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MATERNAL OVERALL DIET AND QUALITY OF FAT IN PROMOTING INFANT HEALTH AND DEVELOPMENT

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(neé Latva-Pukkila)

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To my family

ABSTRACT

Ulla Hautero

Maternal overall diet and quality of fat in promoting infant health and development

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Maternal nutrition during pregnancy is an important determinant of the later health of the offspring. The aim here was to evaluate the effects of maternal dietary intake and dietary counselling in providing a favourable nutritional environment for the developing child. This study evaluated in a mother-child trial (n=256) the impact of maternal dietary intake on maternal and infant serum fatty acids (FA) and infant development (Griffiths Mental Development Scale). The trial involved individual dietary counselling emphasizing the quality of dietary fat and provision of supporting foods with favourable fat and fibre content.

Dietary intervention increased the percentage of maternal serum phospholipid n-3 FA during pregnancy. A further evaluation revealed that an overall healthy diet and particularly the intake of fish increased n-3 FA of the mother and infant when consumed three times weekly or once weekly if the consumption was persistent throughout pregnancy. Maternal dietary n-3 FA did not contribute to child development; instead maternal vitamin D intake from diet and supplements was associated with higher developmental scores at one year of age. Nausea and vomiting during pregnancy resulted in qualitative changes to maternal dietary intake such as a lower intake of meat and protein and a higher intake of sucrose and carbohydrates.

In conclusion, the results demonstrate that pregnancy predisposes to nutritional risks impacting dietary intake, such as nausea and vomiting. Dietary counselling modifying dietary intake may lead to beneficial changes in the FA metabolism of the mother and child with clinical benefits. Thus, balanced versatile dietary intake during pregnancy including sources of n-3 FA and vitamin D, such as fish, is of importance, concerning the benefits for infant development.

Keywords: pregnancy, maternal, dietary intake, nutrition, dietary counselling, breastfeeding, programming, fatty acid, vitamin D, infant

TIIVISTELMÄ

Ulla Hautero

Raskausajan ravitsemus ja rasvan laatu: mahdollisuus edistää imeväisen terveyttä ja kehitystä

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen laitos, Lastentautioppi, Turun kliininen tohtoriohjelma, Turun yliopistollinen keskussairaala, Lasten- ja nuortenklinikka, Turku, Suomi
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Raskaudenaikaisella ravitsemuksella on useita tunnettuja vaikutuksia sikiön ja lapsen terveyteen. Tämän tutkimuksen tavoitteena oli selvittää äidin raskaudenaikaisen ravitsemuksen ja ravitsemusohjauksen mahdollisuuksia tukea kehittyvän lapsen terveyttä edistävää ravitsemusympäristöä. Tutkimuksessa selvitettiin miten äidin (n=256) ravitsemus vaikuttaa äidin ja lapsen seerumin n-3 rasvahappojen osuuksiin sekä lapsen kehitystestin pisteisiin (Griffiths Mental Development Scale) vuoden iässä. Tutkimuksessa annettiin alkuraskaudesta lähtien ravitsemusohjausta, jossa painotettiin ravitsemuksen rasvan laatua ja kuidun määrää. Lisäksi äidit saivat käyttöönsä ohjausta tukevia ruokatuotteita.

Ravitsemusohjaus lisäsi äitien seerumin fosfolipidien n-3 rasvahappojen osuutta loppuraskaudessa. Lisäksi ravintoindeksillä mitattu suositusten mukainen ruokavalio ja erityisesti kalan käyttö, joko säännöllisesti alkuraskaudesta lähtien tai synnytyksen jälkeen kolmesti viikossa, selittivät äitien ja heidän lastensa suurempaa n-3 rasvahappojen osuutta. Äidin n-3 rasvahappojen saanti ei kuitenkaan liittynyt lapsen kehitystestin pisteisiin vuoden iässä. Ravintoaineista äidin D-vitamiinin saanti ravinnosta ja ravintolisistä korreloi lapsen korkeampiin kehitystestin pisteisiin. Raskaudenaikainen pahoinvointi voi asettaa haasteen riittävälle ravinnonsaannille ja tutkimuksessa todettiinkin, että naiset, joilla oli pahoinvointia saivat ravinnosta vähemmän proteiinia ja enemmän hiilihydraatteja verrattuna naisiin, joilla ei ollut pahoinvointia.

Tulokset osoittavat, että raskaus voi altistaa epätasapainoiselle ravintoaineiden saannille, mikäli äiti kärsii raskauspahoinvoinnista. Raskaana olevien naisten ravitsemusohjaus johtaa suotuisiin muutoksiin äidin ja lapsen rasvahappoaineenvaihdunnassa. Monipuolisen ruokavalion ohella erityisesti riittävä n-3 rasvahappojen ja D-vitamiinin saanti edistävät hyödyllisiä aineenvaihdunnallisia muutoksia ja lapsen kehitystä.

Avainsanat: Raskaus, raskaudenaikainen ravitsemus, äidin ruokavalio, ravitsemusohjaus, imetys, ohjelmoituminen, rasvahappo, imeväinen

TABLE OF CONTENTS

ABBREVIATIONS

ALA	Alpha linolenic acid
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
BMI	Body mass index
CE	Cholesteryl ester
CI	Confidence interval
DHA	Docosahexaenoic acid
DOHaD	Developmental origins of health and disease
EPA	Eicosapentaenoic acid
E%	% of total energy
FA	Fatty acid
FFQ	Food frequency questionnaire
GEE	Generalised estimated equations analysis
GW	Gestational week
GWG	Gestational weight gain
HEI	Healthy Eating Index
IQR	Inter quartile range
LA	Linolenic acid
LC-PUFA	Long-chain polyunsaturated fatty acid
MUFA	Monounsaturated fatty acid
NVP	Nausea and vomiting during pregnancy
PL	Phospholipid
PUFA	Polyunsaturated fatty acid
SFA	Saturated fatty acid
SD	Standard deviation
TAG	Triacylglycerol
T1-3	Tertile 1-3

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred in the text by the Roman numerals I-IV. Previously unpublished data are also included.

I Latva-Pukkila Ulla, Isolauri Erika and Laitinen Kirsi. Dietary and clinical impacts of nausea and vomiting during pregnancy. *J Hum Nutr Diet. 2010; Feb;23(1):69-77.*

II Hautero Ulla, Laakso Päivi, Linderborg Kaisa, Niinivirta Katri, Poussa Tuija, Isolauri Erika and Laitinen Kirsi. Proportions and concentrations of serum n-3 fatty acids can be increased by dietary counselling during pregnancy. *Eur J Clin Nutr. 2013 Nov;67(11):1163-8.*

III Hautero Ulla, Poussa Tuija and Laitinen Kirsi. Simple dietary criteria to improve serum n-3 fatty acid levels of mothers and their infants. *Public Health Nutr. 2016 Oct 3:1-8.*

IV Hautero Ulla, Isolauri Erika, Miettinen Reetta, Löyttyniemi Eliisa and Laitinen Kirsi. Clinical evidence substantiating the impact of nutrition during pregnancy on infant development. *Submitted*

1 INTRODUCTION

Already since the 1970s it has been recognized that early life events such as maternal nutrition have long-term effects on the offspring and affect the risk of later diseases (McCance and Widdowson, 1974). This phenomenon is generally known as the programming effect (Barker, 1997). Nowadays, challenges in maternal nutrition in Western countries arise from unbalanced intake of nutrients or excessive intake of energy (Cordain et al., 2005; Sample et al., 2016). As a result, more than half of fertile-aged women in Western countries are overweight or obese causing immediate and long-term health effects during pregnancy for both the mother and the foetus, and this prevalence is increasing (Callaway et al., 2006; Ogden et al., 2014; WHO, 2015; Stang and Huffman, 2016). Along with maternal metabolic disturbances during pregnancy, the metabolic environment of the foetus is disturbed, emerging as unbalanced insulin, leptin and cytokine metabolism and immunological changes before and after birth (Warner and Ozanne, 2010). These disturbances during a sensitive period of development may increase the later risk of chronic diseases for the infant such as asthma, cardiovascular diseases, obesity and type II diabetes through the programming effect (Warner and Ozanne, 2010; Gaillard et al., 2015; Godfrey et al., 2017). Furthermore, the consumption of high-energy density food may lead to the poor intake of essential fatty acids, vitamins and minerals, crucial for optimal infant development (Cordain et al., 2005). There is also increasing evidence pointing to an association between nutritional environment during pregnancy and the neurodevelopment of the infant, although the exact mechanisms are not known (Krakowiak et al., 2012; Rivera et al., 2015a).

As once stated by Hugh Tunstall-Pedoe, -Professor of Cardiology at the University of Dundee in the U.K. and spokesperson for the World Health Organization's 21-nation Monitoring Cardiovascular Disease Project:

"*You have to eat something. If you eat more of one thing, you eat a lot less of something else. So for every theory saying this disease is caused by an excess in* x*, you can produce an alternative theory saying it's a deficiency in* y." (Deddo, 2007)

This quotation by Tunstall-Pedoe summarizes the importance of evaluating diet as a whole in contrast to the individual intake of foods and nutrients. The time from conception to delivery may be perceived as a critical period for preventing adverse pregnancy outcomes, and the risk of long-term diseases and maternal nutrition prior and during pregnancy and during lactation serves as a tool to impact these risks. The prevalence of chronic diseases is increasing worldwide and rather than treating these diseases and their consequences, preventive actions should be

emphasised such as improving maternal diet and health during pregnancy and lactation. In this prospective study, the objective was to modify maternal nutrition during and after pregnancy to provide a favourable metabolic environment such as improved n-3 FA status for the foetus and infant.

2 REVIEW OF LITERATURE

2.1 Pregnancy as a critical period for the offspring

Developmental programming refers to long term or permanent changes in the structure or function of an organism, caused by a stimulus or insult occurring at a critical period of life i.e. during pregnancy or infancy (Lucas, 1991). Programming may be positive, leading to a beneficial pregnancy outcome and a reduced risk of later diseases or negative, resulting in adverse pregnancy outcomes and an increased risk of diseases.

The concept of developmental programming became widely known as the "thrifty phenotype hypothesis" or "Barker hypothesis" by Charles Hales and David Barker (Hales and Barker, 1992). In their study they proposed a well-grounded theory that inadequate early nutrition impairs pancreatic development, and thereby increases the risk of the offspring to develop type II diabetes. In later studies, Barker and his co-authors found further correlations between the low birth weights of infants and their later risk of cardiovascular disease and hypertension (Barker et al., 1993; Barker, 1997). Barker's group also used data from the Dutch Hunger Winter of 1944-1945 to illustrate the long-term effects of nutritional famine during pregnancy; their results connected famine to the decreased glucose tolerance of the child in adult life (Ravelli et al., 1998; Schulz, 2010). Further studies have supported these findings and revealed associations between poor nutrition and growth during pregnancy and metabolic changes in later life for the offspring (Eriksson et al., 2000; Eriksson et al., 2001).

However, the history of research linking early-life environment to long-term health effects dates to the 1970 studies by Elsie Widdowson and Robert McCance (McCance and Widdowson, 1974). Their work provided the foundations of the scientific field called the Developmental Origins of Health and Disease (DOHaD) (McCance and Widdowson, 1974; Buklijas, 2014). In addition, studies by Dörner written in German during 1973 introduced the possible significance of maternal nutrition for the pathogenesis of obesity and arteriosclerosis (references not available). Soon after, occasional studies produced theories of early-life events affecting the later health of the individual (Forsdahl, 1977; Freinkel, 1980).

Initially, these studies examined the long-term effects of maternal undernutrition, but later the focus of research has shifted from quantity to quality and the balance of maternal dietary intake. Furthermore, the multifactorial and complex mechanisms of developmental programming for specific diseases have been widely examined in experimental studies (Aiken and Ozanne, 2014; Langley-

Evans, 2015; Gali Ramamoorthy et al., 2015; Sánchez-Hernández et al., 2016). In brief, studies indicate that a variety of physiological disturbances in the mother may change the epigenetic signature (**Figure 1)** and also the structure and function of multiple organs (**Figure 2)** resulting in adult disease for the offspring. Most of the scientific human evidence from nutritional programming has been produced in recent decades, and nowadays DOHaD is an international society founded by scientists to promote research into the foetal and developmental origins of disease (Silveira et al., 2007). Maternal nutrition during pregnancy is seen as an opportunity to impact the rapid increase in the incidence of allergic and metabolic diseases as well as mental disorders worldwide.

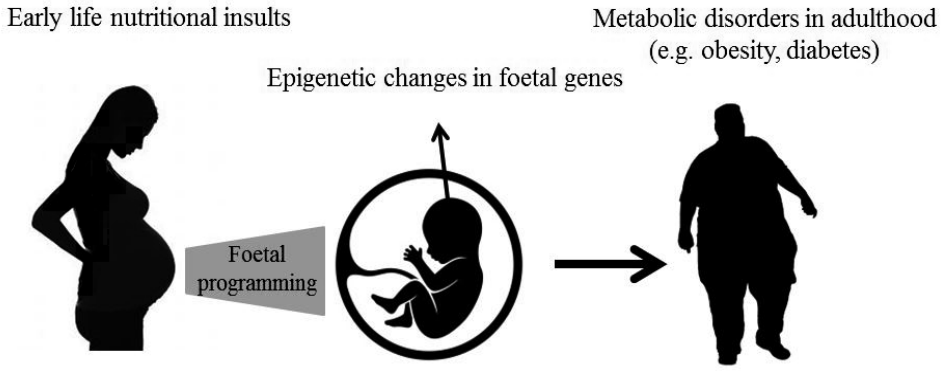

Figure 1 Epigenetic programming of metabolic disorders. Altered nutritional environment at a critical developmental period may program alterations in the epigenetic signature leading to changes in the expression of certain genes and an increased risk of metabolic disorders. Picture modified from Gali Ramamoorthy et al., 2015.

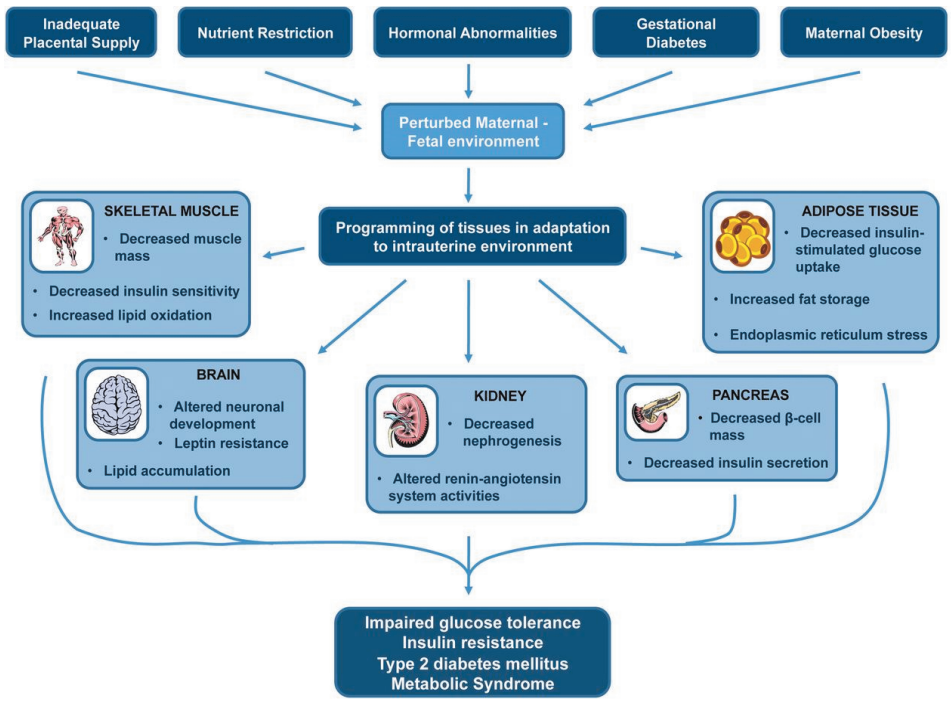

Figure 2 The structural and molecular adaptations in programming of metabolic disease during pregnancy. A schematic representation of how a perturbed intrauterine environment, induced by a variety of physiological disturbances in animal models, can induce changes in the structure and function of multiple organs, subsequently leading to the development of features of metabolic syndrome. Image used with permission from Portland Press Ltd. (Warner and Ozanne, 2010).

2.2 Nutrition recommendations in pregnancy

2.2.1 Background of nutrition recommendations during pregnancy

The first published study on nutrition and pregnancy was published in 1901 by Prochownick, a German researcher according to a report of the Institute of Medicine (Committee on Nutritional Status During Pregnancy and Lactation, 1990). Nutrition recommendations for pregnant women were developed not until decades later. Initially, these recommendations concentrated on limiting the growth of the offspring by restricting food intake. The aim was to deliver a smaller baby, considered favourable in the light of high maternal mortality and the incidence of delivery complications, and also because small gestational weight

gain was considered to prevent toxaemia (Committee on Nutritional Status During Pregnancy and Lactation, 1990). Nutritional famine was associated with the long-term metabolic changes of the offspring, and as a result, attention was increasingly focused on safe and sufficient nutrient intake (Williamson, 2006; Kunz and King, 2007). Furthermore, in several subsequent longitudinal studies, small birth weight has been associated with increased risk of coronary heart disease and type II diabetes in adulthood (Whincup et al., 2008; Eriksson, 2011; Eriksson et al., 2016; von Bonsdorff et al., 2017). Later, scientific research into the consequences of maternal nutrition during pregnancy and lactation has increased globally, and by implication many regional and international recommendations concerning dietary intake during pregnancy have been produced (Williamson, 2006; Nordic Council of Ministers, 2014; National nutrition council VRN 2014; Stang and Huffman, 2016; National nutrition council VRN, 2016).

Nowadays, the primary aim of nutritional recommendations during pregnancy and lactation is to optimize the environment for the mother and the developing foetus and new-born (Nordic Council of Ministers, 2014). The foetus is dependent on the placental transfer of nutrients through maternal dietary intake and metabolism (Larqué et al., 2013; Larqué et al., 2014). As such, the focus of nutrition recommendations during pregnancy has shifted on the one hand to ensuring a balanced diet comprised of essential nutrients and on the other hand to avoiding certain potentially harmful foods (National nutrition council VRN, 2016; Nordic Council of Ministers, 2014). The secondary aim of nutritional recommendations during pregnancy is to permanently improve the diet for the whole family and by implication, to achieve healthier eating habits and better lifelong health for the growing child (National nutrition council VRN, 2016). In addition, preventing excessive energy intake and weight gain is important for both the mother and her offspring, especially in women who are overweight prior to pregnancy (Bhattacharya et al., 2007).

