a focus on monitoring and evaluating the safety of iodine supplementation in pregnant women and the effects on infant growth and neurodevelopment, as well as finding the amount of iodine associated with minimum risk through prospective, randomized controlled studies (Pearce, 2013; Zhou et al., 2013).

2.6 Methods to assess iodine status

2.6.1 Urinary iodine concentration

The WHO, UNICEF and IGN recommends median UIC as the primary tool for assessment of iodine status in pregnancy (WHO, 2007a). The method is cost-efficient and easily obtained and since the majority of iodine (90%) is excreted in the urine, it is considered a marker of current iodine intake. This can be measured either over 24-hours or in spot samples and can be expressed as μg per liter or per gram creatinine. Spot urine samples are the most common measure because 24-hours samples are impractical in large groups (WHO, 2007a; Zimmermann & Andersson, 2012). Measurement of both iodine and creatinine in a spot sample expressed as μg iodine/g creatinine can, however, approximate the value in a 24-hours sample and reduce variation due to hydration status (Zimmermann & Andersson, 2012). UIC is found to correlate well with the urinary iodine/creatinine ratio in well-nourished populations (Scientific Committee on Food, 2002). Age- and sex adjusted iodine/creatinine ratio is shown to correlate even better with 24-hours urinary iodine excretion (UIE) than creatinine ratio alone, where expected creatinine excretion for the group being studied is used (Knudsen, Christiansen, Brandt-Christensen, Nygaard & Perrild, 2000). UIC can only be used to determine iodine status in a population because UIC can vary from day to day and even within a given day (WHO, 2007a; Yarrington & Pearce, 2011). Iodine content of foods varies considerably with relatively few foods having a high content of iodine, and the iodine content in specific foods can vary greatly (Rasmussen, Ovesen & Christiansen, 1999). Furthermore, UIC does not provide direct information about thyroid function (Vanderpas, 2006). It has conventionally been recommended to assess iodine status in SAC because iodine intake in SAC is thought to be representative for the rest of the population. The epidemiological criteria for assessing iodine status in the population are therefore based on median UIC in SAC (≥6 years) (WHO, 2007a). Considering that pregnant and lactating women have an increased need for iodine, there is a risk that these needs will not be met if population levels are too low (Glinoer, 2007; Zimmermann, 2007). When assessing iodine status in pregnant and lactating women, epidemiological criteria for iodine status based on median or range in UIC of pregnant women should be used (Table 2-3) (WHO, 2007a). The UIC cut-offs value for pregnant women used to be the same as for other groups in the population but in 2007, WHO, UNICEF and IGN developed new cut-offs value for pregnant women due to the changed recommendation of iodine intake during pregnancy (Andersson et al., 2007; Skeaff, 2012).

Therefore, a median UIC in the range 150-249 μg/L defines an adequate iodine intake and a median UIC <150 μg/L defines an insufficient iodine intake during pregnancy (Nordic Council of Ministers, 2014; WHO, 2007a). Measuring UIC in pregnant women is complicated because the effects of advancing gestation on excretion of iodine in urine is poorly understood, and studies have found both an increase and decrease in iodine excretion during gestation, which can cause uncertainties in the assessment of iodine status in pregnant populations (Azizi et al., 2003; Bath, Furmidge-Owen, Redman & Rayman, 2015; Fuse, Shishiba & Irie, 2013).

Table 2-3 Epidemiological criteria for assessing iodine nutrition based on the median or range in urinary iodine concentration (μg/L) of pregnant women.

Population group	Median urinary iodine concentration (μg/L)	Iodine intake
Pregnant women	<150	Insufficient
	150-249	Adequate
	250-499	Above requirements
	>500	Excessive

Source: Adopted from WHO (WHO, 2007a).

For children and non-pregnant women the criteria for median UIC are somewhat different, and a median UIC between 100-199 μg/L defines adequate iodine status, 50-99 μg/L defines mild ID, 20-49 μg/L defines moderate ID, and <20 μg/L defines severe ID (WHO, 2007a).

2.6.2 Other measurement of iodine status

Three other methods for assessment of iodine status in a population are goiter prevalence, serum TSH and serum thyroglobulin (Tg). The latter method shows an intermediate response (weeks to months), and measurement of serum Tg can be used as an indirect measurement of goiter because of an increase of Tg in the blood when thyroid volume increases (Skeaff, 2012; Zimmermann, 2008a). Dried blood spots taken by a finger prick can be used to measure serum Tg, making the collection and transportation easy if used in remote areas, but several questions need to be answer before serum Tg can be used as a indicator of iodine status in a larger scale. No cut-offs values for serum Tg for pregnant women exist and the measurement cannot be used to assess iodine status during pregnancy (Skeaff, 2012). Measurement of serum TSH is a good indicator of iodine status in newborn and is often used in screening to

detect congenital hypothyroidism in newborn (Zimmermann, 2008a). Serum TSH is, however, an insensitive indicator of iodine status in SAC and adults, as well as in moderate-to-mild ID, because the serum TSH is higher in iodine-deficient populations than in iodine-sufficient populations, but the difference is small and overlap in TSH values often occurs (Skeaff, 2012; WHO, 2007a). For measurement of goiter rate, two widely used methods exist; neck inspection with palpation and thyroid ultrasonography. Palpation of goiter is often used in SAC (Zimmermann, 2008a). In areas of mild ID palpation of goiter has poor sensitivity and thyroid volume by ultrasound is the preferred method (Zimmermann, Saad, Hess, Torresani & Chaouki, 2000). However, ultrasonography is an impractical method to diagnose ID in pregnant women because there are no cut-offs values for thyroid volume in pregnancy (Skeaff, 2012).

3 OBJECTIVES

The main objective was to describe the iodine status (iodine intake and urinary iodine concentration) in a group of pregnant women in Norway.

The specific objectives were:

1. To describe the calculated iodine intake and compare it to NNR5 and WHO recommendations for pregnant women
2. To examine to what extent pregnant women use iodine-containing supplement and evaluate the contribution from iodine-containing supplements to the total iodine intake and to urinary iodine concentration
3. To describe urinary iodine concentration and compare it to WHO recommendations for pregnant women
4. To examine the correlation between calculated iodine intake and urinary iodine concentration
5. Investigate whether there is a difference in calculated iodine intake and urinary iodine concentration between the pregnant women and a control group of non-pregnant women

4 METHODOLOGY

4.1 Quantitative, cross-sectional study

A quantitative approach was used in the present study and a cross-sectional and descriptive study design was chosen. In cross-sectional studies, the outcome and exposure are measured simultaneously and the study design is used to measure prevalence as they measure the proportion of people with a condition at given point in time, or to describe a population's intake of particular nutrients (Mosdøl & Brunner, 2011; Thompson & Subar, 2013). Advantages with cross-sectional studies are that they are quick and easy to carry out, gives prevalence of a condition in a population and are hypothesis generating. On the other hand, the study design is not suited for hypothesis testing nor for rare conditions or conditions of short duration (Mosdøl & Brunner, 2011).

4.2 Recruitment and sampling

The data set is part of the "Experimental study of deoxynivalenol biomarkers in urine" (Donexpo), study conducted by the Norwegian Institute of Public Health (FHI) and the Norwegian Veterinary Institute (NVI) (Appendix 1). The purpose of Donexpo was to investigate the levels of mycotoxins in urine among different groups in Norway (children, adolescents, adults, elderly, pregnant women, and vegetarians). A consent declaration was made for permission to analyze other substances in urine, like iodine. The data collection was conducted between April and December 2014. Participants for Donexpo were recruited among employees at the FHI and NVI. Information about the study and who to contact for those willing to participate was posted on the internal intranet system within each institution. This information also specifically called for children of employees and for pregnant women/spouses. In order to include also elderly and vegetarians, potential participants were asked to extend the information to family and friends, and to pass on an information leaflet with the contact details on how to contact the project workers. The study sample consists of 257 participants in all age groups (3-85 years), including 40 pregnant women, whereas five were vegetarians. Inclusion criteria were that the participants were healthy at the time of recruitment. In addition to the 40 pregnant women from the Donexpo study, during 2015, five more were recruited to the present study. The recruitment took place from August to

September 2015 and was achieved through convenience sampling of family and friends, and the same inclusion criteria as in the Donexpo study was applied. For this master, a total of 40 pregnant women from Norway were included. The pregnant group included all pregnant women recruited to Donexpo and the master thesis (age range 22-47 years), with the exception of pregnant vegetarians. In addition, a control group of 26 women from the Donexpo study were included, all non-pregnant women in the age range 22-48 years, with the exception of vegetarians. The purpose of including a non-pregnant control group was to examine whether or not pregnant women had higher intake of iodine from food or used more iodine-containing supplements than non-pregnant women. The five pregnant vegetarians were excluded from the present study population because they were included in a master thesis conducted by a fellow student, assessing iodine status in vegetarians (Johansen, 2016).

4.3 Data collection

Before completion of the Donexpo study and this master thesis, the researchers had a meeting with each participant where detailed information about the study was given, including the purpose of the study, what participation in the study entailed and description of the different methods used (e.g. food diaries and urine samples). They were also given materials for data and urine collection. It was mentioned during the meeting that participation in the study was voluntary and that they could withdraw at any time without a reason. All the participants completed a two-day food diary were they recorded all foods, beverages and food supplements consumed during two days, and they were asked to continue with their normal food intake. Each participant was shown how to complete the food diary, both oral information during the meeting and written information (Appendix 2), and they were asked to complete it on two consecutive days. They were asked to give a detailed description of the foods and beverages consumed, including the name, preparation methods, recipes for food courses and portion size, by using a scale or household measures. The researcher checked the completed food diaries for completeness of description. Furthermore, each participant provided two urine samples, which are spot urine taken in the morning after day one and day two of recording the food diary. Information on how the urine samples had to be carried out was given to the participants during the meeting with researcher, and it was specified that the samples had to be collected in the morning. Written information about the urine samples was also provided (Appendix 2). Each participant received two urine cups, which both was marked with ID number and number 1 and 2 in order to separate the two cups, and they were

asked to fill out the date and time of sampling. After the urine samples were completed, the participants had been informed to store the samples either in the fridge or the freezer until the researcher came for collection, normally the same day or the day after the last urine sample was completed. The researchers brought the urine samples to FHI where the samples was stored and frozen prior to analyze at -20^{o}C. The urine samples were transferred to tubes and the rest of the urine was kept in reserve for creatinine testing. The samples were sent to National Public Health Institute of Finland where the urine samples were analyzed for iodine between October 2015 to January 2016. FHI, Department of Drug analysis, analyzed creatinine levels in the urine samples at two occasions.

Each participant completed a background form (Appendix 3) with information about age, weight, height, activity level, restriction in the diet, week of gestation and parity, and signed a consent form, both during the meeting with researcher (Appendix 4). All information provided by the participants was handled with confidentiality.

4.4 Dietary assessment

The Norwegian Food Composition Table (last updated 09.23.2015) was used in the process of coding the food diaries. The Norwegian Food Composition Table provides information about the nutrients- and energy content of foods and beverages in Norway, both unprepared and prepared foods and dishes, and includes 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). The food code of the food items and beverages consumed and ID numbers representing the participants was used in the coding process as well as number 1 and 2 to separate the days of recording (Appendix 5). To code the food diaries, Excel version 14.1.0 (2010) was used (Appendix 5).

All food items and beverages were calculated in gram in the coding process. For items that were described in household measurement (e.g., ml, tablespoons, pieces, a portion or a handful) the diet planner "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 or how much a deciliter of a certain food/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 (The Norwegian Directorate of Health & The Norwegian Food Safety Authority, 2015). For items that were not included in the diet planner, a Google search with the name of the item was

conducted to find the amount in gram. This applied especially to chocolate bars, ice cream and some prepared foods and dishes such as yoghurt with muesli and TORO mixes. For different food courses that were not in The Norwegian Food Composition Table, every ingredient was manually coded. This applied either when the participants had written down the different ingredients used or if only the name of the food eaten was described (e.g. lasagna, spaghetti Bolognese or fish soup). In the latter example, a Google search was used to find the ingredients in the food course. The name of the food 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 items without a value for iodine, the value 0 was sat. This was true for foods and beverages that are probably not significant for iodine intake in the Norwegian diet, like soda and bread. 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. For instance, some specific brands of yoghurt did not have a value for iodine, only the letter M (missing value), and these yoghurts got the same iodine value from a similar brand. The same was true for foods that were cooked because most of the raw products had a value for iodine while the cooked products was marked with M.

FoodCalc is a program developed to calculate intake of nutrients. The program 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 and energy intake (in kJ) in the diet (Lauritsen, 2010).

4.5 Protocol

A protocol (Appendix 6) was developed along with the coding 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 in the food diaries. For items that were not found in The Norwegian Food Composition Table, a similar product was used instead. In cases were the participants only had written the name of the food or beverage consumed, like butter or milk, the same type or brand was always used (in this example; bremykt and lettmelk). The type or brand chosen as reference value in the protocol was based on the most common product in Norway. When the participants had specified the type or brand used for a certain food item or beverage once or more but forgotten to record it other times in the food diary, the

same type or brand was used in the coding process regardless of the protocol. Because of small differences in iodine value within the different food and beverage groups listed in the protocol, the iodine values used will probably not differ significantly from the true values.

4.6 Assessment of urinary iodine concentrations

Urinary iodine concentrations were analyzed at National Public Health Institute of Finland by a microplate method, which is based on the Sandell-Kolthoff reaction (Jooste & Strydom, 2010). In brief, ammonium persulfate digestion was performed in a polypropylene microplate in an oven at 91^{o}C for 90 minutes. After the digestion, part of the mixture was transferred to a transparent polyethene microplate and the Sandell-Kolthoff reaction was performed for 40 minutes. Urinary iodine was measured by a Thermo Scientific Varioskan flash microplate reader at 405 nm. The limit of quantification is 20 µg/L.

4.7 Assessment of urinary creatinine concentrations

Urinary creatinine concentrations were measured at FHI, Department of Drug analysis according to an accredited method using a colorimetric assay (modified kinetic Jaffe method) on a Beckman Coulter AU680 analyser (Peake & Whiting, 2006). The limit of quantification was 0.2 mml/L. In brief, the method is based on a reaction with alkaline picrate forming a red-orange complex. The colour intensity is directly proportional to the creatinine concentration and is measured spectrophotometrically at 505nm.

4.8 Measurement of iodine status

In order to assess iodine status in the group of pregnant women, NNR5 and WHO criteria for iodine intake in pregnancy was used, as described above (Nordic Council of Ministers, 2014; WHO, 2007a). The median UIC for pregnant women was also considered and was compared with WHO cut-offs value for UIC indicating adequate iodine intake in pregnancy (>150 µg/L) (WHO, 2007a). These cut-offs values can, however, not be used to identify ID in an individual due to large intra-individual variation in UIC (WHO, 2007a; Yarrington & Pearce, 2011). Urinary creatinine concentrations from the spot urine samples and age- and sex adjusted iodine/creatinine ratio was applied to correct UIC for variation in daily urine volume (Andersen, Karmisholt, Pedersen & Laurberg, 2008; Knudsen et al., 2000; Ovesen & Boeing,

2002). UIC was calculated from the two morning spot urine samples collected from the participants and expressed as median and mean μg/L. Creatinine levels from the spot urine samples were obtained from all participants, and the mean creatinine levels of the two urine samples were used to calculate iodine/creatinine ratio expressed as μg/g creatinine. Creatinine levels was given in mmol/L, and considering that the molecular weight is 113.12 g/mol corresponding to 0.11312 g/mmol, the creatinine variable was multiply with 0.11312 g/mmol in order to get creatinine expressed as g/L. In order to find iodine/creatinine ratio, the following formula was applied:

$$\frac{\textit{Iodine (μg/L)}}{\textit{Creatinine (g/L)}}$$

In order to find the age- and sex adjusted iodine/creatinine ratio the creatinine (g/L) was divided with expected creatinine excretion, which according to previous literature was found to be 1.09 g/day for pregnant women (Andersen, Moller & Laurberg, 2014). The following formula was applied:

$$\frac{\textit{Iodine (μg/L)}}{\textit{[Creatinine (g/L)/Expected creatinine (g/day)]}}$$

In order to estimate daily iodine intake in the pregnant women by using UIC, the following formula adopted from the Institute of Medicine (Institute of Medicine (US), 2001) was applied:

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

4.9 Iodine supplement use

Use of supplement was recorded in the food diaries by the participants and coded in an own file in Excel. All supplements were coded, and the amount of iodine provided by iodine-containing supplements was calculated separately before converted into a variable in SPSS. All supplement use was taken into consideration during the statistical analysis. Only the name of the supplements used were listed in the food diaries so in the process of finding the iodine content in the supplements recorded, the pharmacy and health shops were approached. For

one supplement recorded as a prenatal supplement (without more information added), the iodine content for a daily dose was sat to 150 µg in the present study. The decision was made by the researcher in lack of enough documentation on the extent and amount of iodine in prenatal supplements in Norway. One participant used both shakes and multivitamins from the brand Herbalife but the specific types was not specified in the food diary. An email was therefore sent out to the participant in order to get the correct amount of iodine in the products. The participant responded by sending a picture of the products and the right amount of iodine was calculated and coded.

4.10 Other variables

Maternal age was divided into three categories (20-29, 30-39, and 40+ years). Self-reported pre-pregnancy weight and height were collected via the background form and were used to calculate body mass index (BMI) (kg/m^2), which was divided into two categories, normal weight (18.5-24.9), and overweight 25+. Parity was divided into three categories (0= nulliparous, 1= primiparous, and 3= multiparous) and was measured as the number of previous pregnancies resulting in a live or stillbirth. Week of gestation when completing the food diary was divided into the three trimesters (1 = 0-12 weeks, 2 = 13-28 weeks, and 3 = 29 weeks-birth), and pre-pregnancy physical activity level was divided into three categories (1= very low, 2= low, and 3= moderate). Iodine contribution from different food groups (e.g. milk and dairy, fish and seafood, eggs etc.) was included in the study. Energy intake was taken into consideration using cut-offs value from the MoBa study to rule out subjects with improbable low (<4500 kJ per day) or high (>20,000 kJ per day) energy intake (Meltzer, Brantsaeter, Ydersbond, Alexander & Haugen, 2008). None of the participants were excluded from the present study due to low or high energy intake.

