Faculty of health sciences / Department of community medicine

The effects of selected toxic elements on birth weight. The Norwegian Mother and Child contamination cohort study (MISA study)

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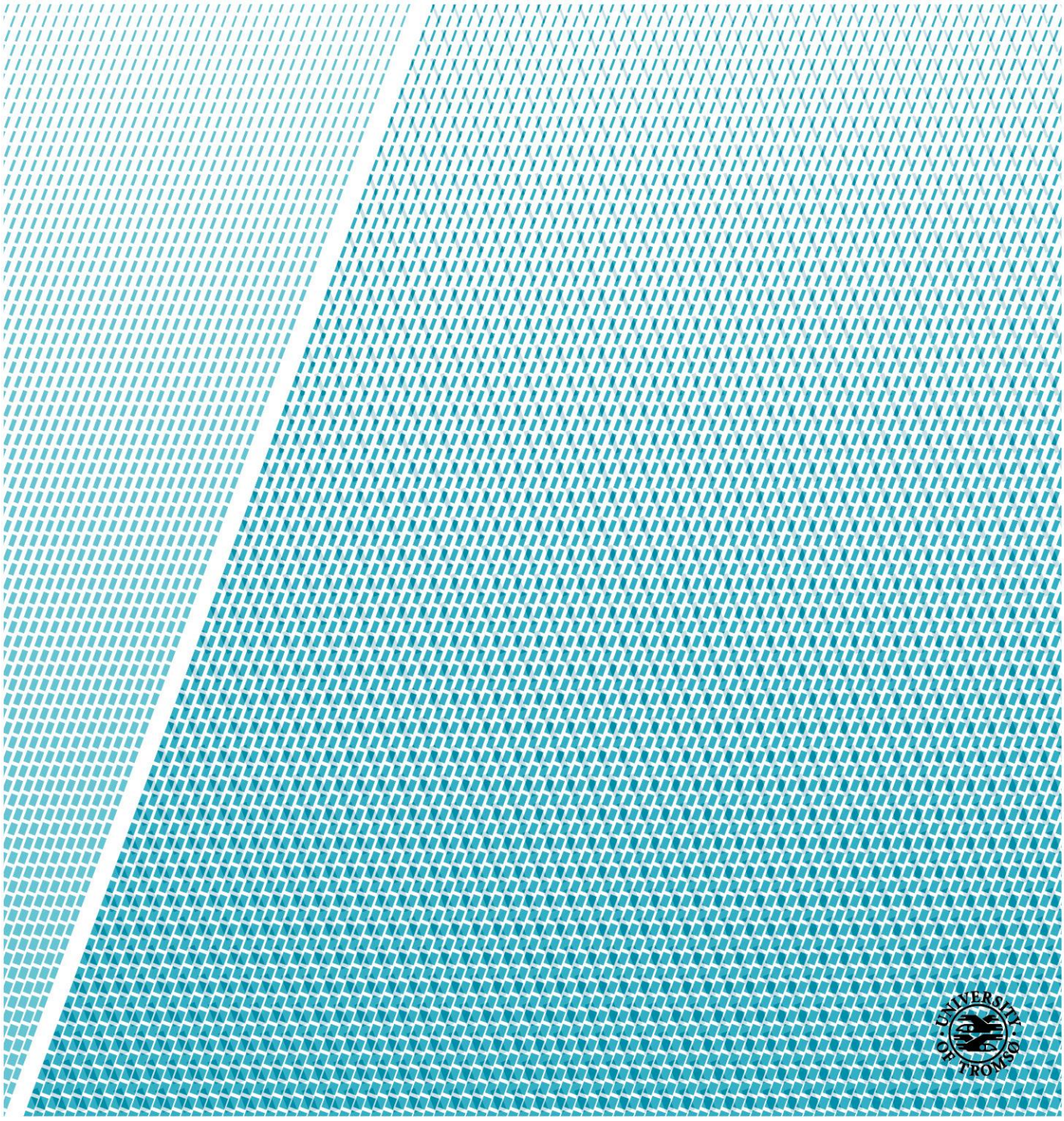

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Abstract

Background

Birth weight is an important indicator for predicting newborn baby's health. Particular toxic elements: lead (Pb), arsenic (As), mercury (Hg), cadmium (Cd) have ability to cross the transplacental barrier and effect the fetal growth and development. These toxic elements exposure during pregnancy have been associated with negative birth outcomes like low birth weight (LBW).

Objectives

The objective of this study was to conduct the assessment of selected toxic elements (Pb, Hg, As and Cd) in the mother's blood sample during the gestational period and their effects on birth weight.

Methods

A subset of 282 pregnant women who delivered their babies from the North Norwegian Mother-and-Child Study (MISA) was included in our study. The participants completed a detailed self-reported information questionnaire supplied by MISA study. Blood samples were collected during the 2nd trimester (P1) and 3rd postpartum (P2) in different regions of Northern Norway, and were analyzed for four selected toxic elements. Both univariate and multivariate analyses were conducted, birth weight was adjusted for a range of potential confounders.

Results

In multivariable model, we revealed that an increasing maternal blood Pb concentration negatively influenced birth weight in baby girls (p-value=0.009). Moreover, elevated maternal blood Cd concentration increased the chances of reduced birth weight in baby boys (p-value=0.045) when adjusted for alone. We also found all the toxic elements peaked at P2 except Hg which is at the P1 time period.

Conclusion

The present study found a significant inverse association between maternal Pb concentration and birth weight in female neonates only. The negative correlation of maternal Cd concentration with birth weight is observed in male neonates but not in female neonates. These significant correlations confirm the potential for sex response differences to Pb and Cd exposure.

List of abbreviations:

AM	Arithmetic mean
ANOVA	Analysis of variance
Arsenic	As
BMI	Body mass index
BW	Birth weight
Cd	Cadmium
Ca	Calcium
CERCLA	Comprehensive Environmental Response, Compensation and Liability ACT
CI	Confidence interval
DMA	Dimethylarsinic acid
DMT1	Divalent metal transporter 1
FFQ	Food frequency questionnaire
GST	glutathione S-transferase
GM	Geometric mean
Hg	Mercury
iAs	Inorganic arsenic
Iron	Fe
IUGR	Intra uterine growth retardation
KJ	Kilo joul
LBW	Low birth weight
Max	Maximum
MBRN	Medical Birth Registry of Norway
MeHg	Methyl mercury
Min	Minimum
MISA	Miljøgifter i svangerskapet og i ammeperioden
MMA	Methylarsonic acid
Mn	Manganese
MoBa	Norwegian Mother and Child Cohort
MT	Metallothionein

µg	Microgram
NILU	Norwegian Institute for Air Research
NIOH	National Institute of Occupational Health
NOWAC	The Norwegian Women and Cancer study
Pb	Lead
PTW1	Provisional Tolerable Weekly Intake
P1	2nd trimester
P2	3rd postpartum day
r	Pearson's correlation coefficient
RI	Recommended intake
SD	Standard deviation
SGA	Small for gestational age
WCBA	Women at child bearing age
WHO	World Health Organization
Zn	Zinc

1 Introduction

Birth weight is an important indicator for predicting newborn baby's health. It is widely accepted that both low birth weight (LBW) and high birth weight (macrosomia) can have either short or long-term effects on a child's health in later life [1] . Under this assumption of interconnection, birth weight is used to rationalize variants in infant mortality and later morbidity, and is also used as an intermediate health endpoint in itself [2]. Of concern, some particular long-term chemical or toxic elements (like Cadmium (Cd), mercury (Hg), lead (Pb), arsenic (As)) exposure during pregnancy have been associated with negative birth outcomes like low birth weight (LBW), prematurity, and small-for-gestational age (SGA) increase the risk of neonatal morbidity and mortality [3-5]. During pregnancy, placenta acts not only as protective organ for fetus but also as a good indicator for dimension of toxic elements exposure. Most of the elements have the ability to pass transplacental barrier and accumulate in the choice of organs in fetal side[6].

Over the centuries, toxic elements, also known as non-essential metals, are recognized for their potential toxicity and easy access to enter the food web. Cadmium (Cd), mercury (Hg), lead (Pb), arsenic (As) are the most common toxic elements according to the WHO's most common public health concern chemicals or chemicals of groups[7]. CERCLA (Comprehensive Environmental Response, Compensation, and Liability Act) ranks As as no.1, Pb as no.2, Hg as no.3 and Cd as no.7 [8]. These elements' feature some properties like:

- Persistence: sustain in the nature under different occurrences for many years and mortifies very slowly.
- Bioaccumulation: concentration increases over the times within a living individual, this feature is very suitable for the human body. With the time or development of age the concentrations also get higher.
- Biomagnification: concentration goes higher along the food chain means single from top of the food chain contains the highest concentration, this property is very common in the food web in the ocean. The members of a top in the chain contains a high amount of toxic substance than rest. However, toxic metals could be toxic even lower concentration [9].

Toxic metals appear or are discharged into nature and afterward, eventually enter the food chain making this a primary route for human exposure [7]. Toxic elements exposures during sensitive windows of development, mainly gestational period and in the first few years of life, could have a role in chronic disease development [10]. Lifestyles, particularly the diet, play a crucial role in personal exposure to environmental toxicants [11]. Cd, Hg, As and Pb have garnered a significant attention because of their widespread exposure worldwide. Fetal exposure through trans-placental passage, evidence of fetotoxicity, multi-organ adverse effects, and ability to interact with the genome and the epigenome [12]. These adverse effects are imperative threats for human life as well as future generation. Thus, maternal exposure is our particular concern because of contaminant concentration during pregnancy, which can give us an indication of the potential risk to the developing fetus [13]. Moreover, fetuses and young children are the most vulnerable to these environmental contaminations. Specifically, concerns are negative birth outcomes like low birth weight and neurodevelopmental disorders with later developmental and other health consequences [13-15]. In a research work, the authors demonstrate that Pb can mobilize from maternal bone into plasma to meet up the extra demand during pregnancy period, without detectable changes in whole blood Pb. So this changes suggest that bone Pb remains in bone for years to decades, even after maternal external Pb exposure has declined, it has equal ability to affect the newborn [16]. Smoking, a valuable source for Cd, affects differently during pregnancy than nonsmoker group [17]. Since, maternal smoking during pregnancy causes the stimulation of maternal catecholamine release; as a result, uterine vasoconstriction occurs. Consequently, less blood supply causes less fetal growth and development[18]. As, a potential toxicant, which has adverse effects on birth outcomes (birth weight, birth length, head and chest circumferences) due to prolong maternal exposure during pregnancy [19]. A cohort study about maternal low levels exposure of Hg during pregnancy period reveals about children's serious and permanent neurobehavioral effect in later life [20]. In this thesis, we are going to study the relationship between fetal birth weight and maternal status of toxic elements in blood. Measurement of these toxic elements through the pregnancy and postnatal time trends in blood have been shown to reflect the changes in the maternal body [21].

1.1 Objectives and the research questions of the study

In this study, we attempt to conduct an estimation of levels of selected toxic elements in the mother's blood sample and their effects on fetal outcome among the north Norwegian mothers. More specifically, the study objectives are:

- To conduct the assessment of selected toxic elements (Pb, Hg, As and Cd) in the mother's blood sample during the gestational period and their effects on birth weight.

The following research questions are formulated to meet the research objectives:

1. Evaluation of selected toxic elements (Pb, Hg, As and Cd) and their effects on birth weight.
2. To find a best model between P1 and P2 to build a multivariable regression model.

The MISA study[21] is aimed to conduct for measurement of concentrations of environmental contaminants in expecting mothers, (and in their new babies) and their effects on birth outcomes like birth weight. These expecting mothers are from the three most northern counties of Norway, namely Nordland, Troms, and Finnmark.

1.2 Organization of the thesis

This thesis comprises of four chapters.

The first chapter introduces detail information about toxic elements including sources, distribution in maternal body, fetal transfer etc. and their effects on birth weight. Furthermore, this chapter includes information about birth weight and its influencing factors, progress of pregnancy, placental development, and mechanism of transfer for different toxic elements through placenta. The research questions (the objectives and justifications for the study) have also been described in this chapter.

Chapter two includes relevant material and methods and shows a brief description of the study area and study population. Dependent and different independent variables which

are significantly associated with our study and a brief description of statistical analysis have been demonstrated in this chapter.

Chapter three contains the results of this study: the different demographic factors and their values. In addition, different birth outcomes and maternal blood toxic elements are also evaluated. Furthermore, the relationship between birth weight and the effects of selected toxic elements and their relationships with the gender of the baby are also described in this chapter. We used several regression methods which include univariate linear regression, and multiple linear regression.

Chapter four concludes the thesis with a review of the themes discussed in the previous chapters and summarizing and analyzing the findings. It has also justified the thesis by discussing different strength and limitation of the study.

1.3 Background

1.3.1 Selected toxic elements, sources and their health effects

1.3.1.1 Human Exposure

The primary exposure for human for these elements are through skin, inhalation, and drinking water or mainly by ingestion of food. Among the food, especially the seafood is a good source for toxic elements like Hg, As, Cd etc. Even at low levels, toxic elements may cause various types of diseases and disabilities, where especially growing fetus and newborn babies are designated as vulnerable groups. However, it is quite difficult to show the negative effects of different elements separately, because of the variety of toxicants and similar source. Here is a brief description of toxic elements, their properties, and how they affect to the birth weight of the newborn babies.

1.3.2 Lead

Sources

Lead (Pb) is a natural occurring neurotoxic metal which is found widespread in the surroundings. The removal of Pb from water pipes, paint and food cans, as well as a ban on Pb additives to petrol in most countries, has reduced exposure to Pb in recent years. Industrial activities such as mining, smelting, Pb shot manufacture and battery manufacture and recycling are still of concern [22]. Particular food, especially game (like duck, goose, woodcock, elk, reindeer, etc.), hunted by leaded ammunition and

contaminated by Pb shot pallets or their bits are usually concerned as the major source of Pb [23]. Other important sources of exposure are paint and ammunition dust contributing to the Pb load in house dust. Smoking also appears to the extra burden of Pb [24, 25]. Pb contaminated drinking water plays a very important role in human exposure [25].

Maternal distribution

This metal is poorly absorbed through the skin but when it inhaled, the Pb containing particles take 24 hours to be absorbed [26] . Nevertheless, it has very low absorption ability through the intestinal tract (only 10% of ingested Pb) [27]. On the contrary, other researchers published reports on mitigating effects of dietary Fe, Zn, Ca and pre-existing serum nutritional status, which have influence on the Pb accumulation and distribution. For example, the role of nutritional status in altering susceptibility to lead toxicity has been documented. Pb uptake increases when Fe- deficiency and/or low calcium intake occurs [27-29]. However, the positive correlation between maternal blood Pb and serum Zn levels have been observed [29]. Once Pb enters into the blood, it is distributed all organs but the particular organ of choice is bones, teeth (almost 94% of stored Pb in the body) because Pb can substitute for calcium (Ca). The half-life of Pb in the peripheral blood and soft tissue compartments is around one month, while in the skeleton it is 9-12 years [30]. Most of the Pb (almost 70%) that enters the body, are excreted by the urine or through biliary clearance (ultimately, in the feces) [26] .

Fetal transfer and health effects

The transfer of maternal Pb either mainly through the placenta or later through the breast milk. Either prenatal exposure or breast milk could be the main source of an infant's total Pb body burden. Contemporarily, a continuous decline has been observed in Pb's concentration in humans [21]. Pb exposure from smoking may have a negative effect on the transplacental flow of micronutrients like glucose. Furthermore, it has an adverse influence on the growth and development of the fetus, and then on children [17, 18]. Pb can readily cross the placenta and can be reserved in fetal brains as early as the first trimester [31]. In another research, the authors indicate that maternal bone Pb burden is inversely related to birth weight [16, 32]. In addition, Pb can mobilize from maternal bone into plasma without detectable changes in whole blood Pb. These findings suggest that bone Pb remains in bone for years to decades, long after maternal external Pb exposure has declined [16]. Pb reaches the fetus by trans-placental transfer approximately at the

beginning of 12th to 14th week of pregnancy by passive diffusion that leads to deleterious effect afterward [12, 33]. Maternal Pb exposure during pregnancy at very low levels may adversely affect fetal bone growth. As Pb compete with Ca for deposition into bone due to similar chemical characteristics, it has a negative effect on child's birth outcomes, particularly preterm birth [28]. In the paper about the relationship between the maternal blood Pb concentration and birth weight points out the significant negative impact of maternal blood Pb level on birth weight, even at concentrations < 5.0 μg/dL regarded as safe for children [34]

1.3.3 Arsenic

Sources

Arsenic (As) is the most common metalloid that found on earth crust. It acquires characteristics of both a metal and a non-metal. The primary route of exposure is the regular diet, or by consumption of contaminated food or drinking water [35]. The highest concentrations of As have been found in seafood, followed by meats, cereals, vegetables, fruit, and dairy products. The non-toxic organic forms of As are mostly found in seafood, fruit, and vegetables, whereas toxic inorganic As forms are present in meat, poultry, dairy products, cereals and most importantly in drinking water. It is estimated that on average, approximately 25% of daily dietary As intake is in the form of inorganic species among the pregnant women in the Pacific Northwest, USA [36].

Maternal distribution

It is believed that over a hundred million people worldwide are exposed to inorganic arsenic due to the exceed levels of As, recommended by the World Health Organization (WHO) which is 10 μg/L[37]. High exposures to inorganic As happen in the form of inhalation or through drinking water in regions of the world that is naturally contaminated with this element. Among the types of natural As, inorganic As is most prevalent. Inorganic As is metabolized in the body and produce methylarsonic acid (MMA) and dimethylarsinic acid (DMA) which are less toxic and readily excreted in urine while reduced forms of the methylated metabolites, are highly toxic and may be responsible for part of the arsenic toxicity [38]. The half-life of inorganic arsenic is 4-6 hours (h) which is quite long for methylated metabolites (20-30 h)[59]. The methylation of arsenic is influenced by dose level, age, and gender [39].

Fetal transfer and health effects

Adverse effects of As contamination include unfavorable reproductive/developmental issues like SGA, pre term birth, growth retardation of fetus etc. [40, 41]. As, which is a potential toxicant, can be correlated with adverse birth outcomes (birth weight, birth length, head and chest circumferences) due to prolong maternal exposure during pregnancy[19]. As can readily cross the placental barrier by glucose transporter 1 (Glut1), which has been shown to catalyze the cellular uptake of both arsenite and its methylated metabolite (like MMA, DMA). After As crosses the placental barrier, it accumulates in the placenta. Subsequently, it produces toxins in placental tissues which are mediated via oxidative stress. These toxin elements interfere with nutrient transport to the fetus and thereby affect fetal growth [41]. Another acceptable explanation is epigenetic alterations. Prenatal arsenic exposure has been associated with deregulation of microRNA expression profiles in umbilical cord blood, and DNA methylation status in maternal and umbilical cord blood. MicroRNAs have an important role in normal placental development; and alteration of microRNA expression profiles have been associated with abnormal placentation and SGA births [42, 43]. In addition, maternal arsenic exposure via drinking water is associated with fetal loss, small size at birth, infant morbidity and mortality [37]. Conversely, in one publication the author reported negative associations between arsenic exposure and birth weight, birth length and gestational age [44].

1.3.4 Mercury

Sources

Mercury (Hg) is an accumulative neurotoxin that exists in the surrounding by natural and anthropogenic sources. These sources include volcanoes, forest fires, fossil fuels such as coal, human activities such as mining, petroleum or discharge from hydroelectric plants, and paper industries contribute to a certain level in the environment[45]. Elemental Hg, transformed into methylmercury by bacteria, exists in lakes and rivers. Methylmercury (MeHg) has the ability to bio-accumulate in aquatic and terrestrial food chains. It is established for the main route of human exposure. So, intake of fish which are long-lived and top in the food chain can correlate with blood Hg levels[20, 46].