2.2.2 Recommended energy and nutrient intake during pregnancy

Energy requirements during pregnancy vary individually depending on body size, body composition and physical activity (Butte and King, 2005). Additional energy is necessary for the growth and maintenance of the foetus, the placenta and maternal tissues. Basal metabolism also increases during pregnancy owing to the increasing mass of metabolically active tissues. The recommended additional energy required daily in the first trimester is considered to be on average 430 kJ, which increases slightly throughout pregnancy to 1375 kJ during the second trimester and 2245 kJ by the third trimester (Nordic Council of Ministers, 2014).

In pregnant women, recommendations for energy-yielding nutrients are identical to other adult populations. In an optimal diet, the intake of energy-yielding nutrients as a proportion of energy intake (E%) is considered to consist of 25-40 E% total fat of which less than 10 E% is saturated fatty acids (SFA), 10-20 E% monounsaturated fatty acids (MUFA) and 5-10 E% polyunsaturated fatty acids (PUFA), 45-60 E% carbohydrates, less than 10 E% added sugars and 10-20 E% protein. Daily fibre intake should be at least 25-35 g (Nordic Council of Ministers, 2014). Furthermore, at least 1 E% of PUFA should consist of n-3 FA and 200 mg daily of docosahexaenoic acid (DHA) (National nutrition council VRN, 2016).

2.2.3 Gestational weight gain and maternal obesity

According to studies since the 1980s, a gestational weight gain of 12-13.8 kg has been considered optimal for pregnancy outcomes (Hytten and Chamberlain, 1980; FAO, 2004; Butte and King, 2005). The current recommendations by the Institute of Medicine also account for the weight of the mother prior to pregnancy and suggest a weight gain of 11.5-16 kg for normal weight, 7-11.5 kg for overweight, 5-9 kg for obese and 12.5-18 kg for underweight women (Rasmussen and Yaktine, 2009). Excessive weight gain during pregnancy predisposes women to being overweight and obese (Mamun et al., 2010; Cohen et al., 2014). This is of importance, because in high-income countries obesity is reaching epidemiological proportions in fertile-aged women (Hanson et al., 2016; Poston et al., 2016).

Actions have been taken to control this worldwide problem, such as dietary interventions to manage gestational weight gain and later obesity, which have had positive results on weight control for the women (Wolff et al., 2008; Ilmonen et al., 2011; Kinnunen et al., 2012; Harrison et al., 2013; Bogaerts et al., 2013; Petrella et al., 2014; Vesco et al., 2014; Poston et al., 2015; Koivusalo et al., 2016; International Weight Management in Pregnancy (i-WIP) Collaborative Group, 2017). However, in some studies, no significant improvement in limiting excessive gestational weight gain has been identified (Guelinckx et al., 2010; Dodd, 2014; Hawkins et al., 2015). In a systematic review article from 2012, nutrition education and counselling during pregnancy seemed to be effective in reducing gestational weight gain (Girard and Olude, 2012). Later, the effects of dietary interventions with and without physical activity before or during pregnancy have been evaluated in another systematic review with no significant improvement in reducing gestational weight gain (Gresham et al., 2016).

Furthermore, maternal obesity prior to conception is a risk for both the mother and child, and results in an increased risk of complications in pregnancy, for example pre-eclampsia, gestational diabetes, stillbirth, pre-term delivery, large-for-

gestational age births and caesarean sections with related problems (Bhattacharya et al., 2007; Stang and Huffman, 2016; Catalano and Shankar, 2017). In further studies, maternal obesity and overweight have also been associated with child long-term diseases such as obesity, coronary heart disease, type II diabetes, stroke, asthma and neurodevelopmental disorders (Pirkola et al., 2010; Gaillard, 2015; Godfrey et al., 2017). Bearing in mind the risks of obesity and related problems such as gestational diabetes and poor nutrition during pregnancy, more effective preventive means are needed and further studies have been initiated.

2.2.4 Vitamins, minerals and dietary supplements during pregnancy

During pregnancy, the need for several vitamins and minerals increases. Although a balanced and versatile diet provides a sufficient supply of micro- and macronutrients, certain supplements are recommended. First, folic acid supplements are recommended for all women, as soon as they discontinue taking their contraceptives, in Finland 400 µg daily until the end of the 12th week of gestation (Nordic Council of Ministers, 2014; National nutrition council VRN, 2016). Dietary folate is received for example from green vegetables, fruits, berries and whole grain products (National nutrition council VRN, 2016). However, the intake of folate in the Finnish population is lower than recommended and significantly lower in women with lower education levels compared to those with the middle and highest educational level (Helldan et al., 2012). Foetal neural tube defects are more common if the intake of folate for the mother is low and supplements are thus recommended for pregnant mothers to maintain an adequate intake of at least 500 µg per day (Wolff et al., 2009; Atta et al., 2015). Sufficiency of this recommended folic acid supplementation should be individually evaluated if the mother is type I or II diabetic, obese, uses certain medicines or has previous children with neural tube defect (National nutrition council VRN, 2016). In addition, lower levels of folic acid during pregnancy have been associated with other consequences, such as neurodevelopmental disorders later in childhood (Steenweg-de Graaff et al., 2012; Valera-Gran et al., 2014).

In addition to folic acid, in Finland and other Nordic countries pregnant women are also recommended to take 10 µg of vitamin D supplements daily throughout the year (Nordic Council of Ministers, 2014; National nutrition council VRN, 2016). In addition to dietary intake, vitamin D is produced by synthesis in the skin depending on sun exposure, which for the majority of the year is inadequate in Northern latitudes (National nutrition council VRN, 2016). Furthermore, this synthesis is limited in pigmented skin and therefore supplements may be especially important, for example, for immigrants (Cashman and Kiely, 2014). However,

according to guidelines by the Word Health Organization and the Institute of Medicine, routine vitamin D supplementation during pregnancy is not recommended (Institute of Medicine, 2011; WHO, 2012). Vitamin D deficiency in pregnant women and their new-born has been, nevertheless, quite common, even in Western countries (Saraf et al., 2016; Tuokkola et al., 2016). In recent studies, the benefits of sufficient vitamin D levels during pregnancy have been explored, and extend over bone metabolism (Garcion et al., 2002; Eyles et al., 2005; Eyles et al., 2011; Miliku et al., 2016). Specifically in pregnant women, vitamin D status may affect the risk of pregnancy complications such as pre-eclampsia and gestational diabetes mellitus (Mirzakhani et al., 2016; Achkar et al., 2015; Meinilä et al., 2015; Zhang et al., 2015; Hyppönen et al., 2013; Hyppönen et al., 2007). Maternal vitamin D status has also been associated with foetal growth restriction, preterm birth and small size for gestational age (Miliku et al., 2016; Tabatabaei et al., 2017). In addition, there has been an on-going debate about whether the recommendations for supplemented vitamin D should be increased (Aghajafari et al., 2016; De-Regil et al., 2016). However, safety aspects should be accounted for, especially during pregnancy, considering that very high doses of vitamin D may cause adverse metabolic or toxic symptoms (Institute of Medicine, 2011). The tolerable upper intake level of vitamin D is considered to be 100 µg per day in non-pregnant populations; however, the definition of safe intake level is difficult due to variations in vitamin D metabolism between individuals (Institute of Medicine, 2011).

Iron is another supplement that may be necessary in late pregnancy if iron stores are deficient prior to pregnancy (National nutrition council VRN, 2016). Iron stores at conception are a good predictor of anaemia in later pregnancy (Casanueva et al., 2003). In addition, iron supplementation is commonly recommended for multipara pregnancies and mothers with risk for anaemia, such as vegetarian mothers (National nutrition council VRN, 2016). A recent study of Portuguese mothers found that younger mothers have an increased risk of anaemia and one-third of all pregnant women have iron deficiency (Gomes da Costa et al., 2016). In addition, iron supplementation may have a wider role for women in developing countries, associated also with a reduced risk for perinatal and early childhood mortality (Choudhury et al., 2015; Abioye et al., 2016; Nisar and Dibley, 2016).

Nutritional recommendations do not routinely guide in using other dietary supplements for normal pregnancies, because their benefits are questionable if the diet is versatile. Nevertheless, pregnant mothers tend to also use additional dietary supplements such as multivitamins, calcium or n-3 fatty acid (FA) supplements, especially older, well-educated and normal weight mothers (Arkkola et al., 2006). Calcium supplementation during pregnancy may be necessary due to its increased

demand if the mother does not consume dairy products (Institute of Medicine, 2011). In previous Cochrane reviews, the use of calcium supplements during pregnancy has also been associated with a reduced risk of pre-eclampsia, with no other clear improvements in pregnancy and infant outcomes (Hofmeyr et al., 2006; Buppasiri et al., 2015).

Nowadays, pregnant women increasingly consume n-3 FA supplementation, which is associated with multiple short- and long-term beneficial effects for the pregnancy outcome and the offspring. For example fish oil supplementation in high-risk women may increase the offspring birth weight and reduce the risk of preterm birth (Makrides et al., 2006). In addition, maternal n-3 FA supplementation has also been shown to improve infant FA status and therefore has the potential to promote the neurocognitive development of the child and decrease the risk of atopic disease and allergy in the offspring (Helland et al., 2008; Furuhjelm et al., 2009; Miyata and Arita, 2015). Low intakes of n-3 FA for women in the United States have given rise to concern, especially in lower socioeconomic classes (Papanikolaou et al., 2014; Nordgren et al., 2017). However, the optimal level of n-3 FA plasma concentration for clinical benefits remains unknown and needs to be defined in further studies before general recommendations for supplementation during pregnancy can be made.

For mothers with restricted diets, such as vegans, vegetarians or very young mothers, additional micronutrient supplements may be necessary (Allen, 2005; Haider and Bhutta, 2006; Black et al., 2008). In a population with micronutrient deficiency, such as mothers in low-income countries, the use of multiple micronutrient supplements may result in a decreased risk of maternal anaemina, low birth weight, and small-for-gestational age (Allen et al., 2009). On the contrary, in the same study the combined use of folic acid and iron was as effective as the consumption of multiple micronutrients (Buppasiri et al., 2015).

2.3 Dietary challenges during pregnancy

2.3.1 Internal challenges

Internal dietary challenges during pregnancy are related to physiological maternal conditions, usually not directly harmful to the mother or foetus. Gastrointestinal tract disorders are common in pregnancy due to alterations in gastrointestinal motility, caused by elevated levels of progesterone and structural changes. These

may present for example as nausea and vomiting, gastro-oesophageal reflux, or constipation (Body and Christie, 2016). In addition, mothers diet may also be affected by health based and other food restrictions, food cravings or aversions related to the pregnancy. As a result, the diet of a pregnant woman may thus be modified either by unintentional elimination or intentional selection of foods in an attempt to improve their well-being.

Mild or moderate nausea and vomiting in pregnancy (NVP) is a common problem affecting approximately 50-90 % of pregnancies (Einarson et al., 2013). There are several aetiological theories for NVP such as fetoprotective, biochemical and immunological theories (O'Brien and Relyea, 1999; Flaxman and Sherman, 2000). However, it is thought to be associated with rising levels of the human chorion gonadotrophin hormone (Louik et al., 2006). NVP is typically manifested between the fourth and seventh week of gestation and is resolved by the 20th week of gestation in majority of the women (Gadsby et al., 1993). The presence of NVP may alter dietary intake for women without affecting energy intake (Lacroix et al., 2000; Chortatos et al., 2013; Crozier et al., 2016). A recent study suggests that mild NVP may result in an increased dietary intake of certain foods in contrast to severe NVP, resulting in decreased food intake during pregnancy (Crozier et al., 2016). According to the findings of Crozier et al., with an increasing severity of NVP symptoms, the intake of vegetables, beans and pulses, rice and pasta decreases and that of white bread and soft drinks increases. This may result in an unbalanced intake of macro- and micronutrients during pregnancy. The current dietary recommendations for pregnant women advice eating several small meals per day, also cold drinks and fruits may relieve the NVP symptoms (National nutrition council VRN, 2016).

Hyperemesis gravidarum, characterised by severe nausea and vomiting during pregnancy, affects approximately 1 % of pregnancies (Einarson et al., 2013). This condition may impact the energy and nutrient intake of the women and therefore essential nutrient supplies for the foetus (McParlin et al., 2016). Fear of NVP may lead pregnant mothers to avoid foods and drinks provoking symptoms, most commonly coffee, meat, poultry, fish, eggs and spicy and fatty foods (Weigel et al., 2011; Crozier et al., 2016). On the other hand, pregnant women may experience cravings for particular foods such as ice cream, chocolate, sweets and fast food, associated with increased excessive weight gain during pregnancy (Orloff et al., 2016). However, according to another recent study, cravings only slightly increased energy intake with no excessive gestational weight gain (Hill et al., 2016). NVP is shown to adversely affect the quality of life and may be associated with some pregnancy complications such as hypertension and pre-eclampsia, but it has not been associated with unfavourable birth outcomes (Koren and Maltepe, 2004; Lacasse et al., 2008; Kramer et al., 2013; Chortatos et al., 2015). However,

in some studies the effect of hyperemesis gravidarum on gestational weight gain has been associated with lower birth weight, small for gestational age and premature birth of the offspring, although later studies have failed to confirm these associations (Dodds et al., 2006; Kuru et al., 2012; Vikanes et al., 2013).

Food allergies may also alter the dietary intake of the mother because of the intentional elimination of foods, which may provoke symptoms. A diet that excludes many specific foods can therefore be restrictive in terms of nutrient intake and should be monitored by professionals with nutritional knowledge if the avoided food is essential (Williamson, 2006). The intake of n-3 PUFA for mothers with fish or shellfish allergies, for example, may remain under the recommended level during pregnancy. The same may be the case with vitamin D and calcium in mothers with cow milk allergy.

Gastroesophageal reflux is a further common condition reported to manifest in 40 to 85 % of pregnancies (Ali and Egan, 2007). A potential cause for this disorder is hormonal changes as elevated progesterone levels leads to lower oesophageal sphincter relaxation and gastric motility reduces (Ali and Egan, 2007; Zia and Heitkemper, 2016). Also, increased abdominal pressure caused by the growing uterus has been hypothesized to affect gastroesophageal reflux symptoms, although this theory lacks scientific evidence. Increased abdominal pressure along with other mechanical changes may also cause other problems. Up to 40 % of pregnant women suffer from constipation during pregnancy (Cullen and O'Donoghue, 2007; Bradley et al., 2007). The causes are often multifactorial including decreased physical activity, low intake of dietary fibre and hormonal and metabolic changes (Prather, 2004; Cullen and O'Donoghue, 2007). In contrast, some pregnant women suffer from diarrhoea, typically presenting in late pregnancy (Zielinski et al., 2015). Collectively, these gastrointestinal tract problems may unintentionally modify the dietary intake of pregnant women and consequently cause indirect health risks or long-term effects for the offspring by maternal food elimination or selection. Thus mothers should be provided with sufficient treatment and care regardless of the generality of the phenomenon.

2.3.2 External challenges

Dietary intake for pregnant mothers may also be affected by external challenges, arising from cultural habits, environmental aspects or maternal lifestyle. Western style dietary intake, a common dietary pattern, is recognized as a problem resulting in the unbalanced dietary intake of foods and nutrients including a high intake of processed foods, such as microwave meals, ready-meals and sausages, red meat,

and saturated fats as well as a low intake of fruits and vegetables, fibre, and polyunsaturated FA (Cordain et al., 2005; Paradis et al., 2009).

Following a Western style diet, may lead to insufficient intake of essential FA, vitamins and minerals, especially considering the needs of pregnancy. For example, low intake of folic acid caused by the Western style dietary pattern increases the risk of neural tube defects and even septal heart defects according to an epidemiological study (Sotres-Alvarez et al., 2013). In addition, high amounts of processed, high-energy dense foods may lead to excessive weight gain or obesity and have been associated with an increased risk of gestational diabetes (Flynn et al., 2016). In a Finnish population of pregnant women seven food patterns were recognised and "Healthy" food pattern was associated with higher maternal age and higher level of education whereas "Fast food" dietary pattern was associated with weight gain rate during pregnancy (Arkkola et al., 2008; Uusitalo et al., 2009). In animal studies, processed food also altered the offspring gut microbiome with substantial effects via the gut-brain axis (Myles et al., 2013). Evidence also suggests that food preparation and manufacturing methods may contribute to adverse health effects (Domingo and Nadal, 2017). In addition to the Western style dietary intake other dietary patterns have also resulted in similar outcomes. In a prospective cohort study conducted in the US, four dietary patterns were characterized in pregnant women (Martin et al., 2015). The results of the study indicated that a less-healthy dietary pattern during pregnancy was associated with the preterm birth and was a risk factor for offspring's overweight and obesity in early childhood (Martin et al., 2015; Martin et al., 2016).

In contrast to the Western style diet, some pregnant women follow restrictive diets such as vegan, gluten-free, dairy-free diets due to health aspects or their view of life. These diets should be carefully planned to ensure sufficient intakes of essential nutrients. However, there is an increasing variety and quantity of these diets without any medical need, which means that individual dietary counselling cannot be provided for all women. In Finnish dietary recommendations, vegan diet is considered safe during pregnancy but should be followed by a nutritionist (National nutrition council VRN, 2016). To date, no studies have focused exclusively on a vegan diet during pregnancy consisting purely of plant food during pregnancy, but findings from studies about vegetarian diets during pregnancy have not found adverse pregnancy outcomes or macronutrient deficiency (Craig et al., 2009). Common problems in vegan diets are deficiency in vitamin D, vitamin B12, iron, n-3 FA, calcium, iodine, and zinc unless the diet is carefully planned (Craig, 2010). In a Finnish non-pregnant vegan population the intakes of vitamin B12 and vitamin D and the serum concentrations of 25-hydroxyvitamin-D, iodine and selenium were lower compared to the non-vegetarian population (Elorinne et al., 2016). On the contrary vegans had lower

levels of serum SFA but also lower of n-3 LC-PUFA compared to the non-vegetarians (Elorinne et al., 2016). Well-executed lacto-ovo-vegetarian diets may be health promoting along with a reduced intake of processed foods and saturated fats and an increased intake of fruits and vegetables (Elorinne et al., 2016).