4.11 Statistical methods

The present study is primarily based on descriptive statistics. For quantitative variables, means, medians, min and max, standard deviations, percentiles and percentages were calculated and presented. The calculated intake of iodine from food and the total iodine intake (food and supplement) did not differ between day 1 and day 2 for the study population and therefore the mean iodine intake for the two days was used in all further analyses. The same was true for UIC and creatinine levels. For the categorical variables BMI and physical activity

level, recoding was performed because there were too few in one or several categories. The calculated iodine intake and total iodine intake for the pregnant women was approximately normally distributed and Independent-Samples T Test for differences in mean iodine intake and total iodine intake according to different maternal characteristics were applied. Calculated iodine intake and the total iodine intake was approximately normally distributed in the control group, and the Independent –Samples T Test was further used for analyzing differences in mean calculated iodine intake and total iodine intake between the pregnant women and the control group. The UIC for the pregnant women was slightly skewed and Mann Whitney U Test for group comparison was used in order to analyze differences in mean UIC between iodine supplement users and non-iodine supplement users. The non-parametric test Spearman's rho correlation coefficient was applied in order to analyze the correlation between calculated iodine intake and UIC, and total iodine intake and UIC. The UIC for the control group was approximately normally distributed and both Independent-Samples T Test and Mann Whitney U Test were applied for analyzing differences in mean UIC between the pregnant women and the control group. The significance level was set at 5% (p<0.05) and all analyses were performed using the statistical software SPSS 23 (SPSS Inc., Chicago, III., USA). Figures and tables were made using SPSS 23 and Microsoft Excel version 14.1.0 (2010).

4.12 Ethical considerations

The Regional Committees for Medical and Health Research Ethics (REK) approved the study (Appendix 7 and 8). The Declaration of Helsinki is a set of ethical guidelines that are used in conjunction with research in many parts of the world (WHO, 2001). The guidelines emphasize the importance of protection of the participants' privacy and confidentiality, and that participants should be well informed about the project. In addition, the participants must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Furthermore, it is important to get a written consent from the participants before participation (WHO, 2001).

The study was carried out in accordance to the Declaration of Helsinki, and no reward was given to the participants (WHO, 2001). They were, however, promised feedback from the researcher with information about their intake of iodine and UIC.

5 RESULTS

5.1 Study population

Mean iodine intake from food in pregnant women is presented by the participants' background characteristics in Table 5-1. The mean age of the pregnant women was 33 years (range 22-47 years). Mean gestational week at time of recruitment was 24 weeks, and 45% and 35% were expecting their first or second child, respectively. Twenty-five percent of the pregnant women reported use of iodine-containing supplement. All were non-smokers prior to pregnancy (data not shown). The mean calculated iodine intake from food differed somewhat within subgroups of maternal background characteristics. The highest iodine intake from food was found in pregnant women between 30-39 years, with normal BMI (18.5-24.9), in second trimester, and with moderate physical activity level. The highest total iodine intake (food and supplement) was found in the pregnant women aged 40 years or older and in those using iodine-containing supplements. The only difference that was statistically significant was the higher total iodine intake (food and supplement) between iodine supplement users and non-supplement users ($p<0.001$) (data not shown).

Table 5-1 Background characteristics by calculated iodine intake (µg/day) and total iodine intake (food and supplement) in a group of pregnant women in Norway (*n*=40).

Characteristics		**Iodine intake**[a]	**Total iodine intake**[b]
	n (%)	Median (P25[†] , P75[†]) µg/day	Median (P25[†] , P75[†]) µg/day
Age, years			
20-29	9 (22.5)	80 (55, 130)	105 (71, 222)
30-39	26 (65)	161 (107, 199)	172 (116, 249)
40+	5 (12.5)	98 (63, 154)	263 (63, 278)
BMI[c] *kg/m*^{2}			
18.5-24.9	30 (75)	145 (96, 199)	186 (107, 252)
25-29.9	10 (25)	107 (83, 149)	116 (83, 180)
Parity			
Nulliparous	18 (45)	111 (93, 176)	136 (103, 238)
Primiparous	14 (35)	172 (86, 203)	197 (107, 252)
Multiparous	8 (20)	135 (92, 162)	142 (96, 238)
Gestational week[d]			
1 trimester	2 (5)	118 (92, -)	118 (92, -)
2 trimester	25 (62.5)	140 (87, 186)	174 (107, 222)
3 trimester	13 (32.5)	118 (89, 200)	130 (90, 270)
Physical activity level			
Very low	4 (10)	142 (96, 165)	142 (96, 165)
Low	19 (47.5)	112 (78, 195)	171 (92, 248)
Moderate	17 (42.5)	144 (101, 193)	177 (111, 260)
Iodine supplement			
No	30 (75)	124 (90, 181)	124 (90, 181)
Yes	10 (25)	130 (86, 182)	265 (230, 293)

[†]P25 = 25th percentile, P75 = 75th percentile

[a]Iodine intake = calculated iodine intake from food

[b]Total iodine intake = calculated iodine intake from food and iodine from supplements

[c]BMI used as a dichotomous variable as only two participants had BMI ≥30 and only 1 person had BMI ≤18.5

[d]1 trimester = 0-12 weeks, 2 trimester= 13-28 weeks, and 3 trimester= 29 weeks-birth

5.2 Calculated iodine intake from food and iodine-containing supplements

The mean calculated intake of iodine from food in the pregnant women was 137 (63) µg/day, and the corresponding median intake was 124 (91, 177) µg/day (Table 5-2). When including supplement to the calculated iodine intake from food (the total iodine intake) the mean and median total iodine intake was 170 µg/day for both. When iodine intake was estimated from

UIC (=UIC*0.0235 x weight (kg)) (Institute of Medicine (US), 2001), the mean and median estimated iodine intake was 135 µg/day and 123 µg/day, respectively.

Table 5-2 Calculated iodine intake from food, total iodine intake (food and supplement) and estimated iodine intake in a group of pregnant women in Norway (*n*=40).

Iodine intake	**Mean (±SD)**	**Median**	**P25**[†]	**P75**[†]
Iodine from food only[a], µg/day	137 (63)	124	91	177
Total iodine intake[b], µg/day	170 (81)	170	105	245
Iodine intake estimated from UIC[c], µg/day	135 (71)	123	77	162

[†]P25 = 25th percentile, P75 = 75th percentile
[a]Mean iodine intake from two days
[b]Calculated iodine intake from food and supplement (mean from two days)
[c]UIC (µg/L) x 0.0235 x weight (kg) = estimated daily iodine intake

Figure 5-1 shows the frequency distribution of the calculated iodine intake and total iodine intake (food and supplement) in pregnant women. Only 30% (22.5% + 7.5%) of the pregnant women had an iodine intake from food of at least 175 µg/day, which is the recommended intake according to NNR5. When including iodine from supplement (total iodine intake), this number increased to 45% (22.5% + 17.5% + 5%). The recommendation from WHO of 250 µg/day was reached by 7.5% and 22.5% of the pregnant women when examining the calculated iodine intake and total iodine intake (food and supplement), respectively. None of the women had excessive (>600 µg/day) iodine intake.

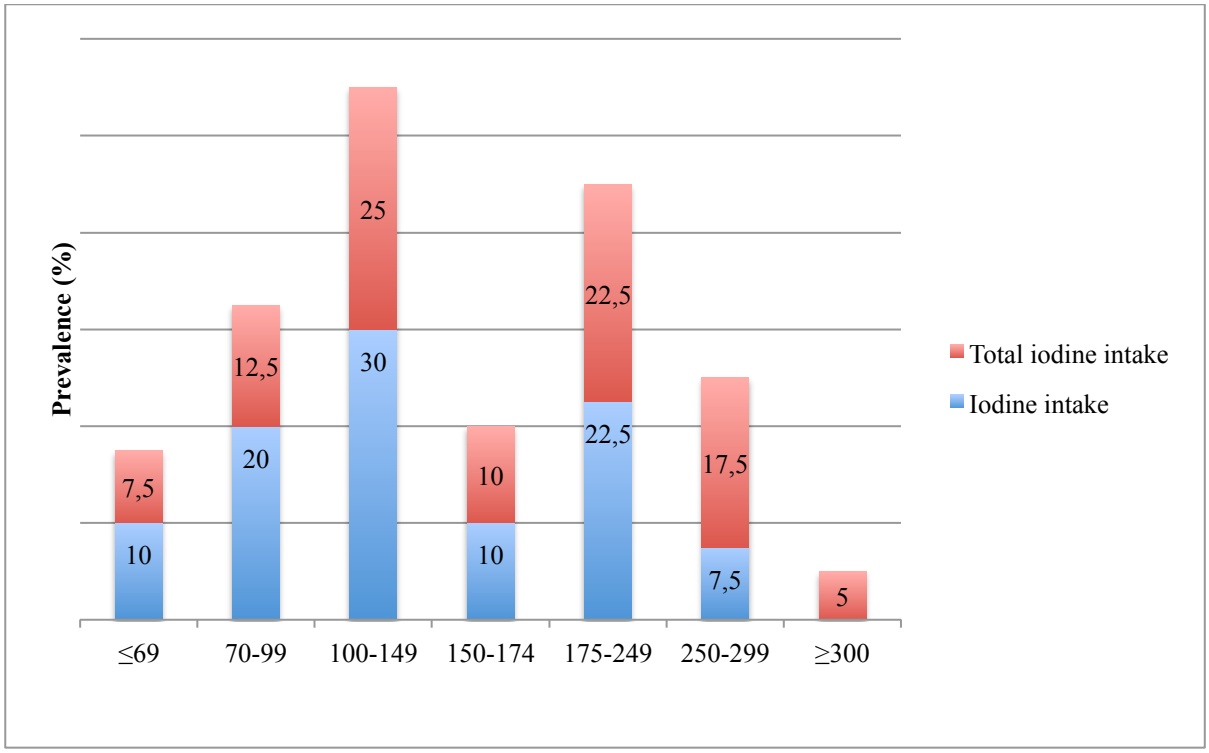

Figure 5-1 Calculated iodine intake and total iodine intake (food and supplement) in a group of pregnant women in Norway given as percent in each category (*n*=40).

5.3 Dietary sources of iodine

Figure 5-2 shows contribution (%) to iodine intake from different food groups in the pregnant women. Milk and dairy products contributed with 58% of iodine from food. Milk (ekstra lett and lettmelk), cheese (Norvegia and Jarlsberg) and yoghurt accounted for most of the milk and dairy intake (data not shown). Seafood contributed with 22% of iodine among the pregnant women. The most common fish and seafood products consumed was salmon, "makrell i tomat" and fish cakes, and the intake of lean fish like cod, haddock and saithe was low (data not shown). Eggs, dishes and ready products, and nuts and cereal products contributed all with 6% of the iodine intake from food. Iodine contribution from other food groups (e.g. fats and oils, vegetables, fruits and berries, and sweets) was 2% of the iodine intake from food.

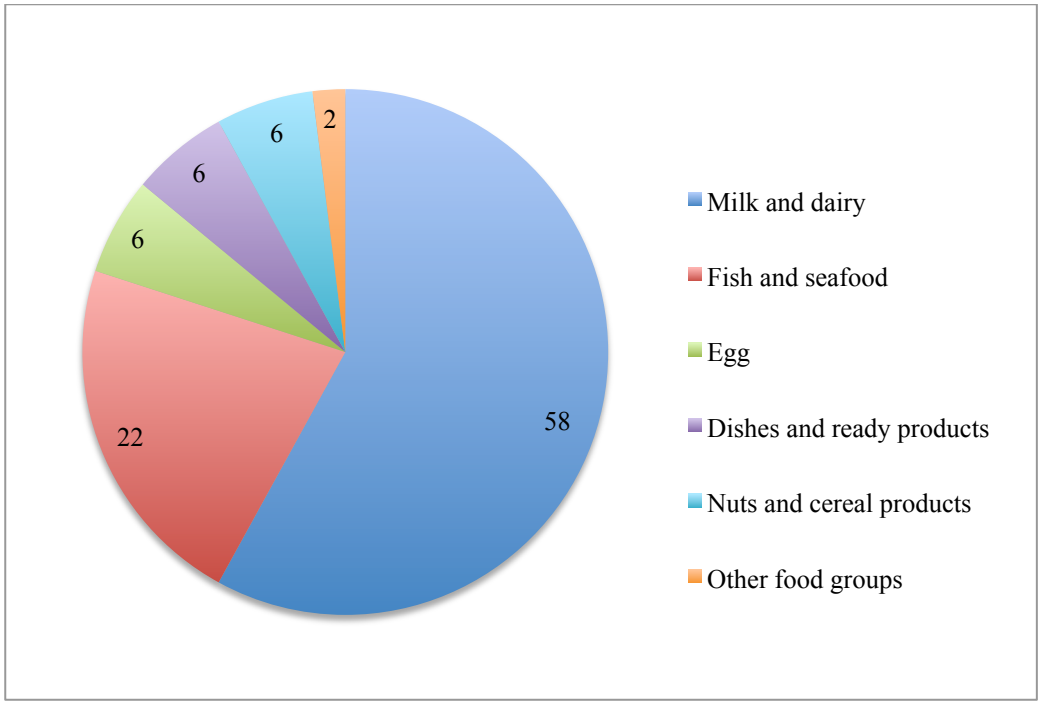

Figure 5-2 The contribution (%) to the calculated iodine intake from different food groups in a group of pregnant women in Norway (*n*=40).

The importance of the different dietary sources and iodine-containing supplement to the total iodine intake (food and supplement) was also examined according to pregnant women with total intake less than the NNR5 recommendation and those who reached the recommendation of 175 µg/day (Figure 5-3).

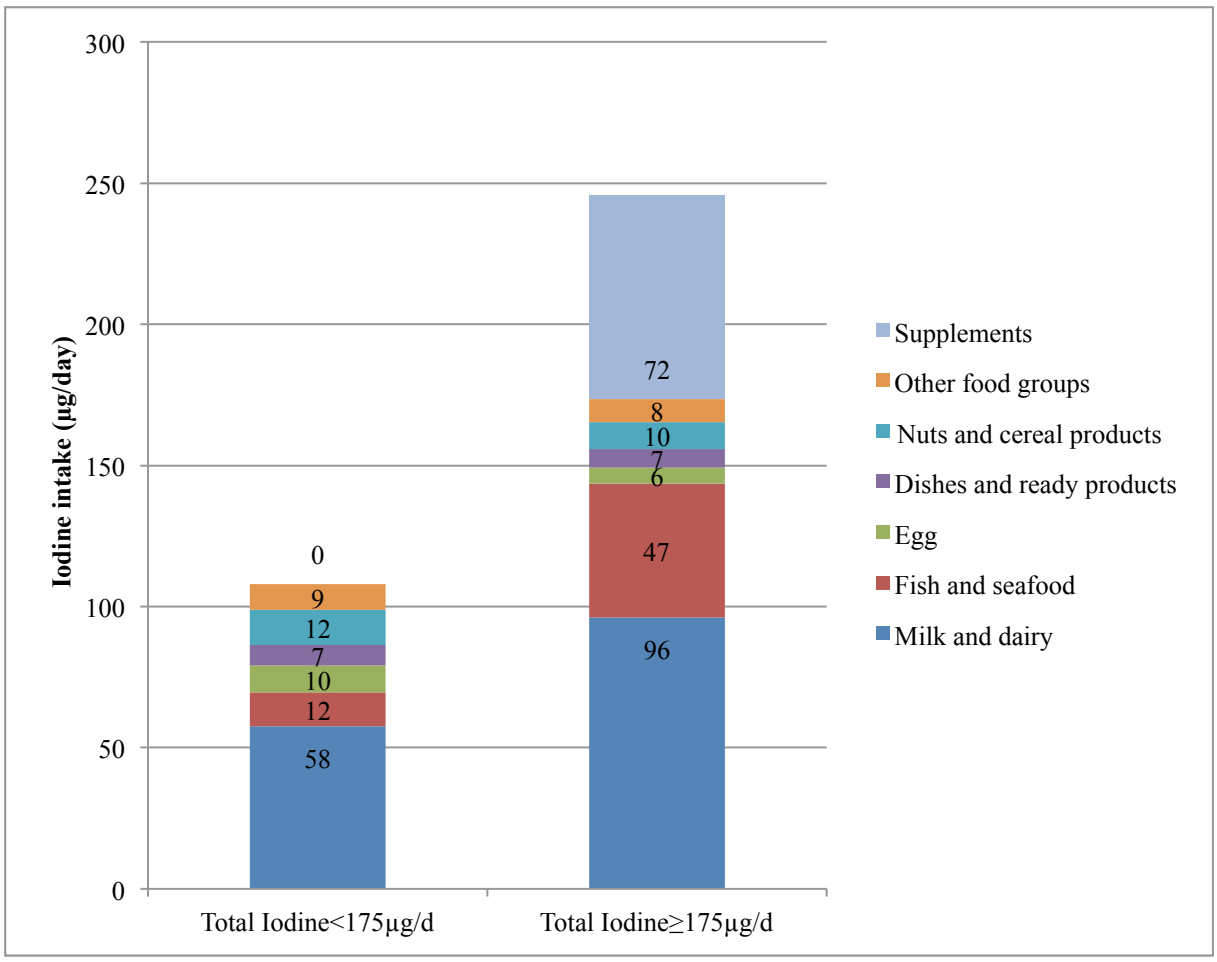

Figure 5-3 The mean contribution by food groups (µg/day) to the total iodine intake (food and supplement) in pregnant women (n=22) with intakes below the NNR5 recommendation (mean total: 108 µg/day) and in women (n=18) who reached the recommendation (mean total: 246 µg/day).

5.4 Iodine supplement use

As shown in Table 5-1, 25% (n=10) of the pregnant women used iodine-containing supplement. When iodine from supplement was included to the total intake, the median iodine intake increased from 124 µg/day to 170 µg/day (Table 5-2). The two most common used supplements were multivitamins for pregnancy called "Lifeline Care Gravid" and "Nycoplus Mamma" purchased at the pharmacy, and the iodine-content in one daily doses is 175 µg for both products. Figure 5-4 shows that pregnant women who used iodine-containing supplement had an iodine intake above the recommended 175 µg/day (NNR5) and 60% reached WHO recommendation of 250 µg/day. Iodine supplement users had a significantly higher (p<0.001) mean total iodine intake (264 µg/day) than non-iodine supplement users (139 µg/day) (data not shown). Figure 5-5 illustrate that women using iodine-containing

supplements had a higher median UIC, as well as iodine creatinine/ratio, than non-iodine supplement users.