Maternal distribution

At room temperature, Hg is a liquid that is volatile, toxic in both its elemental (Hg°) and ionized forms. Elemental Hg is less capable of absorbing from the gastrointestinal tract (less than 0.1%), although 7% and 95% of inorganic and MeHg are absorbed correspondingly [47]. The Hg gas, which is well absorbed in the lung and easily crosses cell membranes, inhaled vapor dissolved in tissue fluids and the bloodstream moves rapidly throughout the body. Afterwards, it readily crosses the blood–brain and placental barriers and sits there. MeHg, which usually ingested, is absorbed into the bloodstream. Then the organ of choice is brain, liver, kidney, hair, biliary tract for distribution. From blood compartment to all the body tissues the process takes about 30 to 40 hours. On average about 5% of the absorbed dose remains in the blood compartment. Hair Hg levels closely follow blood levels. However, in the time of execration, different forms take different pathways. MeHg is excreted through feces, while inorganic Hg through urine with a half-life of 45-70 days [48] .

Fetal transfer and health effects

MeHg is instantly ready to cross placenta so that fetal level have been found greater than maternal levels [49]. Actually, the MeHg binds to the neutral amino acid carriers (such as cysteine). As a result, the fetal side of the placenta has reduced affinity and leads to one-way placental transfer [50]. A study about GSTM1/GSTT1 polymorphism and blood mercury published in 2010 suggested that interactions of Hg with glutathione S-transferase (GST) play a role in reducing birth weight. This study found that both umbilical cord blood Hg and maternal blood Hg were inversely related to birth weight. Further, they specifically examined the significant association between GST polymorphisms in mothers blood Hg and infant birth weight [51]. Another study in Norway called Norwegian Mother and Child Cohort Study (MoBa), investigates the potential association between birth weight and estimated Hg intake based on dietary information from an FFQ. This MoBa study revealed that women with high Hg exposure delivered offspring with reduced birth weight [52]. On the other hand, a cohort study named Birth Cohort 1 in the Faroe Islands was established to investigate the effects of fetal exposure Hg owing to the frequent consumption of whale meat during pregnancy. Follow-ups of the children in this cohort have indicated the serious and permanent neurobehavioral effects of fetal exposure to Hg even at low levels. These are the most

important findings of the present assessment [20]. However, some researchers claim no associations with birth weight and Hg [53]. Counter wise, positive associations are reported in populations with high fish consumptions, suggested as a protective effect of fish and selenium in it. [54].

1.3.5 Cadmium

Sources

Cadmium (Cd) is naturally occurring toxicant found in the earth crust. Main sources for exposure are industrialized release include mining and smelting of Zn, battery manufacturing, pigment production for paints, and in tobacco products [8]. Further, Cd is one of the most important toxicants related to pregnancy outcome largely depend on smoking [55, 56]. For nonsmoker, the main source for Cd is food like cereals, potatoes, and vegetables which grow in soil that is naturally rich in Cd or even from the use of Cd-containing fertilizers and pesticides [57, 58]. Food grows in contaminated soil like wheat, rice, vegetables contain a greater amount of Cd. Other studies also revealed that Cd from the soil was absorbed and retained in rice to a great extent. Further, Cd in rice has been exclusively correlated with Cd body burden [57, 59].

Maternal distribution

Cd can be absorbed via inhalation and ingestion. Absorption is enhanced by dietary deficiencies of Ca and Fe and by low protein diets. Low dietary Ca stimulates synthesis of Ca-binding protein, which enhances Cd absorption. However, human take most of the Cd via cigarette smoking. Through smoking, nearly 10-30% of the Cd content of a cigarette is inhaled. Further, absorption of Cd through the lungs is more effective than through the gut [61]. In blood, Cd can be bound with red blood cells and high-molecular-weight proteins in plasma. The Cd bound protein, metallothionein, portrays most recent exposure with a half-life of 40-90 days while Cd stored in kidney and liver has a half-life of 10 years or more [60, 61].

Fetal transfer and health effects

Cd exposure influences the hormonal release of the pituitary hormones, which play an essential role in reproductive health, fetal growth, and development [58]. Gender differences in susceptibility at lower exposure are uncertain, but recent data indicate that Cd has estrogenic effects and affect female offspring [62]. Another study establish that Cd

concentration in the placenta was inversely associated with birth weight [58]. Cd can express placental gene 11β-HSD2 which is responsible for the transfer of glucocorticoid through the placenta. Consequently, fetal growth retardation may occur [62]. Cd also acts as a competitor with Zn which is essential for fetal growth and development as it is being delivered to the fetus. The proposed mechanism behind a Cd–Zn interaction is the accumulation of Cd in placenta that stimulates the synthesis of the metal binding protein metallothionein (MT). Furthermore, Cd bound MT can cause Zn retention in the placenta with subsequent reduced Zn transfer to the fetus[63]. Some studies reveal that maternal smoking is related to decrease birth weight in comparison to the nonsmoking group. Moreover, mothers who smoke >20 cigarettes/day have high risk to deliver low birth weight, small for gestational age and pre-term babies due to Cd effect [55, 64]. Furthermore, maternal smoking during the third trimester is the strongest predictor of birth weight after adjusting for gestational age. Research about maternal smoking and its association with birth weight shows that each cigarette smoked per day during the third trimester contribute to a 27-g reduction in the birth weight of the infant [56]. A study on heavily Cd polluted area in Myanmar revealed that a higher maternal Cd concentration increased the likelihood of a low birth weight but not preterm delivery [4].

1.3.6 Development of Pregnancy and placental transfer of toxic elements

Critical period of exposure

A critical age period can be defined as one in which an exposure must occur to influence a later outcome, while a sensitive period is one in which an exposure has a larger effect than the same exposure during other periods, and these critical age period can be i.e. preconception, pregnancy, infancy and childhood [10, 65, 66]. In this context, our particular concern is the pregnancy period**.**

1.3.6.1 Development of pregnancy:

Pregnancy is an unusual physiological condition for the female body. During the period of pregnancy, not only the growth of fetus occurs but also tremendous physiological changes for mother happened along with preparation for lactation. These changes include enlargement of mothers' uterus (can be enlarged 5 times of its initial size), changes in plasma volume and erythrocyte, as well as increase in whole blood volume. In cardio vascular systems, it is changed by increasing cardiac output. Besides, renal plasma flow

and glomerular filtration rate (GFR) both increase due to renal vasodilatation, and importantly plasma volume increases progressively throughout normal pregnancy[10]. Most of this 50% increase occurs by 34 weeks of gestation and is proportional to the birth weight of the baby.

Placenta is developed at the time of implantation in the uterine cavity. This occurs around 6 to 7 days after conception and continues throughout the pregnancy with a simultaneous increase in uteroplacental blood flow (up to 40-fold during the course of the pregnancy) [67]. The placenta plays a vital role to keep the fetus connect with the mother via the umbilical cord. The main function of the placenta is providing oxygen and nutrients to the growing fetus and removing waste products from fetal blood [68].

In the first trimester, placental growth is more rapid than the fetus growth. The placental weight is almost same to the fetus around 17 weeks of the conception and approximately one- sixth of it at term[69]. Alongside, maternal placental blood flow continues to increase throughout pregnancy, which is considered to reflect vasodilation [10, 67]**.** For some particular compounds, the placenta functions as a barrier and thereby protects against the infections from the mother to the fetus and for other substance, it can accelerate their passage (Figure 1) [12].

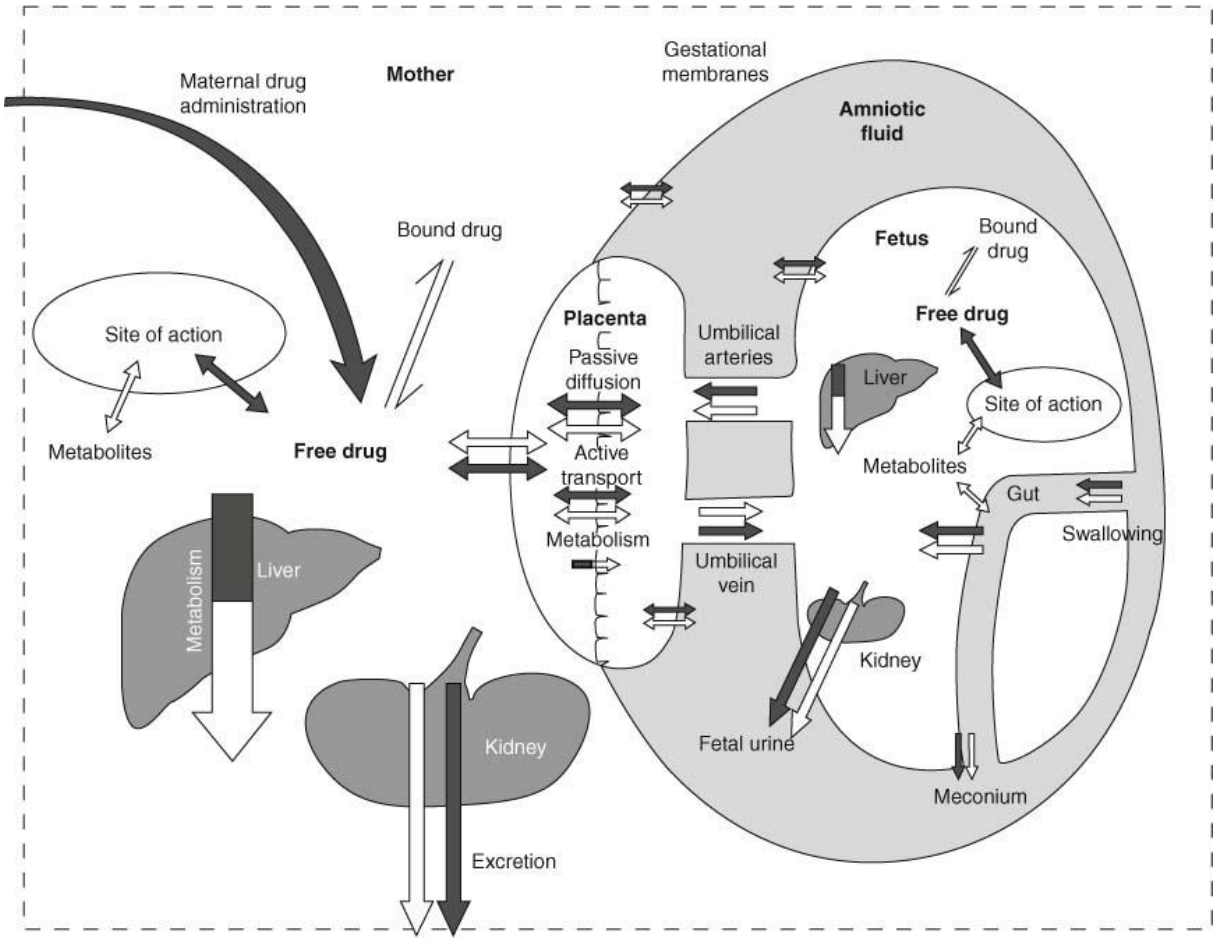

Figure 1: Mechanism of drug transfer across the fetus after maternal drug administration. (Reprinted with permission from Syme et al., 2004).

1.3.6.2 Placental transfer of toxic elements

It is logical to presume a change in levels of different elements during the period of gestation and after delivery because of the expansion in plasma and red blood cells. Though, some studies also suggest that RBCs are better than plasma at reflecting the trans-placental transfer of Pb and Hg from the mother to the fetus [70]. Moreover, the study shows the result for cord/maternal ratios in RBCs that strongly suggest Pb, Hg, and Cd exhibit free trans-placental passage from mother to fetus. However, the result they showed for Cord/maternal ratios in plasma is varied from the result from RBCs. The result for plasma ratio is less reflective than the RBC ratio [71]. So, it is notable that these elements have a strong association with RBCs.

However, unfortunately, a few toxic elements (for example, Pb, Hg, Cd, As etc.) are permissible to the placental barrier. Elements with a molecular weight below 500 are readily transferred across the placenta [27]. Many researchers evaluate metal exposures and consequential maternal fetal health risk by using human placenta [28]. The toxic elements Pb, Hg, As and Cd are the most common toxicants, which are well-known to cross the placenta and to accumulate in fetal tissue. These chemical compounds can cross the placenta by various mechanisms [71]. Maternofetal and fetal-maternal diffusional transfer depend on the thickness of the dividing layers and different stages of pregnancy. During early pregnancy, the maternal-fetal diffusion distance is in the range of 20–38 mm, while at the end of pregnancy, the minimal diffusion distance is about 4 mm. In contrast, facilitated and active as well as vesicular transports are influenced by the number of layers of the placental barrier [49, 71]. Toxicokinetic of Pb, Hg, and Cd is very distinctive in the placenta. Pb is entered by passive diffusion into placenta cells [31]. Meanwhile, accidental exposures of Hg in pregnant women show that the placenta cannot prevent the passage of Hg without exception of any chemical form. The chemical form of Hg determines its cellular uptake. Both Hg vapor (assumed to be transported by passive diffusion) and MeHg (transported by amino acid carriers) can easily pass the placenta [49, 50]. On the other hand, inorganic Hg is more likely to be trapped in placenta tissues [51]. The placental passage of Cd is limited suggesting a partial barrier for this element. The divalent metal transporter 1 (DMT1), is known to mediate intestinal uptake of Pb and Cd, might also play a crucial role in placental uptake of Pb and Cd [72]. The major function of DMT1 is Pb uptake. This transporter is abundantly expressed in human placenta throughout gestation [73].

Figure 1 shows different types of pharmacokinetics including transplacental transport and metabolism that determine the extent of maternal to fetal drug transfer and fetal drug exposure. The size of the arrows approximates relative importance, although this is drug-dependent and will vary during pregnancy with fetal and placental maturation [12]. The fetus is particularly vulnerable to the effects of heavy metals because of the high rate of cell division and differentiation. Therefore, relatively low levels of exposure that do not harm the mother may have a reflective effect on the growth and development of the fetus and development during childhood [5]. Cd, one of important toxic elements that can pass through placental barrier, causes some indirect health effect such as changes in placental hormone production and transplacental nutrient passage of essential trace elements.

These effects may exert a far-reaching impact on human pregnancy and immune processes related to the function of the maternal-fetal interface [63, 74]. In addition, moderate level of prenatal exposure of Cd may have a detrimental effect on birth outcomes [75]. Pb, another toxic element, readily crosses the placenta and sits in fetal brain in the first trimester, and which is a concern for the later life. Low-level Pb exposure in children does not cause overt clinical symptoms but has permanent effects on cognition, behavior and school performance [76]. Some other studies also revealed that both Cd and Pb in placenta were negatively correlated with birth weight, head circumference and placental weight [13, 14]. On the other hand, the relationship between arsenic (iAs) contamination through water and low birth weight, and intrauterine growth retardation is established [19, 35, 40]. In this study, we analyzed birth outcomes especially, low birth weight and measurement of toxic elements in maternal blood during 3rd trimester and 3 postpartum days to establish the alteration in the level of toxic elements in different time period.

1.3.7 Birth weight and influential factors

Birth weight can be defined as body weight just after birth. During pregnancy, babies live in amniotic fluid, and after birth they lose a fraction of their birth weight. According to WHO, children above 2.5 kg are considered as normal birth weight [77] . Low birth weight (LBW) neonates are vulnerable for risk of mortality and morbidity. However, newborns who have a birth weight above 4500 grams considered as macrosomia or high birth weight [78]. Low birth weight (LBW) is a major public health concern for both developed and developing countries, and one of the most frequent causes for child morbidity and mortality in recent years [2, 79]. According to WHO, more than 20 million infants worldwide representing 15.5 percent of all births, are born with low birth weight, and 95.6 percent of them are from developing countries [80]. Usually, it describes if fetus weighted 10% less with respect to gestational age called small for gestational age (IUGR) [3].

Infant birth weight is a strong predictor for recent health status. In general, the lower the birth weight is the higher the risk of infant mortality [81]. Another factor is that, on a population level, mean birth weight is associated with infant mortality. Groups with lower mean birth weight often have higher infant mortality (e.g. the infants of mothers who smoke, or of mothers with lower socioeconomic status) [79]. Finally, birth weight is associated with health outcomes and development later in life. Asthma, low IQ, and

hypertension have all been reported to be more common among those who were small at birth [3, 82].

Newborn baby's weight can vary greatly; it can depend on mother's own health and nutrition during pregnancy, as well as their inbuilt genetic make-up, which comes from both parents [66, 79]. Although smoking, alcohol habits, maternal weight, and pre-pregnancy height are the important determinants for low birth weight [17]. Maternal active smoking during pregnancy induces birth-weight decrease and significantly increases the risk of LBW. Reduced birth weight was found to be adversely correlated with the extent of maternal smoking during pregnancy. One of the authors revealed that maternal smoking of ≥20 cigarettes/day is significantly associated with LBW, small for gestational age (SGA), and preterm birth [64]. The effect of nicotine (found in cigarette smoking) is stimulating maternal catecholamine release. As a result, uterine vasoconstriction occurs. Maternal smoking increases carboxyhemoglobin levels of umbilical arteries and results in fetal hypoxia [18]. Maternal gestational weight gain is one of the most important determinants and has an association with low birth weight compared to those who gain weight within the limit of the American Institute of Medicine guidelines [83]. Many other factors like malnutrition, stress, use of illicit drugs, toxic substance exposure during pregnancy, cesarean delivery, maternal age, prenatal medical visits, obesity, gestational diabetes, eclampsia, and parity also play an important role on determining newborn's birth weight [17]. Moreover, in some studies it reveals that female gender is associated with LBW. The reason for association of LBW with the female infant is biological and inherent and also non-modifiable [1]. Prolonged exposure of toxic elements even at a low-level during pregnancy may adversely affect some childbirth outcomes such as low birth weight. Pre-natal exposure of Pb, associated with reducing fetal birth weight, or ponderal index is established specifically for girls [32, 84]. Besides, many studies have established that the relation of maternal blood Cd level has significant impact on reducing birth weight in baby boys among the smoker mothers [85, 86].

2 Material and methods

2.1 MISA study

The Northern Norway Mother-and-Child Contaminant Cohort Study [in Norwegian: Miljøgifter i svangerskapet og i ammeperioden (the MISA study)] was initiated in 2007 with the goal to measure concentrations of environmental contaminants in expecting mothers (and in their newborn babies) who lived in the three most northern counties of Norway, namely Nordland, Troms and Finnmark. The primary objective was to study the exposure through food intake, as well as examining the influence of maternal anthropometric and 24 socioeconomic factors. The MISA database is considered suitable for exploring associations between contaminant exposure and diet, enhancing understanding of the relationship between physiological changes that occur in mothers and contaminant activity through the body till its fate (including transfer to the infant before and after birth), and conducting prospective health studies of the children[21, 87].

2.2 Geographical description and recruitments

The recruitments for the MISA study took place from May 2007 until December 2009 in different counties of northern Norway. Nordland, Troms and Finnmark as described in Figure 2. Pregnant women in the selected study area were invited by a written invitation administered by ultrasound clinics personnel or midwife consultations in selected region. The participating delivery departments were: Nordland Hospital (Bødo and Lofoten), University Hospital of North Norway Trust (Tromsø and the labour wards of North-Troms (Nordreisa) and Mid-Troms (Lenvik)), and Finnmark Hospital (Kirkenes, Hammerfest and the labour ward of Alta), municipality of Karasjok and Kautokeino in Finnmark [21].