Other modern diets also exist, such as the live-raw food diet consisting of uncooked, often organic or wild foods, and the fruitarian diet consisting only of dried fruits, berries, nuts and seeds. Some raw food may be harmful to the foetus and should be avoided during pregnancy due to the risk of pathogens such as listeria monocytogenes or salmonella in raw fish, meat, and unpasteurized dairy products (Kantsø et al., 2014; Diseases et al., 2014; Acciari et al., 2017). Overall, eliminating individual foods or food groups rarely results in harmful deficiencies, but these modern restrictive diets are poorly studied and thus recommendations have not been made for pregnant mothers.. In extreme cases, they may have similar consequences to eating disorders during pregnancy, and are likely to cause harmful effects on the offspring (Micali and Treasure, 2009).

2.4 Means for optimizing maternal nutrition and pregnancy outcome during pregnancy

2.4.1 Intervention studies to improve dietary intake of pregnant women

Dietary intake for pregnant women may differ from those commonly recommended for several reasons and have potential health consequences for the mother and child. Hence, several randomized dietary intervention trials have been conducted to improve maternal nutrition during pregnancy (**Table 1**). Most of the studies have used Food frequency questionnaires (FFQ) or other questionnaires but also food diaries have been used to evaluate dietary intake of pregnant women. In general, pregnant women are interested in promoting the health of their offspring and are thus responsive to dietary interventions during pregnancy.

Many of the randomized controlled dietary intervention studies studying the impact on maternal dietary intake in pregnant women have been conducted in an obese or overweight population to prevent excessive weight gain or prevent or treat gestational diabetes (Guelinckx et al., 2010; Petrella et al., 2014; Dodd, 2014; Kinnunen et al., 2014; Hawkins et al., 2015; Flynn et al., 2016; Valkama et al., 2016; Opie et al., 2016). These interventions have resulted in targeted improvements in maternal dietary intake, especially in the dietary quality of fat and the consumption of vegetables and fibre (Guelinckx et al., 2010; Dodd et al., 2014; Kinnunen et al., 2014). In a study by Piirainen et al., dietary counselling

during pregnancy was proven to be effective in a normal weight population improving dietary fat quality, reflected in nutrient intakes as a higher intake of PUFA and a lower intake of SFA in the dietary intervention group (Piirainen et al., 2006). Also other beneficial changes in mothers' dietary intake in the intervention groups were observed such as a higher intake of fruits, berries, vegetables, fish, and fibre as well as a lower intake of sugar (Opie et al., 2016; Valkama et al., 2016; Bosaeus et al., 2015; Dodd et al., 2014; Kinnunen et al., 2014; Petrella et al., 2014; Piirainen et al., 2006). One study evaluated the effects of dietary intervention on dietary patterns with reduced "Processed" and "Snacks" pattern scores (Flynn et al., 2016). However, in most of the studies, changes in dietary intake were minor. Some of the interventions also included lifestyle intervention or physical activity programs to support the dietary changes (Petrella et al., 2014; Dodd et al., 2014; Aşcı and Rathfisch, 2016).

In most of the intervention studies, nutritionists advised pregnant women, but trained research assistants or health educators were also used to provide nutritional advice (**Table 1**). In a recent Swedish study, midwives in antenatal care experienced their role in dietary counselling for pregnant women difficult and challenging (Wennberg et al., 2015). The midwives found it especially difficult to interpret the guidance women had received from the Internet. Well-fare clinics play a key role in instructing and guiding families and supporting a healthy lifestyle and thus should be provided with education in nutrition during pregnancy and lactation as well as in counselling delicate issues (Ilmonen et al., 2012; Wennberg et al., 2015).

Table 1 Randomized controlled dietary intervention studies between 2006 and September 2017 affecting maternal dietary intake during pregnancy

Study	*Subjects*	*Type of dietary intervention*	*Aim of the dietary intervention*	*Dietary data collection*	*Main findings*
(Piirainen et al., 2006)	Pregnant mothers (n=209) <17 gestational weeks (GW)	Individual dietary counselling by a nutritionist and supporting food products.	To modify dietary intake towards that recommended by focusing on the type of fat and the amount and type of fat and amount of fibre.	3-day food diary at each trimester of pregnancy.	Intervention increased the consumption of vegetables, fruits, soft margarines and vegetable oils and decreased the consumption of butter. This resulted in a higher intake of PUFA and a lower intake of SFA.
(Guelinckx et al., 2010)	Obese pregnant women (n=195) < 15 GW	Nutritional advice from a brochure or a brochure and lifestyle education by a nutritionist.	To substitute high-energy foods with healthier foods, to increase low-fat dairy and whole-wheat products and reduce the intake of SFA.	7-day food records each trimester of pregnancy.	Total fat intake and SFA intake decreased and protein intake increased in both groups compared to the control group. Calcium intake and vegetable consumption increased in all groups.
(Petrella et al., 2014)	Overweight and obese pregnant women (n=61) during 12 GW	A diet introduced by a nutritionist with energy restriction and physical activity program.	To substitute high-glycaemic index foods with healthier alternatives and to redistribute the number of meals along the day.	Food Frequency Questionnaire (FFQ) at 1st and 3rd trimester of pregnancy.	The intervention group increased the number of snacks, the intake of fruits-vegetables and decreased the consumption of sugar.
(Dodd et al., 2014)	Overweight and obese pregnant women (n=2212) 10-20 GW	Individual dietary and lifestyle intervention by a research dietician and trained research assistants.	To balance intake of carbohydrates, fat and protein; to reduce intake of refined carbohydrates and SFA and increase intake of fibre, vegetables, fruits and dairy.	FFQ at each trimester of pregnancy.	In the intervention group women increased the fruit and vegetables consumed per day, as well as increased consumption of fibre, and reduced percentage energy intake from saturated fats. Maternal HEI was significantly improved at both 28 and 36 weeks.
(Kinnunen et al., 2014)	Pregnant women with risk of GDM (n=726) 8-12 GW	Individual dietary counselling by the public health nurses	To modify diet towards that recommended focusing on dietary fat, fibre and saccharose intake.	FFQ at 2nd and 3rd trimester of pregnancy.	Intervention increased consumption of vegetables, fruits and berries, high-fibre bread and vegetable fats. This resulted in a higher intake of PUFA, LA and fibre and lower intake of SFA.

(Bosaeus et al., 2015)	Pregnant women (n=101) 8–12 GW	Individual dietary counselling by a dietician and phone calls.	To increase adherence to the dietary recommendations by the Swedish National Food Agency and the Nordic Nutrition Recommendations.	A FFQ focusing on intake of fish and meat at each trimester of pregnancy.	Fish intake increased in the intervention group from the first to the second trimester (median difference 113 g, p = 0.03) and from the first to the third trimester (median difference 75 g, p = 0.01).
(Hawkins et al., 2015)	Overweight or obese pregnant women (n= 68) < 18 GW	Individual counselling sessions and five telephone sessions by health educators.	To decrease intake of foods high in saturated fat and increase dietary fibre.	Two 24h dietary recalls three times during pregnancy.	No significant dietary changes between the groups.
(Flynn et al., 2016)	Obese pregnant women (n=1023) 15-18 GW	A behavioural intervention of diet delivered by health trainers by eight one-to-one or group sessions.	To promote a healthier pattern of eating, focusing on a reduction of dietary glycaemic load and a reduction in saturated fat intake.	FFQ at each trimester of pregnancy.	Four dietary patterns at the baseline were defined; Fruit and vegetables, African/Caribbean, Processed, and Snacks. The intervention significantly reduced the Processed and Snacks pattern scores at second and third trimester of pregnancy.
(Valkama et al., 2016)	Pregnant women (n=242) with obesity or previous GDM < 20 GW	One individual counselling session by a trained study nurse and a group counselling session by a dietitian.	To increase the intake of vegetables, fruits, berries, vegetable fats, whole grain, fish, low-fat meat and dairy. To reduce the intake of sugar-rich foods.	Food-intake questionnaire at the 1st and 2nd trimester of pregnancy.	The intake of low-fat products and fish (times/week) was increased in the intervention group compared with the control group.
(Opie et al., 2016)	Obese pregnant mothers (n=92) ≤ 21 GW	Individual face-to-face dietitian delivered consultation with follow-up phone reviews.	To normalize servings sizes and displace energy-dense and nutrient-poor foods with healthier alternatives.	A diet history questionnaire at baseline and follow-up phone reviews.	Intervention increased intake of vegetables and fruits. Amount of women meeting recommended vegetable serves increased from 17.4 % to 27.9 % and fruit serves from 39.1 % to 51.2 %.
(Aşcı and Rathfisch, 2016)	Pregnant mothers (n=102) 12-18 GW	Four meetings regarding healthy lifestyle, nutrition, exercise, and weight follow-up.	To modify dietary intake towards the recommendations in national guidelines.	3-day food diaries at 1st and 2nd trimester of pregnancy.	Intervention increased intakes of protein, calcium, magnesium, iron, zinc and vegetables.

2.4.2 Impact of dietary intake on serum fatty acids

Serum FA composition is considered to reflect the quality of dietary fat intake and it is typically analysed by measuring the FA of serum lipid fractions such as phospholipids (PL), cholesteryl esters (CE), triacylglycerols (TAG) or that of erythrocytes. High proportions of PUFA, with two or more double bonds, are of special importance during pregnancy, because they are considered health promoting for both the mother and infant (Demmelmair and Koletzko, 2015). PUFAs consist mainly of n-6 and n-3 FA of which the human body is incapable of synthesising linoleic acid (LA, 18:2n-6) and alpha linolenic acid (ALA, 18:3n-3). These essential FA have to be received from the diet and can be converted in small amounts to their longer derivatives endogenously, but the intervention between the n-3 and n-6 FA families is not possible (Burdge and Wootton, 2002; Schmitz and Ecker, 2008). However, dietary intake is considered to be the major determinant of serum n-3 long-chain PUFA (LC-PUFA) status (Plourde and Cunnane, 2007). Dietary n-3 FAs are received from vegetable oils, such as rapeseed oil, nuts, seeds, and oily fish. Oily fish is the main source of n-3 LC-PUFA: DHA (22:6n-3) and eicosapentaenoic acid (EPA, 22:5n-3). Dietary n-6 FAs are received from vegetable oils but also from poultry, eggs, nuts and seeds. Due to the health effects of n-3 PUFA, a lower ratio of n-6/n-3 is considered beneficial, presenting as a typical problem of Western dietary intake (Calder, 2006; Simopoulos, 2008).

In pregnant and lactating women the metabolic need of n-3 PUFAs is increased due to their functions for example in cell membrane synthesis in the brain and retina (Campoy et al., 2012). Furthermore, n-3 LC-PUFAs influence the levels of neurotransmitters such as dopamine and serotonin, serve as precursors for anti-inflammatory eicosanoids, and act as immunoregulators, possibly reducing the later risk of allergic disease in the infant (Dunstan et al., 2003; Chalon, 2006; Montes et al., 2013; Calder, 2013). Maternal intake of n-3 LC-PUFA has also been associated with lower risk of pre-eclampsia and preterm delivery in high-risk pregnancies as well as postnatal depression (Szajewska et al., 2006; Oken et al., 2007; Horvath et al., 2007). In addition, n-3 LC-PUFAs are associated with reduced risk of cardiovascular disease, even at a reproductive age (Oken et al., 2007; Strøm et al., 2012).

Several studies conducted in pregnant women have indicated that maternal serum FA composition is dependent on the maternal dietary intake of FAs (De Vriese et al., 2002; Zhang et al., 2013; Bosaeus et al., 2015). Especially maternal intake of fish has been shown to increase EPA and DHA in serum PL (De Vriese et al., 2002; Bosaeus et al., 2015). Also dietary evaluation with Food Frequency Questionnaire estimating the intake of n-3 LC-PUFA has been considered good

indicator of serum EPA and DHA status (Lepsch et al., 2015; Kobayashi et al., 2017). However, serum FAs are altered also by metabolic changes during pregnancy as concentrations of maternal SFA, MUFA and PUFA have been shown to increase from the pre-pregnancy levels (Al et al., 1995; Otto et al., 1997). For example, maternal plasma and erythrocyte levels of DHA increase in early pregnancy, probably due to the synthesis of DHA from the precursors (Otto et al., 2001). This synthesis may however be disturbed in mothers with gestational diabetes or hyperglycaemia and sufficient dietary intake of n-3 LC-PUFA is needed to secure the development of the foetus (Chen et al., 2010).

2.5 Maternal dietary intake and child development

In previous animal studies, protein malnutrition during pregnancy has been associated with impaired neurodevelopment in mice offspring (Belluscio et al., 2014; Akitake et al., 2015). Also in humans, severe protein malnutrition resulting in intra-uterine growth disorder has been associated with poor developmental outcomes (Georgieff, 2007; Prado and Dewey, 2014). Even though severe protein malnutrition for women in Western countries is rare and dietary intake is usually sufficient to support the normal growth of the offspring, the rapidly developing brain may be vulnerable to macro- or micronutrient insufficiencies.

Indeed, epidemiological and experimental studies have produced theories indicating the role of maternal nutrition *in utero* during this critical time period on later development of the offspring. Thus, modifying maternal nutrition and the metabolic environment during pregnancy may potentially improve the neurodevelopment of the foetus. In contrast to malnutrition, a high-fat diet and as a consequence maternal obesity, have been shown to modify the neurodevelopment of the offspring unfavourably in rats and macaques (Giriko et al., 2013; Mendes-da-Silva et al., 2014; Rivera et al., 2015b; Rivera et al., 2015a). The potential mechanisms through which maternal metabolic changes may modify child neurodevelopment are presented in **Figure 3**.

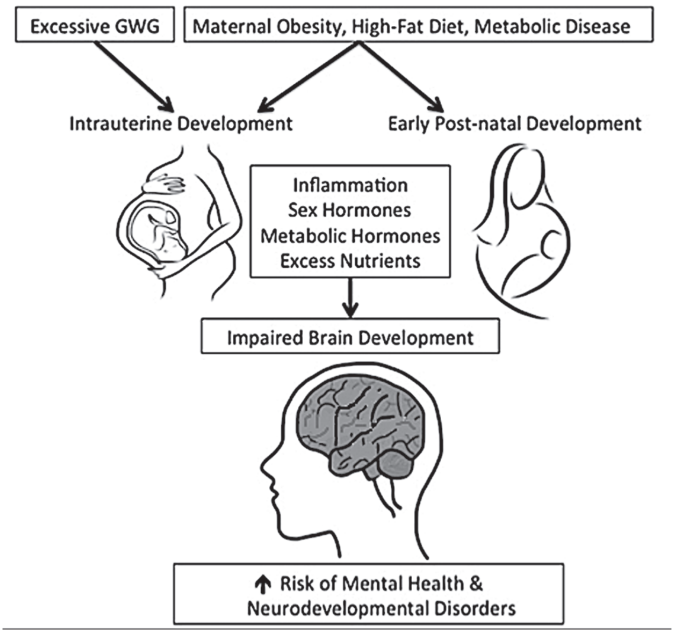

Figure 3 Potential mechanisms through which maternal obesity, metabolic state, high-fat diet, and excessive gestational weight gain may lead to development of mental health disorders in offspring. Modified from Rivera et al., 2015a.

Several studies and reviews focus on separate micronutrients, these include iron, folic acid or vitamin D, and offspring neurodevelopment (Leung et al., 2011; Prado and Dewey, 2014; González and Visentin, 2016). However, there is limited data on the effects of maternal dietary intake on child neurodevelopment in clinical studies, which often focus on the intake of specific nutrients and overlook diet as a whole (**Table 2**). The methods and age for developmental evaluation vary from 14 months to 8 years of age, and thus the comparison of the studies is challenging. The tests used in these studies mostly focus on cognitive or overall development of the children (Daniels et al., 2004; Bayley, 2005; Hibbeln et al., 2007; Oken et al., 2007). A recent study indicated that maternal dietary patterns are associated with the neurodevelopmental outcome of the child (Freitas-Vilela et al., 2017). In the study, the "fruits and vegetables" pattern was associated with a higher IQ for the child at 8 years compared to the dietary patterns "meat and potatoes" and "white bread and coffee". Further, the effects of maternal dietary intake of fish have been previously studied in at least five clinical studies. In two of the studies, the maternal intake of fish and seafood resulted in the improved neurodevelopment of the toddler (Daniels et al., 2004; Julvez et al., 2016) and in one study later in childhood (Hibbeln et al., 2007). However, the remaining two studies resulted in a nonsignificant outcome (Oken et al., 2007; Valent et al., 2013).

As the regulatory systems of neurodevelopment are highly plastic and sensitive to the environment during the foetal period and early infancy, maternal nutrition may be seen as a potential target for preventive measures in an attempt to improve child health through the programming effect.

Table 2 Studies concerning maternal dietary intake during pregnancy and offspring neurodevelopmental outcomes.

Study	Dietary component studied	Used method for developmental evaluation	Primary outcome in the offspring
Daniels et al. 2004	Fish intake	MacArthur Communicative Development Inventory at 15 months, Denver Developmental Screening Test at 18 months	Consumption of fish by the mother during pregnancy and by the infant postnatally, was associated with higher mean developmental scores.
Hibbeln et al. 2007	Fish intake	Weschler Intelligence Scale for Children III^{UK} at 8 years	Maternal seafood intake of more than 340 g weekly resulted in beneficial effects in children's cognitive development.
Valent et al. 2013	Fish intake	Bayley Scale III at 18 months	Maternal intake of fish was slightly but non-significantly associated with child neurodevelopmental scores.
Oken et al. 2016	Fish intake	Kauffman Brief Intelligence Test at 7.7 years	Maternal fish intake or DHA and EPA status were not associated with child verbal or non-verbal intelligence, visual motor function, or visual memory
Julvez et al 2016	Seafood intake	Bayley Scales at 14 months and the McCarthy scale and the Childhood Asperger Syndrome Test at 5 years	Consumption of fatty fish during pregnancy improves child neuropsychological outcome, including cognitive functioning and protection from autism-spectrum traits.
Freitas-Vilela et al. 2017	Dietary pattern	Wechsler Intelligence Scale for Children at 8 years	Fruit and vegetables –dietary pattern during pregnancy was associated with higher IQ of the children

3 AIMS OF THE STUDY

The overall objective of this thesis was to evaluate the impact of maternal nutrition and dietary counselling on maternal and infant metabolism and health in order to provide a favourable metabolic environment during pregnancy and lactation for the foetus and infant. The specific aims were:

1. To evaluate the impact of nausea and vomiting during pregnancy on infant growth and maternal food consumption and nutrient intake. (Study I)

2. To evaluate the effects of dietary challenges such as Western-style dietary intake presenting as a high intake of saturated fatty acids and a low intake of polyunsaturated fatty acids. (Studies II and III)

3. To study the impact of dietary counselling during pregnancy on maternal and infant serum fatty acid status. (Study II)

4. To develop simple dietary criteria to improve the serum n-3 fatty acid status of mothers and their infants. (Study III)

5. To describe the association between maternal nutrition during pregnancy and infant development at one year of age. (Study IV).