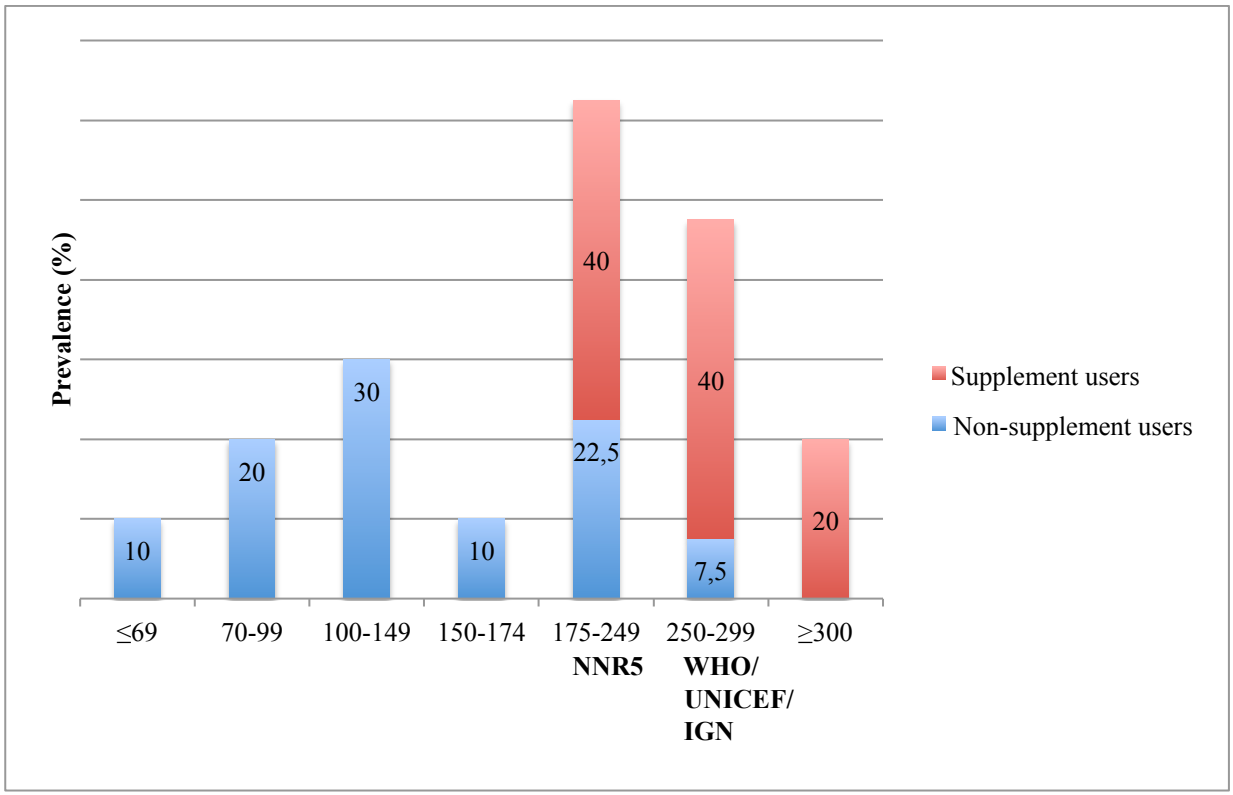

Figure 5-4 Total iodine intake (food and supplement) in non-supplement users (*n*=30) and supplement users (*n*=10) given as percent in each category, in a group of pregnant women in Norway.

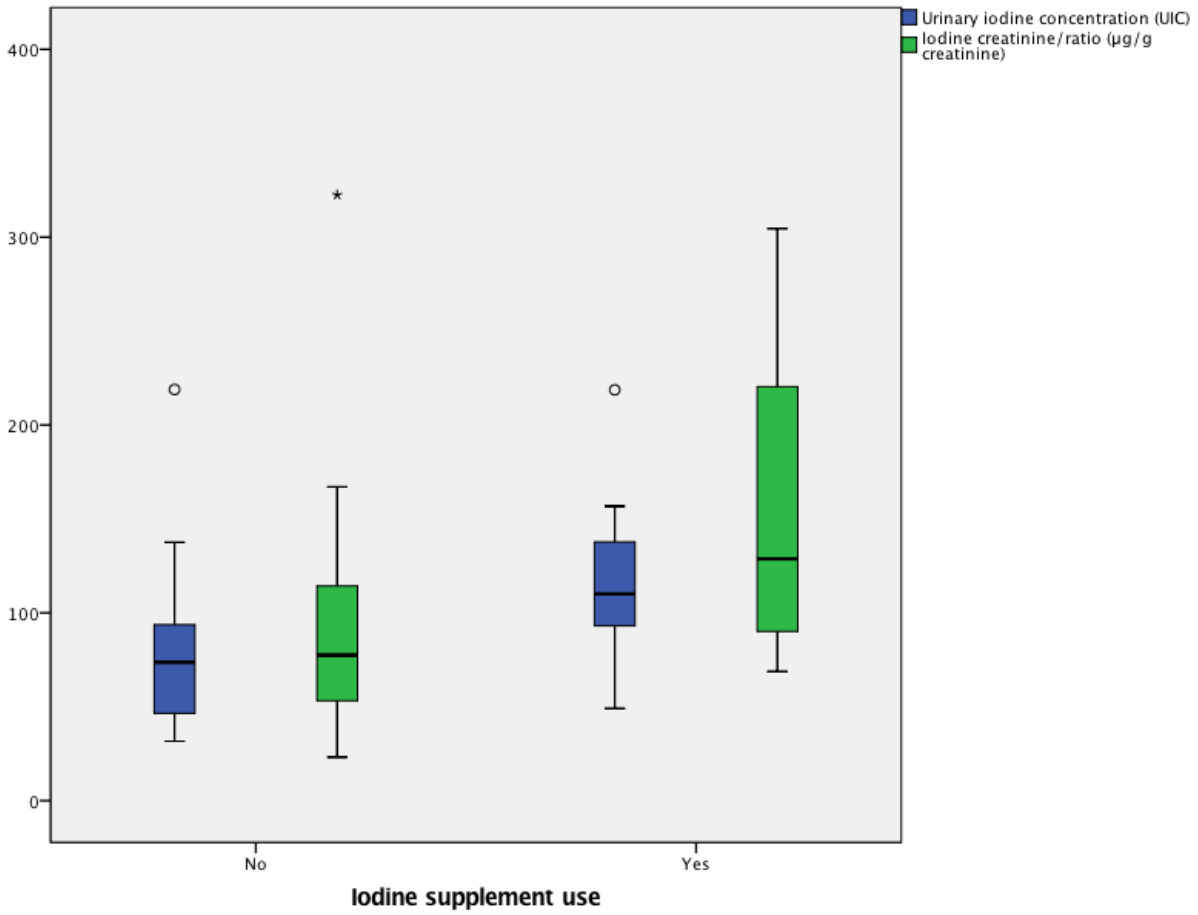

Figure 5-5 Urinary iodine concentration (µg/L) and iodine creatinine/ratio (µg/g creatinine) in iodine supplement users (*n*=10) and non-iodine supplement users (*n*=30) in a group of pregnant women in Norway.

Box plot details: the horizontal line indicates the median; the box indicates the interquartile range (IQR) (IQR: 25th percentile to 75th percentile); the whiskers represent observations within 1.5-times the IQR; and the circles indicate observations more than 1.5-times the IQR away from the box, considered as outliners.

5.5 Any supplement use

A total of 24 out of 40 pregnant women used some sort of dietary supplement, mostly cod liver oil, folic acid and iron, and to a lesser degree vitamin D, vitamin B and magnesium (data not shown). Only ten of the supplement users received iodine from supplements. Figure 5-6 shows the median UIC among non-supplement users, supplement users except those contributing with iodine (all supplement, excluding iodine) and iodine-containing supplement users. The pregnant women using iodine-containing supplement had the highest median UIC

of 110 µg/L, followed by non-supplement users with a median UIC of 76 µg/L. The lowest median UIC was found in supplement users (all supplement, excluding iodine) with a median UIC of 58 µg/L.

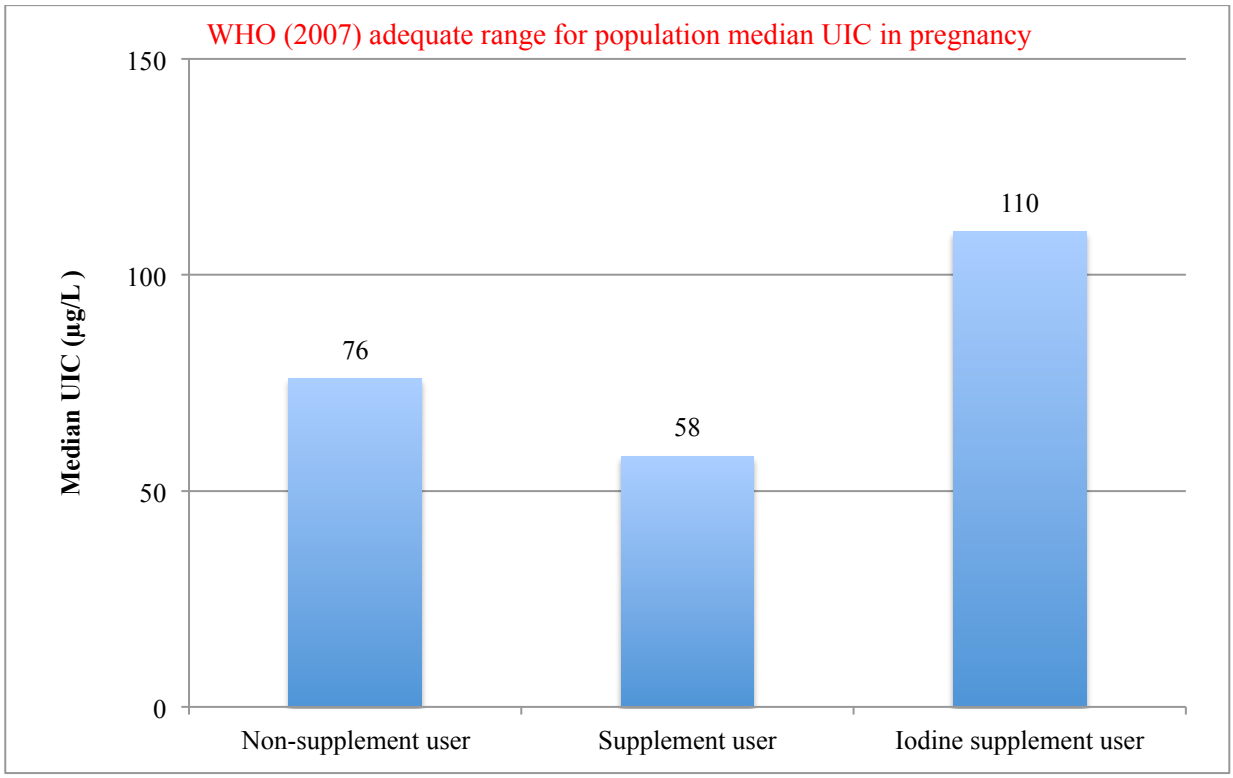

Figure 5-6 Median urinary iodine concentration (µg/L) of non-supplement users (*n*=16), supplement users (all supplement, excluding iodine) (*n*=14) and iodine supplement users (*n*=10) in a group of pregnant women in Norway.

5.6 Urinary iodine concentration

The median UIC in this group of pregnant women was 80 µg/L (range 32-219 µg/L) (Table 5-3). Only 3 (7.5%) of the pregnant women had a UIC in the desired range of 150-249 µg/L (Figure 5-7). After adjusting for creatinine the iodine/creatinine ratio was 80 µg/g (range 23-323 µg/g) and the adjusted age- and sex iodine/creatinine ratio was 87 µg/day (range 25-352 µg/day). Pregnant women consuming iodine-containing supplements had a significant higher (p=0.011) UIC (117 µg/L) than non-iodine supplement users (78 µg/L) (data not shown).

Table 5-3 Urinary iodine concentration (µg/L), iodine/creatinine ratio (µg/g creatinine) and age- and sex adjusted iodine/creatinine ratio (µg/day) in a group of pregnant women in Norway (*n*=40).

Measurement	**Median (min, max)**			**P25**[†]	**P75**[†]	**Mean ± SD**	
Iodine concentration (µg/L)[a]	80	32	219	48	113	88	46
Iodine/g creatinine (µg/g)[b]	80	23	323	63	144	108	70
Adjusted iodine/creatinine ratio (µg/day)[c]	87	25	352	69	157	118	76

[†]P25 = 25th percentile, P75 = 75th percentile
[a]Mean UIC from two days
[b]Iodine (µg/L)/creatinine (g/L)
[c]Iodine (µg/L)/[Creatinine (g/L)/Expected creatinine (g/day)]

Urinary iodine concentration (µg/L), iodine/creatinine ratio (µg/g creatinine) and age- and sex adjusted iodine/creatinine ratio (µg/day) according to WHO cut-off values are presented in Figure 5-7. The UIC was lower than the recommended 150-249 µg/L for 93% of the pregnant women. After adjusting for creatinine ratio and age- and sex adjusted iodine/creatinine ratio, the prevalence with UIC levels below the recommendation was 82.5% and 72.5%, respectively. None of the women had an excessive (> 500 µg/L) UIC.

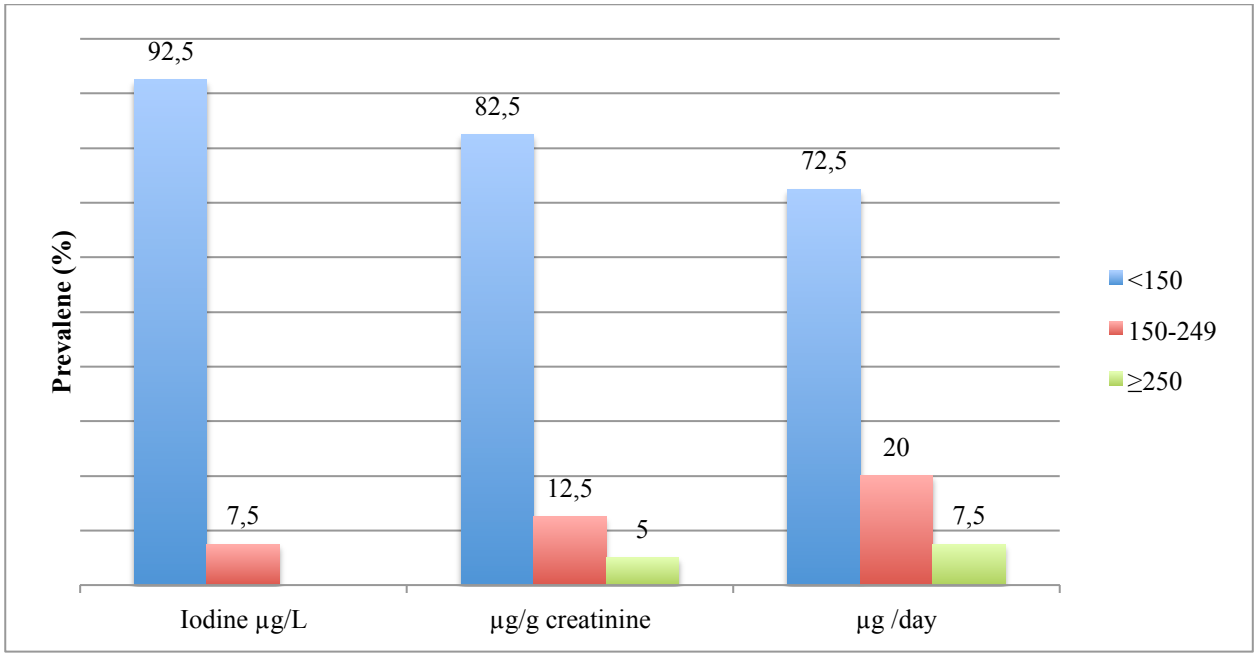

Figure 5-7 Urinary iodine concentration (µg/L), iodine/creatinine ratio (µg/g creatinine) and age- and sex adjusted iodine/creatinine ratio (µg/day) according to WHO cut-off levels in a group of pregnant women in Norway (*n*=40).

Figure 5-8 illustrates the correlation between iodine intake (µg/day) and UIC (µg/L). The spearman's rho was 0.382 (p=0.015), indicating a significant medium correlation between calculated iodine intake from food and UIC. The diagonal line illustrates where the observations should be if there had been a perfect agreement between the methods, i.e. correlation of 1.0. The correlation between total iodine intake (food and supplement) (µg/day) and UIC (µg/L) was 0.541 (p< 0.001), indicating a significant medium correlation (Figure 5-9).

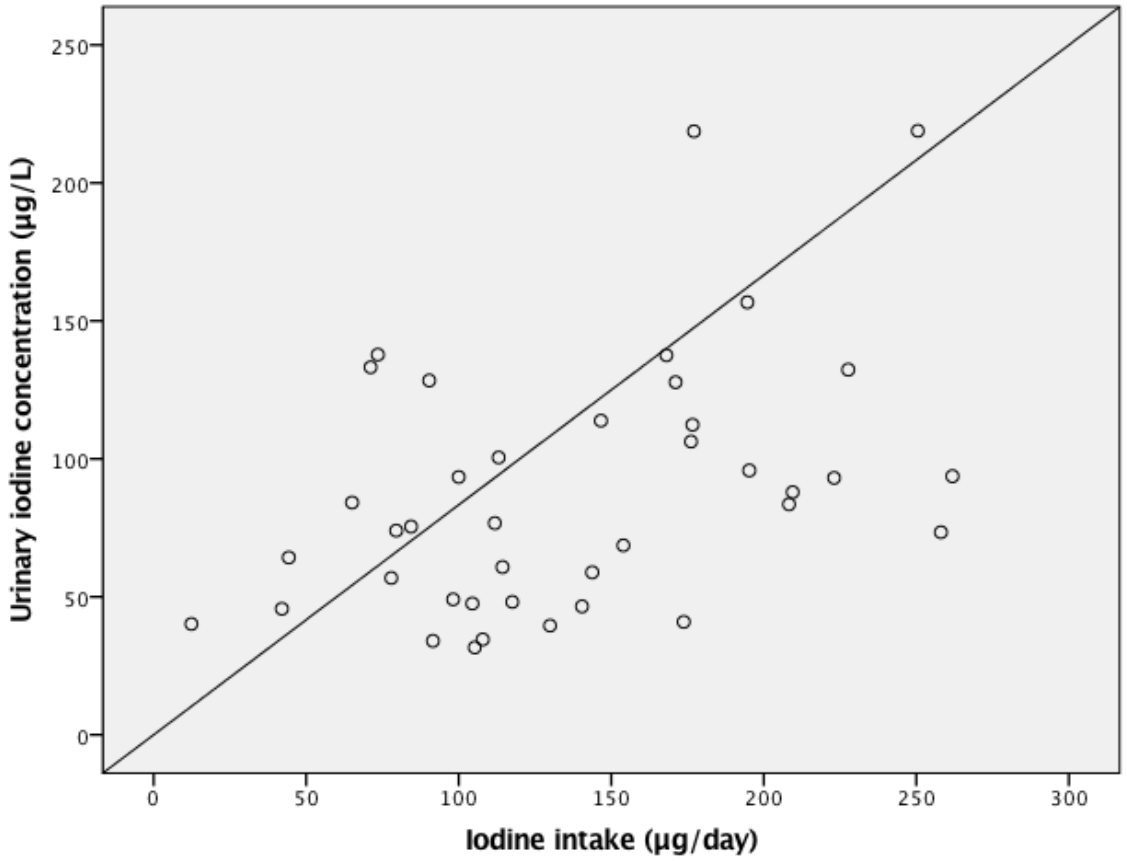

Figure 5-8 Scatter plot illustrating the correlation between iodine intake (µg/day) and urinary iodine concentration (µg/L) in a group of pregnant women in Norway (*n*=40) by Spearman's rho correlation.