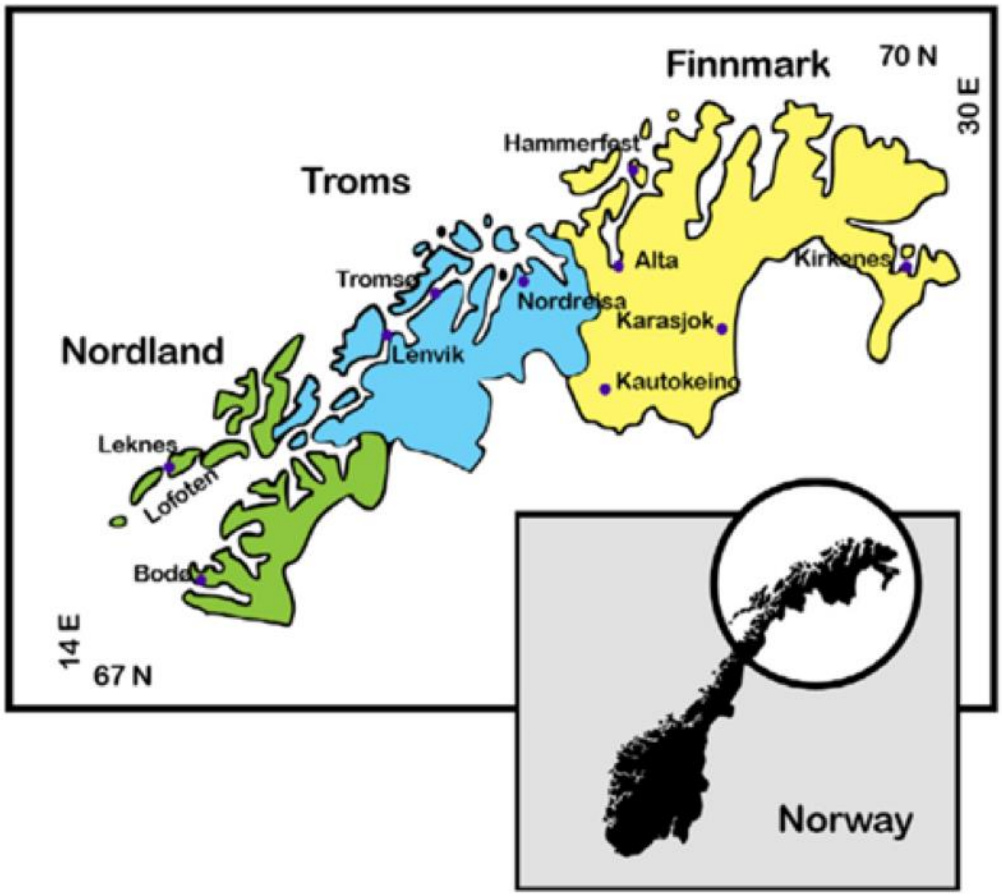

Figure 2: Map of MISA study area[1]
1: Rod Wolstenholm, UiT, Adapted from Veyhe 2016

The MISA study adopted a cohort study design. It had three different sampling points, for instance, P1 –before week 20 in the 2nd trimester, P2 – at the 3 days postpartum and P3 – 6 weeks postpartum but here P1 and P2 sample is our particular concern. Further, in our study we are going to use P1 for 2nd trimester and P2 for 3 days postpartum. A total of 2600 woman were invited to participate, 609 responded of whom 52 avoided further contact. The remaining 557 participants received the project package containing a questionnaire and biological sampling kit. Among 557 participants, 15 did not give blood sample and 27 did not hand in consent form, thereby 515 women were left eligible for study, 461 of these presented at delivery, 395 provided blood sample and 382 provided whole blood sample at each of three points. All whole blood specimen sample collected till end of January 2009 were selected for analysis, and the concentration for essential and toxic elements in a subset of 282 respective donors constituted our primary the study group (see Figure 3). This decision was necessitated by laboratory constrain.

For this study, among the 282 participants we excluded 20 women as they did not meet certain criteria and might have influence on birth weight [88]. Finally, we include 262 women for the study. Among the 20 excluded participants 2 were diabetic (one was type 1 diabetics and another gestational diabetics), 7 pre-eclampsia, 2 hypertensives, 6 twins, 3 had baby with congenital abnormality. The relation between gestational diabetics and increased birth weight (macrosomia) is recognized [17]. Many others factor rather than diabetics also have impact on birth weight, in particular maternal hypertension, pre-eclampsia etc. [79, 89].

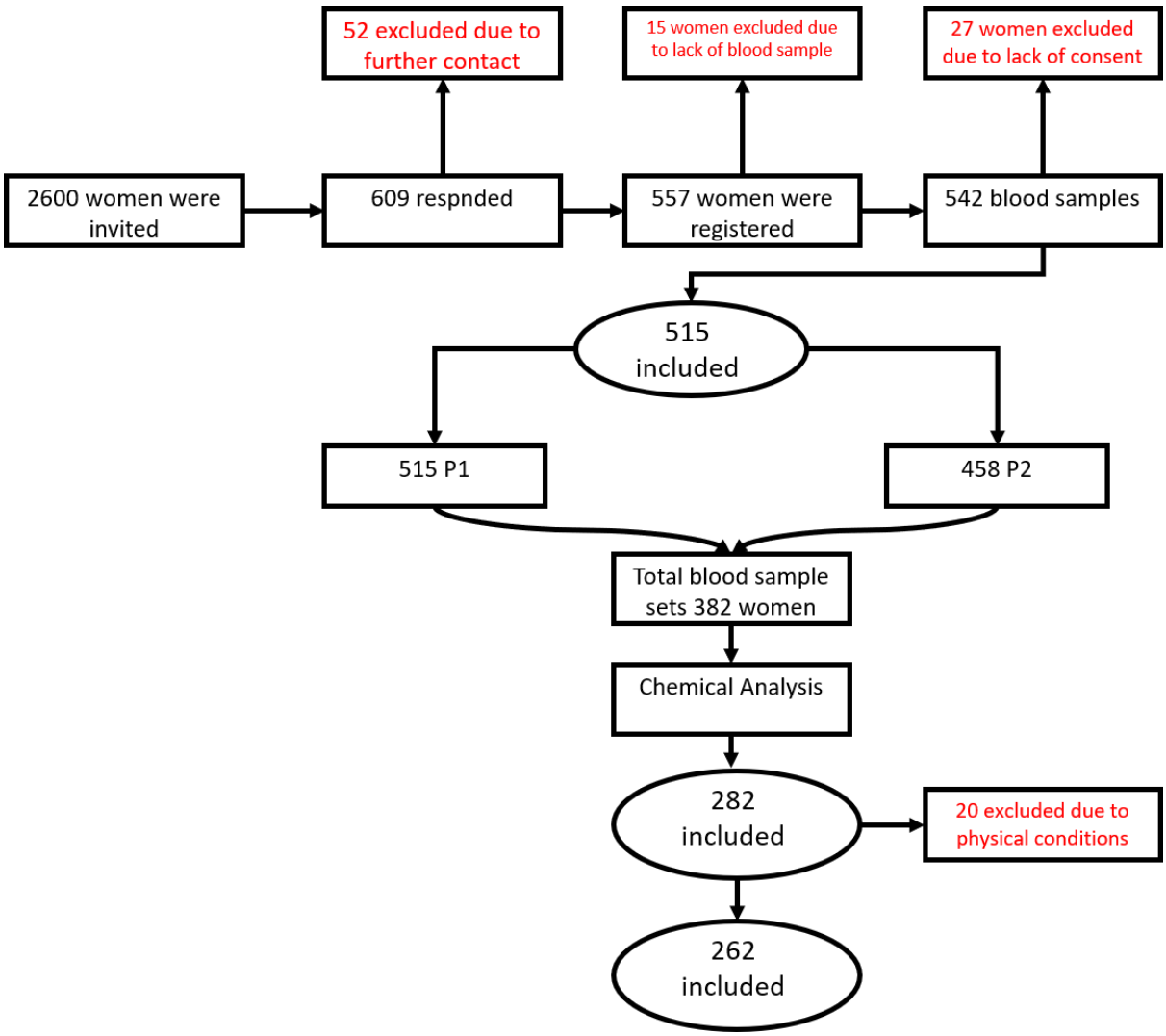

Figure 3: Study population and participants in this study (Adapted from Hansen 2011)

P1, 2nd trimester around 18 gestational weeks; P2, 3 days postpartum

2.3 Enrollment and Data Collection

In the MISA study, the participants completed a detailed self-reported information questionnaire (Appendix 1) relating to personal characteristics, obstetric history, diet and life style. In addition, at all blood sampling points a simple questionnaire (Appendix 2) was administered to obtain personal information about current diet, smoking and alcohol habits, medication and dietary supplements. Maternal weight was measured at each period, and self-reported pre-pregnancy weight and height (verified against that in the medical record) were attained from pregnant women. During assessment of body weight a standard weight machine was used while wearing light clothes and without shoes (rounded to the nearest kilo)[90]. Maternal characteristics like age, smoking status, civil status, medical status and obstetrical data like parity, gestational age, newborn medical status, birth weight, length and head circumference, obtain from Medical Birth Registry of Norway (MBRN)[91].

2.4 Blood Sampling and chemical analysis

The maternal whole blood samples considered in this study were drawn by venous puncture at all three sampling periods (P1, P2 and P3). However, in this experiment, we consider elements analyzed from (P1) and (P2) periods. Samples of maternal whole blood for three collection periods were analyzed for levels of Pb, As, Hg and Cd. Chemical analysis was done by using the inductively plasma- mass spectrometry (ICS-MS) technique, employing a high-resolution magnetic sector field Element 2 mass spectrometer (Thermo Electron, Bremen, Germany) calibrated with whole blood matched standard solution [21, 88]. Analyses for Toxic elements were done by the National Institute for Occupational Health (NIOH), Oslo, Norway[88].

2.5 Description of variables

Mothers age was obtained at delivery, have been reported both as on a ratio scale and as grouped categories (<19, 20-24, 25-29, 30-34, 35-39, >40). Number of years in school were treated both on a ratio scale and categorized into grouped according to Norwegian education system (Primary school <10 years, Secondary school 11-13 years, Higher education >14 years). Household income was measured in yearly income (NOK). Parity was based on deliveries occur after 12 weeks of pregnancy and reported as ratio scale (range 0-4). Gestational age was calculated on basis of ultrasound and were treated as

interval variable (days). Mother's self-reported height (cm) and weight (kg) in 2nd trimester was treated on a ratio scale. Pre-pregnancy BMI was calculated by pre-pregnancy weight in kg/ height in m^2[92]. Data about smoking (before pregnancy, during pregnancy and third post-partum days; yes or no) was self-reported regarding smoking or not, or frequencies of smoking. If missing data on maternal smoking habit, we compared the data from MISA and MBRN and made new variables. Alcohol consumption was treated as teetotaler (yes or not). Daily total energy intake in Kilojoule (KJ) were based on self-reported dietary intake [21].

2.6 Statistical analysis

All statistical analysis was carried out by using the IBM SPSS Statistic for Mac (version 25.0, SPSS Inc., Chicago, IL, USA). Descriptive statistic was run to summarized the data of the study group and were presented as number or percentage, mean, median and minimum to maximum range and standard deviation (SD). One-way ANOVA used for compare birth outcome differences between boys and girls. Chi square test was used to test differences between categorical data like smoking status between gender. Normality and deviations of outcome variables and elements were assessed from histograms and Kolmogorov-Smirnov (KS) tests. Birth weight was normally distributed.

The distribution of maternal concentration of toxic elements were found not normally distributed, so the compounds were Log transform (base 10 logarithm, log10x). Paired sample t-test was done to explore the change in concentrations between 2nd trimesters and 3 days postpartum. To account for the dependency between repeated measurements collected for each participant across time, p-value is reported.

Relationships between concentration of toxic elements and birth weight were visualized by scatter plots. Pearson correlation coefficients (R) were calculated for linear relationship. Simple linear regression was employed to detect association between birth weight with related independent variables included toxic elements. Predictors (p-value 0<.25) from univariate regression were included to build multiple regression model aimed to observe relationship between birth weight and elements adjusted for different characteristic. The independent variables tested by using the enter method regression approach included maternal age, pre-pregnancy body weight, height, parity, gestational age, gender of the baby, and log toxic elements. Six different models were built for the toxic elements, with and without co-existing elements, and including covariates obtained

an overall p-value below 0.1. Models using both 2nd trimester and 3 days postpartum concentrations of elements were tested out to find the best models. The models were both overall and stratified on gender. Unstandardized beta coefficient (ß), confidence intervals (95% Cl) and p-value explained the relationship and the boundaries of the interval. F-test, R2 and overall p-value for total model were reported to observed variability and extent to accuracy of the model**.** p-values< 0.05 were considered as significant.

2.7 Ethical considerations

The MISA study was approved by the Regional Committees for Medical Research Ethics and the Norwegian Data Inspectorate (Appendix 3). Participation of the women were voluntary, and the women signed an informed consent form (Appendix 4) [88].

3 Result and Analysis

3.1 Sample characteristic

Particular characteristics of 262 participating pregnant women are presented in Table 1. The study found that most of the women, 45.4%, were from Troms county, 33.2% from Nordland and rest of them (21.4%) were from Finnmark. The maternal mean age was 31.2 years and ranging from 18 to 43 years. The percentage for nulliparous and para 1 is nearly equal (39.3% and 39.7%, respectively). Majority of women delivered at term with mean gestational age 39.6 weeks. Almost 60% of the respondents' annual household income was equal or more than 600 000 Norwegian kroner while 38.7% had less than 600 000 Norwegian kroner. Majority of the respondents were cohabited (60.7%) followed by married (34.4%) and single (4.6%). The literacy rate of the mothers was relatively high, among them 76.5% and 21.6% had higher education more than 14 years and secondary school education while only 2% were under 10 years of education. Precisely half the study population were within a normal BMI range (BMI 18.6-24.9 kg/m2) while 33.7% were overweight (BMI range 25-29.9) and rest of 15.9% and .4% represent extreme groups (obese and underweight groups). Among the participants, 17.1% had smoking habit in beginning of the pregnancy while only 6.5% smoked at the end of the pregnancy. Moreover, 23% respondents also reported that they were smoked at least 6 months before pregnancy. High frequency of smoking was observed among the mothers carrying baby boys (22.5%) than girls (11.6%) (p-value=0.020). Respectively, only 7% respondent reported about no alcohol use as they were a teetotaler. In dietary portion women reported mean energy or calorie intake was 7873 KJ/day while the range is quite wide from 3135-12857 KJ/day.

Table 1: Characteristics of the study cohort

		Mean (SD) or n (%)	Median	Min-max
County of living at Inclusion (n=262)				
	Troms	119 (45.4)		
	Nordland	87 (33.2)		
	Finnmark	56 (21.4)		
Maternal age (years) at Delivery (n=262)		31.2 (4.8)	31.7	18-43
Age groups: in years				
	<19	3 (1.1)		
	20-24	27 (10.3)		
	25-29	70 (26.7)		
	30-34	102 (38.9)		
	35-39	50 (19.1)		
	40+	10 (3.8)		
Household income, annual (n=245)[b]				
	>600 000 NOK	147(60)		
Education (years of school) (n=255)		15.6 (2.7)	16	9-22
Educational years in groups				
	Primary school, <10	n (2)		
	Secondary school, 11-13	n (21.6)		
	Higher education, >14	n (76.5)		
Parity, all live births (n=262)		1.8 (.302)	1	0-4
	Para 0	103 (39.3)		
	Para 1	104 (39.7)		
	Para 2	39 (14.9)		
	Para 3	12 (4.6)		
	Para 4	4 (1.5)		
Gestetional age (weeks) (n=262)[c]		39.6 (1.4)	40	30-42
	<37 weeks	14 (5.7)		
Body weight of mother at 2nd trimester (kg)[a]		71.84	70	40-120
Height of the mother (cm)[a]		166.7	167	145-183
[c]Pre-pregnancy BMI (n=262): (kg/m^2)		31.2(4.8)	31.7	18.35-43.71
[c]Pre-pregnancy BMI in groups: (kg/m^2)				
	Under weight, <18.5	1 (.4)		
	Healthy,18.6-24.9	126 (50)		
	Overweight,25-29.9	85 (33.7)		
	Obese,>30	40 (15.9)		
Smoking Habits (yes or regularly)[d]				
smoking at last 6 months of pregnancy (n=256)		59 (23)		
smoking at the beginning of pregnancy (n=258)		44 (17.1)		
smoking at the end and after delivery(n=248)		16 (6.5)		
Alcohol Intake				
	Teetotaler (n=258)	15 (6)		
Total energy Intake, KJ (n=257)[e]		7973 (1993)	7891	3135-12857

[a]Maternal body weight, height was taken at 18.2 weeks; [b]Income based on annual household income.
[c]Gestetional age detect by ultrasound; [d]Smoking status is yes/no through 2nd trimester of pregnancy.
[e]In total energy intake data 2 missing data and 3 extreme outliers indicating over-reporting were removed from data

3.2 Pregnancy outcomes

Table 2 shows the major pregnancy outcomes among the north Norwegian newborn's characteristics overall and according to gender. In all 50.4% of the newborns were boys. The overall mean birth weight including both genders was 3653 gm. However, boys appear almost 200 g bit heavier than girls. The overall mean length of the newborns was

50.3 cm and with girls 0.5 cm shorter than boys. Likewise, for head circumference with overall 35.6 cm, girls show 0.6 cm lower circumference compare to boys. There were statistically significant differences between boys and girls for all these outcomes (p-value= <0.05)

Table 2: Primary fetal outcomes among North Norwegian Mothers in the MISA study (2007-2011)

		Overall	Boy	Girl	p-value[a]
Gender (n=262)			50.4	49.6	<0.001
Babies birth weight:					
	mean	3653	3738	3565	0.006
	min- max	1720-5170	1720-4930	2390-5170	
	std. Deviation	509.96	541.39	461.83	
Babies birth length:					
	mean	50.39	50.91	49.84	<0.001
	min- max	41-57	41-57	45-56	
	std. Deviation	2.14	2.29	1.8	
Babies head circumference:					
	mean	35.64	35.93	35.35	0.002
	min- max	27-40	27-40	32-39	
	std. Deviation	1.49	1.5	1.5	

[a]For gender comparison, ANOVA test was used

3.3 Detection of frequencies, normality and outliers of toxic elements

The detection for frequencies for toxic elements were 100% except Hg at P1 (99.1%) and As at P1 (98.6%). Regarding log transformation of every elements, the frequency distributions explore by histogram and detected by test for normality (KS test) were not normally distributed except for Hg at P1 and CD at P2 for smokers. However, the histograms were satisfied. A small number of extreme outliers by using boxplot observed for Cd (2 in both P1 and P2) and Pb (1 at P1) and were keep in dataset during measurement of the concentration. As they not were appraised to represent unusually high concentrations, they were also included during regression analysis.

3.4 Maternal concentrations of toxic elements

The maternal concentration and ranges for the selected toxic elements are reported in table 3. Pb had the highest concentration followed by As > Hg > Cd(smoker) > Cd(nonsmoker) at the point of both P1 and P2. This sequence shows that nearby all the elements (except of Hg), Pb concentration rise at point P2 and smoking has impact on blood Cd levels. Employing the paired sample t-test for log transformed concentrations,

all trends across the 2-different time period were significant (p-value < 0.001). All the elements tend to P2 > P1 pattern except Hg which follow P2 < P1.

Table 3: Maternal Whole blood concentrations of toxic elements during 2nd trimester in pregnancy and 3rd days of postpartum-The MISA study (2007-2011)

	2nd Trimester (P1)					3rd day of postparturm (P2)					
	Concentration (µg/L)					Concentration (µg/L)					
Compound[a]	**n**	**AM**	**SD**	**GM**	**Min-Max**	**n**	**AM**	**SD**	**GM**	**Min-Max**	**p-value[b]**
As	262	2.1	2.11	1.47	0.14-12.77	262	2.4	2.36	1.74	0.14-17.1	<.001
Cd(smoker)[c]	44	0.52	0.51	0.36	0.08-2.74	16	0.72	0.53	0.56	0.13-2.42	<.001
Cd(non-smoker)	214	0.17	0.08	0.15	0.04-.72	232	0.19	0.08	0.17	0.05-0.54	<.001
Hg	262	1.5	1.01	1.21	0.10-6.64	262	1.24	0.72	1.05	0.2-5.5	<.001
Pb	262	8.1	3.84	7.5	2.22-41.09	262	9.4	3.8	8.8	3.6-28.13	<.001

[a]As, arsenic; Cd, cadmium; Hg, mercury; Pb, lead; n, number of participants, GM, geometric mean based on ((log_{10}^{x})); AM, Arithmetic mean; min, minimum; max, maximum.
[b]Analysis for GM values was by the paired sample t test; [c] for the smoking variable in P1 4 data and in P2 14 data was missing.