4 MATERIALS AND METHODS

4.1 Study population and design

The study population consisted of 256 mothers and their infants from a prospective follow-up study. Mothers were recruited between April 2002 and November 2004. The study was originally designed to monitor and optimize maternal nutrition and metabolism by intervention and to evaluate the effects of maternal nutrition on infants. The focus of the present thesis was to detect the impact of maternal dietary intake and dietary counselling on maternal and infant metabolism and health.

The mothers were informed about the study in local newspapers and by leaflets distributed during their first visit at the local maternity and child welfare clinics in the city of Turku and neighbouring areas in Southwest Finland. Interested women contacted the study nurse for further information and to reserve their first visit to the study clinic. The inclusion criteria were 18 years age, pregnancy duration less than 17 weeks and the unborn child having a risk for allergic diseases (mother, father or sibling having a self reported food allergy, atopic eczema, asthma or allergic rhinoconjuctivitis). The mothers in the study were healthy and had no chronic or metabolic diseases except the presence of allergic disease was accepted.

After recruitment, the women were randomized into three groups: dietary intervention receiving food products and probiotic supplementation (diet/probiotics); dietary intervention receiving food products and placebo capsules (diet/placebo); and a control group receiving placebo capsules (control/placebo) **(Figure 4)**. A statistician, not involved in recruitment or the study, carried out randomization according to a computer-generated block randomization of six women, and the study was conducted as a double-blind to probiotics and placebo groups and as single-blind to diet and control groups.

The study visits took place three times during pregnancy at 13.9 (1.6 SD), 23.8 (1.4 SD) and 33.9 (1.4 SD) weeks of gestation and at one, six and 12 months after delivery. Reasons for discontinuing the study were: miscarriage, illness of mother or child, moving, not willing to give child samples and not willing to continue. All mothers and infants also attended routine follow-up at their municipal welfare clinics during and after the pregnancy.

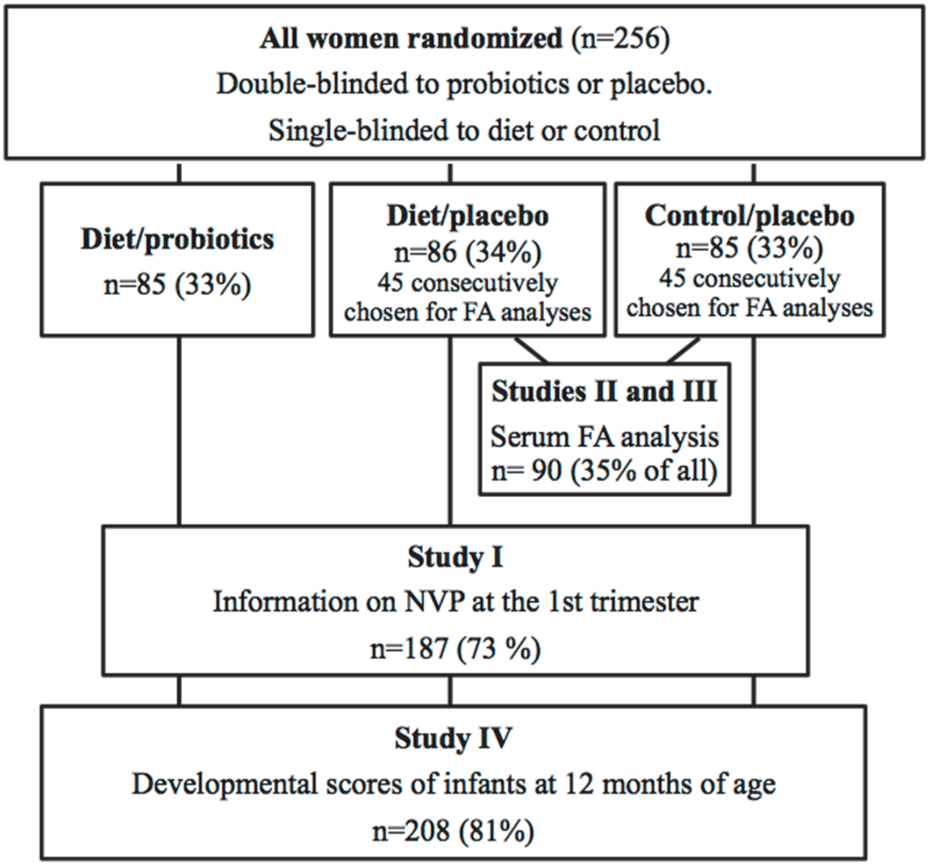

Figure 4 Study design

Information about nausea and vomiting was obtained from 187 mothers (73%) thus comprising the subjects in study I **(Figure 4)**. For the accurate FA analyses in studies II and III a subpopulation of 90 women and infants, 45 from the dietary intervention group and 45 from the control group, were chosen in consecutive order according to the enrolment sequence to keep the original randomization order. All women in the subpopulation for FA analysis received placebo capsules. Developmental tests were successfully performed for 207 infants at one year of age thus comprising the study population in study IV.

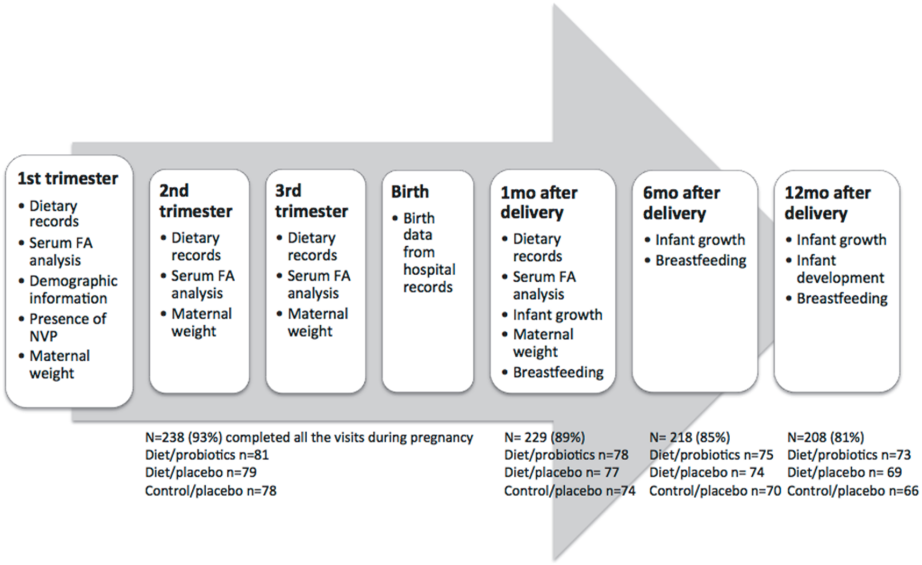

Figure 5 Study visits, samples and measurements

4.2 The probiotic intervention

The impact of probiotic intervention in this study population is reported in previous studies (Huurre et al., 2008; Laitinen et al., 2009; Ilmonen et al., 2011; Luoto et al., 2012; Hoppu et al., 2012). The possible impact of probiotic intervention was, however, taken into account in preparing the analysis for the present study. In study I the presence of NVP was interviewed at the baseline and thus was not affected by the intervention. In studies II and III the study subjects were chosen only from the groups receiving placebo (**Figure 4**). In study IV the hypothesis was that dietary intake during pregnancy may alter infant development. The study was not originally powered to test the effect of probiotic intervention on infant development, however the intervention was taken into account by analysing the impact of dietary intervention on developmental scores with no statistical differences between the groups and developmental total score or the sub scores. In addition, the statistical analyses were adjusted by the results for intervention groups.

4.3 Baseline characteristics and measurements of the mothers

At the first study visit demographic information such as age, parity, smoking, and level of education were recorded by the study nurses. Mothers´ self-reported pre-pregnancy weight was received from maternal welfare records and their height was measured by a research nurse at the first study visit. These measurements were used for calculating pre-pregnancy body mass index (BMI) by dividing weight (kg) by the square of height (m). Information on smoking was derived from interviews at each study visit during pregnancy and information on length of exclusive and total breastfeeding at the study visits at one, six and 12 months after delivery by the study nurses.

The presence of NVP was obtained at the first study visit by interviews with standard questions carried out by a nutritionist. These were: (1) Do you have nausea related to early pregnancy? (2) If you do, have you vomited? (3) If you have vomited, how many times a day? The severity of NVP was assessed as having no nausea or vomiting, only nausea, vomiting once a day or vomiting more than once a day, with the primary outcome being the presence or absence of nausea.

4.4 Maternal dietary evaluation

Maternal dietary intakes of foods, energy, energy-yielding nutrients, vitamins and minerals of all women were measured using 3-day food diaries. The recording days were self-selected, including one weekend day. The food diaries were fulfilled prior to each of the three study visits during pregnancy and one month postpartum. Women received individual oral and written instructions for filling in the food diaries, and the food records were revised for completeness and accuracy by a nutritionist guided by a portion picture booklet. The use of vitamin and mineral supplements was queried in the food diaries. Daily intakes of foods and nutrients were calculated using the computerized program Micro-Nutrica® (version 2.5, Research Centre of the Social Insurance Institution, Turku, Finland). The database in this program has been validated and includes continuously updated data on commercially available foods. The intake of fish was evaluated by three different methods to better estimate the typical fish consumption of the women; quantitatively from 3-day food diaries, as a frequency questionnaire of recent consumption (over two weeks), and a questionnaire of typical fish consumption.

To evaluate the quality of the diet, a healthy eating index (HEI) was calculated based on guidelines given by the European Health Monitoring Program (Steingrímsdóttir et al., 2002). High intakes of vegetables, fruits and berries, fish and bread and low intakes of SFA (E%) and salt were evaluated from the food

diaries and each scored on a scale of 0 to 5, the index score of 25 representing the best health-promoting diet.

4.5 Dietary intervention

The dietary counselling for the dietary intervention group was performed by a nutritionist and aimed to modify the dietary intake of pregnant women according to dietary recommendations, with specific focus on the quality of dietary fat (Becker et al., 2004). To facilitate achieving these recommendations, women received sponsored food products for free use at home such as low erucic acid rapeseed oil-based spreads, salad dressing, fibre-enriched pasta, breakfast muesli and porridge cereals. The women received verbal feedback from a nutritionist during the study visits based on the fulfilled food diaries and the nutritionist suggested improvements for the women in the dietary intervention group. The written feedback was sent home after the study visits for the women in the dietary intervention group. The women in the control group received only routine dietary guidance at the maternity well-fare clinics and fulfilled the 3-day food diaries without individual dietary counselling and food products.

4.6 Birth data and clinical evaluation of the infants

Infants' birth data (length of gestation, weight, length and head circumference) was obtained from hospital records. The weight and length of the infants at one, six and 12 months of age at the study visits were measured by a research nurse.

Infant development at 12 months of age was assessed using Griffiths Mental Development Scale scores consisting of five subscales: locomotor (A), personal-social (B), hearing and speech (C), eye and hand coordination (D) and performance (E) (Griffiths and Huntley, 1996). Subscale A tests gross locomotor skills including the ability to balance and to co-ordinate and control movements. Subscale B measures the developing abilities that contribute to independence and social development. Subscale C tests the sense of active listening, receptive language and expressive language. Subscale D focuses on fine motor skills, and visual monitoring skills. Subscale E draws on the developing ability to reason through performance tests and tests how skills are applied in novel situations. The subscales were evaluated and scored separately and combined to provide an age-standardized overall quotient. The subscale points were also combined to form a total general quotient or a total score. A total score of ≥ 88 is considered to indicate normal development (Griffiths and Huntley, 1996).

4.7 Blood sample collection and storage

Fasting blood samples for mothers were taken from the antecubital vein on the mornings of the study visits at each trimester of pregnancy and one month postpartum. Non-fasting blood samples for the infants at the age of one month were obtained from the antecubital vein after topical lidocaine anaesthesia. The blood samples were collected into plain serum tubes and centrifuged after 30-120 min of cooling at 2500 g for 10 minutes at room temperature. The samples were first stored at – 20 ºC for a maximum of one week and then at – 70 ºC until analysed. The samples of the mothers and infants were used for FA analysis.

4.8 Fatty acid analyses

To analyse FA proportions and concentrations for the mothers and the infants, total lipids were extracted from blood samples with chloroform:methanol and the PL, TAG and CE were separated by solid phase extraction. FA methyl esters were prepared with boron trifluoride using the methanol procedure and FAs were analysed with gas chromatograph. The results of the FA are expressed as a concentration (mg), a percentage of total FA (%) or as a ratio of n-6/n-3 FA.

4.9 Ethical aspects

Written informed consent was received from the mothers at the first study visit and the study was approved by the Ethics Committee of the Hospital District of Southwest Finland. The study complies with the Declaration of Helsinki as revised in 2000.

4.10 Statistical analysis

The data was analysed with SPSS (SPSS Inc., Chicago, IL, USA) version 14.0 in Study I, version 18.0 in Study II and version 23.0 for studies III and IV. In study IV also SAS (SAS Institute, Inc., North Carolina, USA) version 9.4 was used. The distributions of variables were tested using graphical plots and Shapiro-Wilk test for normality. The *P* value was considered significant when $p < 0.05$ in all analyses.

Variables describing the clinical and background characteristics of the mothers and infants were normally distributed and were analysed using parametric methods.

Some variables describing dietary intake were moderately skewed to the right, thus in study I we used nonparametric tests and in studies II and III robust parametric analysis. Comparisons between the two groups were performed with independent samples *t*-test or the Mann-Whitney *U*-test for continuous variables and for dichotomous variables Chi-squared test was used.

Study I

The data was analysed using analysis of variance for repeated measures (repeated measures ANOVA) to evaluate the impact of NVP on dietary intake, the weight gain of the mothers and growth of the infants during the course of pregnancy. Maternal age, smoking status and parity were included as covariates in the analysis based on previous literature. The effect of the intervention (dietary counselling and probiotic supplementation) was analysed, but not included as a covariate because ANOVA did not find significant interaction between NVP and the groups.

Study II

To detect the impact of dietary counselling during pregnancy on maternal proportions and the concentrations of FA at the third trimester and one month after delivery we used analysis of covariance (ANCOVA) with baseline as a covariate. The differences between the groups with and without dietary counselling are presented as the baseline adjusted mean and mean differences between the groups with 95% CI. Intakes of energy, energy-yielding nutrients and foods between the groups were also analysed using the method described above.

Study III

In the initial analysis, correlations between maternal dietary factors and n-3 FA in the serum PL of mothers and infants were evaluated using Pearson and Spearman correlation scores. Based on these initial results, we performed further analysis of the dietary factors with significant *p* values, these being the intake of fish and the Healthy eating index (HEI) (Ilmonen et al., 2011). The HEI scores and intake of fish (g/day) were divided into three equally sized groups T1, T2 and T3 according to tertiles. The division was performed due to the abnormal distribution of these variables and to assist with data presentation. Groups T2 and T3 were compared to the lowest intake or lowest index score group T1 using Dunnett's *t* test. Dunnett's *t* test was also used to compare the n-3 FA in serum PL of women with different frequencies of fish intake compared to the non-consumers. ANOVA was used when comparing the n-3 FA in serum PL for the infants between groups T1-T3.

Generalised estimated equations analysis (GEE) with ANOVA was used to combine the three study points to compare the mothers n-3 FA in serum PL between the groups with different frequencies of fish consumption per week. The frequency of fish consumption for the women was also compared with non-consumers using Dunnett's *t* test pairwise comparison.

Study IV

The relationship between infants' developmental scores and the dietary intervention groups (dietary intervention with probiotics, dietary intervention with placebo and control with placebo) was analysed using the Kruskall-Wallis test. The analyses were adjusted to the intervention groups although no differences were detected. We found no correlation between infant developmental scores and possible confounding factors such as maternal level of education, maternal age, smoking, parity, maternal pre-pregnancy BMI, mode of delivery, presence of gestational diabetes, length of breastfeeding and infant birth size. Thus these were not included as a covariate. However, the analyses were later performed also adjusted to maternal education to ensure the reliability of the results. There were no significant differences compared to the results without adjusting to maternal education and thus the analyses without adjustment were used.

The impact of maternal nutritional during pregnancy on the development of the infant was evaluated with multivariable regression models and backward linear regression models, separately performed for intake of foods and nutrients and dietary and total intake vitamins and minerals. For intake of vitamins and minerals, we also performed separate models on each developmental subscale. A chi-squared test was performed to detect the differences between the intake of foods and nutrients in the highest tertile (T3) and the developmental scores in the highest tertile.

5 RESULTS

5.1 Clinical characteristics and dietary intake at baseline

The clinical characteristics of the mothers and infants are presented in **Table 3**. The women were of normal weight with mean BMI of 23.6 and 75 % had a college or university degree education. The rate of caesarean section (15%) and gestational diabetes mellitus (10%) in the study population were similar to the average Finnish population (National Institute for Health and Welfare, 2016). The infants were born at term with a mean of 39.8 weeks of gestation. The clinical characteristics of the women and infants in the dietary intervention and control groups had no statistically significant differences. The subsample for the FA analysis was representative for the whole population (**Table 3**).

Table 3 Clinical characteristics of the mothers and infants in dietary intervention group (with or without probiotics) and control group and in the subsample groups for FA analysis at the baseline. The results are presented as mean (± SD) or number (%).