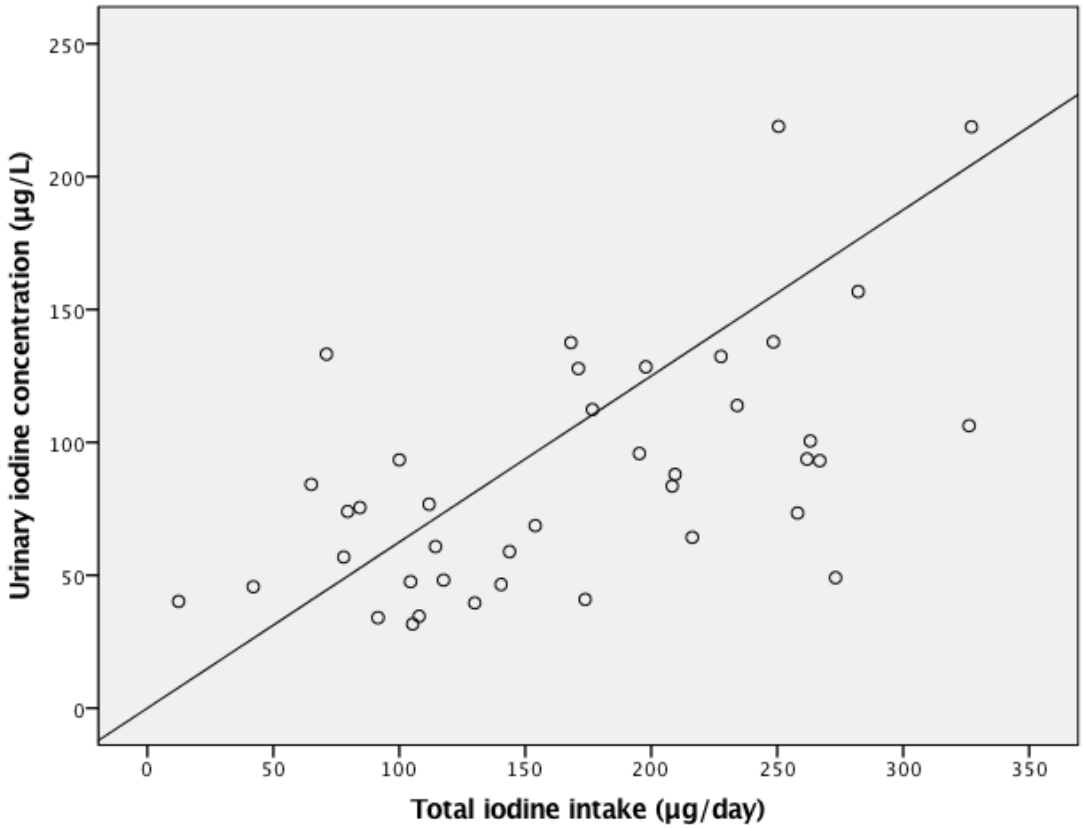

Figure 5-9 Scatter plot illustrating the correlation between total iodine intake (food and supplement) (µg/day) and urinary iodine concentration (µg/L) in a group of pregnant women in Norway (*n*=40) by Spearman's rho correlation.

5.7 Calculated iodine intake and urinary iodine concentration in pregnant women and a control group

A control group of 26 non-pregnant women (age range 22-48 years) was included in the study. The mean age was 36 years and the women had a mean BMI of 23, indicating normal weight (data not shown). No significant difference was found in calculated iodine intake from food between the pregnant women and the control group (p=0.233), and median and mean calculated iodine intake in the non-pregnant group was 93 µg/day and 117 µg/day, respectively. For the pregnant women, the median and mean calculated iodine intake was 124 µg/day and 137 µg/day, respectively. When including iodine from supplement to the calculated intake of iodine from food (total iodine intake), the pregnant women had a significant higher total iodine intake (170 µg/day) compared to (119 µg/day) the control group (p=0.014) (data not shown). In the control group, one woman used shakes from the brand Herbalife, which contains iodine but none used iodine-containing supplements. No

significant difference was found in UIC between the control group (80 µg/L) and the pregnant women (88 µg/L) when analyzed with the parametric test (p=0.557) (non-parametric test; p=0.189).

6 DISCUSSION

Assessing iodine status in pregnant women is of great importance because there is an increased risk of ID during pregnancy due to a greater demand of thyroid hormones, and hence iodine (Zimmermann, 2009). The main objective of the present study was therefore to assess iodine status in a group of pregnant women in Norway based on two-day food diary and measuring median UIC from morning spot urine samples. The findings from the present study indicated that the pregnant women were mild-to-moderate iodine deficient, which can be damaging for the developing fetus and pose a risk to public health.

6.1 Findings

6.1.1 Calculated iodine intake

The consequences of ID remains a worldwide problem and it is estimated that 1.88 billion people have inadequate iodine intakes (Andersson et al., 2012). Severe ID during pregnancy can be damaging for the developing fetus and result in cretinism and mental retardation (Glinoer, 2007). Even mild-to-moderate ID during pregnancy can effect the intellectual, psychomotor and cognitive development in children (Bath et al., 2013; Qian et al., 2005; Trumpff et al., 2013), and it is therefore important to optimizing iodine status previous to pregnancy. Although Norway has been considered iodine replete for decades, the MoBa study showed that pregnant women could be at risk of mild-to-moderate ID (Brantsaeter et al., 2013). The median calculated iodine intake from food (124 μg/day) for pregnant women in the present study is similar to the median iodine intake from food (120 μg/day) estimated from a four day weighed food record in pregnant women who participated in a validation study of the MoBa FFQ in 2003-2004 (Brantsaeter et al., 2009). The findings from the present study is slightly lower than what was found in another master thesis where pregnant Norwegian women had an median iodine intake of 153 μg/day, but the results were conducted from a FFQ (Sanchez, 2015). In the Nordic countries, pregnant women are recommended to consume 175 μg/day of iodine from food in order to meet both here own and the fetus requirement for iodine, which only 30% of the pregnant women in this study achieved (Nordic Council of Ministers, 2014). In comparison, only 3 (7.5%) of the women in the present study reached WHO recommendation of iodine for pregnant women at 250 μg/day (WHO, 2007a). The findings indicate that the present study population had a lower intake of

iodine from food than recommended, and can be seen as mild-to-moderate iodine deficient. The calculated iodine intake in the present study from the food diaries was virtually equal to the estimated iodine intake based on UIC (123 µg/day) in these pregnant women (Table 5-2), which further strengthens the findings of mild-to-moderate ID among the women.

Four studies from Norway have found low intake of iodine among pregnant women and women in childbearing age (Brantsaeter et al., 2013; Dahl et al., 2004; Dahl et al., 2003b; Sanchez, 2015). Studies from other European countries including Sweden, Portugal and Italy have shown inadequate iodine status in pregnant women with a median UIC ranging from 50-98 µg/L (Granfors et al., 2015; Limbert et al., 2010; Mian et al., 2009). According to new data on the prevalence of ID in pregnant women in Europe, two-thirds of the countries that had assessed iodine status in pregnant women reported inadequate iodine intakes (Zimmermann et al., 2015). In the study from UK linking maternal iodine status to reduced child IQ at age eight years, median UIC were 91.9 µg/L indicating mild-to-moderate ID (Bath et al., 2013). Furthermore, a study from New Zealand found that pregnant women were iodine deficient with a median iodine intake of 48 µg/day (Pettigrew-Porter et al., 2011). A study from the US has also shown inadequate iodine status in the pregnant population with a median UIC of 129 µg/L (Caldwell et al., 2013). These results emphasize the importance of monitoring iodine status in pregnant women, as well as developing and implementing strategies to ensure an adequate intake of iodine before and throughout pregnancy.

6.1.2. Dietary sources of iodine

Milk and dairy products were the largest contributor of iodine from food (58%), which is in accordance with findings from other Norwegian studies (Brantsaeter et al., 2013; Dahl et al., 2004; Dahl et al., 2003a; Dahl et al., 2003b). Iodine content of milk and dairy products is earlier found to differ between winter and summer season, with the highest content in winter milk (Dahl et al., 2003a). According to the dairy industry, the seasonal difference in iodine levels between summer and winter milk has diminished because mineral concentrate is now given to cows also during summer season (L, Nordang, personal communication, April 20, 2016). The same was found in a Norwegian study from 2012 analyzing iodine concentration in milk (Haug et al., 2012). The iodine values for milk and dairy products in the updated food composition table are based on a number of analyzed samples and the values represent the weighted mean of a range of analytical values (G, Waage, personal communication, April 19, 2016). According to the references given in the Norwegian Food Composition Table, these

values have been provided by the dairy industry (The Norwegian Food Safety Authority, The Norwegian Directorate of Health & University of Oslo, Undated). For some dairy food items in The Norwegian Food Composition Table, e.g. cheese, the iodine concentration was assigned based on values for similar food items and some values are compiled from other countries. For composite dishes, the iodine concentrations were assigned based on recipes if the item included iodine containing food items or beverages such as milk, fish and eggs. The use of a single iodine value for each food course may be a major source of uncertainty in the assessment of iodine from the diet. Seafood and eggs contributed with 22% and 6% of iodine from food, respectively. The relatively high contribution of iodine from nuts and cereal products (6%) can probably be explained by the inclusion of dishes containing milk and/or dairy products or eggs such as waffles, cakes and similar products. Iodine contribution from other food groups (e.g. fats and oils, vegetables, fruits and berries, and sweets) was 2% of the intake of iodine from food, in concordance with previous findings (Dahl et al., 2004). Pregnant women who did not reach NNR5 recommendation of 175 µg/day had a lower mean iodine intake from milk and dairy products, and fish and seafood than women reaching the recommended 175 µg/day. Dietary sources of iodine are as mention few, and low consumption of milk and dairy products and/or seafood has been shown to be a risk factor for inadequate iodine intake (Brantsaeter et al., 2013; Rasmussen et al., 2002). The fact that the pregnant women in the present study had a low intake of fish, and especially lean fish with a high content of iodine (e.g. cod, haddock and saithe) is therefore of specially concern, and moreover that four of the pregnant women reported no intake of fish and/or seafood (only one explained the restriction with allergy). The low intake of fish is in accordance with a report from the Norwegian Directorate of Health that was published in 2015 with data on the development of the Norwegian diet. It revealed that the consumption of milk and fish are decreasing in some parts of the population (The Norwegian Directorate of Health, 2015). Furthermore, Norkost, a National dietary survey conducted among adults in Norway during 2010-2011, found a decreasing intake of fish (The Norwegian Directorate of Health, 2012b). Especially women in childbearing age (18-39 years) had a low intake of fish and fish products compared to elderly (The Norwegian Directorate of Health, 2012b). The trend is concerning and if it continues it could lead to a further reduction in iodine intake in Norwegian women in childbearing age. The same trend is also seen in Sweden (Livsmedelsverket, 2012). In Denmark, the intake of milk has slightly decreased in women in childbearing age the last years but the intake of iodine is assumed to be adequate because of the iodization of salt and mandatory use of iodized salt in industrial bread (National Food Institute, 2015; Rasmussen et

al., 2007). Even in Iceland, a country known for its high intake of fish and milk, there has been a reduction in the consumption of fish and milk. However, a recent study found that iodine status in pregnant women was adequate (Gunnarsdottir et al., 2013). With the possible decrease in intake of milk and dairy products and fish in women in childbearing age, the use of iodine-containing supplement may be an important source of iodine before and throughout pregnancy, and did in fact contributed substantially to the total iodine intake in the present study population.

6.1.3 Iodine supplement use

When iodine from supplements was included to the calculated intake, the median total iodine intake in the pregnant women increased to 170 µg/day, which is still below the recommended 175 µg/day (Nordic Council of Ministers, 2014). Only 25% of the pregnant women used some sort of iodine-containing supplements. This percentage is slightly higher compared with a large survey from US (22.3%) (Gahche, Bailey, Mirel & Dwyer, 2013), but lower than what was found in Austria (32.1%) (Lindorfer et al., 2015). In the Norwegian MoBa study, 31.6% of the participants reported intake of iodine-containing supplements, which is higher than in the present study population (Brantsaeter et al., 2013). There are no official recommendations on iodine supplementation during pregnancy in Norway. However, there are official recommendations for intake of folic acid and vitamin D during pregnancy. Considering that iodine from supplement was solely obtained by intake of prenatal multivitamins, it is likely that intake of iodine from supplement is due to the other recommendations for supplement intake for pregnant women in Norway (The Norwegian Directorate of Health, 2012a). The government in Australia recommend iodine supplementation of 150 µg/day to all pregnant and breastfeeding women (NHMRC, 2010). Iodine supplement users reached the recommendation from NNR5 of 175 µg/day and 60% reached WHO recommendation of 250 µg/day, indicating that supplements with iodine is a great contributor to the total iodine intake during pregnancy (Nordic Council of Ministers, 2014; WHO, 2007a). A strength of the present study was therefore the information of consumption of iodine-containing supplements. Use of iodine supplement was shown to be a predictor of adequate iodine intake in pregnant women in Norway (Brantsaeter et al., 2013). In the present study, the two most commonly used supplements were prenatal vitamin and mineral supplements, and it is alarming that only 25% of the women took prenatal supplements. A minority of the women took other vitamin and mineral supplements, but none contained iodine. None of the women ate kelp or seaweed

products, which should be avoided during pregnancy due to unacceptable variability in their iodine content and risk of excessive iodine intake (Scientific Committee on Food, 2002; Zimmermann & Delange, 2004). Seaweed is one of the main sources of iodine in some countries in Asia (Wei et al., 2015; Zava & Zava, 2011). In some European countries and in the US most of the prenatal vitamin and mineral supplements do not contain iodine (Leung, Pearce & Braverman, 2009; Zimmermann et al., 2015).

6.1.4 Possible adverse effects of mild-to-moderate iodine deficiency in pregnancy

Several studies have examined the potential adverse effects on children of mild-to-moderate ID during pregnancy. In spite of some inconsistencies between the results, the evidence from these studies underlines the importance of adequate iodine status early in pregnancy. Studies have shown that mild-to-moderate ID during pregnancy can affect the intellectual, psychomotor and cognitive development in children (Costeira et al., 2011; Qian et al., 2005; Trumpff et al., 2013). This include lower scores for verbal IQ, reading accuracy and a reduction in grammar and spelling, and psychointellectual development in children from mothers with a low UIC during pregnancy (<150 μg/L) (Bath et al., 2013; Hynes et al., 2013; van Mil et al., 2012; Velasco et al., 2009; Vermiglio et al., 2004). The findings from a study conducted in Portugal showed that children born to hypothyroxinaemic mothers with low serum fT_4 levels during first trimester had lower psychomotor score than controls (Costeira et al., 2011). A study conducted in Russia found similar results with maternal hypothyroxinaemia during early pregnancy (5 to 9 weeks) correlating significantly with delayed cognitive performance in the offspring, and that the prognosis of the offspring improved if the hypothyroxinaemia was corrected before the ninth week of pregnancy with levothyroxine (synthetic thyroid hormone) (Kasatkina et al., 2006). However, the latter study included only a total of 23 children and the mother was treated with medicine (levothyroxine) rather than iodine supplementation. A newly published pilot study found that children born to mothers with treatment of levothyroxine during pregnancy had different scores in IQs test although the mothers were having similar fT_4 concentration throughout gestation. The differences was explained by the intake of iodized salt, where children born to mothers with both a intake of levothyroxine and iodized salt had better IQ scores than children born to mothers with no intake of iodized salt but only levothyroxine (Moleti et al., 2016). The authors of the study concluded that maternal nutritional status had a greater effect on neuro-intellectual outcomes in the offspring than maternal thyroid function (Moleti et al., 2016). A

study from Netherland indicated that maternal hypothyroxinaemia during early gestation was associated with a delay in infant neurodevelopment (Pop et al., 2003). The findings from the Generation R Study, a population-based cohort study also conducted in Netherland, confirmed the findings of a delay in neurodevelopment in children from hypothyroxinaemic mothers (Henrichs et al., 2010). The results are however inconsistent and depends on the measurement variable applied. For instance, a further study using data from the Generation R Study found no clear association between low maternal UIC and children's cognition (IQ). However, few of the women studied had a UIC below <150 μg/L and maternal thyroid function was not included (Ghassabian et al., 2014). Likewise, in New Zealand, a group of pregnant women was found to have a median UIC of 38 μg/L, indicating ID. The concentration of thyroid hormones was however within normal reference ranges and suggested that the pregnant women had an adequate intake of iodine. Furthermore, the children born to these women had no clear effects on developmental outcomes (Pettigrew-Porter et al., 2011).

Lazarus (2011) suggest that interventions conducting screening of thyroid function in early gestation could be beneficial because low thyroid hormone concentrations is, as discussed above, found to be a possible risk factor for low IQ and a delayed neurodevelopment in young children, although more studies are needed to confirm this (Lazarus, 2011). Maternal thyroid dysfunction (e.g. hypothyroidism, subclinical hypothyroidism and hypothyroxinaemia) and its consequences on the developing fetus are even seen in areas with adequate iodine intake, which increase the need for continuous monitoring of iodine status in the pregnant population (Lazarus, 2011).

6.1.5 Iodine supplementation during pregnancy

WHO recommend every country to assess iodine status in the population with five-year interval. In the case of suboptimal iodine intake, supplement with iodine is recommended to vulnerable groups, regardless if the country has implemented USI (WHO, 2007a). The American Thyroid Association for example recommends supplementation of 150 μg of iodine (as potassium iodide) per day for women in childbearing age before conception and throughout pregnancy and lactation. The recommendations are provided for pregnant women living in the US and Canada (Stagnaro-Green et al., 2011). Some researchers recommend the use of iodine supplementation to women who are planning a pregnancy and to all pregnant and breastfeeding women regardless if the iodine status of pregnant women is been assessed (Berbel et al., 2007; Moleti et al., 2011; Zimmermann et al., 2015). The recommendation is

based on the importance of adequate iodine status during the first trimester, and considering that a lot of women do not find out about the pregnancy before the end of the first trimester it may be to late with iodine supplementation at that point (Morreale de Escobar et al., 2004; Zimmermann et al., 2015). For instance, in Canada where pregnant women are thought to have an adequate intake of iodine, supplementation of iodine are still recommended, as mention above (Katz et al., 2013; Stagnaro-Green et al., 2011).