3.5 Predictors in the linear models

3.5.1 Simple linear regression

In the simple linear regression, no elements were significant related to birth weight. Further according to standardized beta (β standard) with limited contribution. However, both Pb at P1 and P2 met the criteria of a p-value below 0.25 (p-value = 0.190 and p-value= 0.198, respectively, table 4). Scatter plots were also used to illustrate the relationships between the concentration of peaking Pb at P2 and birth weight. According to the plot (Figure 4) the correlation was low and non-significant. Along with log transformed elements, potential confounders were also included in the simple linear regression model on the basis of rational associations in previous studies [4, 44]. In simple linear regression model, there were significant (p-value < 0.05) association with birth weight and mother's age, parity, gestational age, mother's height, pre-pregnancy weight, BMI of the mother, gender of baby and Pb at both P1 and P2 (Table 4). Mother's age one of most significant and relevant positive factor for determining child's birth weight. (p-value = 0.010). It means increasing mother's age by one year 16.5 gm increasing the birth weight. Parity, mother's height and gestational age are constituted as a positive predictor for birth weight (p-value < 0.001). By switching from girls to boys tends reduce birth weight (p-value = 0.006). Maternal pre-pregnancy smoking habits show no association with birth weight. No association between birth weight and education, household income, alcohol and smoking were seen.

Table 4: univariate linear regression of birth weight adjusting for different covariates. Weight Changes gram/unit (95%cl) and P-value

	2nd trimester (P1)					3rd days postpartum (P2)				
	[a]ß	[b]95% Cl	[c]R^2	[d]β standard	p-value	[a]ß	[b]95% Cl	[c]R^2	[d]β standard	p-value
Mother's age (years)	16.53	3.98 to 29.09	0.025	.159	**0.010**					
Education (years)	1.98	−20.9 to 24.9	0.0001	0.01	0.865					
Income >600 000 kr	7.71	−39.5 to 54.9	0.0004	0.02	0.748					
Parity (0-multipara)	124.61	58.94 to 190.24	0.051	0.23	**<0.001**					
Gestetional age (in days)	24.44	19.11 to 29.78	0.24	0.49	**<0.001**					
Mother's Body weight	10.56	6 to 15.13	0.074	.273	**<0.001**					
Mother's height (cm)	14.56	5.3 to 23.78	0.04	0.19	**0.002**					
BMI of mother kg/m^2)	22.78	9.07 to 36.49	0.04	0.19	**0.001**					
Gender of baby (boy/girl)	−173.28	−295.8 to −50.8	0.029	−0.17	**0.006**					
Alcohol	147.7	−94.7 to 390.1	0.006	0.07	0.231					
Smoking (yes/no)	−21.1	−187.6 to 145.3	0.0002	−0.01	0.803					
Cadmium log, **µ**g/L	−76.8	−302.3 to 148.6	0.002	−0.04	0.530	−153.31	−429.36 to 122.73	0.005	−.068	0.275
Arsenic log, **µ**g/L	19.8	−152.8 to 192.5	0.001	0.01	0.821	−40.8	−210 to 128.4	0.001	−.029	0.635
Lead log, **µ**g/L	−237.62	−595.9 to 120.64	0.007	−0.08	**0.190**	−250.02	−631.4 to 131.33	0.006	−0.08	**0.198**
Marcury log, **µ**g/L	81.6	−123.2 to 186.5	0.002	.049	0.433	−40.1	−283 to 202.9	0.0004	−0.02	0.740

Maternal body weight, height and blood sampling were taken at 18.2 weeks
Income based on annual household income.
All the metals are log transformed ((log_{10}^{x}) And taken at 2nd trimester (P1) and 3rd postpartum day (P2) time point.
Gestetional age detect by ultrasound.
Smoking status is yes/no through 2nd trimester of pregnancy.
Alcohol based on drinking habit(teetotaller) through their whole life
[a]ß Unstandradized beta, [b]95% Cl Confident interval, [c]R^2 pearson coralation, [d]β Standardized coefficient

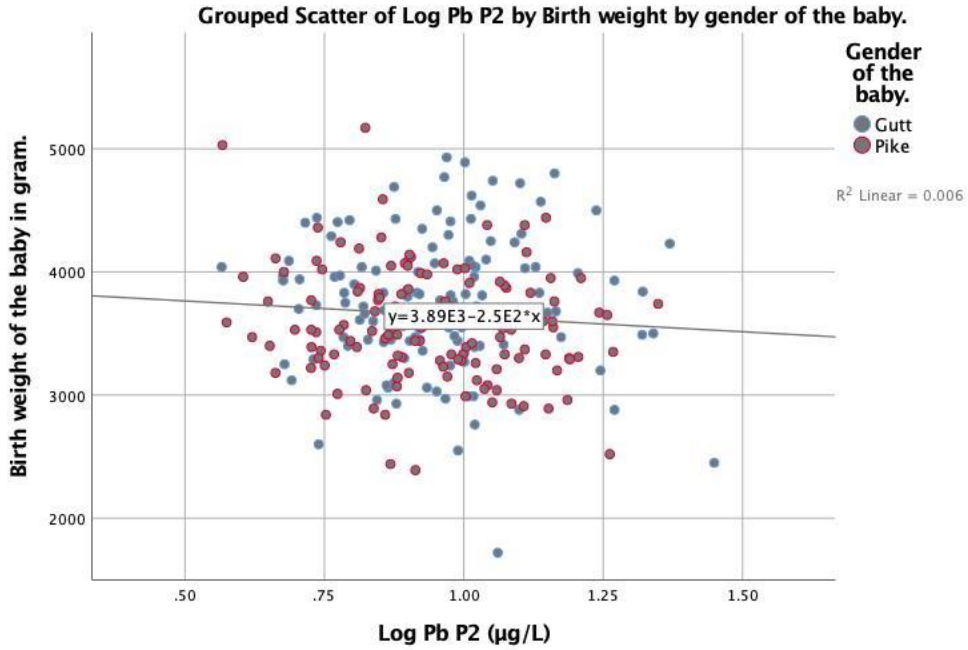

Figure 4: Scatter plot of log Pb 3 days postpartum (P2) versus birth weight of the baby grouped by gender (Pearson's r = 0.080)

3.5.2 Multiple linear regression

The regression model included all log toxic elements, variables with p-value < 0.25 revealed in the simple regression analyses. Due to inter-relation between BMI and height and weight, BMI were excluded from further testing. Age was also excluded in the final overall and stratified multivariable models due to p-value > 0.1. For some models (Pb and Cd separately) we also adjust for smoking due to its relation with the elements [56, 93]. Concentrations of toxic elements from both 2nd trimester and 3 days postpartum were tested. However, we choose to present the best model; all representing the highest maternal concentrations of the toxic elements, namely Pb, As and Hg at P2, and Hg at P1. Thus, data representing the lowest concentrations are not been presented.

The multiple regression model 1 (table 5) was run by all four toxic elements adjusted for the different covariates in both overall and gender stratified models. Moreover, this model suggested a negative association of the toxic element Pb at P2 with birth weight in baby girls (ß = -589.9, p-value = 0.010) meanwhile this level was not significant for boys. Further, maternal blood Cd, As and Hg level were not significant with birth weight in either the overall or the stratified models.

In model 2 (table 6) including Pb and Cd at P2 due to its naturally relationship, the model was, based on the F-test, improved from the initial model. In this model, maternal blood Pb level was strongly associated ß=-573.83, p = 0.009) with birth weight for girls while for boys was not significant (p = 0.931) at all. While maternal blood Cd at P2 was border significant (p = 0.050) for boy's counter wise not significant for girls.

In the model 3 (table 7) including only Pb at P2 and adjusted for the selected relevant variables. Overall, a significant association between Pb with birth weight was observed (ß -359, p-value = 0.020) but when stratified, only an effect for baby girls (ß=-567.7, p-value = 0.008) were found. We also built one model (model 5, table S1 in Supplementary file) including Pb adjusted for smoking habit of mother 6 months before pregnancy as a substitute for Cd. For girls, smoking reduced the effect of Pb on birth weight with 23% (p-value = 0.039). Evaluating the F-test between model 2, 3 and 5, model 3 predicted the best model between Pb and birth weight.

Simultaneously we also built a model 4 (table 8) to explore the birth weight by Cd alone adjusted for the selected covariates. We found significant association of Cd at P2 with birth weight in baby boys only (p-value = 0.045). Further, model 6 (table S2 in Supplementary file) with blood Cd at P2 adjusted for smoking habits was for boys borderline significant (p-value = 0.055). However, the association was not significant for the overall model. According to the F test, model 2 was, compared to model 4, less explained by its predictors.

However, besides the gender, all the models suggested that maternal age, gender, parity, gestational age and height (only boys) (all p-value < 0.001) were strong predictors for the birth weight. They are positive explanatory factors for the birth weight.

To conclude, multiple regression models adjusted for selected covariates, individual or in combinations, demonstrated statistically significant negative association of maternal whole blood Pb concentrations on birth weight for girls only; both in adjusted for all elements, adjusted for Cd, and adjusted for smoking habits and alone. According to the F-test, model including Pb alone, stated the best model. Likewise, Cd at P2, was also a negative predictor of birth weight, but only for boys, and with no association when adjusted for smoking habits or Pb. No significant association of other toxic elements like As and Hg with birth weight were found in the multiple regression models. Moreover, we

built models with As and Hg alone and simultaneously adjusted for associated elements, but these elements remained non-significant (the data is not presented in the thesis).

Table 5: Model 1- Association between maternal whole blood toxic elements Cd, As, Hg and Pb and birth weight adjusted for selected covariates, in a multivariable regression model – The MISA study (2007-2011)

	Overall			**Boy**			**Girl**		
	Birth weight (gm) (n= 257)			Birth weight (gm) (n=131)			Birth weight (gm) (n=126)		
	ß	95% Cl	p-value	ß	95% Cl	p-value	ß	95% Cl	p-value
Body weight at 2nd trimester (kg)	7.1	3.03 to 11.1	**0.001**	7.9	2.2 to 13.6	**0.006**	5.8	–.02 to 11.8	**0.051**
Height of Mother (cm)	8.7	.70 to 16.77	**0.033**	14.8	3.7 to 26.0	**0.009**	1.6	−10.2 to 13.4	0.789
Gender (boy/girl)	−178.8	−279.0 to −78.6	**0.001**						
Gestetional age[a] (in days)	22.9	18.06 to 27.7	**<0.001**	22.38	16.4 to 28.3	**<0.001**	23.6	15.0 to 32.3	**<0.001**
Parity (0-4)	146.2	97.07 to 195.06	**<0.001**	147.6	79.3 to 215.8	**<0.001**	142.1	68.5 to 215.7	**<0.001**
Log Cadmium in P2 (µg/L)	−148.7	−382.5 to 84.9	0.211	−317.5	−621.8 to 13.2	**0.041**	47.2	−342.3 to 436.9	0.811
Log Arsenic in P2 (µg/L)	−60.2	−205.19 to 84.69	0.414	−72.5	−274.8 to 129.8	0.479	−100.4	−322.1 to 436.9	0.371
Log Mercury in P1 (µg/L)	39.2	−137.03 to 215.6	0.661	40.83	−324.1 to 282.5	0.752	28.5	−225.6 to 282.7	0.824
Log Lead in P2 (µg/L)	−282.7	−603.1to 37.7	0.084	70.2	−214.3 to 296.0	0.775	−572.2	−1005.4 to −139.1	**0.010**
F	19.55			14.85			6.8		
R^2	.41			.49			.31		
P (over all)	**<.001**			**<.001**			**<.001**		

Maternal body weight, height and blood sampling were taken at 18.2 weeks
All the toxic elements concentration took in 3rd postpartum day (P2) except Hg which took in 2nd trimester (P1)
Cd, As, Hg and Pb are log transformed (log_{10}^{x}); and whole blood concentration
[a]Gestetional age detect by ultrasound and parity count as nullipara to multipara
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Table 6: Model 2- Association between toxic elements Pb, Cd and birth weight adjusted for other selected covariates, in a multivariable regression model – The MISA study (2007-2011)

	Overall			Boys			Girls		
	Birth weight(gm) (n=257)			Birth weight(gm) (n=131)			Birth weight (gm) (n=126)		
	ß	95% Cl	p-value	ß	95% Cl	p-value	ß	95% Cl	p-value
Body weight at 2nd trimester (kg)	7.2	3.2 to 11.3	**<0.001**	8.2	2.6 to 13.8	**0.004**	6.03	.16 to 11.9	**0.044**
Height of Mother (cm)	8.4	0.51 to 16.4	**0.037**	14.53	3.6 to 25.4	**0.010**	1.16	−10.52 to 12.85	0.844
Gender (boy/girl)	−181.4	−279.9 to −82.86	**<0.001**						
Gestetional age[a] (in days)	22.78	17.96 to 27.59	**<0.001**	22.16	16.3 to 28.01	**<0.001**	23.68	15.1 to 32.2	**<0.001**
Parity (0-4)	147.01	98.2 to 195.8	**<0.001**	146.03	78.3 to 213.69	**<0.001**	148.9	76.3 to 220.07	**<0.001**
Log Cadmium in P2 (µg/L)	−143.24	−375.9 to 89.43	0.226	−296.34	−592.7 to 0.037	0.050	23.59	−360.3 to 407.5	0.903
Log Lead in P2 (µg/L)	−305.02	−619.1 to 8.6	0.057	20.34	−441.6 to 482.2	0.931	−573.83	−1001.9 to −145.7	**0.009**
F	25.16			19.95			9.1		
R^2	0.41			0.49			0.31		
P (over all)	**<0.001**			**<0.001**			**<0.001**		

Maternal body weight, height and blood sampling were taken at 18.2 weeks
Cd and Pb in 2nd postpartum day(P2) are log transformed (log_{10}^{x}); and whole blood concentration
[a] gestetional age detect by ultrasound and parity count as nullipara to multipara.

Table 7: Model 3- Association between toxic element Pb with birth weight adjusted for other selected covariates, in a multivariable regression model – The MISA study (2007-2011)

	Overall			Boys			Girls		
	Birth weight(gm) (n=257)			Birth weight(gm) (n=131)			Birth weight (gm) (n=126)		
	ß	95% Cl	p-value	ß	95% Cl	p-value	ß	95% Cl	p-value
Body weight at 2nd trimester (kg)	7.5	3.5 to 11.6	**<0.001**	8.8	3.2 to 14.4	**0.002**	5.9	.21to 11.7	**0.042**
Height of Mother (cm)	7.9	.02 to 15.9	**0.049**	13.1	2.1 to 24	**0.019**	1.2	−10.4to 12.8	0.837
Gender (boy/girl)	−179.7	−278.3 to 81.1	**0<.001**						
Gestetional age (in days)	22.7	17.9 to 27.4	**<0.001**	22.2	16.3 to 28.7	**<0.001**	23.7	15.2 to 32.2	**<0.001**
Parity (0-4)	143.8	95.2 to 192.4	**<0.001**	141.7	73.2 to 210	**<0.001**	149	78.6 to 219.3	**<0.001**
Log Lead in P2 (µg/L)	−359	−660.7 to −57.2	**0.020**	−126.7	−569.6 to 316.2	0.572	−567.7	−982.2 to −153.1	**0.008**
F	29.0			22.6			10.9		
R^2	0.41			0.47			0.31		
P (over all)	**<0.001**			**<0.001**			<.001		

Maternal body weight, height and blood sampling were taken at 18.2 weeks
Pb in 3rd postpartum day (P2) is log transformed ($\log_{10}x$) and whole blood concentratio
Gestetional age detect by ultrasound and parity count as nullipara to multipara.

Table 8: Table 8: Model 4 Association between toxic element Cd with birth weight adjusted for other selected covariates, in a multivariable regression model- The MISA study (2007-2011)

	Overall			**Boys**			**Girls**		
	Birth weight(gm) (n=257)			Birth weight(gm) (n=131)			Birth weight (gm) n=(126)		
	ß	95% Cl	p-value	ß	95% Cl	p-value	ß	95% Cl	p-value
Body weight at 2nd trimester (kg)	6,8	2.8 to 10.8	**0.001**	8.5	3 to 14.1	**0.003**	5.1	−.97 to 11.3	0.098
Height of Mother (cm)	8.3	.32 to 16.3	**0.042**	14.7	3.8 to 25.7	**0.008**	−.12	−12.4 to 12.1	0.984
Gender (boy/girl)	−176.7	−275.6 to −77.7	**0.001**						
Gestetional age (in days)	22.9	18.1 to 27.8	**<0.001**	21.6	15.7 to 27.4	**<0.001**	23.3	14.2 to 32.3	**<0.001**
Parity (0-4)	145.9	96.9 to 195	**<0.001**	151.8	83.3to 232.8	**<0.001**	111	29.2 to 192.7	**0.008**
Log Cadmium in P2 (µ/L)	−206.2	−430.9 to 18.3	0.072	−287	−567.5 to −6.4	**0.045**	−81	−478.8 to 286.5	0.688
F	28.4			24.8			9.0		
R^2	0.40			0.49			0.27		
P (over all)	**<0.001**			**<0.001**			**<0.001**		

Maternal body weight, height and blood sampling were taken at 18.2 weeks
Cd in 3rd postpartum day (P2) is log transformed (log_{10}^{x}) and whole blood concentration
Gestetional age detect by ultrasound and parity count as nullipara to multipara.

4 Discussion

4.1 Main findings

This study evaluated the association between selected toxic elements exposure to the North Norwegian mothers and birth weight of newborn babies. Concentrations of Pb, Cd, Hg and As both in the 2nd trimester and 3 days postpartum were evaluated against birth weight. All of the toxic elements peaked at P2 except Hg, which was highest at the P1 time period. In multivariable models, those peaking elements were best to predict reduced birth weight. Stratified by gender, we revealed that an increasing maternal blood Pb concentration negatively influenced birth weight in baby girls. Besides, a high concentration of Cd in maternal blood increased the chances of reduced birth weight in baby boys when adjusted for alone.

4.2 Predictors of the best model

In this study, we examined the maternal whole blood concentration of selected toxic elements to attain the peaking level of these elements. We expected that these peaking concentration would have the highest effect. Both P1 and P2 were tested in the models and with the peaking levels as the best models. In multivariable model 1 (table 5) where we used all the log transformed elements with peaking levels, it explains 41% variances by its covariates (according to F test). During the gestational period, lots of physiological and metabolic changes occur to meet this growth and development of the fetus. Changes include the expansion of the volumes of blood and its contents, substantial changes in circulating hormones, essential elements and serum lipids. Consequently, it is rational to assume variations of blood levels of toxic elements during the gestational and postpartum periods. [88]. Earlier, the authors have shown that the decrease in birth weight per 1-µg/L increase in elements was more significant at lower concentrations than at higher concentrations without evidence of a lower threshold of effect [94]. A superlinear dose-response relationship, with the greatest decrement in birth weight occurring at the lowest level of Pb exposure, was predicted in a large data linkage study of Pb <100 µg/L [95]. Although in case of low levels in our study, we have seen an effect of Pb and Cd with birth weight.