	All subjects	***Intervention***	***Control***	***Subsample for FA analysis***	
Mothers	**n=256**	**n=171**	**n=85**	***Intervention* (n=45)**	***Controls* (n=45)**
Age (y)	30.0 ± 4.8	29.9 ± 4.7	30.2 ± 5.0	30.8 ± 5.4	30.0 ± 4.3
Prepregnancy BMI (kg/m^2)	23.6 ± 3.8	23.6 ± 3.9	23.7 ± 3.5	24.2 ± 4.2	23.1 ± 3.4
Gestational weight gain (kg)[1]	14.9 ± 4.8	14.9 ± 4.7	14.8 ± 5.1	15.2 ± 5.0	14.8 ± 5.2
Primigravida	147 (57 %)	99 (58 %)	48 (57 %)	21 (47 %)	25 (56 %)
College or university degree	191 (75 %)	123 (72 %)	67 (79 %)	31 (69 %)	36 (80 %)
Smoking in the first trimester	11 (4 %)	6 (4 %)	5 (6 %)	2 (6 %)	2 (4 %)
Gestational diabetes mellitus [2]	25 (10 %)	16 (9 %)	9 (11 %)	7 (16 %)	5 (11 %)
Cesarean section [3]	35 (15 %)	24 (14 %)	11 (13 %)	7 (16 %)	6 (14 %)
Infants	**n=237**	**n=160**	**n=77**		
Male gender	124 (48 %)	81 (47 %)	43 (51 %)	22 (49 %)	27 (63 %)
Gestation weeks at birth	39.8 ± 3.0	39.7 ± 3.6	40.1 ± 1.3	39.7 ± 2.1	40.0 ± 1.4
Birth weight (g)	3562 ± 465	3543 ± 438	3600 ± 510	3610 ± 480	3590 ± 520
Birth length (cm)	51 ± 1.9	51.0 ± 1.8	51.0 ± 2.2	51.3 ± 1.7	50.8 ± 2.2
Exclusive breast-feeding (months)[4]	3.4 ± 1.8	3.4 ± 1.9	3.1 ± 1.6	2.9 ± 2.3	3.0 ± 1.8
Total breastfeeding (months)[4]	8.3 ± 4.9	8.8 ± 5.6	8.3 ± 4.5	8.4 ± 5.9	7.7 ± 4.2

[1](n=233/256, n=155/171, n=78/85), [2](n=242/256, n=161/171, n=79/85),
[3](n=229/256, n=152/171, n=77/85), [4](n=220/256, n=150/171, n=70/85)

The dietary intake of all mothers during the first trimester is presented in **Table 4** and **Table 5**. The dietary intakes of the dietary intervention and the control groups were comparable at the baseline. Compared to that recommended, the intake of SFA and MUFA were higher and the intake of fibre was lower in the study population.

The mean score for the HEI of all women was 13.8 (3.6 SD; min 5, max 20). The tertiles for the index were: ≤12 (33%), 13-15 (31%) and ≥16 (37%). The median intake of fish for all women was 18 g/day (inter quartile range IQR 0 to 46) and 40 g/day (IQR 21 to 66) including only those women who ate fish during the 3-day food diary recording. During the recording days, 37% of the women did not consume fish. According to the frequency questionnaire, the women consumed a median of 1.5 portions fish per week (IQR 1 to 2). The tertiles for fish intake were: 0 g/day, 1-35 g/day and ≥36 g/day. As determined from the food frequency questionnaire, 19% of the women had consumed fish 0 times, 18% once, 23% twice, 18% 3 times, 22% ≥4 times over the two weeks before the baseline study visit.

Table 4 The maternal dietary intake of foods (g/day) calculated from 3-day food diaries at the first trimester of pregnancy. N=256.

Intake of foods	Median	IQR
Grain products	204.3	159.8-251.4
Milk products	461.0	305.6-682.4
Cheese	45.7	30.5-70.0
Meat products	104.9	76.0-145.4
Fish products	16.5	0-41.1
Eggs	12.5	4.9-23.1
Vegetables	279.2	196.2-365.0
Fruits and berries	288.3	179.3-443.1
Butter	2.2	0.2-8.3
Margarines	12.6	6.0-21.3
Vegetable oils	7.6	2.5-13.8
Drinks	587.8	389.8-795.7
Sugar and sweets	25.8	14.5-42.6

Table 5 The maternal dietary intake of energy, energy-yielding nutrients, dietary fibre, and dietary and total (from diet and supplements) intake of vitamins and minerals at the baseline and the recommended intakes for pregnant women (National nutrition council VRN, 2016). N=256. The dietary intakes are calculated from 3-day food diaries.

Energy and macronutrients		***Mean***	***SD***	***Recommended***	
				2004*	***2016***
Energy	MJ/day	8.2	1.8		
Fat	g/day	69.7	21.6		
	E%	31.7	5.4	25-35	25-40
SFA	g/day	28.8	9.9		
	E%	13.1	2.9		<10
MUFA	g/day	23.3	8.0		
	E%	10.6	2.4		10-20
PUFA	g/day	11.3	4.6		
	E%	5.1	1.6		5-10
Carbohydrates	g/day	458.5	245.6		
	E%	65.2	50.2	50-60	45-60
Sucrose	g/day	43.2	18.4		
	E%	8.8	3.2		<10
Protein	g/day	80.9	19.8		
	E%	16.6	2.7		10-20
Fibre	g/day	19.9	6.5		25-35
Vitamins and minerals		***Median***	***IQR***	***Recommended***	
Vitamin A (RE)	Diet	783.8	551.5 to 1076.1		
	Total	816.0	561.3 to 1137.9		800
Vitamin D (µg)	Diet	3.8	2.3 to 6.2		
	Total	8.3	4.3 to 11.9		10
Vitamin E (mg)	Diet	8.9	7.0 to 10.9		
	Total	14.4	8.8 to 18.9		10
Vitamin C (mg)	Diet	135.1	85.9 to 181.4		
	Total	173.1	121.9 to 238.4		85
Thiamine (mg)	Diet	1.4	1.2 to 1.7		
	Total	2.3	1.4 to 3.6		1.5
Riboflavin (mg)	Diet	2.0	1.6 to 2.4		
	Total	3.1	2.0 to 4.5		1.6
Niacin (mg)	Diet	16.0	12.7 to 19.6		
	Total	26.1	16.5 to 35.4		17
Vitamin B12 (µg)	Diet	5.6	4.2 to 7.1		
	Total	7.0	5.1 to 9.1		2.0
Folate (µg)	Diet	287.4	234.2 to 343.0		
	Total	414.4	294.3 to 577.5		500
Biotin (mg)	Diet	34.1	27.6 to 42.6		
	Total	49.2	33.3 to 71.5		1.4
Iron (mg)	Diet	11.7	9.5 to 13.8		
	Total	12.9	10.3 to 16.9		-
Calcium (mg)	Diet	1229.3	943.1 to 1483.7		
	Total	1351.8	1119.3 to 1734.2		900
Zinc (mg)	Diet	11.6	10.0 to 13.6		
	Total	17.1	11.8 to 24.2		9
Iodine (µg)	Diet	251.7	201.9 to 308.6		
	Total	282.7	220.9 to 341.3		175

*Recommendation at the study conduct if different to current recommendations (Becker et al., 2004)

5.2 Dietary and clinical impacts of nausea and vomiting (I)

5.2.1 NVP in the study population

The majority of the mothers, 72 % (n=134/187) reported that they had experienced nausea during the first trimester of pregnancy; 30 % (n=40) had vomited and 5 % (n=9) had vomited more than once a day. None of the mothers was hospitalized due to hyperemesis gravidarum. Mothers with NVP were older with a mean age of 30.5 (SD 4.4) years compared to those without 28.6 (SD 4.0), p=0.005. There were no significant differences between other clinical characteristics (pre-pregnancy weight, BMI, education, parity, smoking prior to pregnancy or smoking in the first trimester) of the mothers.

5.2.2 NVP and dietary intake at the first trimester of pregnancy

Mothers with NVP consumed less meat products at the first trimester of pregnancy with a median intake of 98 g/day (IQR 66-138) compared to those without, 121 g/day (IQR 95-164), p=0.004 (Mann-Whitney U-test). Vegetable intake tended to be lower in mothers experiencing NVP compared to those without [279 g/day (IQR 181-353) and 294 (234-423), p=0.070). There were no differences in consumption of foods in other categories between mothers with or without NVP.

The differences in the consumption of foods were reflected by the intake of energy-yielding nutrients as a lower intake of protein and higher intake of carbohydrates and sucrose (**Table 6**). However, the intake of energy was similar in both groups. Dietary and total intake (from diet and supplements) of vitamin B12, dietary intake of zinc and total intake of magnesium were significantly lower in women with NVP compared to those without (**Table 7**). There was also a tendency towards a lower dietary and total intake of niacin.

Table 6 Dietary intake of energy, energy-yielding nutrients and dietary fibre calculated from 3-day food diaries in women with (n=134) and without (n=53) NVP in the first trimester of pregnancy. Results are given as medians and IQR. *Mann-Whitney U-test

		With NVP		**Without NVP**		
		Median	IQR	Median	IQR	P*
Energy	kJ	8013	(6620-9021)	8339	(6774-9181)	0.456
Fat	g	66.6	(56.5-79.6)	67.6	(56.8-82.9)	0.474
	E%	32.2	(28.1-35.5)	32.8	(28.5-37.4)	0.271
SFA	g	27.1	(22.0-33.8)	28.8	(23.2-35.8)	0.328
	E%	12.8	(11.1-15.3)	13.6	(11.2-15.8)	0.370
MUFA	g	22.7	(18.0-26.8)	21.3	(18.5-27.9)	0.772
	E%	10.4	(9.0-11.8)	10.8	(8.6-12.9)	0.504
PUFA	g	10.0	(7.8-13.3)	10.8	(7.9-13.7)	0.563
	E%	4.8	(4.0-6.1)	4.8	(4.0-6.1)	0.829
Protein	g	79.4	(66.4-91.1)	89.7	(74.0-102.8)	**0.007**
	E%	16.4	(14.9-18.4)	18.3	(16.3-19.8)	**0.003**
Carbohydrates	g	237.7	(200.3-278.9)	220.2	(190.2-271.0)	0.401
	E%	50.1	(46.7-53.6)	46.8	(43.6-51.9)	**0.008**
Sucrose	g	46.3	(32.5-57.2)	37.8	(26.2-51.5)	**0.031**
	E%	9.7	(7.4-11.7)	7.9	(6.0-10.9)	**0.007**
Fibre	g	19.3	(15.8-24.9)	19.4	(15.9-24.4)	0.944

Table 7 Daily dietary and total (diet and supplements) intake of vitamins and minerals of women with (n = 134) and without (n = 53) NVP in the first trimester of pregnancy calculated from 3-day food diaries. Results are given as medians and interquartile ranges (IQR) *Mann–Whitney U-test

		With NVP		**Without NVP**		
		Median	IQR	Median	IQR	P*
Vitamin A (RE)	Diet	789	(570-1072)	880	(625-1147)	0.289
	Total	795	(570-1113)	913	(664-1164)	0.235
Vitamin D (ug)	Diet	4.0	(2.4-6.2)	4.2	(2.3-6.5)	0.868
	Total	8.0	(4.9-11.8)	8.6	(5.3-11.8)	0.817
Vitamin E (mg)	Diet	8.8	(6.9-10.6)	9.1	(7.4-11.9)	0.298
	Total	14.0	(8.9-18.8)	15.6	(8.4-21.2)	0.675
Thiamine (mg)	Diet	1.4	(1.2-1.7)	1.5	(1.1-1.9)	0.175
	Total	2.2	(1.4-3.4)	2.4	(1.9-3.5)	0.250
Riboflavin (mg)	Diet	2.0	(1.6-2.4)	2.2	(1.6-2.7)	0.195
	Total	2.9	(2.0-4.3)	3.3	(2.3-4.5)	0.361
Niacin (mg)	Diet	15.6	(12.4-19.1)	17.5	(13.0-21.6)	0.052
	Total	23.7	(15.8-34.3)	29.7	(19.3-36.2)	0.080
Vitamin B12 (ug)	Diet	5.3	(4.0-7.0)	6.5	(4.7-7.9)	**0.011**
	Total	6.8	(5.1-8.8)	7.9	(6.4-9.7)	**0.015**
Folate (ug)	Diet	286	(233-337)	305	(249-379)	0.087
	Total	401	(297-548)	471	(329-589)	0.139
Vitamin C (mg)	Diet	137	(87.7-176)	147	(89.5-202)	0.423
	Total	176	(129-227)	185	(142-285)	0.276
Calcium (mg)	Diet	1229	(947-1512)	1281	(1032-1644)	0.192
	Total	1360	(1146-1681)	1481	(1032-1644)	0.220
Magnesium (mg)	Diet	314	(273-380)	350	(269-402)	0.180
	Total	365	(295-437)	409	(342-482)	**0.037**
Iron (mg)	Diet	11.7	(9.4-13.9)	12.4	(10.7-14.3)	0.232
	Total	12.8	(10.1-17.5)	13.6	(11.2-17.6)	0.230
Zinc (mg)	Diet	11.9	(9.9-13.5)	12.4	(10.4-15.2)	**0.038**
	Total	15.7	(11.8-24.9)	19.6	(13.0-26.1)	0.128

5.2.3 NVP and dietary intake of mothers in late pregnancy

The impact of NVP in the first trimester on dietary intake at the second and third trimester of pregnancy was analysed with repeated measures ANOVA. The daily intake of meat remained lower by at 16.8 g (95% CI 2.8 to 30.9) in women with NVP compared to those without. Also the intake of niacin remained lower by 2.5 mg (95% CI 0.2 to 4.9) and zinc by 1.0 mg (95% CI 0.1 to 1.8) if the mother had suffered from NVP.

5.2.4 Clinical impacts of NVP

Regarding the evaluation of the clinical impacts of NVP the results indicated a shorter duration of gestation [39.9 weeks (95% CI 39.6 to 40.1) compared to 40.4 (40.1 to 40.8); p=0.018] in women without NVP. There were no significant changes in gestational weight gain at the first trimester or during the course of pregnancy of the mothers or in birth measurements or growth of the infants at one or six months of age in women with NVP compared to those without.

5.3 Serum fatty acids of mothers and infants

5.3.1 Serum fatty acid variation during pregnancy in three fractions

Serum FA concentrations were measured in three fractions: PL, CE and TAG. The concentrations of all FAs increased from the first trimester to the third trimester of pregnancy and decreased one month postpartum (**Figure 6**). The most extensive variation was seen in serum TAG concentrations. In serum PL and CE the changes were more modest and the concentrations of FA remained at a higher concentration after pregnancy, compared to the baseline. In contrast, serum TAG concentrations of all FAs were lower after pregnancy compared to the first trimester. The time-related changes of these FAs as a proportion of total FAs in serum PL, CE and TAG of pregnant women were only minor and did not follow a clear pattern.

5.3.2 Impact of dietary counselling on maternal fatty acid status (II)

Dietary intervention during pregnancy resulted in an improvement, here defined as an increase in the n-3 FA, of maternal serum PL, CE and TAG FA during the 3rd trimester of pregnancy (**Table 8**).

In serum PL, the proportion of PUFA, sum of n-3 and DHA was higher and that of MUFA lower during the 3rd trimester in the dietary intervention group compared to the controls. In serum CE, the changes were similar as the proportion of sum of n-3 and eicosapentaenoic acids (EPA) were significantly higher in the intervention group. In serum TAG, intervention resulted in a higher proportion of PUFA, sum of n-3 FA, sum of n-6 FA, ALA, LA, dihomogammalinoleic acid and arachidonic acid and lower of SFA. The ratio of n-6/n-3 FA was lower in serum PL and TAG for women in the intervention group.

In the evaluation of the concentrations of FA (mg/l), the mean difference between dietary intervention and the control groups was 1.65 mg/l (95% CI 0.09 to 3.21, p=0.04) for sum of n-3 FA, 3.55 mg/l (-1.45 to 8.54, p=0.16) for PUFA, 1.30 mg/l (0.31 to 2.28, p=0.01) for DHA and -0.52 mg/l (-2.93 to 1.88, p=0.67) for MUFA. At one month postpartum the effects of dietary intervention were perceived only in maternal serum CE as a higher proportion of ALA (**Table 9**).

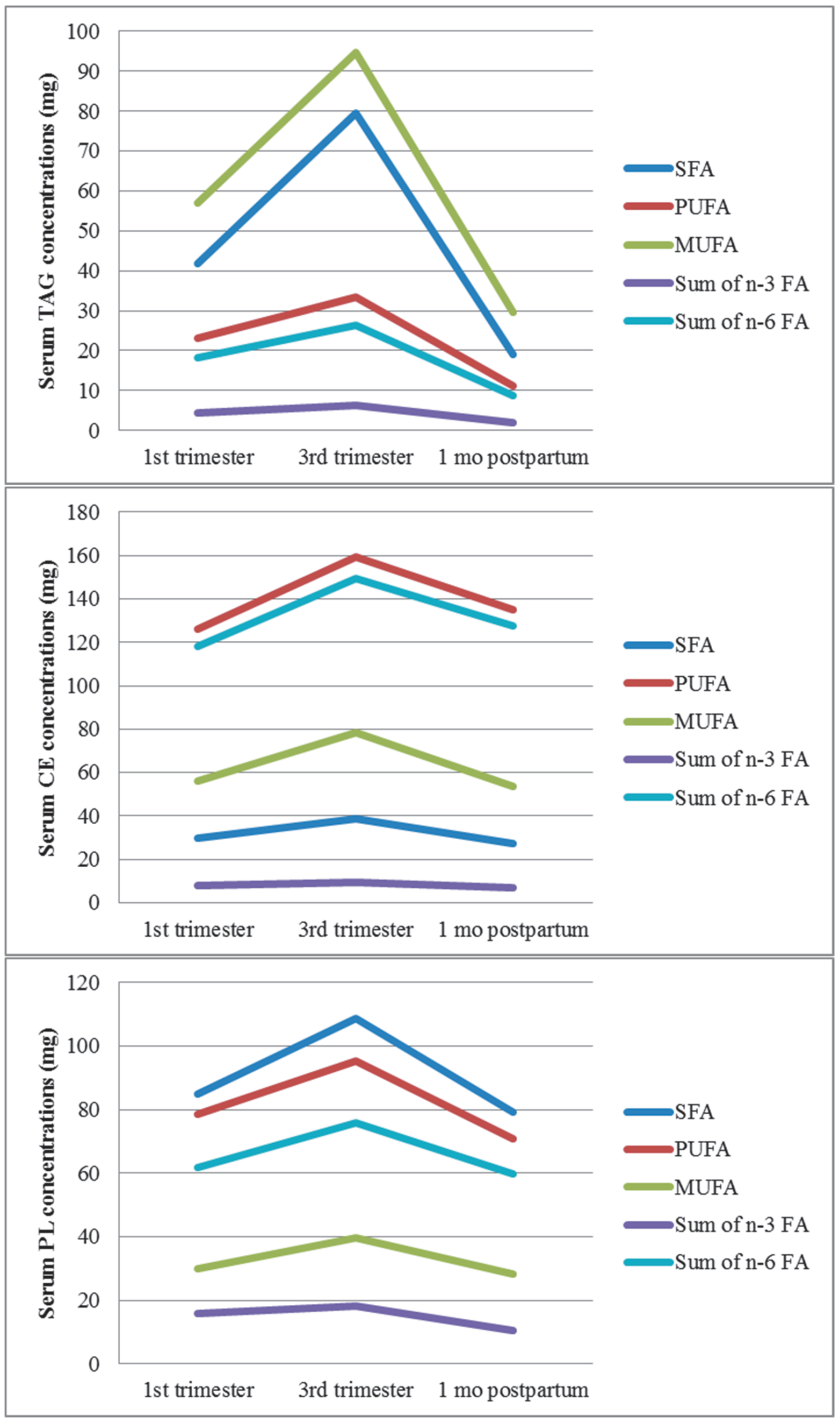

Figure 6 Concentrations (mg/l) of maternal FA of all the study subjects (n=90) in serum phospholipids, cholesterol esters and triacylglycerols from the first trimester to one month postpartum.