In 2014, 16 national coordinators in Europe confirmed that monitoring of iodine status in the country was ongoing, while 17 countries responded that there was no monitoring (Lazarus, 2014). In addition, two-thirds of European countries that had assessed iodine status in pregnant women reported inadequate iodine intake, including Norway (Zimmermann et al., 2015). These findings are of special concern when ID can have serious consequences for the people affected, especially pregnant and lactating women (Skeaff, 2011). Pregnant women have an increased need of iodine and it is of utmost importance that the intake of iodine is adequate before and throughout pregnancy (Glinoer, 2007; Zimmermann, 2007). Several studies have therefore been conducted on the use of iodine supplementation during pregnancy in areas with mild-to-moderate ID, with various results (Pearce, 2013; Zhou et al., 2013). One study from Spain found that children of mothers receiving iodine supplementation of 300 μg/day had better psychometric assessment than children from mothers not receiving supplement (Velasco et al., 2009). A similar study from Spain found however no association between iodine supplementation (200 or 300 μg/day) during pregnancy and maternal thyroid function or children's neurological development (Santiago et al., 2013). Although the methods used in the two studies from Spain were similar, the study conducted in 2009 was not randomized as opposed to the study from 2013. Another study did not find any difference in neurodevelopment in children of mothers receiving iodine-containing supplement (150 μg/day) during pregnancy and the placebo group (Zhou et al., 2015), and some studies have even found adverse effects on child development in children from mothers receiving iodine-containing supplement (150 μg/day or more) during pregnancy or an increased risk of maternal thyroid dysfunction (Moleti et al., 2011; Rebagliato et al., 2013). It is important to note that the different methods used to measure the effect of iodine supplementation and the various amount of iodine in the supplement used, will cause limitation in the comparisons across studies (Brownie & Myers, 2004).

Because the safe UL for iodine during pregnancy is not been clearly defined and the fetal thyroid is vulnerable to iodine excess, some researchers are more skeptical in the recommendation of iodine supplementation during pregnancy (Pearce, 2013). It is especially

the risk of iodine-induced thyroid dysfunction that is of concern, because it has been seen in relation to iodine intake in excessive form. It is however elderly people and other groups in the population with preexisting goiters and/or abnormalities of the thyroid that are most susceptible, and it may even occur in cases of adequate iodine intake (Laurberg et al., 2010; Leung & Braverman, 2014; WHO, 2007a). Likewise, a systematic review from 2013 found no evidence of an excess of thyroid dysfunction in conjunction with iodine supplementation in pregnancy in the studies investigated (Taylor, Okosieme, Dayan & Lazarus, 2014). On the other hand, in Belarus the incidence of iodine-induced hyperthyroidism increased among adults after the introduction of salt iodization in 2001 but by 2009 the incidence had return to pre-supplementation levels (Petrenko, Mokhort & Gerasimov, 2014). In Denmark where salt iodization was implemented in 2000, follow-up studies have shown that an increase in iodine intake over time may lead to fewer cases of hyperthyroidism and more cases of hypothyroidism, even though the population is changing from ID to adequate iodine status (Carle et al., 2006; Laurberg et al., 2006). Another study found also both an appearance and disappearance of thyroid nodules after the iodization of salt in Denmark (Krejbjerg et al., 2014). The latter studies are however based on USI and the general population, and it is uncertain if these results are transferable to the implementation of iodine supplementation during pregnancy.

To the best of my knowledge, there has not been conducted any study in Norway addressing the effects of iodine supplementation during pregnancy, nor is there a recommendation for use of iodine-containing supplement during pregnancy. The evidence base of long-term outcomes of moderate-to-mild ID during pregnancy is scarce and the results of using iodine-containing supplement during pregnancy are inconsistent as discussed above. The lack of data and evidence could be the reason why health authorities have not given a higher priority to monitor and secure optimal iodine status during pregnancy (Zimmermann et al., 2015). Large scale controlled trials are therefore needed, both in Norway and in other countries, to clarify the efficacy and safety of iodine supplementation use during pregnancy (Lazarus, 2015; Taylor et al., 2014). Therefore, two randomized controlled trials, one in India and another in Thailand, was started in 2008 with the aim of measuring the effect of iodine supplementation during pregnancy on birth outcomes and child development in areas of mild ID (Melse-Boonstra et al., 2012). Furthermore, the Pregnancy Iodine and Neurodevelopment in Kids (PINK) Trial is ongoing, a randomized control trial in Australia comparing women receiving supplement of 150 μg iodine with placebo (NHMRC, undated). The findings of these ongoing trials are thought to be of importance in deciding the safety and efficacy of

iodine supplementation in pregnancy, as well as causing an increased interest for iodine status in pregnancy (Taylor et al., 2014).

6.1.6 Urinary iodine concentration

We found a correlation between total iodine intake (food and supplement) and UIC of 0.54, which can be considered a medium or fair correlation. The strength of the correlation depends on the width of the values of the two variables. Still, a correlation above 0.5 is a clear indication that the calculated total iodine intake can be seen as valid and reliable. The correlation is comparable to the correlation of 0.52 between total iodine intake from a 4-day food diary and urinary iodine in the MoBa validation study (Brantsaeter et al., 2007). In that study, UIC was analyzed in 24-hours urine and expressed as 24-hours UIE. Correlation coefficients above 0.5 is actually in the upper end of what can be expected given the uncertainty in both the calculated intake and the use of spot urine samples for UIC. In the current study, food and supplement intake was based on self reported food diaries, which can be exposed to misreporting, and the iodine values in The Norwegian Food Composition Table does not take into account the variation in iodine content within food groups. Furthermore, UIC measured in spot urine samples are less representative of the iodine intake than 24-hours urine collections.

The median UIC in the group of pregnant women was 80 μg/L, which is below WHO cut-off values for adequate iodine status in pregnant women (150-249 μg/L) (WHO, 2007a). No UIC cut-off values for severe and moderate/mild ID during pregnancy exist today, but according to existing literature the pregnant women in the present study can probably be defined as mild-to-moderate iodine deficient based on median UIC (Zimmermann, 2007). Low UIC in pregnant women or women in childbearing age is found in three other studies from Norway, with a median UIC between 69-112 μg/L (Brantsaeter et al., 2013; Dahl et al., 2003b; Sanchez, 2015). The median UIC in the pregnant women is similar to the results from a cross-sectional study conducted in two counties in Sweden, where pregnant women had a median UIC (98 μg/L) indicating mild-to-moderate ID (Granfors et al., 2015), but lower than what was found in a large cross-sectional study from China, where pregnant women had a median UIC of 130 μg/L (Mao et al., 2015). None of the women had UIC levels above >250 μg/L, which would have indicated an intake of iodine above the recommendation (WHO, 2007a). A lower UIC was found in the group of supplement users (all supplement, excluded iodine) with a median UIC of 58 μg/L, compared to the women consuming iodine-containing

supplements (110 µg/L). There were a significant difference (p=0.011) in UIC between iodine supplement users and non-iodine supplement users. Similar results are found in other European studies. Andersen et al. (2013) found that Danish pregnant women who were iodine supplement users had a significant higher median UIC (109 µg/L) than non-iodine supplement users (68 µg/L) (Andersen et al., 2013). In Austria, pregnant women taking iodine-containing supplement had a significant higher median UIC (97.3 µg/L) compared to non-iodine supplement users (80.1 µg/L) (Lindorfer et al., 2015). However, iodine supplement users in the present study and the above mention studies still had a lower UIC than recommended, which can indicate that doses of 150-175 µg/day from supplement are insufficient for adequate excretion of iodine in urine during pregnancy.

In order to adjust and correct UIC for daily urine volume, iodine/creatinine ratio from the two spot urine samples and age- and sex adjusted iodine/creatinine ratio was applied (Knudsen et al., 2000). The results showed a comparable median UIC for urinary iodine (80 µg/L), iodine/creatinine ratio (80 µg/g creatinine) and age- and sex adjusted iodine/creatinine ratio (87 µg/day), which can indicate that the morning spot urine samples were only affected by the hydration status to a smaller degree.

Because only two spot urine samples were collected from each participant in the present study, the prevalence of ID in the pregnant women cannot be accurately described based on UIC, and the WHO reference ranges for defining optimal iodine status based on UIC are, however, for larger population groups. Furthermore, UIC cannot be used to measure long-term intake of iodine (WHO, 2007a). However, UIC is a good indicator for recent iodine intake and was in accordance with the calculated iodine intake in the pregnant women.

6.1.7 Calculated iodine intake and urinary iodine concentration in pregnant women and a control group

No significant difference in calculated iodine intake from food was found between the pregnant women and a control group of non-pregnant women. The pregnant women had a higher intake of iodine from food than the control group, although not significant, a result that is advantageous considering the higher need of iodine during pregnancy. When iodine from supplement was included in the calculated iodine intake, there was a significant difference (p=0.014) in total iodine intake between the pregnant women and the control group, with the pregnant women having the highest intake of iodine. The result can be explained by the fact that none of the women in the control group consumed iodine-containing supplement,

compared to ten of the pregnant women. No significant difference was found in UIC between the pregnant women and the control group. The women in the control group had a lower intake of iodine (93 µg/day) than recommended (150 µg/day) for non-pregnant women, which is of concern considering that most of the women were in childbearing age. The sample size of the control group is however too small to draw valid conclusions.

6.1.8 Improving iodine status in pregnancy

In order to improve iodine status in pregnant women with inadequate iodine intakes, three strategies can be used and are as follows; dietary diversification, fortification and supplementation (Skeaff, 2012). The first strategy requires a change in the diet with an increased intake of iodine rich foods like milk and dairy products, fish and seafood, and eggs (Brantsaeter et al., 2009; Skeaff, 2012; Zimmermann, 2009). Some women may however found this as a challenge because of a changed appetite and perhaps nausea during pregnancy, as well as dislikes and/or allergy to certain foods (National Institutes of Health, 2007). Furthermore, two studies from Australia assessing iodine status in pregnant women also found low level of knowledge about iodine (e.g. function during pregnancy, dietary sources and recommendations), which shows the importance of increasing the knowledge of iodine in order to achieve an improved iodine intake in pregnant women (Charlton et al., 2012; Charlton et al., 2013).

Fortification and supplementation

The most common used method is USI, and it is also the preferred method to eliminate ID worldwide because it is an effective and relatively affordable method. A systematic review conducted by WHO in 2014 showed that USI is an effective contributor in reducing the risk of goiter, cretinism, low cognitive function and ID (Aburto, Abudou, Candeias & Wu, 2014). WHO has earlier recommended that iodine concentration in salt when consumed should be 20-40 mg of iodine per kg of salt in order for the general population to meet the recommended level of iodine (150 µg iodine/day), and it should be in the form potassium iodate (WHO, 2007a). In 2014, WHO issued a new report recommending mandatory USI in all countries (WHO, 2014a). The report state that the amount of iodine added to salt should be assessed within each country due to differences in production, climate, packaging and storage, which all can influence the amount of iodine in the salt available for the consumers (WHO, 2014a). During pregnancy, the intake of iodized salt is often not enough to ensure an adequate intake

of iodine and if the iodine intake is found to be low in pregnant women, iodine supplementation should be recommended (Moleti et al., 2016; WHO, 2014a). USI are implemented in several European countries such as Denmark, Netherland, Switzerland and the UK, as well as Canada (Lazarus, 2015). The effectiveness and safety of salt iodization can however be discussed. In Belarus, the intake of iodine during pregnancy is now adequate because of a national strategy where the food industry uses iodized salt (amount of iodine not available), and the government recommends use of iodized salt to the population (Petrenko et al., 2014). Moreover, in Switzerland where there is a high-iodized salt coverage (20 mg iodine per kg salt) and good monitoring, pregnant women have an adequate intake of iodine (Andersson et al., 2010; Zimmermann, Aeberli, Torresani & Burgi, 2005). The same is seen in Canada where USI has been mandatory since the 1920s with 77 μg of iodine/g of salt, which is a higher concentration than that used in most other countries (Katz et al., 2013). On the other hand, in Denmark, where salt fortification was implemented in 2000, a study found no difference in iodine status before and after fortification in pregnant women with no intake of iodine-containing supplement (Andersen et al., 2013; Rasmussen et al., 2008). The fortification of 13 mg iodine per kg salt is however probably lower than the recommended amount from WHO (Rasmussen et al., 2008; WHO, 2007a, 2014a). In contrast, Lazarus (2014) refer to the salt law in Croatia from 1996 with the introduction of 25 mg iodine per kg salt, which has led to steadily increase in the UIC values in the population, but which also shows the need for continuing monitoring in order to avoid iodine excess and its consequences (Lazarus, 2014; WHO, 2014b). WHO further state that there has been a rapid global progress in the elimination of ID because of USI, but warns that poorly monitoring of iodine status can cause iodine excess in populations (WHO, 2007a, 2014a). It is therefore important to monitor the iodine status in the population through UIC to detect deficiency or excessive intakes, and then adjust the level of iodine fortification. Salt iodization should be regulated by governments through an efficient system to ensure that iodine is added in an acceptable range, and that the strategy is accepted, adopted and sustained by the population (WHO, 2014a). In Finland, where USI has been implemented for several decades, the consumption of iodized salt has decreased and the intake of iodine is inadequate in the population. The National Nutrition Council in Finland therefore now recommends that salt should contain 25 μg/g of iodine, iodized salt is to be used in mass catering, in homes and should gradually be used in all food preparation, including the food industry (National Nutrition Council, 2015; WHO, 2007b). In a recent study conducted by Bath et al. (2015) in the UK, only 6% of the pregnant women reported use of iodized salt, which again shows the

importance of monitoring iodine status in the population, as well as the coverage of USI (Bath et al., 2015). These conflicting results and the various level of iodine added to salt shows the importance of evaluating and monitoring the effectiveness and safety of USI, as well as the importance of adding iodized salt to foods frequently consumed by the population.

In Norway, only some brands of salt are fortified with iodine, regulations permit the addition of 5 μg of iodine per gram of NaCI and the food industry is not allowed to use fortified salt. The intake of iodine from salt is therefore thought to be insignificant in the Norwegian diet (Andersson et al., 2007; Dahl et al., 2004). In countries without USI (e.g. Norway) and a suboptimal iodine intake, salt iodization should be implemented in adequate doses in order for the general population to meet the need for iodine. In addition, iodine supplementation should be recommended to pregnant women in order to ensure an adequate intake of iodine (Skeaff, 2012; WHO, 2007a; Zimmermann et al., 2015).

6.1.9 Salt iodization and public health

The use of iodized salt as a vehicle for combating ID raises a public health question when high intake of salt is seen as a risk factor for cardiovascular diseases (Aburto et al., 2013). One of the main strategies for reducing salt intake in the population is a reduction in salt added to processed foods. For instance, there is an ongoing campaign in Norway to reduce the intake of salt in the population, and hence the prevalence of cardiovascular diseases (The Norwegian Directorate of Health, 2014). The food industry is an important part of this goal and they have already begun the reduction of added salt to processed foods. The plan is of great importance and will in the longer-term benefit the public health in Norway. Because the iodine content in iodized salt is low and use of iodized salt is very limited in Norway, the salt campaign will not affect the iodine status in the population. However, in countries with a higher contribution of iodine from salt, a reduction of salt will probably have a greater impact on iodine status. For instance, in the UK where iodized salt is implemented, only 15% of all salt consumed comes from processed foods because of a successful salt reduction program (He, Brinsden & MacGregor, 2014). This may be the reason for the reappeared ID in the UK and the fact that only 5% of the iodine intake comes from salt (Lazarus, 2014; Vanderpump et al., 2011). Zimmermann et al. (2015) therefore state that in order for iodized salt programs to be successful but not interfere with the public health goal of reducing salt intake in the population, the food industry need to use iodized salt in processed foods and salt used in homes should be fortified with iodine, as for example recommended in Finland (Campbell et

al., 2012; National Nutrition Council, 2015; Zimmermann et al., 2015). WHO further state that because salt reduction and salt iodization are compatible, each country needs to monitor salt intake and iodine intake in the population in order to adjust salt iodization over time, and increased salt intake should not be promoted to the public (WHO, 2014a).

6.2 Methodological considerations

6.2.1 Recruitment of study participants

A majority of the participants in the present study were recruited to the Donexpo study conducted by FHI and NVI, and only five of the pregnant women were recruited exclusively for assessment of iodine status in pregnant women in this master thesis. In order to make sure that all information and materials given to the participants recruited to this master thesis was the same as in Donexpo, a meeting with the researcher from Donexpo was conducted in advance of recruitment. The background form, the food diary, the bottles for collection of morning spot urines and the consent form given to the participants were the same as those used in Donexpo. However, some differences in the recruitment might have occurred. External validity, or generalizability, measure to what extent the study captures accurately the phenomenon as it exist in the target population (Gibson, 2005). 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 be 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 media value), and it is important to take bias into consideration because it cannot be removed by statistical analysis (Gibson, 2005). Selection bias is a systematic bias that is common in nutritional studies 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 (Mosdøl & Brunner, 2011; Thompson & Subar, 2013). Considering that the recruitment was done through convenience sampling, mostly through information on intranet at FHI and NVI (Donexpo), this may further have resulted in selection bias considering the high level of education among the people working at the two institutes. However, the recruitment method included also family and friends of employees at the two institutes, and a weakness of the present study was therefore the lack of information of socio-demographic variables such as education, work and income levels. These

variables are further seen in relation to misreporting of the actually dietary intake (Gibson, 2005). Higher education among women also seems to decrease underreporting (Livingstone & Black, 2003). There were no exclusion criteria's in the Donexpo study and the only inclusion criteria were that the participants were healthy at the time of recruitment. Previous studies assessing iodine status in pregnancy have excluded women taken thyroid hormone drugs (Bath et al., 2015; Bath et al., 2013; Travers et al., 2006) or with diseases related to the thyroid (Granfors et al., 2015; Lindorfer et al., 2015; Pettigrew-Porter et al., 2011), but considering that the present study did not include measurement of thyroid hormones, the lack of this information should not have affected the results. Furthermore, the fact that the study sample consisted of only 40 pregnant women whereas all lived in Oslo or Akershus can limit the external validity of the study to the rest of the pregnant population in Norway. However, there was a wide range in the age among the pregnant women (age range 22-47 years) and all three trimesters and parity were included, which can have strengthened the external validity.

6.2.2 Dietary assessment

In the present study, food diary was the chosen dietary record method, which has the potential of providing quantitatively accurate information on food consumed during the recording period. Because the women reported foods prospectively throughout the day when consumed, the problem of omissions (forgotten foods) may have been reduced and the foods eaten were more detailed described (Thompson & Subar, 2013). There is however, no way to know whether or not participants changed their intakes due to the food recording. Two days of recording are often not enough to adequately measure an individual's usual intake but regardless of which method applied to measure usual intakes it is difficult to validate the results due to large day-to-day variability of individual's diets (Gibson, 2005; Thompson & Subar, 2013).