4.3 Gender difference in the models

4.3.1 Lead

Models for Pb

In this study, when we tested out the effects Pb separately (in model 3), it shows, Pb causing reduce birth weight in the baby girl (ß =–567.8, p-value=.008). Stratification by gender appeared to explain more of the variability. Interestingly in model 1 (all four elements), 2 (Pb and Cd), 3 (Pb alone) and S1 (Pb and smoking), maternal whole blood Pb at P2 were significant for girls but reversibly non-significant for boys. Moreover, when we adjusted Pb with smoking the association becomes weaker because smoking heightens the effect of Pb. On the other hand, in model 2 (Pb and Cd) maternal whole blood Pb at P2 is significant for girls but not for boys since we have a high frequency for smoker mother of baby boys (22.5%).

Gender difference

Our study indicated that the adjusted maternal blood Pb levels (mean = 8.8 µg/L) were associated with statistically significant decrease in birth weight in baby girls (p-value = 0.008) when it alone or adjusted for other log transformed elements or with smoking. Interestingly, this association has not been observed for boys. However, when the model for girls adjusted with Cd, it shows 9.8 % effect change of Pb 573 gm of reducing birth weight compare to 567 g for Pb alone. However, the effect on the β-estimate was rather small (<10 %) and thus, not considered as a confounder or modifier [96]. In contrast, the Pb model adjusted with smoking showed a 20% reduced effect (> 20%) of Pb on birth weight compare to adjustment for Pb alone. Since smoking contributes to Pb concentrations, the adjustment either may mask the total effect of Pb on birth weight or smoking may also act as a confounder due to other toxic effects of smoking on birth weight [18]. Hence, based on both the β-effect, p-value, and the F-test, the model which was adjusted with the birth weight for Pb alone may be preferable to observe the real effect of Pb. Even though the frequency of smoking has observed more in boy's mother (22.5%) than in girl's mother (11.6%), there were no effects of Pb on birth weight for baby boys. So, we also consider the finding may be by chance as sometimes we could not deny the null hypothesis or unable to exclude unexplained confounding which is not detected.

However, our particular interest about the gender effect can be explained by the biological mechanism. Only a few other studies demonstrate gender differences of Pb effect on birth weight [84, 97]. An epidemiological study on the newborn in Port Pirie, South Australia has shown that girls are more vulnerable to post-natal Pb exposure. The author explains some of the factors and reasons for the variation. One of the primary justifications behind the gender inconsistency is the timing of exposure. Biologically founded that girls develop earlier than boys during early childhood; there may be a greater intrinsic biological susceptibility for the gender difference in mother womb [97]. So, it could be a reason for baby girls in the womb have higher susceptibility by Pb from their beginning. One study about low birth weight and macrosomia from Northern Ethiopia showed that along with other variables regarding mother bearing female neonates are at higher risk to deliver low birth weight neonates [1]. However, other studies found uneven result from our study [98-100]. The study about associations between prenatal lead exposure and birth outcomes modification by sex and GSTM1/GSTT1 polymorphism showed a significant inverse association of maternal blood Pb with birth weight and head circumference in baby boys [98]. The impaired placental function caused by prenatal Pb exposure may put male fetuses in a more disadvantageous position due to their higher growth rate and greater demands for nutrients compared with females [100].

Contrast with other studies

A counter association between prenatal Pb exposure and birth weight has been found in several studies. Three sequential longitudinal birth cohorts in Mexico City found that blood Pb concentration was correlated with lower birth weight with evidence that the decrease in weight is sustained until age 5[16, 71, 86]. A study about population included upstate New York found maternal Pb < 100 µg/L were associated with a small but statistically significant decrease in birth weight[95]. In another study of disadvantaged mother-infant pairs with a mean second trimester blood Pb level of 28 µg/L showed infants whose Pb levels changed from above to below the median were larger than infants whose Pb levels went from below to above the median[85].

In our study, a statistically significant ($p = <0.001$) rise in maternal blood lead from the P1 to P2 has been observed. Furthermore, research about the mobilization of lead from human bone tissue during pregnancy and lactation reports the geometric mean (GM) of blood Pb approximately 29 µg/L in Australian women. They calculated the rise in blood

Pb through the term of the whole pregnancy and found that blood Pb increases about 20% from the second trimester to delivery[101]. In contrast, in our study north Norwegian mothers has quite low levels of Pb in the 2nd trimester (P1) 7.5 µg/L and 3rd postpartum day (P2) 8.8 µg/L. Therefore, we calculated the Pb rise in blood through the 2nd trimester of pregnancy to 3rd postpartum day and found that blood Pb increases <10% from the second trimester to delivery [88]. Similar to our finding, previous evidence shows that even at very low levels, maternal blood Pb throughout pregnancy and the transportation of blood Pb from mother to child does not occur at random. It follows superlinear dose-response patterns established in cohorts with higher lead levels [95]. Moreover, in the earlier study by Taylor, the authors suggest that the decrease in birth weight per 1-µg/L increase in Pb was more significant at lower concentrations than at higher concentrations without evidence of a lower threshold of effect [75]

Safe levels

Pb is a readily permeable toxic element, and the adverse effects of low-level prenatal Pb exposure are associated with negative impacts in early childhood and later life [32]. Although in the case of low levels (mean= 8.8 µg/L), we have seen an effect of Pb on birth weight and the low contribution of the variation of birth weight. Health Canada has described the margin of safety between exposures and effects, giving sufficient evidence that health effects occur below 100 µg/L. Moreover, health effects have been associated with Pb level even as low as 10-20 µg/L [95, 102]. So, these reports provide evidence that the safety level for Pb is either very narrow or nonexistent [103-105]. Whereas, the CDC published a statement indicating that there is no threshold below which Pb exposure is acceptable. Later they have requested explicitly for additional research into pregnancy outcomes related to prenatal exposure [106].

4.3.2 Cadmium

Model for Cd

In this study, Cd had significant (p-value = 0.045) role in reducing baby boys' birth weight when adjusted for alone. But when Cd adjusted for smoking habits before pregnancy then there is no longer association with birth weight, meaning that smoking variable masks the effects of Cd on birth weight. By contrast, when Cd adjusted for smoking habits before pregnancy the effects of Cd on birth weight was elevating in model S2 (ß =−296.3, p-

value=0.055) than in the Cd only model 4 (ß =−287, p-value=0.045). However, the effects of Cd on birth weight tremendously elevated but significance level reached into no significance. When we adjusted the model Cd with the smoking variable the effect of Cd disappeared, and hence, was modified by the smoking variable. Therefore, the Cd was no longer associated with birth weight. Hence, smoking was not associated with birth weight [107].

Gender difference

In our study, 22.5% of pregnant women carrying baby boy smoke during the pregnancy, while this is 11.6% for the pregnant women carrying baby girls. For that reason, when we run a model for Cd alone it shows the association. However, when we adjusted the model Cd with smoking variable the effect of Cd disappeared, this was probably modified by the smoking variable. Therefore, Cd has no association with birth weight. In contrast, other studies found the most distinct consequences of cigarette smoking during pregnancy like restrictions to fetal growth, low birth weight, reduced fetal length, head circumference. These effects are stronger for male offspring [85, 86]. Additionally, the male fetus carrying women who smoke more than a ½ packet of cigarettes per day delivered neonates with reduced birth weight and smaller in size. However, we could not relate this observation to baby girls [85].

One explanation for gender susceptibility for Cd could be an increased intrauterine growth velocity in the male fetus than in females. So, it might be more vulnerable for growth retardation in the male fetus [85]. Additionally, the gender differences in the hormonal background could be an important consideration. High levels of gonadotrophins and testosterone appear in the male fetus in the second trimester. Further, the important barrier mechanism like skin barrier and lung maturation process is delayed in the male fetus while comparing to a female fetus. Estrogen accelerates the barrier process, while testosterone delays development of the barrier mechanism [108]. In contrast, some studies found the association of maternal blood Cd level with birth weight in baby girl [75, 93]. It has also been reported in few studies that the negative effect of maternal smoking in pregnancy is more pronounced in males than in females [33, 85, 86]. The author provides possible explanations about the effect of prenatal glucocorticoid exposure, which is appeared to be sex specific. Mothers, receiving glucocorticoid treatment, for asthma, 11β-HSD2 activity was significantly decreased in placentas of

female but not in male fetuses. This reduced 11β-HSD2 activity was associated with increased umbilical cord blood cortisol levels as well as, birth weight can be reduced in the female fetus[62]. In other epidemiologic studies, the authors explained that Cd might also interfere with the insulin-like growth factor (IGF) axis and thereby may reduce fetal growth in a sex-specific manner [109, 110]. In human pregnancies, both IGF-1 and insulin-like growth factor-binding protein 3 (IGFBP-3) are positively associated with birth weight [68]. Furthermore, the studies have found that IGF-1 and IGFBP-3 levels in umbilical cord blood/plasma were higher in female than in male infants[109, 110].

Contrast with other studies

Maternal blood Cd levels were significantly associated with the reduced birth weight of baby boys (p-value=0.045). Other studies also reported that maternal blood Cd has associations with newborn birth weight[111]. There is abundant evidence showing that maternal active smoking during pregnancy profoundly alters placental weight, morphology, and function [56, 112]. In our study, most of the pregnant women (22.5%) carrying boy smokes during the pregnancy than women who carrying girl (11.6%). Cd is not an essential element in humans, but due to a variety of industrial and other anthropogenic activities, it becomes one of the primary heavy metal contaminants in the environment. In our study, the peak mean concentration of Cd for smoker was 0.56 µg/L. But mother's whole blood concentration does not represent the fetal exposure. Some researchers claim a threshold value for the passage of Cd through the placenta. It seems that the human placenta serves as a selective barrier to Cd with an average attenuation of 40–50% [113]. However, other studies reveal cord blood Cd was only about 10% of that in maternal blood, confirming the findings of other studies that placenta acts as a relatively impermeable barrier to this element[114, 115]. Some research has also shown that maternal smoking during pregnancy can promote Cd accumulation in the placenta. However, those placental Cd concentrations are inversely correlated with neonates' birth weight in both smokers and nonsmokers. [17, 116].

Safe levels

In this study, we observed the peaking levels for both smoker and non-smoker at P2 time point. For the smoker, the mean value was 0.56 µg/L and for non-smokers 0.17 µg/L. The

margin of safety of exposures has been described by Federal Environmental agency, Germany. The reference value for non-smoking adults aged 18–69 years is 1 µg/L[117]. Though below the recommended levels, we have seen an effect of Cd on birth weight.

4.3.3 Mercury

Model for Hg

In our study, Hg was not associated with birth weight alone or adjusted by other log transformed elements (p-value=0.661). Some studies are constant with our study as they found no association between birth weight and maternal blood or cord blood Hg [53, 118]. Some other studies have found a negative association between Hg exposure and birth weight [51, 52]. However, high maternal blood Hg levels also a reason for association with low birth weight[119].

Contrast with other studies

We have not found any significant relationship between maternal blood Hg with birth weight. Similar to our study, some other studies also do not support the relationship between Hg exposure and birth weight [53, 118]. A study in a fishing community in Denmark found that total Hg in neither cord nor maternal blood was related to newborn size [11]. A recent British study showed that total Hg levels in umbilical cord blood were not related to birth weight [30]. Genetic predisposition, dietary patterns, the difference in concentrations and environmental factors could be the reasons behind the differences among studies [120, 121]. However, some studies found an inverse association between birth weight and prenatal Hg exposure in Poland and South Korea, and some studies suggest possible effects on child growth afterward [13]. Norwegian Mother and Child Cohort Study (MoBa) relates the dietary Hg exposure negatively with the birth weight of offspring significantly. They have stated that the highest exposure group has an increased risk of giving birth to babies being small for gestational age (SGA). If we compare the mean blood Hg level with our study, we found quite lower value 1.21 µg/L than MoBa study (1.88 µg/L) for pregnant women [52]. Birth cohort in Mexico City reported mean average blood Hg level for pregnant women 3.4 µg/L [121, 122]. A potential dose-response relationship between mercury exposure and adverse reproductive outcomes like the low birth weight has been mentioned by this publication [123]. Thus it is evident that high Hg

level relates with birth weight. Unlike MISA study group (n=282), MoBa study group which is also from the same location where the participation level was quite high, and the Hg level is also a bit higher from our participants level (n=62,941, MoBa level 1.88 µg/L)[52]. People in the Arctic region are usually exposed to Hg mainly through seafood consumption. Other sources, such as elemental Hg in the air and inorganic Hg in food items are minor sources of exposure. Consequently, the highest exposure levels to methylmercury (MeHg) in the Arctic region are found in coastal populations who consume more fish on a regular basis. These fishes are mainly top on the food chain like the whale, shellfish and freshwater fish [124]. Mercury levels in fish vary greatly according to species and origin [87]. Farmed fish generally contain less Hg than free-ranging fish from the open ocean. The highest values have been reported for wild fish catches in the Mediterranean Sea [87]. One important plausible mechanism for Hg exposure results decrease in birth weight via oxidative stress. Hg has been reported to cause oxidative stress, which may lead to lipid peroxidation and the generation of reactive oxygen. The study also suggested that heavy metals, such as Hg might induce oxidative stress caused by changes in the GSH and ATP metabolism [50]. However, in this study the participants of these food groups are low due to Norwegian national dietary advice regarding fish and seafood intake especially for pregnant and lactating women could be one of the reasons [19].

Safe levels

In this study, the mean Hg level 1.21 µg/L have been observed at P1 time point. The mean value is lower than the recommended value by Federal environmental agency, Germany which is 2.0 µg/L[117]. However, Safe levels for women at reproductive age recommended by US environmental protection agency is slightly higher than Federal environmental agency, Germany. The cut-off level for women is 5.8 µg/L [46, 117]. However, the joint FAO/WHO Expert Committee on Food Additives established the recommended safe level for Hg as Provisional Tolerable Weekly Intake (PTWI), which is 1.6 µg of MeHg/kg body weight per week [125].

4.3.4 Arsenic

Model for As

In our study, we did not find any association of As alone or adjusted for other log transformed elements with birth weight (p-value = 0.414), neither overall nor stratified by gender. In this study, the form of the As is a non-toxic form called inorganic arsenic [21]. This inorganic As methylate into the body and quickly passes through urine. Similarly, fish consumption was a positive predictor of blood As concentrations ($p < 0.01$) among women from our previous finding in the North Norwegian Mother-and-Child Study [21]. On the other hand, other studies where the As is in the toxic form found a significant association of As with birth weight, IUGR and small fetus [40, 41, 44]. Further, other studies have demonstrated that maternal high As exposure (measured by urinary total arsenic concentrations) is associated with birth weight, birth length, and risk of SGA for baby girls only [44, 126].

Contrast with other studies

We did not find any association between As and birth weight in the study group. Similar to our study other studies from China also did not find any association between mother blood As and birth weight [5, 44]. However, the link between As exposure and its effect on birth weight is established in many studies [35, 41, 42, 127]. One prospective cohort study from Ottawa County, Oklahoma estimated negative associations between maternal blood arsenic concentrations and birth outcomes while adjusting for exposure to Pb and Mn. However, their dietary source was different from our population [127]. Additionally, some studies found strong connection of As exposure during pregnancy and its association with fetal loss, small size at birth, infant morbidity and mortality [43, 128]. In other population, researchers have found that maternal blood As is significantly interrelated with birth weight. The reason behind this interrelation is due to higher As levels and metabolites in, different form and various sources [19, 129]. The mechanism of As and growth retardation involved pathways mediated via gestational age as well as pathways independent of gestational age. As has a possible role of shortening of gestation and intrauterine growth restriction. The biologic effects of inorganic As exposure support the biological plausibility of findings. As can generate reactive oxygen species and deplete antioxidant enzymes (e.g. glutathione) which leads to oxidative stress. Oxidative damage in early pregnancy can disrupt placental development, function and cause alteration, afterward which is responsible for hamper oxygen and nutrient supply to the growing fetus. Further, it also reasons for interruption of production and metabolism of fetal

growth regulating hormones leading to preterm delivery and IUGR [41]. Another acceptable explanation is epigenetic alterations. Prenatal arsenic exposure has been found associated with deregulation of microRNA expression profiles in umbilical cord blood and DNA methylation status in maternal and umbilical cord blood. MicroRNAs have an important role in normal placental development; and alteration of microRNA expression profiles have been associated with abnormal placentation and SGA births [42, 43]. As has a very common source which is fish, the person with the highest level of arsenic also had the highest level of fish consumption. Most of the blood As is in the form of arsenobetaine, which is considered nontoxic form, also able to passes readily (half-life is hours) [14]. In Norway, As, we detect in maternal blood, is nontoxic (arsenobetaine) organic form and also present in relatively low concentration [21, 88, 115]. Thus, we assumed that no clarifications are needed for its risk measurement.

Safe levels

According to WHO provisional guideline the safe levels for As is 10 µg/L[37] . This level is only for drinking water. While in our study the highest mean As was 1.74 µg/L which is far less than WHO recommended level. However, in North Norway main source of As is seafood in the form of arsenobetaine and nontoxic form [88, 115].

4.4 Effect of covariates on birth weight

Demographic characteristics are found to be associated with birth weight in other studies [79]. In our study maternal age, height, weight, BMI, parity, gestational age and gender of the baby has significantly associated with birth weight. Maternal body weight, gestational age, and parity were a recurring positive explanatory variable in all multivariable linear models. Gender plays an interesting role in birth weight. The reverse relation reveals that baby boys are more prone to low birth weight. However, boys appear to be heavier than girls respectively 3739 gm and 3566 gm. This result is confirmed by the preliminary report from the MISA cohort study [21]. These three predictors (gestational age, parity, and gender) for birth weight are well established[130]. Other cohorts, establish parity as a strong predictor for birth weight [21, 75, 130].

4.5 Strength and Limitation of the study

The strength of the study is that it has prospective longitudinal aspects. In our study, we collected data at a specific time point, namely at 2nd trimester (P1) and 3rd postpartum day (P2). For prospective aspect, we collected the baseline data from the day of 1st visit and afterward we collected the data from the follow-ups. During follow-ups, sample collections were done [90]. Since an objective of this study was to detect patterns of change in the concentrations of the selected toxic elements during gestational periods to detect the highest concentration throughout the period, external validity, in this case, maybe less critical. On the other hand, the statistically different concentration of the toxic elements through the P1 and P2 validated the strength of the study by choosing the best model [88]. Another strength of the study is that data for mother and newborn characteristics have been obtained from the Medical Birth Registry of Norway (MBRN).

Confounding usually measured as bias and often termed as mixing or blurring of effects. It commonly happens when the effect of an exposure intends to determine the occurrence of an outcome. But then actually it measures the effect of another factor, a confounding variable. In this study, we controlled for several factors like age, gestational age, parity, gender of the baby including smoking as a confounder for elements or predictors of birth weight. This cofounder, smoking, is suspected to hide the actual effect of Cd on birth weight. Confounding can also be controlled by adjusting it after completing a study using stratification or multivariate analysis[96]. Here, in this study, we ran several multivariable models with or without adjusting the smoking variable and at the end stratified by gender. As our study population is quite small, the model was not further stratified into a smoking group. But we controlled for several factors, which have an influence on birth weight. However, we might have missed adjusting for some relevant confounders related to elements or interaction terms.

Selection bias is actually termed as non-distinction and refers to a selection pattern where the dependence of the outcome category is conditional on across exposure categories [131, 132]. It is assumed that non-differential selection is rather harmless and does not cause serious bias. Nevertheless, if any dependence on the outcome category is not consistent across exposure categories then a termed called differential in selection or bias of estimation may arise. Selection bias due to loss to follow- up is also known as informative censoring. But in our previous report we have demonstrated relatively high

follow-ups, but bias can't be ruled out[21]. The selection bias could be controlled by the techniques such as stratification-based methods, weighted methods.