Table 8 The proportions of maternal serum phospholipids, cholesteryl esters and triacylglycerols during the 3rd trimester of pregnancy in the dietary intervention and control groups (% of total FA). Analysed by ANCOVA, where the intake during the 1st trimester was included as a covariate. The results are presented as adjusted mean (95% CI).

	Phospholipids			**Cholesteryl esters**			**Triacylglycerols**		
	Intervention	Control	P	Intervention	Control	P	Intervention	Control	P
SFA	44.6 (44.3-44.9)	44.6 (44.3-44.8)	0.93	14.0 (13.5-14.5)	13.9 (13.4-14.4)	0.69	36.7 (35.4-38.0)	39.3 (38.0-40.6)	**0.005**
MUFA	16.0 (15.6-16.3)	16.6 (16.2-16.9)	**0.02**	28.1 (27.4-28.7)	28.9 (28.3-29.6)	0.07	46.1 (45.1-47.0)	45.4 (44.5-46.4)	0.33
PUFA	39.5 (39.1-39.9)	38.9 (38.4-39.2)	**0.03**	57.9 (57.1-58.8)	57.2 (56.3-58.0)	0.20	17.3 (16.5-18.0)	15.3 (14.5-16.0)	**<0.001**
18:3n-3	0.53 (0.48–0.57)	0.50 (0.45-0.54)	0.31	1.41 (1.31-1.51)	1.32 (1.23-1.41)	0.17	1.8 (1.7-2.0)	1.6 (1.4-1.7)	**0.01**
20:5n-3	1.4 (1.3-1.6)	1.4 (1.2-1.6)	0.53	1.08 (0.93-1.23)	0.85 (0.70-1.00)	**0.04**	0.26 (0.18-0.34)	0.25 (0.17-0.34)	0.92
22:6n-3	5.2 (4.9–5.4)	4.7 (4.4-4.9)	**0.01**	-	-	-	-	-	-
22:5n-3	0.68 (0.64–0.71)	0.65 (0.62-0.69)	0.33	0.06 (0.04-0.09)	0.07 (0.04-0.10)	0.78	0.17 (0.15-0.20)	0.14 (0.12-0.16)	0.05
Sum n-3	7.8 (7.4–8.2)	7.2 (6.8-7.6)	**0.03**	3.50 (3.27-3.72)	3.13 (2.91-3.36)	**0.03**	3.35 (3.05-3.65)	2.83 (2.53-3.13)	**0.02**
18:2n-6	19.5 (19.0–20.0)	19.6 (19.1-20.2)	0.71	47.1 (46.2-48.0)	46.8 (45.9-47.7)	0.66	12.2 (11.6-12.7)	10.8 (10.3-11.4)	**0.001**
18:3n-6	0.05 (0.04-0.05)	0.05 (0.04-0.06)	0.55	0.49 (0.43-0.55)	0.50 (0.45-0.56)	0.76	0.10 (0.09-0.12)	0.10 (0.09-0.12)	0.81
20:3n-6	3.4 (3.3–3.6)	3.5 (3.4-3.6)	0.64	0.89 (0.84-0.94)	0.88 (0.83-0.93)	0.61	0.23 (0.22-0.25)	0.21 (0.20-0.23)	**0.04**
20:4n-6	7.6 (7.4–7.9)	7.3 (7.1-7.6)	0.06	5.8 (5.6-6.0)	5.5 (5.3-5.7)	0.05	0.81 (0.76-0.86)	0.73 (0.68-0.78)	**0.04**
Sum n-6	31.1 (30.6–31.7)	31.0 (30.5-31.6)	0.78	54.3 (53.4-55.1)	53.7 (52.9-54.6)	0.39	13.6 (13.0-14.2)	12.1 (11.5-12.7)	**0.001**
n-6/n-3	4.2 (3.9–4.4)	4.6 (4.3-4.9)	**0.03**	16.7 (15.5-18.0)	18.1 (16.9-19.4)	0.13	4.34 (3.95-4.73)	5.02 (4.61-5.42)	**0.02**

Table 9 The proportions of maternal serum phospholipids, cholesteryl esters and triacylglycerols at 1 month postpartum in the dietary intervention and control groups (% of total FA).

Analysed by ANCOVA, where the intake during the 1st trimester was included as a covariate. The results are presented as adjusted mean (95% CI).

	Phospholipids			**Cholesteryl esters**			**Triacylglycerols**		
	Intervention	Control	P	Intervention	Control	P	Intervention	Control	P
SFA	44.4 (44.1-44.8)	44.2 (43.8-44.6)	0.44	12.6 (12.4-12.8)	12.6 (12.4-12.9)	0.83	30.8 (29.6-31.9)	32.0 (30.8-33.2)	0.15
MUFA	15.8 (15.2-16.3)	15.9 (15.3-16.5)	0.74	25.1 (24.4-25.9)	24.6 (23.9-25.3)	0.31	50.0 (49.1-50.9)	49.5 (48.6-50.5)	0.47
PUFA	39.8 (39.3-40.3)	39.9 (39.4-40.4)	0.76	62.3 (61.5-63.1)	62.8 (61.9-63.6)	0.44	19.4 (18.4-20.3)	18.3 (17.4-19.3)	0.13
18:3n-3	0.43 (0.40-0.46)	0.39 (0.36-0.42)	0.11	1.1 (1.0-1.1)	1.0 (0.9-1.0)	**0.03**	1.9 (1.7-2.0)	1.7 (1.5-1.8)	0.14
20:5n-3	1.5 (1.3-1.8)	1.4 (1.2-1.6)	0.32	1.6 (1.4-1.7)	1.4 (1.2-1.6)	0.24	0.56 (0.45-0.67)	0.45 (0.34-0.57)	0.18
22:6n-3	3.3 (3.1-3.6)	3.1 (2.8-3.4)	0.22	-	-	-	-	-	-
22:5n-3	0.88 (0.83-0.93)	0.85 (0.79-0.90)	0.33	0.04 (0.04-0.04)	0.04 (0.04-0.04)	0.22	0.48 (0.42-0.53)	0.41(0.35-0.46)	0.07
Sum n-3	6.2 (5.8-6.6)	5.8 (5.3-6.2)	0.17	3.3 (3.0-3.5)	3.0 (2.8-3.2)	0.11	3.8 (3.4-4.2)	3.3 (2.8-3.7)	0.07
18:2n-6	21.8 (21.2-22.4)	22.4 (21.8-23.0)	0.15	51.3 (50.4-52.3)	52.3 (51.3-53.2)	0.14	13.0 (12.4-13.6)	12.7 (12.1-13.3)	0.55
18:3n-6	0.09 (0.07-0.10)	0.09 (0.08-0.11)	0.73	0.93 (0.81-1.05)	0.90 (0.77-1.02)	0.69	0.41 (0.36-0.46)	0.39 (0.34-0.45)	0.69
20:3n-6	3.1 (2.9-3.2)	3.0 (2.9-3.2)	0.74	0.75 (0.71-0.78)	0.74 (0.70-0.78)	0.84	0.27 (0.25-0.29)	0.26 (0.23-0.28)	0.54
20:4n-6	8.0 (7.7-8.3)	7.8 (7.5-8.2)	0.51	5.8 (5.5-6.1)	5.5 (5.2-5.8)	0.20	1.2 (1.1-1.3)	1.2 (1.1-1.2)	**0.37**
Sum n-6	33.3 (32.8-33.8)	33.7 (33.2-34.3)	0.23	58.8 (58.0-59.5)	59.5 (58.7-60.4)	0.22	15.1 (14.5-15.6)	14.7 (14.1-15.4)	**0.36**
n-6/n-3	5.8 (5.4-6.2)	6.3 (5.9-6.8)	0.10	19.3 (17.9-20.7)	21.0 (19.6-22.5)	0.08	4.3 (4.0-4.7)	5.0 (4.6-5.4)	**0.02**

5.3.3 Improving maternal n-3 fatty acid status (III)

We evaluated which dietary factors correlated with higher serum PL n-3 PUFA for the mother one month after delivery. The initial analysis revealed that intake of fish ($R=0.477$, $p<0.001$) and HEI ($R=0.337$, $p=0.002$) were the best determinants of higher maternal serum n-3 PUFA.

N-3 FA proportions increased along with increased HEI score. In the analysis of tertiles of HEI, in women with HEI scores in the middle and highest tertiles, total n-3 FAs [mean difference 1.31% of total FA (0.37-2.24) and 1.26% (0.37-2.15)] and DHA [0.75% (0.18-1.31) and 0.63% (0.09-1.17)] in serum PL were higher, and the ratio of n-6/n-3 FA lower [-1.4% (-2.47 to -0.33) and -1.59% (-2.62 to -0.57)] than those of women in the lowest tertile.

When the intake of fish was specifically analysed, the highest tertile of fish intake, above 36 g/day (equivalent to 2.5 portions weekly) as calculated from food diaries, was related to a significant increase in total n-3 FAs and DHA as a percentage of total FA, as well as a lower ratio of n-6/n-3 FAs in serum PL (**Table 10**) compared to the lowest tertile, i.e., the women who did not consume fish at all. Further, fish consumption at least three times per week resulted in an increase in the percentage of n-3 PUFA in serum PL (**Table 10**).

Persistent intake of fish once per week during the follow-up period from the first trimester of pregnancy to one month after delivery (GEE analysis), resulted in a significant increase in total n-3 FAs and DHA and a decrease in the ratio of n-6/n-3 FA compared to women who did not eat fish (**Figure 7**).

GEE analysis was performed also for HEI-scores, whereas the sum of n-3 FAs and DHA in serum PL increased significantly and ratio of n-6/n-3 decreased when the HEI-score was higher (**Figure 8**).

Table 10 Serum phospholipid fatty acids (% of total FA) according to fish consumption tertiles in the women one month after delivery. Fish intake is presented quantitatively from 3-day food diaries (tertiles T1=0 g/day, T2=1-35 g/day, T3≥36 g/day) and as frequency of fish consumption received from a query (times per week). *Dunnett's T-test

	Fish consumption (g/day)	**Mean (SD)**	**Mean difference**	**(95 % CI)**	***P****
Sum n-3	T1	5.38 (1.30)			
	T2	5.70 (0.97)	0.32	(-0.58 to 1.21)	0.642
	T3	6.93 (1.94)	1.55	(0.67 to 2.42)	**<0.001**
22:6n-3	T1	2.92 (0.92)			
	T2	3.09 (0.75)	0.17	(-0.38 to 0.72)	0.709
	T3	3.74 (0.98)	0.82	(0.29 to 1.36)	**0.002**
22:5n-3	T1	0.83 (0.16)			
	T2	0.85 (0.17)	0.03	(-0.08 to 0.13)	0.790
	T3	0.91 (0.19)	0.08	(-0.02 to 0.18)	0.125
n-6/n-3	T1	6.61 (1.54)			
	T2	6.11 (1.35)	-0.50	(-1.48 to 0.47)	0.411
	T3	5.24 (1.85)	-1.38	(-2.33 to -0.42)	**0.003**
	Fish consumption (times per week)	**Mean (SD)**	**Mean difference**	**(95 % CI)**	***P****
Sum n-3	0 times	4.72 (0.71)			
	Once	5.17 (0.81)	0.46	(-0.65 to 1.56)	0.686
	Twice	5.26 (0.79)	0.55	(-0.56 to 1.65)	0.543
	3 times	6.44 (1.42)	1.72	(0.68 to 2.76)	**<0.001**
	> 4 times	7.55 (1.61)	2.83	(1.82 to 3.83)	**<0.001**
22:6n-3	0 times	2.43 (0.47)			
	Once	2.77 (0.53)	0.34	(-0.32 to 1.00)	0.516
	Twice	2.85 (0.57)	0.42	(-0.24 to 1.08)	0.324
	3 times	3.56 (0.78)	1.12	(0.50 to 1.75)	**<0.001**
	> 4 times	4.12 (0.96)	1.69	(1.09 to 2.29)	**<0.001**
22:5n-3	0 times	0.80 (0.15)			
	Once	0.82 (0.14)	0.02	(-0.13 to 0.17)	0.989
	Twice	0.80 (0.15)	0.01	(-0.14 to 0.15)	1.000
	3 times	0.87 (0.17)	0.08	(-0.06 to 0.22)	0.423
	> 4 times	0.97 (0.17)	0.17	(0.04 to 0.31)	**0.008**
n-6/n-3	0 times	7.51 (1.25)			
	Once	6.80 (1.29)	-0.71	(-1.90 to 0.48)	**0.376**
	Twice	6.70 (1.22)	-0.81	(-2.00 to 0.38)	**0.265**
	3 times	5.42 (1.48)	-2.09	(-3.20 to -0.97)	**<0.001**
	> 4 times	4.48 (1.15)	-3.03	(-4.11 to -1.95)	**<0.001**

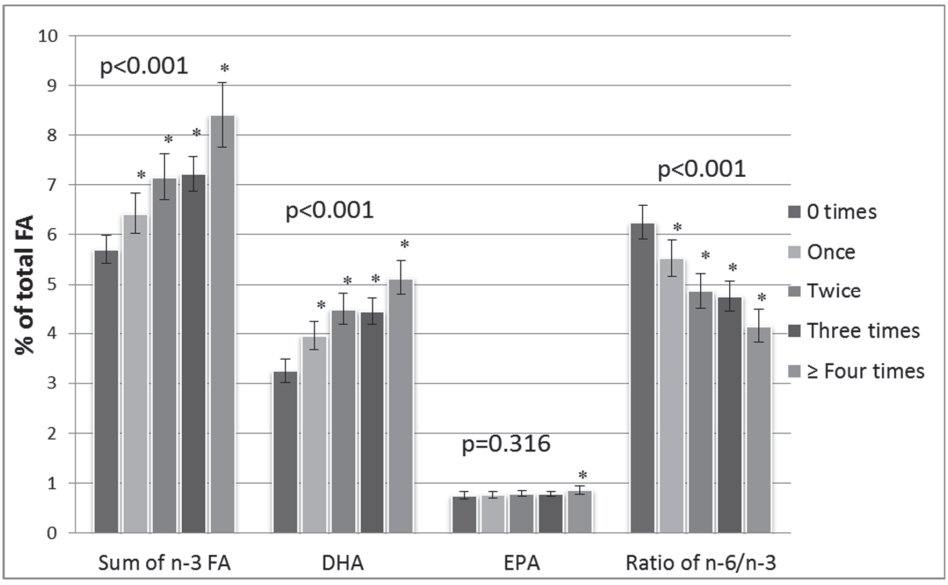

Figure 7 Proportion of n-3 PUFAs and ratio of n-6/n-3 FA in serum PL according to persistent frequency of fish consumption per week of the women from the 1st trimester of pregnancy to one month after delivery (ANOVA).

*denotes p<0.05 compared to 0 frequency in fish consumption (GEE)

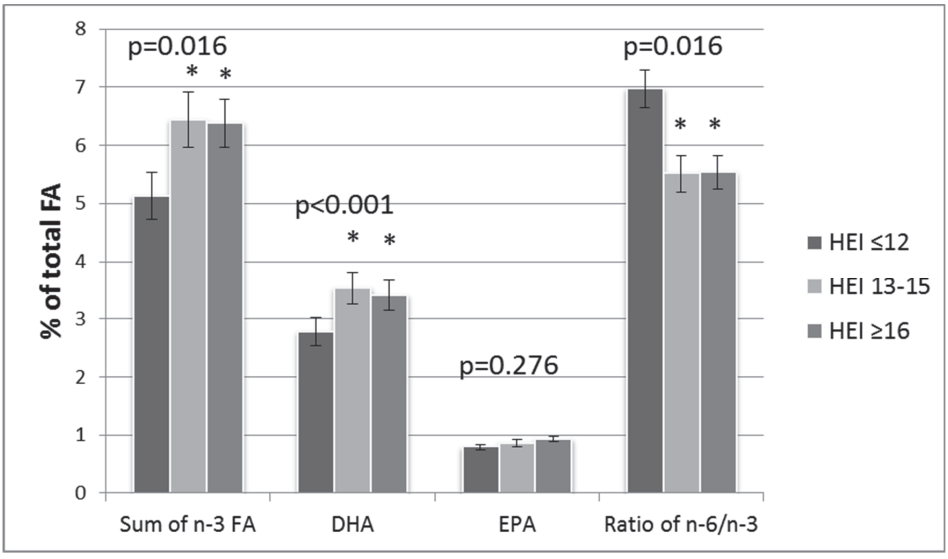

Figure 8 Proportion of n-3 PUFAs and ratio of n-6/n-3 FA in serum PL according to Healthy eating index score of the women (divided in tertiles) from the 1st trimester of pregnancy to one month after delivery (ANOVA).

*denotes p<0.05 compared to lowest tertile of Healthy eating index score (GEE)

5.3.4 Association of maternal dietary intake and infant fatty acids (III)

The impact of maternal diet and diet induced changes in n-3 FAs in serum PL in infants was evaluated by correlating the maternal and infants' serum FA at one month of age. Blood samples were available from 64 infants. A linear test demonstrated that higher HEI scores were significantly related to an increased total n-3 FA, DHA and EPA and a decreased ratio of n-6/n-3 FAs in infants' serum PL (**Table 11**). Furthermore, maternal higher fish intake (g/day) was significantly correlated to increased total n-3 FAs, DHA and a decreased ratio of n-6/n-3 FAs in infants' serum PL (**Table 11**).

Table 11 Relationship of Healthy Eating Index score and fish intake (g/day) of the mothers (divided in tertiles) to infant's serum PL FA (% of total FA) at one month of age. The results are presented as mean (SD). *ANOVA

	Healthy eating index score				**Fish intake g/day**			
	≤12	**13-15**	**≥16**	***P****	**0**	**1-36**	**≥36**	***P****
Sum n-3	4.87 (1.20)	6.10 (1.28)	6.21 (1.32)	0.002	5.20 (1.30)	5.64 (1.17)	6.42 (1.41)	0.015
22:6n-3	3.54 (0.94)	4.38 (0.86)	4.40 (0.97)	0.004	3.76 (1.02)	4.03 (0.84)	4.59 (0.93)	0.009
22:5n-3	0.65 (0.15)	0.72 (0.15)	0.80 (0.17)	0.010	0.69 (0.16)	0.73 (0.17)	0.77 (0.17)	0.257
n-6/n-3	7.53 (3.20)	5.46 (1.33)	5.56 (1.43)	0.004	6.97 (3.10)	6.22 (1.48)	5.22 (1.38)	0.038

5.4 The association of maternal dietary intake and infant development (IV)

5.4.1 Developmental evaluation

The developmental evaluation was performed at 12 months of age. The infants were normally developed as evaluated by the median developmental scores (**Table 12**). The intervention did not affect the developmental total score or the subscale scores A-E (**Table 12**).