Internal validity indicates to what degree the results are valid for the particular group being studied, and includes collection and processing of data as well as interpretation of the results (Gibson, 2005). There are several possible steps that can have caused errors to the results during the coding process, usually referred to as coding errors, and hence affected the internal validity of the present study. Random errors such as coding and data entry errors are difficult to avoid (Cadmus-Bertram & Patterson, 2013). During the coding process we took random samples to minimize the chance of errors. This included checking to make sure that day 1 and day 2 and ID numbers were recorded in order, and that all items were recorded in

gram. If an error was detected we looked over the food diary again to correct the error. Furthermore, FoodCalc, the nutrient analysis program used to quantify iodine and energy intake, only recognized the codes of items found in The Norwegian Food Composition Table and the program reported any code not found in the table, which then was corrected by the researcher. Some coding errors may however have occurred. The Norwegian Food Composition Table is not complete and has its shortcomings, and both random and systematic errors may occur when using food composition data (Gibson, 2005). The Norwegian Food Composition Table does not account for losses of iodine through food preparation or other processing factors, which can result in inconsistencies in the food composition values (Gibson, 2005). Some of the nutrient values in The Norwegian Food Composition Table may be incorrect or incomplete, and they are compiled from a variety of sources, including direct chemical analysis, imputed values and literature reporting analytical values from other countries. This may further lead to error in the estimates of iodine intake due to the differences in iodine content in soil and farming practices across countries (Cadmus-Bertram & Patterson, 2013; Gibson, 2005). However, the majority of the food composition data in The Norwegian Food Composition Table used in the present study was based on national data. This is particularly important for milk and yoghurt, which were the main contributors to iodine intake. In the present study, the latest updated version of The Norwegian Food Composition Table (September 2015) was used in order to minimize the chance of errors but some of the iodine values in the table are still obtained from old references, and some items had still not got a value for iodine (Gibson, 2005; The Norwegian Food Safety Authority et al., 2015). Furthermore, the iodine values in The Norwegian Food Composition Table indicate the total amount of iodine in foods and beverages, rather than the amount actually absorbed by the body (Gibson, 2005). The bioavailability of dietary iodine has been quantified to 92% of iodine from the diet being absorbed by the body (Hurrell, 1997). Moreover, The Norwegian Food Composition Table does not take the composition of the total diet into consideration, and therefore goitrogens and other substances that may limit the uptake of iodine by the thyroid (Gibson, 2005; Zimmermann, 2009). According to Zimmermann (2009), the intake of goitrogenic substances is not thought to have a major impact in iodine status in the general population, unless there is coexisting ID (Zimmermann, 2009). Although there is no national data on the intake of goitrogenic substances in the Norwegian diet, the calculated intake of iodine from the diet in the present study is thought to be the approximately iodine absorbed by the body.

All foods and beverages were converted from household measurement into gram in the coding process, which may have lead to miscalculation, as well as an increased risk of coding errors (Gibson, 2005). In some of the diaries the writing was hard to understand or it was unclear, but because the completed food diaries were checked for completeness of description, it did not cause any problems during the coding process. Several times during the coding process it was necessary to use other items than those actually consumed because multiple items reported in the food diaries were not found in The Norwegian Food Composition Table. In those cases the most similar food items or beverages to the one actually consumed were chosen, as listed in the protocol. The iodine values of the items chosen as references will probably not differ significantly from the truth because of small differences in iodine value between the food groups listed in the protocol. The protocol can further have lead to a more accurate description of intake of foods and beverages, and hence iodine, compared to if random items were chosen throughout the coding process. For different food courses that were not found in The Norwegian Food Composition Table, every ingredient was manually coded or a similar product was used. Handling of mixed dishes can lead to error when breaking down the dish into raw ingredients, and this may have led to errors when the actual ingredients used and the amount eaten could be somewhat else (Gibson, 2005). Furthermore, the risk of data entry errors may have increased during this process. Not all food items and beverages in The Norwegian Food Composition Table had a value for iodine and as described in the method section, the value 0 or a value from a similar product was given to these items. Because the exact values for iodine for these items are unknown there might be some foods and beverages that have inaccurate iodine value. Additional information that was collected from the participants during the meeting with researcher (e.g. height and weight, physical activity level and supplement use), as well as urine samples, may however enhance the interpretation of the dietary data (Gibson, 2005). The collection of the food diaries also made it possible to compare the agreement between iodine intakes calculated from the diet with the UIC. The correlation was moderate at the individual level, showed good agreement on the group level, with good agreement between the median calculated intake, median UIC and median intake estimated from UIC.

6.2.3 Food diaries

The assessment of dietary intake is complex and often contains large measurement errors (Baranowski, 2013). One of the main problems with food diaries is information bias where

the participants have under- or overestimated the actually dietary intake, partly due to incomplete recording and/or the impact dietary recording can have on dietary choices, called reactivity, including undereating (Baranowski, 2013; Maurer et al., 2006). Thus, the foods and beverages recorded in the food diaries by the women might be the one actually consumed, but not be representative for the usual diet to the participants (Baranowski, 2013). Foods and beverages that are often underreported includes items that are perceived as unhealthy like cakes, savory snacks, soft drinks, meats, condiments and fat-type spreads, and women tend to more frequently underreport energy intake (Bingham et al., 1995; Krebs-Smith et al., 2000). Susceptibility to social desirability bias where participants are responding in a socially desirable way or is in denial of the actually consumption is another common problem with self-reported dietary intake (Maurer et al., 2006; Thompson & Subar, 2013). Being pregnant can further increase the awareness of nutrition, food habits and supplement consumption, and social desirability bias may be a greater issue in this group (National Institutes of Health, 2007). However, this often applies to assessment of more unhealthy foods like sugar and food high in fat, as well as alcohol (Maurer et al., 2006; Thompson & Subar, 2013). Considering that the highest iodine content is found in what is often perceived as healthy foods as milk and dairy products, fish and eggs, underreporting might only have interfered with the results to a smaller degree (Dahl et al., 2003a). Likewise, the participants in Donexpo was not aware that the food diaries would be used in the present study to assess iodine status, which could have reduced the risk of information bias compared to if they had been exclusively recruited to this study of iodine. The participants were instructed to record the portion size of the foods and beverages eaten or drank but considering that only some of the participants followed this request, some under- or overestimating may have occurred. In addition, the risk that some of the women had problem with conceptualize the portion size cannot be ruled out, which further can have caused miscalculations in the coding process (Cadmus-Bertram & Patterson, 2013; Maurer et al., 2006). On the other hand, no description of portion size would have made it even more difficult to estimate the amount eaten and drank according to the food diaries. Another challenge that occurred during the coding process was the different ways the food diaries were completed. Some of the participants had measured and/or weighed all foods eaten during the two days, including beverages. Others had only described the portion size, and in some cases the only information given about the food consumed was the name and no more information about the content. For instance, one of the participants ate salad both of the days, but no more information was given. The lack of information about the content of the

salad and other foods and beverages or food courses can have affected the results when it was impossible to know the amount and ingredients actually used and consumed.

In an effort to reduce the extent of underreporting or misreporting, all participants were provided with both written and verbal instructions for recordkeeping and they were encouraged to keep usual eating habits during the two days of recording (Baranowski, 2013). In order to avoid the problem with omissions, the participants were asked to record food times and beverages along with the consumption. It is, however, almost impossible to make sure that this was followed and a possible consequence of underreporting or misreport the actual dietary intake can be low energy intake, which further can lead to an underestimation of the iodine intake among the study population (Livingstone & Black, 2003). Although none of the participants had low (or high) energy intake according to the cut-off values (adopted from the MoBa study), one needs to be cautious about the possibly bias with self-reports of diet and some under- or overestimation may have occurred.

When assessing iodine status by calculating the iodine intake from the diet, all major sources need to be taken into consideration. The present study has not considered the contribution from iodized salt or the iodine content in water because the contribution to the intake of iodine are assumed to be limited in the Norwegian diet, and data for iodized salt and drinking water are often lacking (Dahl et al., 2004; Nordic Council of Ministers, 2014). The calculation of iodine intake from food is further complicated because fish, which is one of the major sources of iodine, is normally not consumed every day. The exclusion of some dietary sources of iodine, regardless the contribution size, can cause uncertainties in the interpretation of the results.

6.2.4 Supplement use

Recording of supplement is an important factor in dietary assessment methods because of its nutritional contribution to the total diet, and the participants in the present study were asked to record any use of supplements (Gibson, 2005). Accurately recording of the supplements brand names are of critical importance due to the differences in content. Failure to quantify the correct dose of iodine from a supplement can have great impact on the calculated total iodine intake. A number of the participants reported use of iodine-containing supplements but in many cases the use of supplement was only written down one of the two days of recording. This may have lead to an underestimation in total iodine intake for some of the participants if the supplement actually was used both days. However, the total iodine intake (food and

supplement) seemed to correlate well with the UIC in the pregnant women, which can indicate that the recorded supplements are close to the actually intake. Not all had written the name or brand on the supplement taken so a standard amount of 150 µg I/tablet was used, which may not be the true amount of iodine. However, this applied only for one of the participants and should not have affected the results. Some under- or overestimation of iodine intake may however have occurred due to misreporting of supplement use, which should be taken into consideration when interpreting the results.

6.2.5 Urinary iodine concentration

UIC is the recommended biomarker in evaluating the iodine status in a population (WHO, 2007a). Spot urine samples are simple to obtain and were used in the present study, expressed as the median µg/L. However, several factors may challenge the interpretation of the results and cause analytical biases (Gibson, 2005; Laurberg et al., 2007; Skeaff, 2012). Firstly, UIC can vary greatly from day-to-day in relation to an individual iodine intake, and spot UIC cannot be used to classify iodine status of individuals because it only reflects short-term iodine intake (Als et al., 2000). Multiple spot urine samples are therefore needed to evaluate an individual iodine status (Andersen et al., 2008; Laurberg et al., 2007; WHO, 2007a). Secondly, spot UIC is not interchangeable with 24-hours UIE, which is the recommended measurement, unless the volume of urine passed in 24-hours is one liter (Laurberg et al., 2007). For SAC the urine volume is often one liter, but for an adult, this volume is approximately 1.5 liter a day meaning that median UIE given as µg per 24-hours will be 50% higher than the median UIC given as µg/L (Laurberg et al., 2007). Another reason, of particular importance for this study, is that ingested iodine will appear in the urine around 4-5 hours after a meal and morning spot urine samples will therefore have the lowest concentration of iodine compared to 24-hours UIE (Als et al., 2000; Chen et al., 2016; Knudsen et al., 2000; Rasmussen et al., 1999). Morning urine samples are not representative of the average iodine intake in an individual or a population, which have to be taken into account when interpreting the results. Iodine measurement in morning spot urine samples will, however, results in lower intra-individual variation than spot urine samples collected at random time points and will not be affected by resent food intakes because the samples are collected fasting (Ovesen & Boeing, 2002).

It has further been argued that the time and location of spot urine sampling can affect the results leading to methodological challenges when assessing iodine status with UIC

(Andersen, Sorensen, Krejbjerg, Moller & Laurberg, 2014; Rasmussen et al., 1999). A Danish study from 2014 found that the median UIC differed depending on the time of supplement intake prior to sampling, where the highest UIC was measured the same day as supplement was taken (Andersen, Sorensen, et al., 2014). In the present study, only a few of the participants reported time of supplement intake, and the time span from supplement intake to collection of the urine samples has not been considered. Still, the total iodine intake (food and supplement) correlated well with the UIC, which can indicate that the time of supplement intake only interfered with the findings in the present study to a smaller degree.

In order to adjust for intra-individual variation in the UIC calculated from the two morning spot urine samples, urinary creatinine concentration was used, as well as age- and sex adjusted iodine/creatinine ratio. Age- and sex adjusted iodine/creatinine ratio is a more precise estimate of iodine intake based on spot urine samples than median UIC alone, especially when expected creatinine excretion for pregnant women is used (Knudsen et al., 2000). The use of iodine/creatinine ratio and age- and sex adjusted iodine/creatinine ratio can therefore have given a more correct assessment of iodine status in the pregnant women.

Thirdly, in the present study the excretion of iodine in the urine is calculated to be the same in all trimesters because the results in studies investigating the difference in UIE across pregnancy are conflicting (Azizi et al., 2003; Bath et al., 2015; Fuse et al., 2013). A majority of studies assessing iodine status in pregnant women have focused on early gestation because it is thought to be the most critical time for fetal brain development, and the effect of advancing gestation on UIE is therefore poorly understood (Bath et al., 2015; Morreale de Escobar et al., 2004). Furthermore, there is some evidence indicating that estimation of iodine intake from UIC in pregnancy can be less valid because of the increase in glomerular filtration rate and renal iodine clearance but the evidence is ambiguous (Zimmermann, 2009). One must take into account that the excretion of iodine in the urine might differ between trimesters, which can have influenced the results.

6.2.6 Assessment of urinary iodine concentrations and creatinine concentrations

Urinary iodine is found to be relatively stable and the urine samples should not have been affected if they were not stored in the fridge or the freezer immediately after collection (Soldin, 2002). However, the laboratory in Finland informed about concerns regarding a possible contamination of the instrument used for measuring urinary iodine concentration in our study, which may have resulted in slightly lower values of iodine.

Considering that the creatinine analyzes were conducted on two separate occasions it cannot be excluded that differences have occurred during the analyses. Furthermore, urinary creatinine needs to be stored soon after collection because it may decompose if not stored maximum three days after collection (Soldin, 2002). The participants were instructed to store the urine samples in the fridge or the freezer immediately after collection, but it is uncertain if all the participants followed this request.

7 CONCLUSION AND FUTURE WORK

The findings of the present study indicate mild-to-moderate iodine deficiency in the group of pregnant women in Norway, shown through low intake of iodine from food and a low median urinary iodine concentration, and the study confirms previous findings of inadequate iodine intake in pregnant women in Norway. In regard to the specific objectives:

1. The calculated iodine intake in the pregnant women was lower than NNR5 and WHO recommendations for pregnant women. Milk and dairy products were the main source of iodine from the diet to the pregnant women.
2. Twenty-five percent of the pregnant women reported use of iodine-containing supplement. The total iodine intake (food and supplement) in the group of pregnant women was lower than recommended. Iodine supplement users had an adequate intake of iodine according to NNR5 recommendations, indicating that supplements with iodine is a great contributor to the total iodine intake during pregnancy. The use of iodine-containing supplement was, however, not adequate to ensure an acceptable urinary iodine concentration in the pregnant women.
3. The median urinary iodine concentration in the pregnant women was lower than WHO recommendations for pregnant women. The low median urinary iodine concentration further strengthens the findings of mild-to-moderate iodine deficiency in the pregnant women.
4. A significant correlation was found between total iodine intake (food and supplement) and urinary iodine concentration.
5. A significant difference was found in total iodine intake (food and supplement) between the pregnant women and a control group of non-pregnant women. The result can probably be explained by the intake of iodine-containing supplement in the group of pregnant women. No significant difference in urinary iodine concentration was found between pregnant women and the control group.

The findings of the present study cannot be generalized to the pregnant women in Norway because the women were not randomly selected and the total number of participants was low. A nationally representative study on iodine status in pregnant women is therefore needed to confirm the findings.

Future work

The findings from the present study suggest that the Norwegian health authority should assess iodine status in the population as recommended by WHO, especially among vulnerable groups such as women in childbearing age. If the population or some sub-groups of the population is found to have inadequate iodine intakes, strategies should be implemented in order to prevent an increase in iodine deficiency in the Norwegian population. Iodization of salt and recommendation of iodine-containing supplement are approaches that have been successfully implemented in other European countries, and which the health authority should take into consideration. Considering the higher need of iodine during pregnancy, recommendation of iodine-containing supplements should be the main approach to ensure an adequate intake of iodine in pregnant women. If the government put a high priority on ensuring an adequate iodine status in women in childbearing age, this may benefit the promotion of health and economic development in Norway. Furthermore, healthcare professionals need an increased attention to ensure sufficient iodine status in pregnant women, trough an increased intake of iodine from food and/or supplement. Well-designed, randomized, clinical intervention trials are needed to assess the safety and effectiveness of implementation of iodine-containing supplements in pregnancy, and continuous monitoring of iodine status in the population is needed in order to avoid iodine deficiency or excess.

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Appendix 1 Project description Donexpo

Prosjektbeskrivelse – Norsk delundersøkelse i samarbeidsprosjektet «Experimental study of deoxynivalenol biomarkers in urine»

Sammendrag
Bakgrunn: Muggsopper fra sopper av Fusarium slekten er et problem i kornproduksjon både i Norge og internasjonalt. Klimaendring i retning av mildere og våtere klima har økt problemet. Muggsopper produserer muggsoppgifter (mykotoksiner) som kan utgjøre en helserisiko for mennesker og dyr ved konsum av korn og kornprodukter. Eksponeringsberegninger som er gjort så langt tyder på at vi får i oss mer av noen mykotoksiner enn det som er vurdert som trygt, men beregningene innehar store usikkerheter. Mengden mykotoksiner i urin er et godt mål på eksponeringen. Nivå av mykotoksiner som deoksynivalenol i urin har hittil ikke vært målt i den norske befolkningen. Dette prosjektet omfatter den norske deltakelsen i et samarbeidsprosjekt med partnere i Italia, England og Norge. Prosjekt utgår fra det Det europeiske mattrygghetsorganet (European Food Safety Authority, EFSA) som har bevilget midler til å framskaffe kvalitetssikrede data for human eksponering for mykotoksiner. Folkehelseinstituttet og Veterinærinstituttet er ansvarlige for den norske delen av prosjektet.
Formål: Hensikten med prosjektet er å framskaffe data som viser nivåene av muggsoppgifter, og spesielt deoksynivalenol (DON), og metabolitter av muggsoppgifter i urin fra ulike grupper i den norske befolkningen. Videre å framskaffe data om sammenheng mellom matinntak og nivå av mykotoksin-metabolitter i urin.
Metoder: Prosjektet sikter mot å rekruttere minimum 200 deltakere som er villige til å gi to urinprøver (morgenurin) og svare på et spørreskjema for kartlegging av kostvaner og bakgrunnsfaktorer av betydning for eksponeringsnivå (vedlegg). Deltakerne skal representere ulike grupper av befolkningen og omfatte barn, ungdom, voksne, gravide, eldre og vegetarianere. Urinprøvene skal analyseres ved Veterinærinstituttet som innehar ekspertise og utstyr for å analysere mykotoksin-metabolitter i urin. Datainnsamlingen vil starte våren 2014 og gjennomføres som angitt i søknaden til EFSA.
Deltakere vil bli bedt om å underskrive informert samtykke. Alle data vil behandles avidentifisert. Resultatene, det vil si analyserte nivåer av muggsoppgifter og rapporterte matinntak vil bli innrapportert til EFSA Belastningen på deltakerne er ansett å være relativt liten og det er ingen etiske betenkninger med prosjektet.
Finansiering: Prosjektet har mottatt finansiering fra EFSA etter søknad som ble innvilget i henhold til GP/EFSA/CONTAM/2013/04
Kontaktpersoner:
Folkehelseinstituttet: Anne Lise Brantsæter, seniorforsker
Veterinærinstituttet: Gunnar Sundstøl Eriksen, seniorforsker

Protokoll og prosjektopplysninger

Generelle opplysninger

a. Prosjekt tittel: Undersøkelse av muggsoppgifter i urin.