The study group was smaller than targeted even though enthusiastic campaign strategy like advertising through media, posters, web publications, encouragement by health professionals and field workers, etc. have been executed. Although several attempts were made to increase the participant's rate, the acceptance rate was slow-moving. So, this inescapable low participation rate can be a limitation. Study tiredness (request the participants for too many studies) among those eligible members were visible. The final sample size was less than targeted. Therefore, the study is likely less representative as small numbers might have reduced the chance of detecting a real effect. Another drawback of this study is involving a high percentage of older well-educated women than the MBRN registered mother that could further lead to selection bias [90, 132]. Because well-educated women are more aware of healthy food selection including fish [118] . Moreover, a direct comparison of the 262 subsets of the current study with the full cohort (n = 515) indicated lower mean for educational level average (15.6 and 15.9), but in contrast higher parity (respectively 1.8 and 1.0) and age (31.6 and 31.0). This is encouraging in terms of internal validity. The decision to analyze a subset of the study population has reduced the statistical impact of the result and thus places some restraint.

Information bias in general is a result of measurement errors. For the outcome variable birth weight, we collected data from MBRN with no missing data which is a strength of the study. However, for the measurement of birth weight, no standardized equipment was supplied, but measured by local hospital own electronic or beam scale. Hence different weight scale and human error may introduce to measurement bias. Self-reported information may have a high degree of intrinsic improbability. For example, the self-reported smoking habit has more probability for under report, likewise the FFQ and calculation of the amount of food may be under or over reported relying on the grade of healthy content. Another thing is the null value or smallest amount attribution on missing value could lead underestimation and misclassification [133]. Another type of bias of our concern is recall bias by the members to assemble FFQ or other lifestyle habits. A selective memory could lead to underreporting or overestimation. To minimize the recall bias FFQ focuses foods consumption on regular basis, so that it helps to identify consumers' trend in the population but still other factors could lead to bias. Further, and in addition to a

larger study group, a more sophisticated analysis may have brought more strengths into the results; and also including the mixture effect of elements. Essential elements, not included in this study, are due to the limitation of the content. But we have the concern about the influence of essential elements on the toxic elements; e.g. regulation of uptake, distribution and toxic effects [88].

4.6 Conclusion

A significant inverse association was found between maternal Pb concentration and birth weight in female neonates only. This significant correlation confirms the potential for sex response differences to Pb exposure. The relationship of maternal Cd concentration with birth weight in male neonates is reverse, but not for female neonates. However, when Cd is adjusted for smoking the relationship was not significant anymore. Further, we found a significant rise of toxic elements from P2>P1 except for Hg (P2<P1). This ascending pattern of maternal blood toxic elements establishes the maternal physiological and metabolic changes during pregnancy, at delivery and after delivery. Although the measured maternal concentrations of the toxic contaminants were relatively low, more substantial exposures would be a concern. This is especially a worry for mothers who smoke cigarettes during pregnancy.

Based on our findings, we emphases the significance of biomonitoring studies for reporting the gender differences for different toxic elements. From a public health perspective, we appraise the biomonitoring study as an important tool for organizing human health risks from exposure to environmental pollutants.

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Supplementary tables

Table S1: Model 5- Association between toxic element Pb with birth weight adjusted for other selected covariates, in a multivariable regression model- The MISA study (2007-2011)

	Overall			Boys			Girls		
	Birth weight(gm) (n=257)			Birth weight(gm) (n=131)			Birth weight(gm) (n=126)		
	ß	95% Cl	P-value	ß	95% Cl	P-value	ß	95% Cl	p-value
Body weight at 2nd trimester (kg)	7.08	3.05 to 11.1	**0.001**	8.1	2.2 to 13.8	**0.007**	5.5	.24 to 11.8	**0.054**
Height of Mother (cm)	8.06	−.034 to 16.15	**0.051**	14.02	2.6 to 25.7	**0.017**	1.2	−10.2 to 13.07	0.825
Gender (boy/girl)	−185.4	−285.2 to −85.6	**<0.001**						
[a]Gestetional age (in days)	22.5	17.7 to 27.6	**<0.001**	23.2	16.9 to 29.4	**<0.001**	22.2	15.2 to 32.3	**<0.001**
Parity (0-4)	149.9	100.9 to 198.87	**<0.001**	146.5	76.3 to 216.8	**<0.001**	158.2	79.5 to 220.8	**<0.001**
Smoking for 6 before pregnancy	−10.29	−129.4 to 108.8	0.865	−66.4	−228.2 to 95.4	0.418	61.2	−358.5 to 196.04	0.502
Log Lead in P2 (µ/L)	−292.2	−598.7 to 14.2	0.062	−105.4	−562 to −199.7	0.648	−439.2	−980.7 to −148.9	**0.039**
F	23.96			17.62			8.58		
R^2	0.40			0.46			0.30		
P (over all)	**<0.001**			**<0.001**			**<0.001**		

Maternal body weight, height and blood sampling were taken at 18.2 weeks
Pb in 3rd postpartum day (P2) is log transformed (log_{10}^{x}); and whole blood concentration
[a]Gestetional age detect by ultrasound and parity count as nullipara to multipara.
Smoking status is yes/no 6 months before pregnancy

Table S2:Model 6- Association between toxic element Cd with birth weight adjusted for other selected covariates, in a multivariable regression model- The MISA study (2007-2011)

	Overall			Boys			Girls		
	Birth weight(gm) (n=257)			Birth weight(gm) (n=131)			Birth weight(gm) (n=126)		
	ß	95% Cl	p-value	ß	95% Cl	p-value	ß	95% Cl	p-value
Body weight at 2nd trimester (kg)	6.3	2.3 to 10.4	**0.002**	7.6	1.9 to 13.4	**0.009**	4.5	−1.1 to 10.3	0.118
Height of Mother (cm)	8.8	0.71 to 17	**0.033**	15.7	4.2 to 27.2	**0.008**	1.3	−10.3 to 13	0.825
Gender (boy/girl)	−179.8	−279.4 to −80.2	**<0.001**						
[a]Gestetional age (in days)	22.8	1797 to 27.8	**<0.001**	23	16.3 to 29.2	**<0.001**	22.4	13.9 to 30.9	**<0.001**
Parity (0-4)	155.8	106 to 205	**<0.001**	151.8	82.3 to 221.2	**<0.001**	159.1	86. to 232.1	**<0.001**
Smoking for 6 before pregnancy	26.5	−100.5to 153.7	0.681	−13.1	−182.1 to 155.8	0.878	87.9	−110.1 to 285.9	0.381
Whole blood lg cadmium in p2	−231.2	−469.6 to 7.2	0.057	−297.3	−600.3 to 6.2	0.055	−157.1	−556.3 to 242	0.437
F	23.96			18.7			7.7		
R^2	0.40			0.48			0.28		
P (over all)	**<0.001**			**<0.001**			**<0.001**		

Maternal body weight, height and blood sampling were taken at 18.2 weeks
Cd in 3rd postpartum day (P2) is log transformed (log_{10}^{x}); and whole blood concentration
[a]Gestetional age detect by ultrasound and parity count as nullipara to multipara.
Smoking status is yes/no 6 months before pregnancy.

APPENDICES

Appendix 1	Spørreskjema MISA
Appendix 2	MISA LAB følgeskjema
Appendix 3	27.03.2007 REK
Appendix 4	Informasjosskriv MISA

2007
KONFIDENSIELT

MILJØGIFTER I SVANGERSKAPET OG I AMMEPERIODEN

ID-nr:

Universitetet i Tromsø

Romssa universitehta

Universitetet i Tromsø — Romssa universitehta

MILJØGIFTER I SVANGERSKAPET OG I AMMEPERIODEN

Vi ber deg fylle ut spørreskjemaet så nøye som mulig.

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, forhøy 0,5 til 1. Bruk blokkbokstaver.

Dersom du får for liten plass på enkelte spørsmål, vennligst noter på siste side, eller ta i bruk et ekstra ark.

Venligst besvar skjema innen en uke etter oppstart i prosjektet. Sendes sammen med blodtrykkssjema til UiT i vedlagte returkonvolutt.

Dato for utfylling av spørreskjema: dag mnd år

Dato .....

SOSIALE FORHOLD

Hva er ditt postnummer? .....

Hva er ditt fødselsår: .....

Hvor mange års skolegang/utdanning har du i alt,
ta også med grunnskole og videregående? Antall år

Hvor mange personer er det i ditt hushold? Voksne Barn

Hvor høy er den samlede bruttoinntekten i ditt hushold?

- ☐ Under 150 000 kr
- ☐ 150 000-300 000 kr
- ☐ 301 000-450 000 kr
- ☐ 451 000-600 000 kr
- ☐ 601 000-750 000 kr
- ☐ 751 000-900 000 kr
- ☐ Over 900 000 kr

Hva er ditt yrke?

.....

(Ikke skriv her →)

Beskriv kort din arbeidsplass og arbeidsoppgaver så nøyaktig som mulig:
(Eksempel: skole/undervisning, sykehus/ pasientarbeid/cellegift, butikk/ klær, renseri/renser klær, kontor/dataarbeid, frisør/kunder)

.....

(Ikke skriv her →)

Hva er din arbeidssituasjon? (Sett om nødvendig flere kryss)

- ☐ Arbeider heltid
- ☐ Arbeider deltid
- ☐ Hjemmeværende
- ☐ Under utdanning
- ☐ Arbeidssøkende
- ☐ Under attføring
- ☐ Uføretrygdet

Er du sykemeldt? (Sett ett kryss i hver kolonne)

- ☐ Nei
- ☐ Delvis sykemeldt
- ☐ Fullt sykemeldt

Hvordan er du sykemeldt?

- ☐ Sykemeldt korttids
- ☐ Sykemeldt langtids

OPPVEKST

Hva var din bostedskommune da du ble født, og i hvilke kommuner i Norge har du bodd lengre enn ett år?

Kommune	Fra årstall	Til årstall	*(Ikke skriv her →)*
1 Ved fødsel:			
2			
3			
4			
5			
6			
7			

FAMILIE- OG SPRÅKBAKGRUNN

I Nord-Norge bor det folk med ulik etnisk bakgrunn. Det vil si at de snakker ulike språk og har ulike kulturer. Eksempler på etnisk bakgrunn eller etnisk gruppe er norsk, samisk og kvensk.

Hvilket hjemmespråk har/hadde du, dine foreldre og besteforeldre? (sett ett eller flere kryss)

	Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
Morfar	☐	☐	☐	☐	☐	.....
Mormor	☐	☐	☐	☐	☐	.....
Farfar	☐	☐	☐	☐	☐	.....
Farmor	☐	☐	☐	☐	☐	.....
Far	☐	☐	☐	☐	☐	.....
Mor	☐	☐	☐	☐	☐	.....
Jeg selv	☐	☐	☐	☐	☐	.....

Hva er din, din fars og din mors etniske bakgrunn?
(sett ett eller flere kryss)

	Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
Min bakgrunn	☐	☐	☐	☐	☐	.....
Mors bakgrunn	☐	☐	☐	☐	☐	.....
Fars bakgrunn	☐	☐	☐	☐	☐	.....

Hva regner du deg selv som? (sett ett eller flere kryss)

Norsk ☐ Samisk ☐ Kvensk ☐ Annet ☐ Dersom annet beskriv .....

SVANGERSKAPET

Var dette svangerskapet planlagt?

☐ Ja ☐ Nei

Dersom JA, hvor mange måneder tok det før du ble gravid?

Antall mnd. ☐☐

Trengte du hjelp til å bli gravid i dette svangerskapet?
(Behandlet for barnløshet; hormonstimulering, IVF, mikroinjeksjon ol.)

☐ Ja ☐ Nei

Dersom JA, hva var årsaken?

.....

Hvilken behandling fikk du da?

.....

MORSMELK SOM BABY

Ammet din mor deg da du var baby?

☐ Ja ☐ Nei

Dersom JA, hvor mange måneder til sammen fikk du morsmelk?

Totalt antall mnd. med morsmelk ☐☐ Vet ikke ☐

SELVOPPLEVD HELSE

Oppfatter du din helse som:

☐ Meget god ☐ God ☐ Dårlig ☐ Meget dårlig

VEKT

Hvor mye veide du før svangerskapet? *(I hele kg)*.... ☐☐☐

Hva var din egen fødselsvekt som nyfødt baby?

(Gram) ☐☐☐☐ Vet ikke ☐

Har du noen gang hatt vekttap på 5 kg eller mer, i så fall hvor mange ganger?

☐ Ja ☐ Nei Antall ganger ☐☐

FYSISK AKTIVITET

Vi ber deg angi din fysiske aktivitet etter en skala fra svært liten til svært mye ved 14 års alder, før svangerskapet og i dag. Skalaen nedenfor går fra 1-10. Med fysisk aktivitet mener vi både arbeid i hjemmet og i yrkeslivet samt trening og annen fysisk aktivitet som turgåing ol.

	Svært lite									Svært mye
Alder	1	2	3	4	5	6	7	8	9	10
14 år.....	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Før svangerskapet.....	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
I dag.....	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

RØYK OG ALKOHOL

Beskriv dine røykevaner før og i dette svangerskapet?
(Sett ett kryss)

	Ikke røyker	Av og til	Daglig
6 mnd før svangerskapet.....	☐	☐	☐
Ved svangerskapets start.....	☐	☐	☐
I dag.....	☐	☐	☐

Dersom du røyker eller har røykt, angi antall pr. dag eller pr uke?

	Antall pr dag	Antallpr uke
6 mnd før svangerskapet.....	☐☐	☐☐
Ved svangerskapets start.....	☐☐	☐☐
I dag.....	☐☐	☐☐

Dersom du røyker daglig eller tidligere har røykt daglig, hvor mange år har du da røykt til sammen? Antall år ☐☐

Er du til daglig utsatt for passiv røyking?

☐ Ja ☐ Nei Antall timer daglig ☐☐

Er du totalavholdskvinne?

☐ Ja ☐ Nei

Hvis NEI, hvor ofte og hvor mye har du drukket før dette svangerskapet?
(sett ett kryss for hver linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-4 pr. uke	5-6 pr. uke	1+ pr. dag
Lettøl/cider *(0,5 l)*.....	☐	☐	☐	☐	☐	☐	☐
Øl/rusbrus *(0,5 l)*.....	☐	☐	☐	☐	☐	☐	☐
Vin *(glass)*.....	☐	☐	☐	☐	☐	☐	☐
Brennevin *(drink/shot)*.....	☐	☐	☐	☐	☐	☐	☐
Likør/Hetvin *(glass)*.....	☐	☐	☐	☐	☐	☐	☐

Dersom NEI, hvor ofte og hvor mye har du drukket i dette svangerskapet?
(sett ett kryss for hver linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-4 pr. uke	5-6 pr. uke	1+ pr. dag
Lettøl/cider *(0,5 l)*.....	☐	☐	☐	☐	☐	☐	☐
Øl/rusbrus *(0,5 l)*.....	☐	☐	☐	☐	☐	☐	☐
Vin *(glass)*.....	☐	☐	☐	☐	☐	☐	☐
Brennevin *(drink/shot)*.....	☐	☐	☐	☐	☐	☐	☐
Likør/Hetvin *(glass)*.....	☐	☐	☐	☐	☐	☐	☐

TRAN, OMEGA-3 OG FISKEOLJE

Bruker du flytende tran/omega-3/fiskeolje?

☐ Ja ☐ Nei

Hvis JA, hvor ofte tar du flytende tran/omega-3/fiskeolje?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-6 pr. uke	daglig
Om vinteren.....	☐	☐	☐	☐	☐
Resten av året.....	☐	☐	☐	☐	☐

Hvilken type flytende tran/omega-3/fiskeolje bruker du vanligvis, og hvor mye pleier du å ta hver gang?

	1 ts	½ ss	1+ ss
Navn:	☐	☐	☐
Navn:	☐	☐	☐
Navn:	☐	☐	☐

Bruker du kapsler/piller med tran/omega-3/fiskeolje?

☐ Ja ☐ Nei

Hvis JA, hvor ofte tar du kapsler/piller med tran/omega-3/fiskeolje (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-6 pr. uke	daglig
Om vinteren	☐	☐	☐	☐	☐
Resten av året	☐	☐	☐	☐	☐

Hvilken type kapsler/piller med tran/omega-3/fiskeolje bruker du vanligvis, og hvor mange pleier du å ta hver gang?

Navn ..... Antall ☐

Navn ..... Antall ☐

Navn ..... Antall ☐

KOSTTILSKUDD

Bruker du kosttilskudd?

☐ Ja ☐ Nei

Hvis JA, hvor ofte bruker du kosttilskudd? (Sett ett kryss pr. linje)

Navn på kosttilskudd	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-6 pr. uke	daglig
.....	☐	☐	☐	☐	☐
.....	☐	☐	☐	☐	☐
.....	☐	☐	☐	☐	☐
.....	☐	☐	☐	☐	☐

KOSTHOLD

Påvirker noen av følgende forhold kostholdet ditt?
(Sett om nødvendig flere kryss)

- ☐ Er vegetarianer/veganer
- ☐ Spiser ikke norsk kost til daglig
- ☐ Har allergi/intoleranse
- ☐ Kronisk sykdom
- ☐ Har anoreksi
- ☐ Har bulimi
- ☐ Prøver å gå ned i vekt
- ☐ Lav glykemisk mat

Vi er interessert i å få kjennskap til hvordan kostholdet ditt er vanligvis. Kryss av for hvert spørsmål om hvor ofte du i gjennomsnitt siste året har brukt den aktuelle matvaren, og hvor mye du pleier å spise/drikke hver gang.

DRIKKE

Hvor mange glass melk drikker du vanligvis av hver type?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-4 pr. uke	5-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Helmelk *(søt, sur)*	☐	☐	☐	☐	☐	☐
Lettmelk *(søt, sur)*	☐	☐	☐	☐	☐	☐
Ekstra lettmelk	☐	☐	☐	☐	☐	☐
Skummet *(søt, sur)*	☐	☐	☐	☐	☐	☐

Hvor mange kopper kaffe/te drikker du vanligvis av hver sort?
(Sett ett kryss for hver linje)

	aldri/ sjelden	1-6 pr. uke	1 pr. dag	2-3 pr. dag	4-5 pr. dag	6-7 pr. dag	8+ pr. dag
Kokekaffe	☐	☐	☐	☐	☐	☐	☐
Traktekaffe	☐	☐	☐	☐	☐	☐	☐
Pulverkaffe	☐	☐	☐	☐	☐	☐	☐
Presskanne kaffe	☐	☐	☐	☐	☐	☐	☐
Anne kaffe *(latte, espresso ol.)*	☐	☐	☐	☐	☐	☐	☐
Svart te	☐	☐	☐	☐	☐	☐	☐
Grønn te	☐	☐	☐	☐	☐	☐	☐

Bruker du følgende i kaffe eller te:

	Kaffe		Te	
Sukker *(ikke kunstig søtstoff)*	☐ Ja	☐ Nei	☐ Ja	☐ Nei
Melk eller fløte	☐ Ja	☐ Nei	☐ Ja	☐ Nei

Hvor mange glass vann drikker du vanligvis?

	aldri/ sjelden	1-6 pr. uke	1 pr. dag	2-3 pr. dag	4-5 pr. dag	6-7 pr. dag	8+ pr. dag
Springvann/flaskevann	☐	☐	☐	☐	☐	☐	☐

Hvor mange glass juice, saft og brus drikker du vanligvis?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. uke	4-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Appelsinjuice	☐	☐	☐	☐	☐	☐
Annen juice	☐	☐	☐	☐	☐	☐
Saft/brus med sukker	☐	☐	☐	☐	☐	☐
Saft/brus sukkerfri	☐	☐	☐	☐	☐	☐

YOGHURT/KORNBLANNING

Hvor ofte spiser du yoghurt (1 beger)? (Sett ett kryss)

- ☐ Aldri/sjelden
- ☐ 1 pr. uke
- ☐ 2-3 pr. uke
- ☐ 4+ pr. uke

Hvor ofte spiser du kornblanding, havregryn eller müsli?
(Sett ett kryss)

- ☐ Aldri/sjelden
- ☐ 1-3 pr. uke
- ☐ 4-6 pr. uke
- ☐ 1+ pr. dag

BRØDMAT

Hvor mange skiver brød/rundstykker og knekkebrød/ skonrokker spiser du vanligvis?
(1/2 rundstykke = 1 brødskive) (Sett ett kryss for hver linje)

	aldri/ sjelden	1-4 pr. uke	5-7 pr. uke	2-3 pr. dag	4-5 pr. dag	6+ pr. dag
Grovbrød	☐	☐	☐	☐	☐	☐
Kneip/halvfint	☐	☐	☐	☐	☐	☐
Fint brød/baguett	☐	☐	☐	☐	☐	☐
Knekkebrød o.l.	☐	☐	☐	☐	☐	☐

Nedenfor er det spørsmål om bruk av ulike påleggstyper. Vi spør om hvor mange brødskiver med det aktuelle pålegget du pleier å spise. Dersom du også bruker matvarene i andre sammenhenger enn til brød (f. eks. til vafler, frokostblandinger, grøt), ber vi om at du tar med dette når du besvarer spørsmålene.