Table 12 Maternal dietary intervention and probiotics use during pregnancy and Griffith's Mental Development Scale scores at 12 months of age.

Results are given as median (IQR). N=203.

	Dietary intervention and probiotics	Dietary intervention and placebo	Control group	*P* *
Total score	107.3 (103.5-112.7)	106.7 (102.2-111.8)	105.7 (102.2-110.8)	0.47
Locomotor (A)	109.9 (100.7-126.2)	108.7 (99.9-123.5)	109.4 (100.7-127.0)	0.41
Personal-Social (B)	111.5 (106.6-113.4)	108.3 (103.8-113.4)	110.9 (105.3-114.7)	0.18
Hearing and speech (C)	109.6 (97.2-118.4)	105.9 (96.7-116.7)	101.8 (97.1-114.4)	0.47
Hand and eye coordination (D)	99.9 (95.2-109.6)	99.4 (95.3-109.6)	99.9 (95.5-108.6)	0.96
Performance (E)	104.5 (99.9-108.6)	104.2 (99.9-108.6)	104.3 (99.9-108.2)	0.89

* Kruskall-Wallis

5.4.2 Maternal nutrition and infant developmental scores

Initial inspection of correlations revealed that some maternal dietary factors were related to infant developmental scores such as intake of fruits and berries, PUFA, dietary intake of biotin and intakes of vitamin D, vitamin C, calcium and iron from diet and supplements (data not shown).

Multivariate and backward linear regression models were performed separately for maternal intakes of foods, energy-yielding nutrients, and vitamins and minerals.

Considering the consumption of foods during pregnancy, a higher intake of meat and a lower intake of margarine were associated with high developmental scores in both the multivariable model (meat P=0.029, margarine P=0.009) and in the backward linear regression model (meat P= 0.056, margarine P=0.004l), although the Pearson correlations were weak (meat R=0.112, margarine R=-0.188). Contrary to our assumption, higher habitual fish consumption was not associated with higher developmental scores or sub-scores A-E (Table in study IV). None of the maternal intake of energy-yielding nutrients correlated with infant developmental scores in either the multivariable models or backward regression models (data not shown).

In the backward linear regression analysis of dietary and total intakes of vitamins and minerals the best dietary determinant of higher infant developmental scores was the total intake of vitamin D i.e. the intake calculated from diet and supplements (**Table 13** and **Figure 9**). When all dietary and total intakes of vitamins and minerals were evaluated together with the multivariable model, the dietary intake of iron and total intake of vitamin D, calcium, and biotin correlated positively with the developmental scores of the infants (**Table 13**).

Table 13 The association between maternal dietary and total intake of vitamins and minerals during pregnancy with infant developmental scores. N=203.

Initial *P* describes the association between the intake of vitamins and minerals and total developmental score in a multivariable regression model where all vitamins and minerals are included in the model. Final *P* describes the association after backward stepwise model with Pearson correlations where all nonsignificant (NS) variables have been removed.
Modified from study IV.

	Dietary intake	**Initial**	**Final**	**Total Intake**	**Initial**	**Final**
	Median (IQR)	***P***	***P***	**Median (IQR)**	***P***	***P***
Vitamin A (RE)	855 (658-1077)	0.89	NS	857 (676-1104)	0.93	NS
Vitamin D (µg)	4.8 (3.5-6.5)	0.88	NS	9.8 (7.6-12.3)	**0.05**	**0.002***
Vitamin E (mg)	10.0 (8.2-11.8)	0.50	NS	14.8 (11.1-19.0)	0.15	NS
Vitamin C (mg)	145 (99-184)	0.72	NS	190 (143-245)	0.39	NS
Thiamine (mg)	1.5 (1.3-1.7)	0.58	NS	2.6 (1.7-3.5)	0.57	NS
Riboflavin (mg)	2.1 (1.7-2.5)	0.84	NS	3.2 (2.4-4.3)	0.29	NS
Niacin (mg)	16.5 (14.3-19.9)	0.18	NS	26.9 (18.7-35.7)	0.92	NS
Vitamin B12 (µg)	5.6 (4.7-7.0)	0.97	NS	7.0 (5.5-9.0)	0.51	NS
Folic acid (µg)	292 (253-346)	0.94	NS	453 (325-540)	0.18	NS
Biotin (mg)	36.0 (30.1-42.9)	0.36	NS	56.5 (40.8-72.8)	**0.06**	NS
Iron (mg)	12.3 (10.5-14.1)	**0.07**	NS	43.6 (16.3-78.6)	0.21	NS
Calcium (mg)	1220 (999-1461)	0.87	NS	1384 (1187-1654)	**0.08**	NS
Zinc (mg)	11.8 (10.2-13.7)	0.50	NS	18.2 (13.6-23.0)	0.51	NS
Iodine (µg)	248 (217-296)	0.81	NS	277 (231-325)	0.27	NS

*Pearson correlation R=0.214

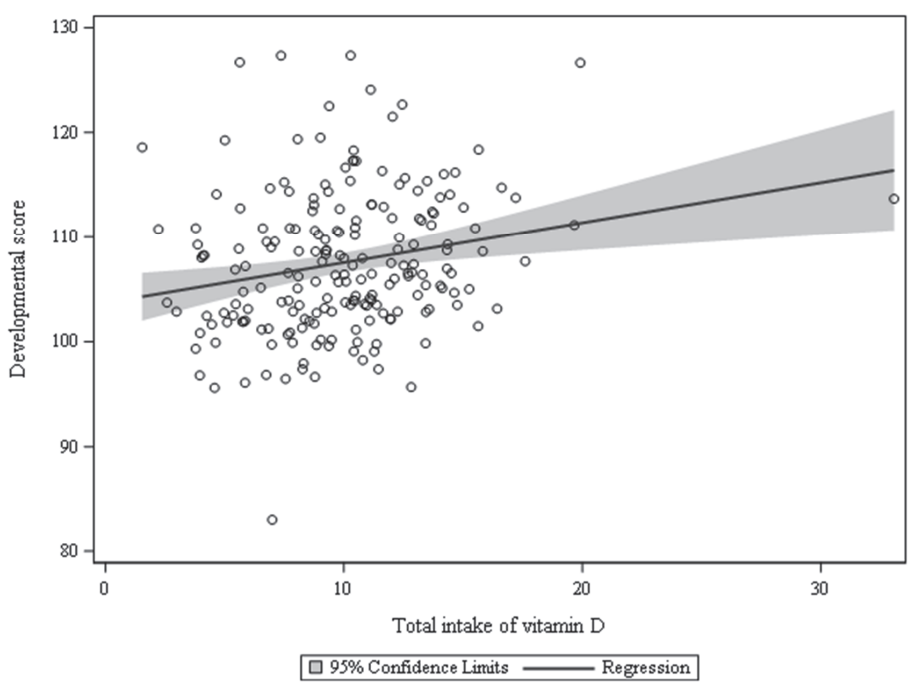

Figure 9 The association between maternal total intake of vitamin D from diet and supplements during pregnancy and infant developmental scores as detected by a fit plot. Picture modified from study IV.

5.4.3 Maternal intakes of vitamins and minerals and infant developmental sub scores

We examined the association between maternal total intake of vitamins and minerals during pregnancy and infant developmental sub scores A-E with a stepwise backward linear regression model (**Table 14**). Locomotor development (A) was associated with total vitamin C intake. Personal-social development (B) was associated with increased total intake of calcium, vitamin D and iodine. Hearing and speech development (C) and eye and hand coordination (D) were associated with a higher total vitamin D intake. Finally, performance (E) was associated with a higher total intake of calcium and lower of vitamin C.

Table 14 The association between maternal total intake of vitamins and minerals during pregnancy and infant development on Griffiths mental development subscales. The table shows only significant results, with final P-value describing the association after backward stepwise model with Pearson correlation scores (R). n=203-207.

Modified from study IV.

	Total intake	**Final *P***	***R***
Locomotor (A)	Vitamin C	0.0125	0.179
Personal-social (B)	Vitamin D	0.0377	0.136
	Calcium	0.0568	0.100
	Iodine	0.0336	-0.022
Hearing and speech (C)	Vitamin D	0.0017	0.215
Hand and eye coordination (D)	Vitamin D	0.0492	0.139
Performance (E)	Calcium	0.0086	0.144
	Vitamin C	0.0206	-0.113

6 DISCUSSION

6.1 Study population and maternal dietary intake (I-IV)

The subjects for this study were recruited between the years 2002 to 2005. However, the women represent quite well the pregnant population at present. The mean age of women giving birth in Finland nowadays is 30.7 years, 29.9 years for primipara, which is similar to that of the study subjects, 30.0 years (National Institute for Health and Welfare, 2016). The mean BMI of the study subjects (24.7 kg/m^2 compared to 23.6 kg/m^2), rate of caesarean sections (16.4 % compared to 15 %) and incidence gestational diabetes (12.6 % compared to 10 %) were slightly lower in our study subjects (National Institute for Health and Welfare, 2016). The definition of gestational diabetes mellitus has changed through the years and thus we used the glucose limits according to current definition (Current Care Guideline, 2013). It is of note, that the mothers in this study were homogenous in terms of baseline characteristics and were healthy, mostly highly educated, and well-nourished. Thus the differences between compared groups were minor and the impact of maternal dietary intake seen in this kind of population may be more distinct if repeated in a more varied population.

Comparing to the recommended maternal dietary intake during pregnancy the challenge for the study subjects at the baseline was the poor quality of dietary fat as the intake of SFA was higher than recommended and the intake of PUFA at the lowest recommended level (National nutrition council VRN, 2016). The effects of dietary counselling during pregnancy in this population have been published previously in more detail (Piirainen et al., 2006). Western dietary intake is commonly associated with poor fat quality in the diet and thus interventions are needed (Cordain et al., 2005). The dietary intake of PUFA 5.1% of energy, in our study subjects at the baseline was similar to previously reported concentrations of PUFA in pregnant women in Finland and in other Western countries (Innis and Elias, 2003; Lof et al., 2009; Kinnunen et al., 2012). As a result of the dietary intervention in this study, PUFA intake increased, enabling better achievement of the recommended dietary intake level of n-3 FA (Koletzko et al., 2007; Nordic Council of Ministers, 2014). These changes are of importance for both to the mother and child considering the previously studied effects of n-3 FA on pregnancy outcome, risk of cardiovascular disease for mothers and, growth and neurodevelopment of the foetus and infant (Uauy et al., 2001b; Uauy et al., 2001a; Strøm et al., 2012; Horvath et al., 2007; Campoy et al., 2012). However, women in this study were from allergic families, that may explain the particularly good

response to dietary intervention because allergic diseases have been previously associated with lower serum n-3 levels (Sala-Vila et al., 2008).

Concerning micronutrients, the dietary and total intakes of folic acid and vitamin D at the baseline were lower than recommended in the study population, although a micronutrient supplementation is recommended for all pregnant women in Nordic countries (Nordic Council of Ministers, 2014; National nutrition council VRN, 2016). The intake of vitamin D has been low also in other studies in Finnish pregnant populations (Tuokkola et al., 2016; Meinilä et al., 2015). However, it has to be taken into account that the dietary information in this study was collected several years ago and currently, actions have been taken to correct the insufficient intake of vitamin D at a population level. The actions taken including recommendation for oral vitamin D supplementation for pregnant and lactating mothers throughout the year instead of the winter period as was the case when the study was executed, and the increase in the level of vitamin D enrichment in liquid dairy products and spreads production on sale on the market (Calvo and Whiting, 2013; Nordic Council of Ministers, 2014; National nutrition council VRN, 2016). In a recent study vitamin D status of non-pregnant sample of Finnish adults was considered sufficient based on the serum concentration of 25-hydroxyvitamin-D (≥50 nmol/l) (Jääskeläinen et al., 2017). Otherwise, the dietary recommendations given at the enrolment of the study are the same at present, despite a minor increase in the recommended proportion of intake of fat from 25-35 E% to 25-40 E% and decrease in intake of carbohydrates from 50-60 E% to 45-60 E% (National nutrition council VRN, 2016; Becker et al., 2004).

6.2 NVP and maternal dietary intake (I)

This study showed that NVP resulted in qualitative changes in maternal dietary intake during pregnancy. The intake of meat was lower for women suffering from NVP, which resulted in a lower intake of protein and a higher intake of carbohydrates compared to the control group. There was also a tendency towards a lower intake of vegetables in the women with NVP. These changes were reflected in the lower intake of vitamin B12, zinc and magnesium in women with NVP compared to the women without NVP. However, intake of these micronutrients was adequate compared to the recommended intake. In previous studies, the number of days with nausea has been associated with a lower intake of niacin and a higher intake of sodium and vitamin C (Tierson et al., 1986). We found only a tendency towards a lower intake of niacin and no differences in the intake of sodium and vitamin C were detected. Another more recent study reported a lower intake of vegetables and a higher consumption of white bread in women with NVP

(Crozier et al., 2016). These observations may result in a low intake of essential dietary components such as folic acid and fibre, already at lower levels than recommended in this study population. The changes in dietary intake of women in early pregnancy may also remain throughout pregnancy even though NVP symptoms are usually relieved after the first trimester (Jwa et al., 2016). This may have effects for example to gestational weight gain of the pregnant mothers (Chortatos et al., 2013). In a Norwegian large cohort study also changes in pregnancy complications were observed such as higher blood pressure and proteinuria in women with NVP (Chortatos et al., 2015). In this study population intake of meat and niacin remained lower throughout pregnancy in women with NVP. However, no differences in the pregnancy outcome were detected despite a minor difference in the duration of gestation. There is a clear need for resources for dietary guidance in maternity well-fare clinics in early pregnancy to direct eating habits towards safe and adequate dietary intake despite NVP.

6.3 Modification of maternal and infant n-3 FA (II and III)

Maternal dietary counselling to lower the intake of SFA and increase PUFA, led to favourable changes reflected in the increased proportions of serum PL n-3 PUFA and sum n-3 FA in the third trimester of pregnancy. A typical approach to modifying n-3 FA status in clinical studies has been to increase intake by supplementing n-3 LC-PUFA, particularly with fish oil (de Groot et al., 2004; Dunstan et al., 2004; Helland et al., 2006; Krauss-Etschmann et al., 2007; Escolano-Margarit et al., 2012). Miles et al used an alternative approach by providing pregnant women with two portions of fish weekly during the study, increasing their EPA and DHA levels significantly (Miles et al., 2011). Modification is needed due to the low intake of LC-PUFA in fertile-aged women. Also, according to a Canadian study, only 27 % of the women in their study met the recommended dietary intake of DHA, but the likelihood of achieving the recommended level increased if mothers consumed n-3 FA supplementation (Jia et al., 2015). In this study, the quality of dietary fat was emphasized and intake of fish was recommended at least twice per week as one of the main meals in dietary counselling. The increase in the sum of the n-3 FA proportion of total FA by 0.6 % was more modest than in studies providing LC-PUFA supplementation by about 2 grams daily (Helland et al., 2006). However, this approach to modifying maternal nutrition with changes in dietary intake rather than providing supplements may produce more long-lasting changes if dietary changes persist after the intervention and is also feasible within the public health setting.

In this study, the intervention resulted in similar changes also in other serum FA fractions: CE and TAG compared to serum PL. In all three fractions, the proportions of n-3 FA were higher in the intervention group compared to the control group. However, the changes in the serum proportions of CE were not evident in the ratio of n-6/n-3. In contrast, TAG n-6 PUFAs were significantly higher in the intervention group. This may demonstrate divergence in the FA fractions, as TAG is considered to present the dietary intake over days and PL over weeks (Thiébaut et al., 2009). As observed also in our study subjects, the variation in TAG FA concentration in the course of pregnancy were greater than in the other two FA fractions, possibly influencing the results at a specific time point. The analysis for concentrations of serum PL, CE and TAG supported the findings of increased n-3 FA during pregnancy; however, these changes were more moderate. Interestingly, there were no differences between the intervention and control groups in serum PL and TAG proportions or concentrations of serum n-3 FA one month after delivery. This may be explained by the rapid metabolic changes in a woman's body after delivery as there is a swift decrease in concentrations of n-3 FA after late pregnancy (De Vriese et al., 2003). It remains to be seen if the long-term impacts of dietary intake and subsequently FA composition were induced by the counselling initiated in early pregnancy with a longer follow-up.

We also evaluated the dietary changes needed to significantly improve maternal serum PL n-3 FA status. The results indicated that a persistent consumption of fish at least once weekly from early pregnancy onwards improves the proportion of n-3 PUFA in serum PL of the mothers. In the shorter term, when examining fish intake in a certain time point one month after delivery, a higher consumption of at least three times weekly is needed to increase maternal n-3 PUFA in serum PL. Maternal dietary intake and increased n-3 PUFA in serum PL increased also the serum PL n-3 PUFA of the infant at 1 month of age. In addition an overall healthy diet evaluated according to the HEI improved maternal and infant PL FA one month after delivery. In this study, the proportion of DHA increased by 26 % and EPA by 24 % in infants at 1 month of age by raising the maternal Healthy Eating Index score from the lowest to the highest tertile. Further, by increasing the maternal fish intake the proportion of DHA in serum PL of the infants increased by 17% and EPA by 7%. These changes in n-3 PUFA status of the mother may improve the health of the offspring, for example by reducing the risk of asthma and allergic diseases (Sala-Vila et al., 2008).

As the intake of fish appears to be crucial in increasing the serum FA levels of both mothers and infants, it is of concern that as many as 37% of the women according to the food diaries and 19 % of the women according to the food frequency questionnaire did not consume fish at all. The subjects of this study were from allergic families that may be related to low intake of fish. However, according to

a national Findiet survey fish intake in average non-pregnant population of women aged 25-65 years was remarkably low as only 42% of the women consumed fish in their diet and the daily mean intake of fish was only 27 grams per day (Helldan et al., 2012). The consumption of fish has remained equal to previous national survey from 2007 (Paturi et al., 2007). Nevertheless, the low frequency of fish intake may be caused by several factors, such as high expense and the relatively poor preservability of fresh fish compared to meat products. Pregnant women may also be concerned about environmental toxins such as mercury (Valent et al., 2013; Gil and Gil, 2015). However, when the instructions of limiting high-mercury species are followed according to the recommendations the benefits of fish consumption are considered to overcome the risks (National nutrition council VRN 2014; Gil and Gil, 2015). More guidance is needed in well-fare clinics to obtain a safe and adequate intake of fish during pregnancy.