Norsk delstudie i prosjektet «Experimental study of deoxynivalenol biomarkers in urine» (awarded EFSA grant under the call for proposal GP/EFSA/CONTAM/2013/04.

b. Prosjektleder: Anne Lise Brantsæter, PhD, Seniorforsker, Nasjonalt folkehelseinstitutt, Pb 4404 Nydalen, 0403 Oslo, telefon 21076326, mobil: 91303207, e-post: anne.lise.brantsaeter@fhi.no

c. Forskningsansvarlig Institusjon: Folkehelseinstituttet, Kontaktperson Anne Lise Brantsæter
d. Andre opplysninger: Oppdragsforskning, European Food Safety Authority EFSA.
e. Prosjektmedarbeidere:
    a. Gunnar Sundstøl Eriksen, PhD, Seniorforsker, Veterinærinstituttet, ansvarlig for analyse av muggsoppgifter i innsamlede urinprøver
    b. Silvio Uhlig, PhD, Seniorforsker, Veterinærinstituttet, prosjektmedarbeider analyse
    c. Per-Erik Clasen, Overingeniør, Veterinærinstituttet, prosjektmedarbeider analyse
    d. Helle Katrine Knutsen, PhD, Seniorforsker, Nasjonalt folkehelseinstitutt, prosjektmedarbeider kosthold og databearbeiding

Prosjektopplysninger

Bakgrunn
Mykotoksiner er muggsoppgifter som forurenser korn og kan utgjøre en helserisiko for mennesker ved konsum av korn og kornprodukter. Muggsoppdannelse og mykotoksin produksjon i korn har økt de siste årene som følge av mer fuktig klima. Muggsoppgifter finnes både i norsk og importert korn. En risikorapport fra Vitenskapskomiteen for mattrygghet (VKM) publisert i april 2013 viser at nivået av mykotoksiner(muggsoppgifter) i kornet er et betydelig problem [VKM rapporten tilgjengelig fra http://www.vkm.no/dav/eee04d10c4.pdf]. Særlig har nivået av mykotoksinet DON steget kraftig de senere årene. Dyrestudier har vist at høyt inntak av de mykotoksinene som er et problem i Norge, over tid blant annet kan føre til nedsatt matinntak, vekstreduksjon og svekket immunforsvar. Slike negative effekter på forsøksdyr er en indikasjon på at høyt inntak av mykotoksiner kan være skadelig for mennesker. VKM beregnet at norske barn får i seg for mye DON gjennom brødet og grøten som de spiser. Korn og kornprodukter er viktige matvarer i barna kosthold og de spiser mye i forhold til kroppsvekten. Beregningen antydet at barn får i seg mer mykotoksiner enn det som anses som trygt, men beregningene må underbygges av objektive målinger i human urin.
Rapporten identifiserte at det er stor mangel på data. Per i dag finnes det ingen objektive data som viser human eksponering Norge. Måling av mykotoksin-metabolitter i urin er en etablert metode som Veterinærinstituttet nå har ekspertise til å anvende, men hittil har humant materiale (urin) ikke vært tilgjengelig. Mangel på data har også vært påpekt i Det europeiske mattrygghetsorganet EFSA i forbindelse med eksponeringsberegning og vurdering av øvre grenseverdier for forekomst mykotoksiner i matvarer. EFSA utlyste derfor i 2013 midler til innsamling av mer data om eksponering for mykotoksiner i Europeiske befolkninger, inkludert analyse av mykotoksin-metabolitter i urin. For best mulig utnyttelse av urin-data vil vi også analysere konsentrasjonen av kreatinin og grunnstoffer.. Veterinærinstituttet og Folkehelseinstituttet bidro som norske partnere i en søknad om midler til å framskaffe slike data og søknaden ble innvilget (vedlegg).

Formål
Formålet med prosjektet er å framskaffe data som viser nivåene av muggsoppgifter, spesielt deoxinivalenol (DON) og metabolitter av denne i urin fra 200 deltakere som representerer ulike grupper i den norske befolkningen.
Prosjektet inngår i et samarbeidsprosjekt med England og Italia (vedlegg). Data som framskaffes skal være av høy kvalitet og skal rapporteres til Det europeiske mattrygghetsorganet EFSA.

Delmål:

1. Å rekruttere 200 deltakere i Norge som representerer ulike aldersgrupper og undergrupper av befolkningen (små barn, barn/ungdom, voksne, eldre, gravide og vegetarianere)
2. Å kartlegge deltakernes inntak av matvarer som bidrar til eksponering for mykotoksiner, spesielt deoxinivalenol
3. Å analysere konsentrasjonen av muggsoppgifter i urinprøver fra deltakerne
4. Å undersøke hvilke matvarer som har betydning for nivået av disse stoffene i urin
5. Å gjennomføre datainnsamling og analyse i henhold til EFSA's krav til prosjektet og ved å benytte samme metodikk som i de andre deltakerlandene i prosjektet.

Forskningsdata
Forskningsdata vil omfatte:

1. Analyserte verdier av muggsoppgifter i urinprøver fra deltakerne.
2. Data på individnivå for konsum av kornbaserte matvarer av betydning for eksponering for muggsoppgift og data på individnivå for alt matinntak over to dager.
3. Selvrapportert personlig informasjon om alder, kjønn, vekt, høyde, aktivitetsnivå og eventuelle kostrestriksjoner av betydning for eksponeringsnivå.

Nye helseopplysninger: Kjønn, alder vekt, høyde, aktivitetsnivå og eventuelle kostrestriksjoner av betydning for eksponeringsnivå og urin-konsentrasjon.
Humant biologisk materiale: urin
Klinisk undersøkelse: å motta to urinprøver fra hver deltaker
Spørreskjema: Deltakelse i prosjektet innebærer å svare på et spørreskjema som omfatter spørsmål om matvaner og informasjon om alder, kjønn, vekt, høyde, aktivitetsnivå og eventuelle kostrestriksjoner av betydning for eksponeringsnivå og urin-konsentrasjon (vedlegg).
Begrunnelse for valg av data og metode: Metodene i prosjektet er valgt i henhold til EFSA's utlysning GP/EFSA/CONTAM/2013/04. Spørreskjemaet og metodikk for urinanalyse skal harmoniseres mellom deltakerlandene Norge, Italia og England. Veterinærinstituttet har utstyr og ekspertise for analyse av mykotoksiner i urin. Kvalitetssikring og validering av analysemetode inngår i prosjektet. Analysemetodene vil bli harmonisert med de tre deltagende laboratoriene og vil bli basert på metoden publisert og validert av det ene deltagende laboratoriet (University of Leeds, UK). Metoden er basert på en LC-MS metodikk og alle prøvene vil bli analysert med og uten enzymatisk dekonjugering for bestemmelse av andel en av konjugerte toksinmetabolitter.

Utvalg
Allmennbefolkning: menn, kvinner (inkludert gravide) og vegetarianere. Gravide inkluderes spesielt fordi svangerskapet er en spesielt sårbar periode og vegetarianere inkluderes spesielt fordi disse er forventet å ha høyere konsum av kornbaserte matvarer
Mindreårige med mangelfull samtykke kompetanse – under 12 år: Foreldre må gi samtykke for barn under 16 år, men barna skal selv få uttale seg om de ønsker å delta og barn fra 12 år og eldre skal underskrive samtykke-erklæringen i tillegg til en av foreldrene.

Antall forskningsdeltakere
Antall forskningsdeltakere er basert på avtalen med EFSA. Målet er å rekruttere minimum 200 deltakere i Norge med like mange av hvert kjønn og fordelt på disse gruppene:

-Barn 3-9 år: 30 deltakere
-Barn og ungdom 10-17 år: 30 deltakere
-Voksne 18-64 år: 30 deltakere
-Voksne 65+ år: 30 deltakere
-Vegetarianere: 40 deltakere
-Gravide: 40 deltakere

Informasjon om rekruttering, samtykke og personvern
Av praktiske årsaker ønsker vi å rekruttere deltakere først og fremst med utgangspunkt i ansatte ved Folkehelseinstituttet og Veterinærinstituttet og deres familier. Dette fordi urinprøver skal innhentes fra to ulike dager og deltakere som arbeider på instituttet vil ha mulighet til å ta med prøven og levere til prosjektmedarbeider ved arbeidsdagens begynnelse. Det skal ikke etterspørres om sensitiv personlig informasjon utover kosthold, vekt, høyde og aktivitet.
For å sikre tilstrekkelig antall deltakere av begge kjønn i alle undergrupper vil vi i tillegg søke om å få rekruttere *små barn* via kontaktperson i foreldreutvalget i en barnehage på Østlandet og *større barn* via kontaktperson i foreldreutvalget på en skole på Østlandet. *Gravide* vil bli rekruttert i samarbeid med jordmødre ved Ullevål eller Bærum sykehus, og *vegetarianere* vil bli rekruttert i samarbeid med kontaktperson i Adventistmiljøet i Oslo. Det er ikke viktig at prøvene samles fra en representativ gruppe av hele befolkningen, men at vi får best mulig kunnskap om eksponeringen i ulike aldersgrupper og livsfaser blant dem som deltar.
Alle deltakere vil få skriftlig og muntlig informasjon om formålet med studien og hva deltakelse innebærer for dem. De som deretter velger å delta vil bli bedt om å underskrive samtykke-erklæringen (vedlegg).
Deltakere vil få en egen studie-identifikasjons id og alle data vil være avidentifisert fram til datainnsamling er over og deretter anonymiseres. Kodenøkkel for identifisering vil kun være tilgjengelig for prosjektleder og slettes senest når prosjektperioden er fullført (10.02.2018).

Forskningsetiske utfordringer ved prosjektet
Fordeler: Prosjektet er av stor betydning og gi viktig kunnskap om eksponering for muggsoppgifter i ulike aldergrupper i den norske befolkningen. Prosjektet vil bidra til å framskaffe data på et felt der det er stor mangel både i Norge og Europa.
Ulemper: Deltakelse innebærer relativt liten belastning, men det kan oppleves tidkrevende å rapportere matinntak, men noen kan oppleve ubehag ved håndtering av urinprøver.
Tiltak: Alle data vil behandles avidentifisert fram til datainnsamling er over og deretter anonymiseres.
Forsvarlighet: Det er få forskningsetiske utfordringer ved prosjektet.

Sikkerhet, interesser og publisering
Personidentifiserbare opplysninger. All informasjon vil behandles konfidensielt, alle data vil avidentifiseres. Kun prosjektleder har tilgang til kodenøkkel som knytter opplysninger til personnavn
Internkontroll og sikkerhet: Personidentifiserbare opplysninger finnes kun i form av kodenøkkel som knytter opplysninger til personnavn. Alle andre opplysninger vil behandles avidentifisert. Det er bare prosjektleder som har tilgang på kodenøkkelen som knytter opplysninger til personnavn, og denne vil oppbevares i låst arkiv. Kodenøkkelen vil bli slettet når datainnsamlingen avsluttes. Etter dette vil innhentede data og analyseresultater kun foreligge anonymisert og benyttes etter interne retningslinjer fram til prosjektslutt (10.2.2018).

Finansiering
Finansieringen dekker de utgifter som skissert fra Veterinærinstituttet og Folkehelseinstituttet og overføres via prosjektansvarlig partner i den internasjonale delen av prosjektet som er Istituto Superiore di Sanità (ISS) i Roma.
Forskningsdeltakerne vil ikke motta økonomisk kompensasjon.

Publisering
Resultater fra den norske datainnsamlingen skal rapporteres til EFSA i henhold til avtale med alle partnere i konsortiet. Norske data skal benyttes i forskningsartikler og andre fagpublikasjoner som utgår fra Veterinærinstituttet og Folkehelseinstituttet.

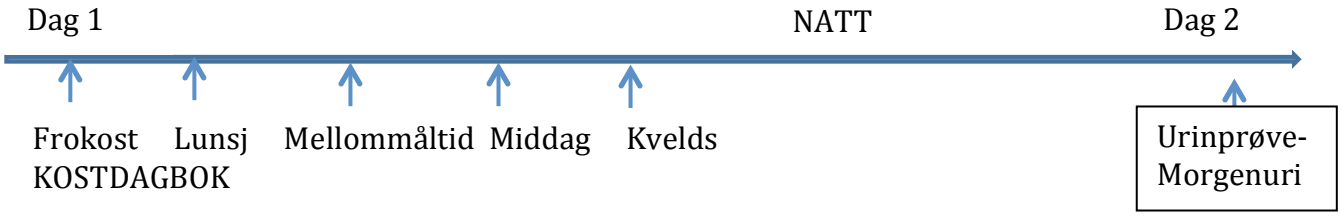
Tidsramme
Prosjektet fikk bekreftet tildeling av midler fra EFSA i desember 2013. Planlegging av harmoniserte metoder for innsamling av kostdata startet umiddelbart. Offisiell start markeres med et prosjektmøte (Kick-off møte) i Parma (EFSA-hovedkvarteret) 10. februar 2014 der partnerne fra Italia, Norge og England vil møtes sammen med representanter fra EFSA. Datainnsamling og urinanalyse skal være ferdig i løpet av 12 mnd, nøkkel til personidentifisering vil slettes senest ved prosjektslutt 10.02.2018. Etter prosjektslutt vil kun anonymiserte data foreligge, og disse vil bli slettet når informasjonen ikke lenger er av betydning for videre vitenskapelig publisering.
Prosjektstart: 10. Februar 2014
Prosjektslutt: 10. Februar 2018

Appendix 2 Instruction

INSTRUKSJON

Denne kostdagboken skal brukes til å registrere all mat fra du står opp om morgen til du legger deg om kvelden. Dette gjelder for begge dagene før du samler morgenurinprøve. Denne studien handler ikke om hvorvidt du spiser sunt eller ikke, men at du spiser mest mulig slik du vanligvis gjør.

PLAN FOR DATAINNSAMLINGEN: Må gjennomføres to påfølgende dager



I dagboken ber vi deg skrive dag og dato og deretter å notere alt du spiser og drikker i løpet av dagen før du samler morgenurin-prøven. Det er best om mengde kan angis i vekt, men hvis du ikke har vekt kan du angi enhet (f eks en skive, ett glass). **Skriv også opp kosttilskudd som tran, vitamintilskudd, mineraltilskudd etc.**

For brød, middagsporsjoner og drikke ber vi deg angi om du anser mengde spist som en liten, middels eller stor porsjon. For sammensatte retter kan du gjerne bruke flere linjer.

For urinprøvene: samle urinen om morgenen med en gang du våkner. Om du må tisse før du trenger å stå opp er det den første urinen du skal samle. Benytt en ny flaske til hver prøve og noter dato og klokkeslett. Flaskene er merket med Prøve 1 og Prøve 2.

Detaljer for hvordan urinprøven skal samles:

1. Vask hendene med såpe og vann, og tørk dem.
2. Skru av lokket på flasken og ta ut den ekstra forseglingen.
3. Avgi urinen direkte i plastflasken. Pass på at du ikke fyller flasken mer enn halvfull.
4. Legg tilbake forseglingen og skru lokket på flasken, sjekk at lokket er skrudd godt til.
5. Noter dato på etiketten utenpå flasken.
6. Oppbevar flasken(e) i kjøleskapet til du skal levere den til.

På neste side er et eksempel på registrering:

Dag og dato: _Tirsdag 23. september 2014__

Tid	Matvare	Detaljer	Mengde, angi om det er liten, middels eller stor porsjon		Økologisk
7.30	Appelsinjuice	Fra kartong, Synnøve	1 lite glass (1,2 dl)	Liten	
	Havregrøt av 1,5 dl havre gryn og 3 dl lettmelk	Store havregryn, Axa	1 stor tallerken 340 gram	Stor porsjon	
	Sukker på grøten	Vanlig hvitt	1 ts		
	Kaffe	Filterkaffe	1 krus (2 dl)	Middels	
	Melk, ekstra lett lettmelk		1 stort glass (2 dl)	Middels	
	Tran	Møllers	1 spiseskje		
10.30	Knekkebrød	Husmann, rug fullkorn	2 stk	Middels	
	Smør, bremykt	Tynt lag	3 gram		
	Brunost	G35	To skiver, 20 g totalt	Middels	
12.00	Brødskiver	Kornbrød grovt brød, mest hvetemel	2 tykke skiver, 60 gram totalt	Middels	X (=Ja)
	Smør, bremykt	Tynt lag på begge	6 gram		
	Jarlsberg ost		To skiver, total 18 g		
	Servelat		1 skive, 9g		
	Agurk	Rå	2 skiver		
	Te	Vanlig tepose	2 dl vann, 1 pose	Middels	
15.30	Eple	Grønt, med skall	1 middels stort	Middels	
16.30	Middag: To poteter	Skrelt og kokt	2 middels ca 150 g	Middels	
	Lakseskiver	Fra frysedisk, 2 stk pakket individuelt	Vekt før tilbereding: 100 g per stykke	Middels	
	Rømmesaus	Rømme, løk og urter	3 spiseskjeer		
	Salat	Salat laget av issalat, agurk, og rocculasalat	1 stor porsjon, 60 g		
	Vann	Fra springen	2 glass, 4 dl		
19.00	Kaffe	Filterkaffe	1 kopp, 1,5 dl		
	Bolle	Gjærbakst, bakt med hvetemel, siktet	2 stk, 80 g		
22.00	Brødskive	Flerkorn brød Bakers, Grovhet: 45%. Ingredienser: hvetemel, sammalt hvete (12,7 %), rug (10,0 %), havre helkorn (3,6 %), havremel (3,6 %)	1 tykk skive, 35 g		
	Brie ost		2 tykke skiver		

Det er satt av tre sider til hver dag. Har du spørsmål underveis kan du ringe Nina eller Kristine på telefon: 90638258 eller 41452222

Appendix 3 Background form

BAKGRUNN OG KOSTVANER

ID KODE: limes i høyre hjørne

PERSONLIG INFORMASJON:

Navn:
Født: (dag/mnd/år):
Kjønn: Mann Kvinne
Høyde (cm):
Vekt (kg):

Røykevaner
Røyker ikke: [ ]
Av og til: [ ]
Daglig: [ ]

Aktivitetsnivå Velg det som best beskriver ditt nåværende daglige aktivitetsnivå:
[ ] Stillesittende/Veldig lavt
[ ] Lett
[ ] Moderat
[ ] Høyt
[ ] Eksepsjonelt høyt
FORKLARING TIL AKTIVITITETSNIVÅ:
STILLESITTENDE/VELDIG LAVT: veldig lite eller ingen aktivitet (sittende og stående aktivitet, lett husarbeid (stryke, lage mat, feie gulv), bilkjøring, arbeid ved datamaskin eller på laboratorium, spille musikkinstrument.
LETT: Lett aktivitet eller sport 1 til 3 ganger per uke (Rolig gange uten motbakker, mekanisk arbeid, lett dans, snekkerarbeid, stående og gående arbeid, servering, rengjøring, barnepass, golf, seiling og bordtennis)
MODERAT: Moderat aktivitet eller sport 3 til 5 ganger per uke (Rask gange, hagearbeid, tunge løft, sykling, tennis, dansing, slalåm)
HØYT: Hard aktivitet eller sport 6 til 7 ganger per uke (hoppe tau, tungt fysisk arbeid, ballspill, fotball, jogging, langrenn)
EKSEPSJONELT HØYT: Virkelig hard daglig aktivitet eller sport tilsvarende to harde treningsøkter daglig (idrett på toppnivå)

Har du spesielle restriksjoner i kostholdet ditt?
Nei:
Ja: Hvis ja, vennligst spesifiser_____ _

Bare for vegetarianere:
Hvor lenge har du praktisert et vegetarisk kosthold? (antall år) _____

Bare for gravide:
Svangerskapsuke nå ved datainnsamling: _____

Antall tidligere svangerskap (sett kryss):
[ ] 0 (ikke vært gravid tidligere)
[ ] 1 (ett tidligere svangerskap før dette)
[ ] 2-3
[ ] 4 eller mer

Bruker du noen gang økologisk mat?