På hvor mange brødskiver bruker du? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. uke	4-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Syltetøy	☐	☐	☐	☐	☐	☐
Brunost helfet	☐	☐	☐	☐	☐	☐
Brunost halvfet/mager	☐	☐	☐	☐	☐	☐
Hvitost helfet	☐	☐	☐	☐	☐	☐
Hvitost halvfet/mager	☐	☐	☐	☐	☐	☐
Kjøttpålegg, leverpostei	☐	☐	☐	☐	☐	☐
Rekesalat, italiensk o.l.	☐	☐	☐	☐	☐	☐

På hvor mange brødskiver pr. uke har du i gjennomsnitt siste året spist? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. uke	2-3 pr. uke	4-6 pr. uke	7-9 pr. uke	10+ pr. uke
Makrell i tomat, røkt makrell	☐	☐	☐	☐	☐	☐
Kaviar	☐	☐	☐	☐	☐	☐
Sild/ansjos/sardiner	☐	☐	☐	☐	☐	☐
Laks/ørret *(gravet/røkt)*	☐	☐	☐	☐	☐	☐
Svolværpostei/Lofotpostei	☐	☐	☐	☐	☐	☐
Krabbepålegg	☐	☐	☐	☐	☐	☐
Annet fiskepålegg	☐	☐	☐	☐	☐	☐

Hva slags fett bruker du vanligvis på brødet?

- ☐ Bruker ikke fett på brødet
- ☐ Smør
- ☐ Hard margarin *(f. eks. Per, Melange)*
- ☐ Myk margarin *(f. eks. Soft, Vita, Solsikke)*
- ☐ Smørblandet margarin *(f.eks. Bremyk)*
- ☐ Brelett
- ☐ Lettmargarin *(f. eks. Soft light, Letta, Vita Lett)*
- ☐ Middels lett margarin *(f. eks. Olivero, Omega)*

Dersom du bruker fett på brødet, hvor tykt lag pleier du å smøre på? (En kuvertpakke med margarin veier 12 gram).
(Sett ett kryss)

- ☐ Skrapet (3 g)
- ☐ Tynt lag (5 g)
- ☐ Godt dekket (8 g)
- ☐ Tykt lag (12 g)

FRUKT OG GRØNNSAKER

Hvor ofte spiser du frukt? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-4 pr. uke	5-6 pr uke	1 pr dag	2+ pr dag
Epler/pærer	☐	☐	☐	☐	☐	☐	☐
Appelsiner o.l.	☐	☐	☐	☐	☐	☐	☐
Bananer	☐	☐	☐	☐	☐	☐	☐
Annen frukt	☐	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du ulike typer grønnsaker? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2 pr. uke	3 pr uke	4-5 pr uke	6-7 pr uke
Gulrøtter	☐	☐	☐	☐	☐	☐	☐
Kål	☐	☐	☐	☐	☐	☐	☐
Kålrot	☐	☐	☐	☐	☐	☐	☐
Brokkoli/blomkål	☐	☐	☐	☐	☐	☐	☐
Blandet salat	☐	☐	☐	☐	☐	☐	☐
Tomat	☐	☐	☐	☐	☐	☐	☐
Grønnsakblanding *(frossen)*	☐	☐	☐	☐	☐	☐	☐
Løk	☐	☐	☐	☐	☐	☐	☐
Andre grønnsaker	☐	☐	☐	☐	☐	☐	☐

For de grønnsakene du spiser, kryss av for hvor mye du spiser hver gang: (Sett ett kryss for hver sort):

Gulrøtter *(stk)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+
Kål *(dl)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+
Kålrot *(dl)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+
Brokkoli/blomkål *(buketter)*	☐ 1-2	☐ 3-4	☐ 5+	
Blandet salat *(dl)*	☐ 1	☐ 2	☐ 3	☐ 4+
Tomat *(stk)*	☐ ¼	☐ ½	☐ 1	☐ 2+
Grønnsakblanding *(frossen) (dl)*	☐ ½	☐ 1	☐ 2	☐ 3+

Hvor mange poteter spiser du vanligvis (kokte, stekte, mos)?
(Sett ett kryss)

- ☐ Aldri/sjelden
- ☐ 1-4 pr uke
- ☐ 5-6 pr. uke
- ☐ 1 pr dag
- ☐ 2 pr dag
- ☐ 3 pr dag
- ☐ 4+ pr dag

RIS, SPAGHETTI, GRØT, SUPPE

Hvor ofte bruker du ris og spaghetti/makaroni?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2 pr. uke	3+ pr uke
Ris	☐	☐	☐	☐	☐
Spaghetti, makaroni, nudler	☐	☐	☐	☐	☐

Hvor ofte spiser du grøt?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-6 pr. uke	1+ pr. dag
Risengrynsgrøt	☐	☐	☐	☐	☐	☐
Annen grøt *(havre o.l.)*	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du suppe?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2 pr. uke	3+ pr uke
Som hovedrett	☐	☐	☐	☐	☐
Som forrett, lunsj eller kveldsmat	☐	☐	☐	☐	☐

FISK

Vi vil gjerne vite hvor ofte du pleier å spise fisk, og ber deg fylle ut spørsmålene om fiskeforbruk så godt du kan. Tilgangen på fisk kan variere gjennom året. Vær vennlig å markere i hvilke årstider du spiser de ulike fiskeslagene.

	aldri/ sjelden	like mye hele året	vinter	vår	sommer	høst
Torsk, sei, hyse, lyr	☐	☐	☐	☐	☐	☐
Steinbit, flyndre, uer	☐	☐	☐	☐	☐	☐
Laks, ørret	☐	☐	☐	☐	☐	☐
Kveite	☐	☐	☐	☐	☐	☐
Makrell	☐	☐	☐	☐	☐	☐
Sild	☐	☐	☐	☐	☐	☐
Tunfisk *(ikke på boks)*	☐	☐	☐	☐	☐	☐
Ferskvannsfisk (*Abbor, gjedde, røye, sik, harr)*	☐	☐	☐	☐	☐	☐
Annen fisk	☐	☐	☐	☐	☐	☐

Med tanke på de periodene av året der du spiser fisk, hvor ofte pleier du å spise følgende til middag? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Kokt torsk, sei, hyse, lyr	☐	☐	☐	☐	☐
Stekt torsk, sei, hyse, lyr	☐	☐	☐	☐	☐
Steinbit, flyndre, uer	☐	☐	☐	☐	☐
Laks, ørret	☐	☐	☐	☐	☐
Kveite	☐	☐	☐	☐	☐
Makrell	☐	☐	☐	☐	☐
Sild	☐	☐	☐	☐	☐
Tunfisk *(ikke på boks)*	☐	☐	☐	☐	☐
Ferskvannsfisk (*Abbor, gjedde, røye, sik, harr)*	☐	☐	☐	☐	☐
Annen fisk	☐	☐	☐	☐	☐

Dersom du spiser fisk, hvor mye spiser du vanligvis pr. gang? (1 skive/stykke = 150 gram)

Kokt fisk *(skive)*	☐ 1	☐ 1,5	☐ 2	☐ 3+
Stekt fisk *(stykke)*	☐ 1	☐ 1,5	☐ 2	☐ 3+

Hvor mange ganger pr. år spiser du fiskeinnmat? (Sett ett kryss for hver linje)

	aldri	1-3	4-6	7-9	10-15	16+
Rogn	☐	☐	☐	☐	☐	☐
Fiskelever	☐	☐	☐	☐	☐	☐

Dersom du spiser fiskelever, hvor mange spiseskjeer pleier du å spise hver gang? (Sett ett kryss)

☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Hvor ofte bruker du følgende typer fiskemat? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Fiskekaker/pudding/boller	☐	☐	☐	☐	☐
Plukkfisk/fiskegrateng	☐	☐	☐	☐	☐
Frityrfisk/fiskepinner	☐	☐	☐	☐	☐
Andre fiskeretter	☐	☐	☐	☐	☐

Hvor stor mengde pleier du vanligvis å spise av de ulike rettene? (Sett ett kryss for hver linje)

Fiskekaker/pudding/boller *(stk.)* *(2 fiskeboller=1 fiskekake)*	☐ 1	☐ 2	☐ 3	☐ 4+
Plukkfisk, fiskegrateng *(dl)*	☐ 1-2	☐ 3-4	☐ 5+	
Frityrfisk, fiskepinner *(stk.)*	☐ 1-2	☐ 3-4	☐ 5-6	☐ 7+

I tillegg til informasjon om fiskeforbruk er det viktig å få kartlagt hvilket tilbehør som blir servert til fisk.
Hvor ofte bruker du følgende til fisk? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Smeltet/fast smør	☐	☐	☐	☐	☐
Smeltet/fast margarin/fett	☐	☐	☐	☐	☐
Seterrømme *(35%)*	☐	☐	☐	☐	☐
Lettrømme *(20%)*	☐	☐	☐	☐	☐
Saus med fett *(hvit/brun)*	☐	☐	☐	☐	☐
Saus uten fett *(hvit/brun)*	☐	☐	☐	☐	☐

For de ulike typene tilbehør du bruker til fisk, vær vennlig å kryss av for hvor mye du vanligvis pleier å spise.

Smeltet/fast smør *(ss)*	☐ ½	☐ 1	☐ 2	☐ 3	☐ 4+
Smeltet/fast margarin *(ss)*	☐ ½	☐ 1	☐ 2	☐ 3	☐ 4+
Seterrømme *(ss)*	☐ ½	☐ 1	☐ 2	☐ 3	☐ 4+
Lettrømme *(ss)*	☐ ½	☐ 1	☐ 2	☐ 3	☐ 4+
Saus med fett *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+
Saus uten fett *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+

Hvor mange ganger i året spiser du hval-/selkjøtt? (Sett ett kryss)

aldri	1-3	4-6	7-9	10-15	16+
☐	☐	☐	☐	☐	☐

Hvor mange ganger i året spiser du det brune kjøttet i krabbe (utenom krabbepålegg)? (Sett ett kryss)

aldri	1-3	4-6	7-9	10-15	16+
☐	☐	☐	☐	☐	☐

Hvor mange ganger i året spiser du andre skalldyr (reker og skjell)? (Sett ett kryss)

aldri	1-3	4-6	7-9	10-15	16+
☐	☐	☐	☐	☐	☐

Hvor mange måseegg eller egg fra annen sjøfugl spiser du i året? (Sett ett kryss)

aldri	1-3	4-6	7-9	10-15	16+
☐	☐	☐	☐	☐	☐

KJØTT

Hvor ofte spiser du følgende viltprodukter? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Reinkjøtt	☐	☐	☐	☐	☐	☐
Andre matvarer fra rein *(lever, nyre, margebein, hjerte, tunge, blod og annet)*	☐	☐	☐	☐	☐	☐
Elgkjøtt, andre matvarer fra elg	☐	☐	☐	☐	☐	☐
Rype, annen viltfugl	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du følgende kjøtt- og fjærkreretter? (Sett ett kryss for hver rett)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Steik *(okse, svin, får)*	☐	☐	☐	☐	☐
Koteletter	☐	☐	☐	☐	☐
Biff	☐	☐	☐	☐	☐
Kjøttkaker, karbonader	☐	☐	☐	☐	☐
Pølser	☐	☐	☐	☐	☐
Gryterett, lapskaus	☐	☐	☐	☐	☐
Pizza med kjøtt	☐	☐	☐	☐	☐
Kylling	☐	☐	☐	☐	☐
Bacon, flesk	☐	☐	☐	☐	☐
Innmat får/storfe	☐	☐	☐	☐	☐
Andre kjøttretter	☐	☐	☐	☐	☐

Dersom du spiser følgende retter, oppgi mengden du vanligvis spiser: (Sett ett kryss for hver linje)

Steik *(skiver)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5+
Koteletter *(stk.)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+	
Kjøttkaker, karbonader *(stk)*	☐ 1	☐ 2	☐ 3	☐ 4+	
Pølser *(stk à 150g)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+	
Gryterett, lapskaus *(dl)*	☐ 1-2	☐ 3	☐ 4	☐ 5+	
Pizza m/kjøtt *(stykke à 100 g)*	☐ 1	☐ 2	☐ 3	☐ 4+	

Hvilke sauser bruker du til kjøttretter og pastaretter?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Brun saus	☐	☐	☐	☐	☐
Sjysaus	☐	☐	☐	☐	☐
Tomatsaus	☐	☐	☐	☐	☐
Saus med fløte/rømme	☐	☐	☐	☐	☐

Hvor mye bruker du vanligvis av disse sausene?
(Sett ett kryss for hver linje)

Brun saus *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+
Sjysaus *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+
Tomatsaus *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+
Saus med fløte/rømme *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+

ANDRE MATVARER

Hvor mange egg spiser du vanligvis i løpet av en uke (stekte, kokte, eggerøre, omelett)? (Sett ett kryss)

☐ 0 ☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Hvor ofte spiser du iskrem (til dessert, Krone-is osv.)?
Sett ett kryss for hvor ofte du spiser iskrem om sommeren, og ett kryss for resten av året

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Om sommeren	☐	☐	☐	☐	☐
Resten av året	☐	☐	☐	☐	☐

Hvor mye is spiser du vanligvis pr. gang? (Sett ett kryss)

☐ 1 dl ☐ 2 dl ☐ 3 dl ☐ 4+ dl

Hvor ofte spiser du bakevarer som boller, kaker, wienerbrød eller småkaker? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4-6 pr. uke	1+ pr. dag
Gjærbakst *(boller ol.)*	☐	☐	☐	☐	☐	☐
Wienerbrød, kringle	☐	☐	☐	☐	☐	☐
Kaker	☐	☐	☐	☐	☐	☐
Pannekaker	☐	☐	☐	☐	☐	☐
Vafler	☐	☐	☐	☐	☐	☐
Småkaker, kjeks	☐	☐	☐	☐	☐	☐
Lefser, lomper	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du dessert? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Pudding sjokolade/karamell	☐	☐	☐	☐	☐	☐
Riskrem, fromasj	☐	☐	☐	☐	☐	☐
Kompott, fruktgrøt, hermetisk frukt	☐	☐	☐	☐	☐	☐
Jordbær *(friske, frosne)*	☐	☐	☐	☐	☐	☐
Andre bær *(friske, frosne)*	☐	☐	☐	☐	☐	☐

Hvor ofte spiser/drikker du ville bær, inkludert syltetøy og saft? (Ikke industrifremstilt)? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Multebær	☐	☐	☐	☐	☐	☐
Tyttebær	☐	☐	☐	☐	☐	☐
Blåbær	☐	☐	☐	☐	☐	☐
Krøkebær	☐	☐	☐	☐	☐	☐
Andre bær	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du selvplukket sopp? (Sett ett kryss pr. linje)

aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
☐	☐	☐	☐	☐	☐

Hvor ofte spiser du sjokolade? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4-6 pr. uke	1+ pr. dag
Mørk sjokolade	☐	☐	☐	☐	☐	☐
Lys sjokolade	☐	☐	☐	☐	☐	☐

Dersom du spiser sjokolade, hvor mye pleier du vanligvis å spise hver gang? Tenk deg størrelsen på en Kvikk-Lunsj sjokolade, og oppgi hvor mye du spiser i forhold til den.

☐ ¼ ☐ ½ ☐ ¾ ☐ 1 ☐ 1 ½ ☐ 2+

Hvor ofte spiser du snacks? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4-6 pr. uke	1+ pr. dag
Potetchips	☐	☐	☐	☐	☐	☐
Peanøtter	☐	☐	☐	☐	☐	☐
Andre nøtter	☐	☐	☐	☐	☐	☐
Annen snacks	☐	☐	☐	☐	☐	☐

VARM MAT

Hvor mange ganger i løpet av en måned spiser du varm mat?

Til frokost ____ Til middag ____
Til lunch ____ Til kvelds ____

KOSTHOLD GJENNOM ULIKE LIVSFASER

Det kan være vanskelig å huske eksakt hva du har spist gjennom tiden, men fyll ut sånn omtrent.

Hvor ofte har du spist fisk? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Når du har spist fisk, hvor ofte har du da spist fet fisk (laks, ørret, kveite, makrell, sild, ål)? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Når du har spist fisk, hvor ofte har du da spist ferskvannsfisk (abbor, gjedde, røye, sik, harr)? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor ofte har du spist fiskepålegg (Makrell, sild, ansjos, sardiner, røkt eller gravet laks/ørret, kaviar, fiskeleverpostei (Lofotpostei, Svolværpostei) krabbepålegg)?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4-6 pr. uke	Daglig
Barndom	☐	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐	☐

Hvor mange ganger i året har du spist fiskelever?
(Sett ett kryss pr. linje)

	aldri	1-3	4-6	7-9	10-15	16+
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor mange ganger i året har du spist hval-/selkjøtt?
(Sett ett kryss pr. linje)

	aldri	1-3	4-6	7-9	10-15	16+
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor mange ganger i året har du spist det brune kjøttet i krabbe (utenom krabbepålegg)? (Sett ett kryss pr. linje)

	aldri	1-3	4-6	7-9	10-15	16+
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor mange måseegg eller egg fra annen sjøfugl har du spist i året? (Sett ett kryss pr. linje)

	aldri	1-3	4-6	7-9	10-15	16+
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor ofte i nevnte livsfaser har du tatt tilskudd av tran/ omega-3/fiskeolje (flytende/kapsler/piller)?
(Sett ett kryss pr. linje)

	Aldri	1-3 pr. mnd.	1 pr. uke	2-6 pr. uke	Daglig
Barndom vinter	☐	☐	☐	☐	☐
Barndom resten av året	☐	☐	☐	☐	☐
Ungdom 13-19 vinter	☐	☐	☐	☐	☐
Ungdom 13-19 resten av året	☐	☐	☐	☐	☐
Voksen vinter *(før siste året)*	☐	☐	☐	☐	☐
Voksen resten av året *(før siste året)*	☐	☐	☐	☐	☐

BARNEFAR

I forbindelse med sammenligning av ultralydmål, er det viktig å ha noen opplysninger om far til barnet i dette svangerskapet:

Hva var barnefars fødselsvekt som nyfødt baby?
(Gram) ☐☐☐☐ Vet ikke ☐

Hva er barnefars høyde i dag? *(cm)* ☐☐☐ Vet ikke ☐

Hvilket hjemmespråk har/hadde barnefar, hans foreldre og hans besteforeldre? (sett ett eller flere kryss)

	Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
Morfar	☐	☐	☐	☐	☐	
Mormor	☐	☐	☐	☐	☐	
Farfar	☐	☐	☐	☐	☐	
Farmor	☐	☐	☐	☐	☐	
Far	☐	☐	☐	☐	☐	
Mor	☐	☐	☐	☐	☐	
Barnefar	☐	☐	☐	☐	☐	

Hva er barnefars, hans fars og hans mors etniske bakgrunn?
(sett ett eller flere kryss)

	Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
Barnefars bakgrunn	☐	☐	☐	☐	☐	
Mors bakgrunn	☐	☐	☐	☐	☐	
Fars bakgrunn	☐	☐	☐	☐	☐	

Hva regner barnefar seg selv som? (sett ett eller flere kryss)

Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
☐	☐	☐	☐	☐	

ANGÅENDE SPØRSMÅLENE

Var noen av spørsmålene vanskelige eller nærgående? Hvis ja oppgi hvilke spørsmål og evt. kommentarer.