6.4 Maternal nutrition and infant development (IV)

In this study setting, the key determinant in maternal diet during pregnancy associated with infant development was the intake of vitamin D from diet and supplements. Indeed, also in previous clinical studies gestational vitamin D status has been associated with positive changes in child neurodevelopment evaluated by the Bayley Scales of Infant and Toddler Development III, Mental Development Index and Psychomotor Development Index (Whitehouse et al., 2012; Morales et al., 2012; Zhu et al., 2015; Tylavsky et al., 2015; Gould et al., 2017). On the other hand, low gestational vitamin D levels in serum have been related to autism-related traits (Vinkhuyzen et al., 2016). However, in a study with a long follow-up time of up to 22 years, higher maternal vitamin D serum levels during pregnancy were not associated with neurodevelopmental outcomes such as ADHD and depression, although, scholastic achievement was slightly but not statistically higher (Strøm et al., 2014).

Despite the name, vitamin D metabolites are considered to function as neuroactive steroid hormones and have the capacity to cross placental barriers and to bind nuclear vitamin D receptors in the neural cells of the foetus (Garcion et al., 2002; Eyles et al., 2005; Eyles et al., 2011). Further, vitamin D metabolites function in neuronal cell differentiation, endocrine organs and affect foetal brain growth (Eyles et al., 2011; Miettinen, 2017). The results indicating the role of maternal vitamin D intake in infant development have been worrying because of the deficient intake among pregnant women (Hollis and Wagner, 2006; Saraf et al., 2016; Cashman et al., 2016; Aghajafari et al., 2016). In a Finnish study population collected from 1983 forward, more than two thirds of pregnant women had lower

plasma 25-hydroxyvitamin D concentration (≤50 nmol/l) than considered optimal (Miettinen, 2017). Increased intake is needed especially in Northern latitudes where the synthesis of vitamin D is limited for most of the year (National nutrition council VRN, 2016). During the conduct of the study, vitamin D supplementation was routinely recommended only during the winter season (October to March) for all pregnant women and in this study population the intake of vitamin D was low, despite 89 % of the women using vitamin D supplements (Piirainen et al., 2006). The sufficiency of vitamin D intake during pregnancy at present has been recently evaluated in a Finnish study and the results indicated that vitamin D deficiency is nowadays scarce (Hauta-Alus et al., 2017). The serum 25-hydroxyvitamin D concentration of a subgroup from this study population has been reported previously and was sufficient both in dietary intervention (62.1 nmol/l) and control groups (61.8 nmol/l) (Vähämiko et al., 2013). However, the association of maternal vitamin D intake and infant development presented in this study was linear, and a higher concentration of serum vitamin D than considered adequate (50 nmol/l) may produce beneficial effects on infant development. Nevertheless, safety aspects should be considered when supplementing vitamin D doses exceeding those recommended during a vulnerable period of foetal development and regular supplementation exceeding 20 µg daily is not recommended (Institute of Medicine, 2011; National nutrition council VRN, 2016). Even though the vitamin D status in Finland on average has improved (Jääskeläinen et al., 2017), this may not be the case with all pregnant women and thus the results indicating the role of vitamin D in infant development should be noted.

Maternal n-3 PUFA and fish intake have previously been associated with improved child brain- and neurodevelopment (Lauritzen et al., 2001; Daniels et al., 2004; Demmelmair and Koletzko, 2015; Julvez et al., 2016). In our study the intakes of PUFA correlated with higher infant developmental scores in the initial correlation analysis, but in the multivariable models, maternal fish or PUFA intake were not associated with infant developmental scores. However, it should be taken into account that the women in the study were well-nourished and healthy and therefore the detected impact of maternal dietary intake may be subtle. The effects of higher PUFA intake could have been detected in a more varied population including undernourished mothers and their children and families from lower socioeconomic classes with poor dietary intake.

The original study randomization provided probiotic or placebo capsules for the mothers. In this study population, the provision of probiotics for the mother during pregnancy was not associated with infant development at 12 months of age. However, the modification of maternal gut microbiota by probiotic supplementation or altered maternal dietary intake is an interesting object for future research (El Aidy et al., 2014; Sampson and Mazmanian, 2015).

Some other dietary factors were moderately associated with infant developmental sub scores such as vitamin C along with calcium and iodine. There are potential mechanisms explaining these associations for example, the antioxidative mechanisms of vitamin C and the functions of calcium in cell membrane synthesis and neurotransmitter release (Coveñas et al., 2015; González and Visentin, 2016). Also interactions between vitamins and minerals may occur and thus the evaluation of the versatility of maternal diet is of importance. The possible associations between the dietary factors were taken into account by performing the multivariate models first for all the variables in the groups simultaneously (foods, nutrients, and vitamins and minerals) and then by stepwise backwards analysis. This enables the evaluation of the dietary components both simultaneously and independently. Overall, the effect of maternal dietary intake on infant developmental scores in this study was subtle as expected, bearing in mind that the study participants were healthy, highly educated and well-nourished. Yet, maternal dietary intake was shown to be associated with infant cognitive and locomotor development underlining the importance of the quality of nutrition during pregnancy. The concept of a health promoting diet may not be clear for all pregnant women and thus dietary counselling is needed. Also mothers following a selective or a restricted diet may be unaware of the potential risks of unbalanced dietary intake for the offspring.

6.5 Methodological aspects

6.5.1 Dietary recording and use of diet quality indexes (I-IV)

Food diaries are commonly used for this kind of food recording and are considered to be suitable for similar sample sizes. Here, one weekend day was included in the recording to better estimate the intake over a week. The recording days were self-chosen, which may affect the reliability of the results. However, the short-term validity of food recording depends on the number of days recorded and on the sample size, especially when the typical intake of foods or intake of vitamins and minerals is evaluated (Basiotis et al., 1987). Keeping in mind that completing food diaries is time-consuming, by totalling the number of recording days the relatively low number of drop-outs among the study subjects may have increased as previously demonstrated (Gersovitz et al., 1978). Thus 3-day recording has been generally considered as an appropriate recording time for evaluating dietary intake of most of the foods and nutrients on a group level. For foods not consumed daily, such as fish, additional methods are needed such as frequency questionnaire used here. If the consumption of fish is irregular or the frequency of fish intake is low,

3-day food diaries solely may be an inadequate method for evaluating fish consumption. Because of this possibility, multiple methods were used to allow fish consumption to be evaluated over a longer period. Nevertheless, underreporting is quite common in food diaries, especially amongst obese persons but presents also amongst pregnant women (Pietiläinen et al., 2010; McGowan and McAuliffe, 2012). However when comparing groups with comparable baseline characteristics, underreporting should not affect the results of comparison. The strengths of dietary recording in this study are the individual face-to-face training for the mothers, using both oral and written instructions, and a review of the food records supported by a portion-picture booklet. In addition, the recording was repeated multiple times to detect variation during study follow-up and in the group comparison. However, for vitamin and mineral intake, measuring the serum levels of vitamins and minerals may have produced more accurate information on the vitamin levels. Especially when interpreting the results for intake of vitamins and minerals, it has to be taken into account that the intakes were not adjusted to the intake of energy. Here, the quantitative intake of vitamins and minerals was considered more relevant than the nutrient density of dietary intake of mothers' and no differences were detected in energy intake between the groups compared in studies I and II.

We also used a diet quality index called the Healthy Eating Index to evaluate the overall healthy diet of the women. The use of dietary quality indexes has been investigated also in pregnant and non-pregnant population (Bodnar and Siega-Riz, 2002; Mariscal-Arcas et al., 2009; Leppälä et al., 2010; Meinilä et al., 2016). The aim of the indexes is to provide a quick but comprehensive general view of the typical diet of the population. These indexes may be used for research purposes and in screening diets as a whole to detect deficient or unbalanced dietary intakes and to further direct resources for dietary counselling for the population in need. In this study the index emphasized a high intake of vegetables, fruits and berries, fish and rye bread, and a low intake of salt and SFA as a percentage of energy aimed at providing an easy overall view of the healthiness of maternal dietary intake. Considering n-3 PUFA in serum PL, the intake of fish may have been the most important factor determining the correlation of higher index scores along with low intake of SFA. However, in vegetarians not consuming fish, the intake of ALA has been shown to increase serum n-3 PUFA levels (Harris, 2014).

6.5.2 FA analysis (II and III)

In previous studies, the proportion of n-3 FA in plasma and serum PL has been considered a good marker of n-3 FA intake(Serra-Majem et al., 2012). We used here a commonly described gas chromatograph analysis and the samples were

stored at – 70 degrees C until analysed. Matthan et al demonstrated that freezing is a valid method as plasma FA composition remains unchanged up to ten years when stored at – 80 degrees C (Matthan et al., 2010). There are no current reference ranges for pregnant and lactating population in terms of serum FA composition, but general reference rates for serum PL FA have been determined in a cross-sectional study (Bradbury et al., 2011).

As different plasma FA fractions have been shown to vary remarkably, we performed the analysis for three commonly used serum FA fractions. The choice of FA analysis method may significantly influence the results and providing results both in concentration and proportion increases the reliability of results (Mocking et al., 2012). In this study, the concentrations of serum FA in these fractions followed the same pattern as previously demonstrated increasing from first to third trimester and decreasing after pregnancy (De Vriese et al., 2003; Stuebe and Rich-Edwards, 2009). Thus the proportional analysis of serum FA may be more stable and thus useful for this kind of group comparison. The FA composition of serum PL and CE has been considered more solid, providing relatively reliable information of the nutritional status over past weeks or months (Zock et al., 1997; Kobayashi et al., 2001; Thiébaut et al., 2009; Serra-Majem et al., 2012). On the other hand, the FA composition of serum TAG provides information on FA metabolism in the shorter-term for the fat intake relating to the last few meals and, for example, the food products provided in this study (Moore et al., 1977). Further, it has been suggested that FA composition of TAG may reflect the endogenous metabolism of FA in the liver rather than FA composition of PL and CE (Venäläinen, 2017). Moreover, the analysis of erythrocyte FA composition could have provided additional information due to an even slower turnover rate compared to PL and CE, used in this study (Sun et al., 2007; Serra-Majem et al., 2012). Analysis of serum FA has still been considered as a valid method for evaluating serum FA status (Serra-Majem et al., 2012). Yet, due to methodological aspects we were unable to analyse the amount of DHA in serum CE and TAG.

6.5.3 Infant developmental evaluation (IV)

In this study the developmental evaluation of the infants was performed with the Griffiths Mental Development Scale at 12 months. The index consists of five subscales to provide a comprehensive picture of child cognitive and locomotor development: locomotor, personal-social, hearing and speech, hand and eye coordination and performance (Griffiths and Huntley, 1996). The test has been used for screening the neurological disabilities of infants and toddlers as well as for research purposes (Kothari et al., 2014; More et al., 2014; Cirelli et al., 2015;

Rohlwink et al., 2016). An ideal age for developmental testing reflecting later cognitive skills would have been at 18 or 24 months of age with repeated testing (Wong et al., 2016). The testing was performed already at 12 months of age because during the second year of life the lifestyle of the children rapidly changes and many of the children attend day care outside the home environment meaning that their eating habits change. In most of the studies, the test is used for following-up individual child, usually born preterm (Wong et al., 2016). Furthermore, always when evaluating infants or toddlers it should be taken into account that any developmental evaluation at one time point is only an estimate of the development of the child and may be impacted by various factors, such as tiredness or hunger of the child.

For studies of this nature evaluating the effects of foetal or early life environment on child development, a widely used method for testing infant cognitive and psychomotor development has been the Bayley Scales of Infant Toddler Development III (Bayley, 2005). This is a commonly used test for evaluating the overall development of preterm infants and toddlers and is considered to be applicable also for term-infants. It may be preferable to evaluate infant development using the Bayley scale, as it is comparable to most of the other similar studies. Nevertheless, Griffiths Mental Development Scale is also currently used for neurodevelopmental testing in clinical studies and considered a valid testing method (Cirelli et al., 2015).

We tested the effect of possible confounding factors typically used in previous similar studies in advance, and found no correlation between the developmental score. These were not included as a covariate in the multivariable models. However, as the study population comprised a majority of well-educated women, the effect of maternal education was further evaluated, by including it as a covariate in the models. There were no significant differences in the multivariable models and the stepwise backwards models compared to the results without adjusting to maternal education. This kind of research frame is sensitive to confounding factors and thus the results should be interpreted with caution. Nevertheless, this study population is homogenous in terms of maternal and child confounding factors and the sample size relatively large to provide reliability to the results. The associations seen in this kind of homogenous population may be more distinct in a more varied population. We also chose to concentrate on total score rather than the sub scores, providing more reliable results for child development at this age.

6.6 Future considerations

This study showed that by increasing the consumption of fish during pregnancy, the serum n-3 FA of mothers and infants increased one month postpartum. The definition of reference rates for serum n-3 and n-6 FA during the different stages of pregnancy and lactation would also be an interesting research target. Moreover, we did not specify in the analysis the intake of lean fish and fatty fish in the dietary intake of the mothers. More specific information on the type of fish consumed would perhaps produce more distinct differences among the study subjects. Also types of fatty fish differ in terms of fat composition, for example, farmed salmon has been shown to include less n-3 PUFA and also less environmental toxins than wild salmon (Lundebye et al., 2017). In many of the analyses we used the mean intakes of the three time points during pregnancy to provide more accurate information on the typical consumption of foods and nutrients. However, in a study with a larger number of study subjects it would be possible to perform more accurate analyses for each different trimester of pregnancy.

An interesting research target for future studies is to define the association of early gut microbiota and child development, as the maternal nutritional status is shown to affect both directly and indirectly the development of gut microbiota in the offspring (Thum et al., 2012; Isolauri et al., 2016; Chu et al., 2016). Previous studies have demonstrated interesting mechanisms in brain development and function through gut-brain-axis, even though the significance of modifying maternal gut microbiota on infant development remains to be elucidated (El Aidy et al., 2014; Sampson and Mazmanian, 2015). Moreover, maternal gut microbiota composition during pregnancy further influences the developing immune system of the offspring and may affect the risk of allergic diseases (Di Costanzo et al., 2016; Gray et al., 2017). The nutritionally poor Western style dietary pattern and following obesity of fertile-aged women changes gut microbiota, and it would be interesting to study the effects of maternal obesity on offspring later cognitive development (Segata, 2015; Nagpal et al., 2016).

There may also be associations between maternal dietary intake and other chronic diseases for the offspring detectable with further follow-up. Non-communicable diseases are a result of genetic, physiological, environmental and behaviours factors (WHO, 2017). The prevalence of, for example, inflammatory bowel diseases, type I and II diabetes and obesity are increasing and further research is needed to evaluate the possibilities for impacting the risk of these diseases by modifying early-life nutritional environment.

In future it would be interesting to see these dietary modifications implemented in a public health setting within a multicentre education program. The targets for

health professionals at maternal and child welfare clinics would consist of educating about the quality of dietary fat, along with underlining the benefits of adequate consumption of fish, fibre and certain vitamins and minerals such as vitamin D, folate and calcium. The development of an easy-to-use diet quality index for well-fare clinic nurses would help in the screening of mothers with nutritional deficiencies. Many of the diet quality indexes, such as the HEI used in this study, exclude vitamin and mineral intake and the calculation of dietary intake of nutrients and energy are needed. A diet quality index specifically designed for dietary needs during pregnancy such as that by Bodnar and Siega-Riz with the addition of vitamin D would provide an overall picture of the dietary intake of pregnant women (Bodnar and Siega-Riz, 2002). However, also in this index for pregnancy, the measurement of energy intake is required and therefore it is not usable for quick screening purposes during routine maternal welfare appointments. However, the Finnish national food recommendations for young families provide compact practical instructions for dietary guidance during pregnancy and for special conditions during pregnancy such as gestational diabetes and NVP (National nutrition council VRN, 2016).

Here we studied the associations of maternal dietary intake and infant developmental scores at the age of 12 months. This is a relatively short time for follow-up and further information on the longer-term effects of maternal nutrition in this extent to child development and health would be an interesting research target. In addition evaluation of the effects of the improved maternal intake of vitamin D at present on infant development would be of interest.

7 CONCLUSIONS

This study provides valuable information on the effects of maternal dietary intake and dietary counselling on maternal and infant FA metabolism and infant development. First we demonstrated that mild or moderate nausea and vomiting during pregnancy resulted in qualitative changes in maternal dietary intake over pregnancy but did not produce alterations leading to an immediate threat to the mother or her infant. This was evaluated by the pregnancy outcome, growth of the infant, and maternal dietary intake compared to those without NVP.

Further, this study showed that dietary counselling focusing on the quality of fat increases maternal serum n-3 FA in three fractions; PL, CE and TAG, also without PUFA supplementation. The dietary intervention in this study combined dietary counselling with advice on commercially available food products providing n-3 FA. This type of dietary counselling may be clinically practicable for example in maternity-child welfare clinics. We also demonstrated that an overall healthy diet that includes fish is likely to ensure sufficient n-3 PUFA intake and beneficially affect maternal and infant serum PL n-3 FA one month after delivery. Thus mothers should be encouraged to eat fish regularly at least once per week during pregnancy and lactation to improve their own n-3 PUFA levels and those of their infants through breast milk. Furthermore, fish consumption more often than three times per week or above 36 g daily (equivalent to 2.5 portions per week) increases the n-3 FA levels in serum PL more rapidly. In cases of fish allergies or a vegetarian diet, n-3 PUFA supplementation may be needed.

In evaluating the association of maternal dietary intake and infant development, intake of vitamin D was the best determinant of higher developmental scores. Sufficient intake of vitamin D along with supplements may produce benefits for the neurodevelopment of the offspring. A versatile diet also providing adequate intake of other vitamins and minerals such as calcium, iodine and vitamin C may have positive effects concerning infant development although further studies are needed.

In conclusion, the results demonstrate that by modifying maternal nutrition during pregnancy it is possible to affect maternal and infant wellbeing. Along with a versatile diet, sufficient intake of sources of n-3 FA and vitamin D, such as fish, should especially be ensured during pregnancy, to benefit infant development. This can be achieved by consumption of fish three times per week if a rapid increase of n-3 FA is desired, or at least once per week if consumption is persistent throughout the pregnancy and by supplementing vitamin D especially in cases of inadequate dietary intake.

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