Økologisk matvare	Sjelden/aldri	Noen ganger	Ofte	For det meste
Melk, melkeprodukter, ost	☐	☐	☐	☐
Brød og kornprodukter, f eks mel, müsli	☐	☐	☐	☐
Egg	☐	☐	☐	☐
Grønnsaker	☐	☐	☐	☐
Frukt	☐	☐	☐	☐
Kjøtt	☐	☐	☐	☐

Appendix 4 Consent form

UNDERSØKELSE AV JODKONSENTRASJON I URIN

folkehelseinstituttet

HØGSKOLEN I OSLO OG AKERSHUS

Veterinærinstituttet
Norwegian Veterinary Institute

Forespørsel om deltakelse i forskningsprosjektet:
"Undersøkelse av jodkonsentrasjon i urin hos gravide og vegetarianere"

Bakgrunn og hensikt
Jod er et viktig sporstoff for produksjonen av stoffskiftehormoner, som er nødvendig for at skjoldbruskkjertelen fungerer. Det finnes få studier her i Norge om jodinntak hos vegetarianere og gravide. Derfor ønsker vi å undersøke dette nærmere i våre masteroppgaver. Dette er en forespørsel til deg om å delta i en studie hvor vi ønsker å finne ut hvor mye jod gravide og vegetarianere får i seg gjennom kostholdet. Dette kan undersøkes ved å analysere mengden jod i prøver av urin. Studien vil også framskaffe data om matvarers betydning for mengde jod i urinen. Studien inngår i en del av en større undersøkelse ved Folkehelseinstituttet. Kunnskapen er nyttig i videre arbeid for å kartlegge inntak av jod hos vegetarianere og gravide.

Hva innebærer studien for deg?
Deltakelse i denne studien innebærer at du kan levere to urinprøver og svare på et bakgrunnsskjema. De to urinprøvene skal tas om morgenen på to ulike dager. I tillegg ber vi deg registrere fortløpende maten du spiser de to dagene *før* du tar urinprøve i en kostholdsdagbok.

Mulige fordeler og ulemper
Studien vil kunne gi deg informasjon om ditt jodinntak. Deltakelse innebærer å avgi urinprøver og å bruke tid til å rapportere kostvaner, hvilket kan oppleves noe belastende.

Hva skjer med prøvene og informasjonen om deg?
Prøvene du gir fra deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun prosjektledere som har adgang til navnelisten og som kan finne tilbake til deg.

Personvern

All informasjon om deg vil behandles konfidensielt, og kodenøkkelen som kan identifisere deg med de innsamlede opplysningene vil bli slettet når prosjektperioden er avsluttet. Etter dette vil opplysninger og analysesvar kun foreligge anonymisert.

UNDERSØKELSE AV JODKONSENTRASJON I URIN

folkehelseinstituttet HØGSKOLEN I OSLO OG AKERSHUS Veterinærinstituttet Norwegian Veterinary Institute

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. **Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side.**
Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke. Dersom du senere ønsker å trekke deg eller har spørsmål til studien kan du kontakte prosjektleder Kristine Nyheim (41452222) eller Nina Johansen (90638258).

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre kodenøkkelen er slettet eller opplysningene brukt i vitenskapelige sammenheng.

Nærmere opplysninger om undersøkelsen kan fås ved henvendelse til prosjektledere Kristine Nyheim og Nina Johansen, tlf 41452222 eller 90638258, e-post: kristinen91@hotmail.com eller nina_c_johansen@hotmail.com.

Vennlig hilsen
Kristine Nyheim og Nina Johansen
Høgskolen i Oslo og Akershus
Postboks 4 St. Olavs plass

Samtykke til deltakelse i studien

Jeg har mottatt skriftlig informasjon om studien «**Undersøkelse av jodkonsentrasjon i urin hos gravide og vegetarianere**» og er villig til å delta i studien

---

(Signert av prosjektdeltaker, dato)

NAVN: _____

ADRESSE:_____

E-postadresse:_____

Mobiltelefon:_____

Dersom deltakelsen gjelder ditt barn (for barn< 12 år):
Stedfortredende samtykke dersom barnet er innforstått med å delta

---

(Signert av foreldre, dato)

Dersom deltakelsen gjelder ditt barn (for barn 12-16 år):
Stedfortredende samtykke i tillegg til barnet selv, dersom barnet ønsker å delta

---

(Signert av barnet selv, dato) (Signert av foreldre, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Appendix 5 Example - coding process

1	matkode	mat	Iodine_µg
2	1001	Milk, whole milk, 3,5 % fat	20
3	1002	Milk, semi-skimmed, 1,2 % fat	20
4	1003	Milk, skimmed	19
5	1008	Milk beverage, chocolate flavour	18
6	1013	Milk, goat, UHT-treated	60
7	1079	Milkshake, chocolate flavour	17
8	1082	Milk, cultured, plain, organic	20
9	1083	Milk, whole milk, cultured, Kulturmelk	20
10	1084	Milk, whole milk, cultured, Kefir	20
11	1085	Milk, skimmed, cultured, Skummet kulturmelk	20
12	1104	Milkshake, strawberry flavour	15
13	1109	Milk, for coffee, 3,5 % fat	20
14	1118	Milk, 1,2 % fat, lactose reduced	20
15	1119	Milk, 1,2 % fat, UHT-treated	20
16	1127	Milk beverage, with chocolate flavour, Litago	15
17	1170	Milk, low-fat, cultured, Biola	20
18	1171	Milk, skimmed cultured, blueberry, Biola	16
19	1192	Milk, semi-skimmed, 0,7 % fat, with vitamin D	20
20	1196	Cocoa, prepared with low-fat milk	18

Example of milk and dairy products as listed in The Norwegian Food Composition Table (2015).

ID person	Matvarekode	Mengde, g	Dag
22	5342	30	1
22	8102	6	1
22	6763	35	1
22	5217	70	1
22	5291	15	1
22	5342	60	1
22	8102	12	1
22	3106	12	1
22	8009	8	1
22	3157	27	1
22	6779	275	1
22	3309	236	1
22	6738	40	1

Example of the coding process in Excel.

Appendix 6 Protocol

Foods/beverages	Code	Name	Explanation
Milk and dairy products			
Milk	1002	Lettmelk	If not specified
Butter	8102	Bremykt	If not specified
"Brunost"	1052	Geitost, brunost	If not specified
Cheese	1039	Norvegia	If not specified
"Rømme"	1087	Lettrømme	If not specified
Ice cream	1018	Iskrem, fløtebasert	If not specified
Philadelphia	1150	Kremost, naturell	Not in FCT
Meat, chicken and fish			
Chicken	3242	Kylling, brystfilet, stekt i fett	If not specified
Minced meat	3138	Kjøttdeig, stekt uten fett	If not specified
Salmon	4226	Laks, oppdrett, skiver, stekt i fett	If not specified
Tuna	4108	Tunfisk, i vann, avrent, hermetisk	If not specified
"Fiskekaker"	4061	Fiskekaker, kjøpt	If not specified
Ham	3106	Kokt skinke	If not specified
Egg	2027	Egg, fra frittgående høns, kokt	If cooked
Egg	2021	Egg, fra frittgående høns, rå	If raw
Fiskegrateng	4292	Fiskegrateng, med egg og makaroni, ovnsstekt	
"Kaviar"	4089	Kaviar, av torskerogn	
Bread, rice, pasta, pastry			
Pasta	5130	Pasta, naturell, makaroni/spagetti o.l, kokt	If cooked
Rice	5337	Ris, Basmati, kokt	If not specified
Müsli	5236	Kornblanding, med frukt, type Go´dag Fruktmüsli	If not specified
Bread	5341	Brød, halvgrovt (25-50%), uspesifisert, kjøpt	If halvgrovt, not specified
Bread	5342	Brød, grovt (50-75%), uspesifisert, kjøpt	If grovt, not specified
Bread	5343	Brød, ekstra grovt (75-100%), uspesifisert, kjøpt	If ekstra grovt, not specified
Nan bread	5188	Pitabrød, fint, kjøpt	Not in FCT
Tortilla/tacolefse	5371	Tortilla, wraps, hvetemel, type Santa Maria	If not specified
Hamburger bread, grovt	5341	Brød, halvgrovt (25-50%), uspesifisert, kjøpt	Not in FCT

Knekkebrød m/frø og kjerner	5143	Knekkebrød, ekstra fiber	Not in FCT
Waffle	5085	Vafler, med egg, helmelk	If not specified
Pain au chocolate	5312+9017	Croissant, uten fyll, kjøpt + melkesjokolade	Not in FCT
"Bolle"	5217	Hveteboller, uten rosiner, kjøpt	If not specified
Chocolate cake	5108	Sjokoladekake, med glasur	
Chocolate	9017	Melkesjokolade	If not specified
Pizza	3203	Pizza, med kjøtt, fryst, kjøpt	
Pizza Italian style/vegetarian	6734	Pizza, med tomatsaus og ost	
Others			
"Vingummi"	9128	Geléfrukter, type Seigmenn	
"Lakris"	9030	Lakris, søt	If not specified
Oil	8112	Olivenolje, Extra Virgin, Jomfruolje	If not specified
Mayonnaise	8009	Majones, ekte	
Mayonnaise, light	8011	Majones, lett, 40% fett	
"Rekesalat"	8014+4098	Majonessalat, ekte majones, 45% fett + Reker, i lake, avrent	Not in FCT
"Italiensk salat"	8014	Majonessalat, ekte majones, 45% fett	Not in FCT
Pesto	6144	Pesto, grønn, kjøpt	
Tomato saus	6706	Grønnsaksrøre, med tomat, Ratatouille	If specified with vegetables
Tomato saus	6070+6038 +6042	Tomat, hermetisk + Hvitløk, rå + Løk, gul/rød, norsk, rå	
Jam	6763	Syltetøy, 60% bær, 30% sukker	If not specified
Potato	6096	Potet, lagringspotet, kokt med skall	If not raw
Salad	6058	Bladsalat, norsk, rå	If not specified
Olives	6611	Oliven, sorte, i olje, hermetisk	If not specified
Tacosaus	6141	Tacosaus, medium, type Santa Maria	If not specified
Tacokrydder	12112	Taco kryddermix, type Santa Maria	If not specified
Soltørkede tomater	6103	Tomater, soltørkede innlagt i olje, avrent	
Linser	6130	Linser, grønne, hermetiske	If not specified
Bønner	6133	Bønner, røde, kidney, hermetiske	If not specified

Appendix 7 Application – REK

Prosjektendring Skjema for søknad om godkjenning av prosjektendringer i de regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK)

2014/207-8
Dokument-id: 602178 Dokument mottatt 18.05.2015

Undersøkelse av muggsoppgifter i urin (2014/207)

1. Generelle opplysninger

a. Prosjektleder

Navn:	Anne Lise Brantsæter
Akademisk grad:	PhD
Klinisk kompetanse:	Autorisert klinisk ernæringsfysiolog
Stilling:	Seniorforsker
Hovedarbeidsgiver	Nasjonalt folkehelseinstitutt
Arbeidsadresse:	Pb 4404 Nydalen
Postnummer	0403
Sted	Oslo
Telefon	21076326
E-post adresse	anne.lise.brantsaeter@fhi.no

b. Prosjekt

Hvilket prosjekt skal endres?	Undersøkelse av muggsoppgifter i urin (2014/207)

c. Ny Prosjektleder?

Skal prosjektet ha ny prosjektleder?	Nei

d. Forskningsansvarlig(e)

Forskningsansvarlig(e) som beholdes

Institusjon	Kontaktperson	Stilling	E-post adresse
Nasjonalt folkehelseinstitutt	Anne Lise Brantsæter	Seniorforsker	anne.lise.brantsaeter@fhi.no

e. Prosjektmedarbeider(e)

Prosjektmedarbeider(e) som beholdes

Navn:	Stilling:	Institusjon:	Akademisk rolle:	Rolle:
Gunnar Sundstøl Eriksen	Seniorforsker	Veterinærinstituttet	PhD	Ansvarlig for analyse av muggsoppgifter i innsamlede urinprøver
Helle Katrine Knutsen	Seniorforsker	Folkehelseinsituttet	PhD	Prosjektmedarbeider
Silvio Uhlig	Seniorforsker	Veternærinstituttet	PhD	Prosjektmedarbeider
Per-Erik Clasen	Overingeniør	Veterinærinstituttet	Cand Scient	prosjektmedarbeider urinanalyse

Ny(e) prosjektmedarbeider(e)

Navn	Stilling	Institusjon	Akademisk rolle	Rolle
Sigrun Henjum	Førsteamanuensis	Høyskolen i Oslo og Akershus	PhD	Medarbeider i delundersøkelse av jod i urin hos deltakerne
Kristine Aastad Nyheim	Masterstudent	Høyskolen i Oslo og Akershus	Bachelor	Masterstudent som skal bruke data fra undersøkelsen i sin masteroppgave

2. Endring(er)

a. Endringen(e) innebærer

Ny(e) prosjektmedarbeider(e) som angitt

Økning i antall forskningsdeltakere

Antall nye deltakere relatert til prosjektets utvalgsgrupper

I forbindelse med tilleggsundersøkelse av konsentrasjonen av jod i urin hos deltakerne i dette prosjektet ønsker vi å rekrutterere ytterligere 20 vegetarianere og 10 gravide slik at disse undergruppene vil inkludere 50 deltakere i hver gruppe.

Hovedprosjektets mål er undersøkelse av muggsoppgifter i urin, men tilleggsundersøkelse av jod og eventuelt andre stoffer i urin var allerede inkludert i opprinnelig forsøksprotokoll, informasjonsmateriell til deltakerne og samtykke-erklæring.

Endring i rekrutteringsprosedyre(r)

Redegjør nærmere for ny(e) rekrutteringsprosedyre(r)

Dersom prosjektet gis tillatelse til rekruttere flere deltakere ønsker vi å rekruttere disse blant studenter og ansatte ved Høyskolen i Oslo og Akershus. Rekruttering vil foregå viaintranett og gjennom oppslag på samme måte som opprinnelig rekruttering ble gjort via intranett og oppslag på Folkehelseinstituttet og Veterinærinstituttet

b. Begrunnelse for endringen(e)

Praktisk, faglig og vitenskapelig begrunnelse for endringen(e)

Dersom deltakerantallet i gruppen "Vegetarianere" og gruppen "Gravide" økes til 50 vil det vil styrke muligheten til å gjøre statistiske sammenlikninger og vitenskapelig publisering.

3. Avveining av nytte og risiko ved prosjektendringene

Hvorfor er det forsvarlig å gjennomføre endringene? Gi en begrunnet avveining av fordelene og ulempene ved prosjektendringene.

Det er forsvarlig å gjennomføre endringene fordi denne studien innbærer liten belastning for deltakerne. Fordelen er at flere deltakere gir økt mulighet til å gjøre statistiske analyser og vil gi ny masterstudenten innsikt og erfaring i rekruttering og gjennomføring av datainnsamlingen.

4. Vedlegg

Ingen vedlegg

5. Ansvarserklæring

Jeg erklærer at prosjektet vil bli gjennomført

- i henhold til gjeldende lover, forskrifter og retningslinjer
- i samsvar med opplysninger gitt i denne søknaden
- i samsvar med eventuelle vilkår for godkjenning gitt av REK

Appendix 8 Approval from REK

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Hege Holde Andersson	22845514	21.05.2015	2014/207/REK sør-øst B
			Deres dato:	Deres referanse:
			18.05.2015	

Vår referanse må oppgis ved alle henvendelser

Til Anne Lise Brantsæter
Nasjonalt folkehelseinstitutt

2014/207 Undersøkelse av muggsoppgifter i urin

Forskningsansvarlig: Nasjonalt folkehelseinstitutt
Prosjektleder: Anne Lise Brantsæter

Vi viser til søknad om prosjektendring datert 18.05.2015 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i REK sør-øst på delegert fullmakt fra REK sør-øst B, med hjemmel i helseforskningsloven § 11.

De omsøkte endringene er beskrevet i skjema for prosjektendringer og dreier seg om to nye medarbeidere i prosjektet. I tillegg ønsker man i forbindelse med tilleggsundersøkelse av konsentrasjonen av jod i urin hos deltakerne å rekrutterer ytterligere 20 vegetarianere og 10 gravide slik at disse undergruppene vil inkludere 50 deltakere i hver gruppe.

Komiteens vurdering
Komiteen har ingen innvendinger til de omsøkte endringene.

Vedtak
Komiteen har vurdert endringsmeldingen og godkjenner prosjektet slik det nå foreligger med hjemmel i helseforskningsloven § 11.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i endringsmeldingen.

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.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Knut W. Ruyter

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

avdelingsdirektør
REK sør-øst

Hege Holde Andersson
komitésekretær

Kopi til: Nasjonalt folkehelseinstitutt ved øverste administrative ledelse: reksoknad@fhi.no