☐ Ja ☐ Nei

Andre kommentarer:

Takk for hjelpen!

2007
KONFIDENSIELT

MILJØGIFTER I SVANGERSKAPET OG I AMMEPERIODEN

Følgende opplysninger fylles ut i forbindelse med blodprøvetaking.

Dette skjema **må** følge blodprøven!

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, bruk blokkbokstaver.

ID-nr:

LAB-kobling.

Urinprøve levert i dag: Ja: ☐ Nei: ☐ **Prøvesett:** P1: ☐ P5: ☐ P6: ☐

PRØVETAKINGSDAGEN

Fyll inn tidspunkt når blodprøven er tatt: dag mnd

Dato ..... | | | | |

Klokkeslett ..... | | | | |

Prøvetakingssted .....

STILLING NÅR BLODPRØVEN BLE TATT

☐ Sittende ☐ Liggende

MÅLTID FØR BLODPRØVEN

Når spiste du siste måltid før blodprøven ble tatt: dag mnd

Dato ..... | | | | |

Klokkeslett ..... | | | | |

Når drakk du siste kaffe før blodprøven ble tatt: dag mnd

Dato ..... | | | | |

Klokkeslett ..... | | | | |

RØYKEVANER SISTE UKEN

Har du røykt i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Hvor mange sigaretter røykte du? Antall

I dag ..... | | |

I går ..... | | |

ALKOHOL SISTE UKEN

	Antall Siste uke	Antall i går
Øl *(0,4 l)*, rusbrus		
Vin *(glass)*		
Brennevin *(drinker/shots)*		
Likør/Hetvin		

HØYDE OG VEKT

Hvor høy er du *(cm)* ..... | | |

Er høyden målt i svangerskapet?

☐ Ja ☐ Nei

Hvor mye veier du i dag? *(I hele kg)* ..... | | |

Er vekten tatt i dag?

☐ Ja ☐ Nei

Hvor ble den i så fall tatt:

☐ Lab ☐ Legekontor ☐ Fødeenhet/fødestue

MEDISINER SISTE UKEN

Har du tatt medisiner i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Angi medikament og dato for siste tablett

dag mnd

Dato ..... | | | | |

Preparatnavn: .....

(Ikke skriv her →) | | | | | | |

dag mnd

Dato ..... | | | | |

Preparatnavn: .....

(Ikke skriv her →) | | | | | | |

dag mnd

Dato ..... | | | | |

Preparatnavn: .....

(Ikke skriv her →) | | | | | | |

dag mnd

Dato ..... | | | | |

Preparatnavn: .....

(Ikke skriv her →) | | | | | | |

TRAN OG FISKEOLJE SISTE UKEN

Har du brukt flytende tran/omega-3/fiskeolje i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Angi dato du sist tok flytende tran/Omega-3/fiskeolje

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

Preparatnavn: .....

(Ikke skriv her →)

Angi mengde

☐ 1 ts ☐ 1/2 ss ☐ 1+ ss

Har du brukt kapsler/piller med tran/omega-3/fiskeolje i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Angi dato du sist tok kapsler/piller med tran/Omega-3/fiskeolje

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

Angi mengde

☐ 1 stk ☐ 2 stk ☐ 3 stk

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

Angi mengde

☐ 1 stk ☐ 2 stk ☐ 3 stk

KOSTTILSKUDD SISTE UKEN

Har du brukt andre kosttilskudd (vitaminer/mineraler) i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Angi dato for siste tablett

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

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dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

Takk for hjelpen!

Jon Øyvind Odland
ISM
Med fak
UiT
9038 TROMSØ

Deres ref.: 5.2006.3758 Vår ref.: 200607370-9/IAY/400 Dato: 27.03.2007

P REK NORD 06/2007 MILJØGIFTER I SVANGERSKAPET OG I AMMEPERIODEN - SLUTTVURDERING - KOMITEEN HAR INGEN INNVENDINGER MOT AT PROSJEKTET GJENNOMFØRES

Vi viser til skjema for protokolltillegg og endringer datert 22.3.2007, revidert biobankskjema datert 22.3.2007, samt revidert protokoll og forespørsel om deltakelse i forskningsprosjektet.

Tilbakemeldingen på komiteens merknader til prosjektet i brev av 19.3.2007 og protokoll-endringen som beskrevet i skjema datert 22.3.2007 tas til etterretning.

Regional komité for medisinsk forskningsetikk, Nord-Norge (REK Nord) har ingen innvendinger mot at prosjektet gjennomføres.

For at det ikke skal være tvil om hvilken informasjon samtykket relateres til, bør samtykket ikke skilles ut på eget ark. Informasjonsskriv med forespørsel om deltakelse og samtykke-erklæring bør foreligge som et samlet dokument som sendes ut i to eksemplarer.

Det forutsettes at prosjektet er godkjent av aktuelle formelle instanser før det settes i gang. Det forutsettes at prosjektet forelegges komiteen på nytt, dersom det under gjennomføringen skjer komplikasjoner eller endringer i de forutsetninger som komiteen har basert sin avgjørelse på. Komiteen ber om å få melding dersom prosjektet ikke blir sluttført.

Komiteen oversender dokumenter til Sosial- og helsedirektoratet for behandling av søknad om oppretting av forskningsbiobank.

Vennlig hilsen

Ingunn Ytrehus
førstekonsulent
77645347

Kopi:
Solrunn Hansen (Solrunn.Hansen@ism.uit.no)
Sosial- og helsedirektoratet (postmottak@shdir.no) vedlagt biobankskjema og forespørsel om deltakelse i forskningsprosjektet.

Til deg som er gravid

Universitetet i Tromsø · Romssa universitehta
Senter for samisk helseforskning, Institutt for samfunnsmedisin, Universitetet i Tromsø

Til deg som vil delta

Du må kontakt **ditt nærmeste** innsamlingssted for å avtale tid for oppstart. Du kan starte opp umiddelbart eller **helst** innen uke 20. Du kan også avtale å starte opp i forbindelse med ultralydundersøkelsen (ca. uke 18).

Innsamlingssted	Telefonnummer
Kirkenes fødeavdeling	78 97 32 35
Hammerfest fødeavdeling	78 42 15 12
Alta Fødestue	78 45 54 00
Karasjok legesenter	78 46 85 00
Kautokeino legesenter	78 48 72 50
UNN barselavdeling	77 62 64 60
Sonjatun fødestue	77 77 08 25
Fødestua i Midt-Troms, Lenvik	77 87 14 90
Lofoten fødestue	76 06 01 22
Gynekologisk senter, Bodø	75 52 39 00

Ved oppstart:
Du skal måle blodtrykk og vekt, ta blodprøve og levere urinprøve. Vi ber deg derfor om å:

- Møte fastende. Om du ikke klarer å faste, kan du spise en lett, fettfattig frokost (brød, salat, grøt) uten kaffe.
- Ta med en morgenurinprøve tatt på følgende måte: Den første porsjon av urinstrålen kastes, den neste porsjon urin samles i egnet beholder og den siste porsjon urin kastes.
- Ta med "Helsekort for gravide" da vi vil merke helsekortet med prosjektets ID

Før oppstart ber vi deg om å sende inn underskrevet samtykke (Miljøgifter i svangerskapet og i ammeperioden + Morsmelksundersøkelsen) i vedlagte svarkonvolutt til Universitetet i Tromsø.

Dersom du har spørsmål, kan du ta kontakt med:
solrunn.hansen@ism.uit.no
Telefon 920 69 700

På forhånd takk og vel møtt!

Vennlig hilsen
Solrunn Hansen
Prosjektleder / Jordmor

http://uit.no/med-nord/misa

Forespørsel om deltakelse i forskningsprosjekt

Miljøgifter i svangerskapet og i ammeperioden

Det er for tiden økende fokus på miljøgifter og hvilke effekter disse har på omgivelsene og helsen til oss mennesker. Befolkningen i arktiske områder er spesielt utsatt siden miljøgifter fra den øvrige verden fraktes nordover til våre områder med globale hav- og luftstrømmer. Nivået av miljøgifter i Norge er sammenlignet med andre land, generelt lave.

Kosten er den viktigste kilden for spredning av miljøgifter i tillegg til det vi finner i miljøet forøvrig. Vi er særlig sårbare for miljøgifter på fosterstadiet og i de første årene av livet. Fettløselige, organiske miljøgifter passerer lett fra mor til foster gjennom morkaka og navlesnora, og de utskilles også i morsmelk. Nivåene av disse stoffene i mors blod gjennom svangerskapet og senere i brystmelk, gir indikasjoner på den risiko vi utsetter våre barn for. Målinger viser at de fleste miljøgifter heldigvis er på vei ned, men vi har mangelfull kunnskap om hvordan mennesker påvirkes over tid.

Vi har ennå liten informasjon om situasjonen i Nord-Norge. Vi ønsker derfor å gjennomføre en undersøkelse som skal måle nivåer av disse langsomt nedbrytbare stoffene hos om lag 1000 gravide og ammende mødre i vår landsdel.

Hensikten er å:

- Kartlegge miljøgifter i mors blod, navlestrengsblod og morsmelk.
- Undersøke hvilken risiko gravide og nyfødte utsettes for gjennom påvirkning av miljøgifter og spesielt hva som tilføres gjennom kostholdet og morsmelk.
- Se om det er noen sammenheng mellom miljøgifter og helsen til mor og barn.
- Å lage grunnlag for retningslinjer i forebyggende helsearbeid for å beskytte mennesker mot miljøgifter og spesielt kostholdsråd for gravide, ammende og kvinner i fertil alder.
- Lage grunnlag for oppfølgingsstudier til barna når 12-årsalder.
- Lagre prøvemateriale i biobank for å ha mulighet til å analysere på "nye" miljøgifter eller faktorer som kan virke beskyttende mot skadelige effekter av miljøgifter.
- Prosjektet vil spesielt sammenligne den samiske og den norsk etniske befolkningen.
- Tilleggsundersøkelse: Undersøke om det er forskjell mellom den samiske og den norske befolkning vedrørende fostermål utført ved ultralyd ved 18. svangerskapsuke.

Forespørsel om å delta sendes til alle gravide som:

- Har time hos jordmor eller time til rutineultralyd
- Er i første halvdel av svangerskapet
- Skal føde ved følgende fødesteder: Kirkenes, Hammerfest, Alta, UNN, Sonjatun, Lenvik, Lofoten eller Bodø.

Frivillig deltagelse

Deltakelse i undersøkelsen er frivillig og bygger på skriftlig informert samtykke. Alle data behandles strengt fortrolig, og resultater blir formidlet slik at ingen opplysninger kan føres tilbake til enkeltpersoner. Dersom du blir med, kan du trekke deg uansett tidspunkt, og du kan be om at dine opplysninger og prøveresultater slettes inntil data er publisert.
Du trenger ikke å begrunne hvorfor du trekker deg, og det medfører ingen konsekvenser for deg. Om du trekker deg i løpet av svangerskapet eller etter fødselen, ber vi deg om å gi tilbakemelding for å unngå utsendelse av nye spørreskjema/innsamlingsutstyr og purring.

Hvis du blir med, spør vi deg om:

1. Spørreskjema:

- Å svare på et spørreskjema i første halvdel av svangerskapet

2. Prøver av deg til analyse av miljøgifter, fettstoffer og hormoner:

Tungmetaller: Kvikksølv, bly, kadmium
Organiske miljøgifter: DDT, HCH, Toxaphenes, HCB, PCB, dioksiner, bromerte flammehemmere, ftalater og PFOS
Jernlagre, kolesterol, triglyserider
Hormoner: FSH, LH, prolaktin, TSH, FT4, FT3, østradiol og progesteron

- Blodprøve i første halvdel av svangerskapet, etter fødsel og 6 uker etter fødsel
- Navlestrengsblod ved fødsel
- Hårprøve ved fødsel for biobank
- Urinprøve ved hver blodprøvetaking til biobank
- Blodtrykk, høyde og vekt i forbindelse med prøvetaking

3. At vi av ditt nyfødte barn kan få:

- Måle omkretsen rundt magen og genitale lengdemål
- Avføringsprøve (mekonium) til biobank
- Blodprøve av barnets hæl til eventuelt hormonanalyse og biobank. Blodprøven tas samtidig med rutineprøven "Nyfødtscreening" 3. dag etter fødselen. Vi ber dersom det er nødvendig, å få stikke barnets hæl en ekstra gang for å få nok blod.

4. Morsmelkundersøkelsen:

- Å levere en morsmelksprøve samlet i løpet av barnets første levemåned, til analyse av miljøgifter
- I forbindelse med morsmelksundersøkelsen spør vi deg også om å svare på spørreskjema når barnet er 1, 6 og 12 måneder og 2, 7 og 12 år gammel.

Folkehelseinstituttet (FHI) er ansvarlig for denne delen av prosjektet. Personopplysninger utlevers til FHI, slik at de kan kontakte deg direkte for utlevering av utstyr og spørreskjema. Vi ber deg om å lese eget vedlagt informasjonsskriv med egen samtykkeerklæring.

5. Ditt samtykke:

- Til å oppbevare prøvematerialet av deg selv og barnet i biobank. Blod- og urinprøver, navlestrengsblod, mekonium og hårprøve vil lagres i en biobank til utgange av år 2022 ved Universitetet i Tromsø med prosjektansvarlig som ansvarlig.
- Til at prøvematerialet kan sendes avidentifisert til utlandet når det er nødvendig av hensyn til å få utført analyser av prøvene og for kvalitetskontrollanalyser (Canada).

6. Innhenting av opplysninger:

- Tillatelse til innhenting av nødvendige journalopplysninger om deg og ditt barn i forbindelse med svangerskapet og fødselen. Kopi av svangerskapsjournal, ultralydskjema, barnets epikrise som sendes til helsestasjonen og skjema til Medisinsk Fødselsregister. Alle opplysninger behandles etter at personopplysninger er fjernet og erstattet med et ID-nummer før utlevering til Universitetet.

7. Tillatelse til å koble innsamlede opplysninger om deg:

- Fra denne delen av prosjektet mot data fra Morsmelksundersøkelsen og Mor-/barnundersøkelsen.
- Mot Medisinsk Fødselsregister vedrørende data fra pågående og eventuelt tidligere svangerskap og fødsler.
- Mot Norsk pasientregister som registrerer diagnoser barnet ditt har fått ved innleggelse på sykehus.
- Mot Nyfødtscreeningregisteret som gir prøvesvar på barnets stoffskifte (TSH).
- Datatilsynet har godkjent disse koblingene.

8. Kontakte deg senere for å:

- Invitere dere til ekstra undersøkelse når barnet er blitt eldre. Du forplikter deg ikke til å delta i dette, men kan ta stilling til dette når du får invitasjonen som vil inneholde detaljert informasjon om hva vi ønsker å undersøke.

Utstyr, ID-nummer
Ditt og barnets navn og fødselsdato er byttet ut (avidentifisert) med et nummer når det brukes i forskning. Ved oppstart får du utlevert alt utstyr merket med et ID-nummer. Både prøver og innsamlet informasjon blir derfor avidentifisert på innsamlingsstedet dersom du har med ID-merket utstyr. Om du ikke har med forhåndsmerket utstyr, skjer avidentifiseringen etter ankomst Universitetet i Tromsø. Data vil anonymiseres etter prosjektslutt år 2022.

Din sikkerhet og tilbakemelding

Opplysninger du gir og svar på prøver du tar, blir kun brukt til forskning. Vi forplikter oss til å gi tilbakemelding til deg dersom du ønsker svar på dine egne blodprøver. Du får svar på for eksempel nivåer av miljøgifter, hormoner og fettstoffer. Vi gir deg automatisk svar på avvikende fettstoffer og hormonprøver vedrørende stoffskifte. Din fastlege får også prøvesvar dersom du tillater det, og fastlege kan gi deg videre oppfølging. Det tar noen måneder før resultatene foreligger pga. tidkrevende analyser.
Vi lager rapporter fra prosjektet, og hvis du ønsker det, kan gir vi deg prosjektets resultater og konklusjoner. Datainnsamlingen pågår fra juni 2007 til høsten 2008, og de første rapporter beregnes ferdig i 2009.

Godkjenninger

Undersøkelsen er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk (REK Nord) og Datatilsynet. Hvis det senere blir aktuelt å bruke prøvene til andre problemstillinger enn de som er skissert her, skjer det kun etter ny godkjenning fra datatilsynet og ny vurdering av REK.

Ansvarlig

Ansvarlig for dette prosjektet er dr. med. Jon Øyvind Odland ved Institutt for samfunnsmedisin, Universitetet i Tromsø. Oppdragsgiver er Institutt for samfunnsmedisin og Senter for samisk helseforskning ved Universitetet i Tromsø. Norges Forskningsråd, Norske Kvinners Sanitetsforening, Helse Nord og Senter for samisk helseforskning ved UiT finansierer prosjektet.

Påmelding, samtykke

Dersom du sier ja til å delta i studien, ber vi deg om å avtale tid for oppstart med ditt innsamlingssted (se oversikt side 2). Før oppstart ber vi deg om å underskrive samtykke og returnere de i vedlagte returkonvolutt. Du beholder selv ett eksemplar.

Dersom du har behov for mer informasjon før oppstart eller har spørsmål underveis, ta kontakt med:

- Prosjektets kontakttelefon:
  920 69 700
- Prosjektansvarlig Jon Øyvind Odland:
  E-post jon.oyvind.odland@ism.uit.no
  telefon 909 53 887
- Prosjektleder Solrunn Hansen:
  E-post solrunn.hansen@ism.uit.no
  telefon 77 64 48 36 / 992 71 762

Du kan også finne informasjon om prosjektet på vår nettside: http://uit.no/med-nord/misa

Vennlig hilsen

Jon Øyvind Odland (sign.),
Prosjektansvarlig / Dr. med.,
Institutt for samfunnsmedisin, UiT

Merete Eggesbø (sign.),
Prosjektleder Morsmelksundersøkelsen/ Dr. med,
Divisjon for epidemiologi, Folkehelseinstituttet

Solrunn Hansen (sign.),
Prosjektleder / Jordmor,
Institutt for samfunnsmedisin, UiT

Samtykke [din kopi]

Miljøgifter i svangerskapet og i ammeperioden

ID- nummer:

Fornavn:.....

Etternavn:.....

Adresse:.....

Postnummer:.....

Poststed:.....

Fødselsnummer 11 siffer:....

E-post:.....

Telefon privat:.....

Telefon mobil:.....

Termin (DD|MM|ÅÅÅÅ):.....

Sett kryss:

☐ Jeg har lest informasjon om prosjektet og samtykker til å delta.

Dato: _____ Signatur: _____

Dato: _____ Signatur foresatte: _____

Dersom du er under 16 år, må du også ha underskrift fra din foresatte.

Tilbakemeldinger

☐ Jeg ønsker tilbakemelding om mine egne prøveresultater.

☐ Jeg ønsker tilbakemelding om prosjektets resultater og konklusjoner.

☐ Jeg tillater at min fastlege får resultater på avvikende prøvesvar med hensyn til hormoner og fettstoffer.

Navn på fastlege: _____

Adresse: _____