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DIETARY CHANGE, OBESITY, AND METABOLIC MARKERS IN PREGNANCY

STUDIES IN WOMEN AT RISK FOR GESTATIONAL DIABETES MELLITUS

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ACADEMIC DISSERTATION

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CONTENTS

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This thesis is based on the following publications:

I The effect of dietary counselling on food intakes in pregnant women at risk for gestational diabetes: a secondary analysis of a randomised controlled trial RADIEL. *European Journal of Clinical Nutrition* 2016;70:912-7.

II Body size modifies the relationship between maternal serum 25-hydroxyvitamin D concentrations and gestational diabetes in high-risk women. *European Journal of Clinical Nutrition* 2018;72:460-463.

III The effect of pre-pregnancy lifestyle counselling on food intakes and association between food intakes and gestational diabetes in high-risk women: results from a randomised controlled trial. *Journal of Human Nutrition and Dietetics* 2018;31:301-305.

IV Diet quality as assessed by the Healthy Food Intake Index and relationship with serum lipoprotein particles and serum fatty acids in pregnant women at increased risk for gestational diabetes. *British Journal of Nutrition* 2018;120:914-924.

The publications are referred to in the text by their Roman numerals. The publications are reprinted with the permission of the copyright holders. In addition, some unpublished results are presented.

ABBREVIATIONS

25(OH)D	25-hydroxyvitamin D
$1,25(OH)_2D_3$	1,25-dihydroxyvitamin D
ADA	American Diabetes Association
aHEI	alternate Healthy Eating Index
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
CVD	Cardiovascular disease
ECLIA	Electrochemiluminescence immunoassay
FFA	Free fatty acid
FFQ	Food frequency questionnaire
OGTT	Oral glucose tolerance test
DALI	Vitamin D And Lifestyle Intervention for Gestational Diabetes Mellitus Prevention
DASH	Dietary Approaches to Stop Hypertension
DBP	Vitamin D binding protein
DHA	Docosahexaenoic acid
GDM	Gestational diabetes mellitus
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
IQR	Interquartile range
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HFII	Healthy Food Intake Index
HOMA-IR	Homeostatic model assessment of insulin resistance
hs-CRP	high-sensitivity C-reactive protein
HUSLAB	Helsinki University Hospital laboratory
LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
MJ	Megajoule
MUFA	Monounsaturated fatty acid
NHANES	National Health and Nutrition Examination Survey
NHS	Nurses' Health Study
NMR	Nuclear magnetic resonance
NNR	Nordic Nutrition Recommendations
PREDIMED	PREvención con DIeta MEDiterránea
PUFA	Polyunsaturated fatty acid
RCF	Relative centrifugal force
SD	Standard deviation
SFA	Saturated fatty acid
SPSS	Statistical package for social sciences

T2D	Type 2 diabetes
TGA	Triacylglycerol
TNF-α	Tumor necrosis factor alpha
VDR	Vitamin D receptor
VDRE	Vitamin D response element
VLDL	Very low-density lipoprotein
WHO	World Health Organization

ABSTRACT

The prevalence of obesity and gestational diabetes mellitus (GDM) are increasing simultaneously worldwide. GDM increases the risk of adverse pregnancy and neonatal outcomes and future type 2 diabetes. Obese women and women with GDM in previous pregnancies are at increased risk of future GDM. In addition, poor diet quality may increase the risk of GDM. However, the optimal diets for prevention of GDM are yet to be discovered.

Both obesity and GDM may increase the risk for cardiovascular disease (CVD). Healthy diets are known to promote cardiovascular health. Studies on diet-lipid associations have usually focused on standard lipid measurements. However, the use of alternative lipid parameters may help in cardiovascular risk assessment.

The study objectives were to investigate the differences in dietary intakes between the intervention and control groups after lifestyle counselling and the role of diets and obesity in maternal metabolism. The hypothesis was that food intakes are improved in the lifestyle intervention group compared with the control group during the follow-up and that diets and obesity are related to maternal glucose, lipoprotein, and vitamin D metabolism. The participants were part of the Finnish Gestational Diabetes Prevention trial (RADIEL) which included diet and physical activity intervention for women at increased risk for GDM due to obesity or a history of GDM. Women were recruited either in early pregnancy or before pregnancy. The inclusion criteria were BMI ≥30 kg/m^2, a history of GDM, or both.

In study I, the objective was to assess the differences in food intake changes from early to mid-pregnancy between the intervention and control groups. The study population consisted of 242 pregnant women. Evaluation of food intakes was based on a 48-item food frequency questionnaire (FFQ) collected in early and mid-pregnancy. Twelve (12) foods or food groups relevant in the Nordic Nutrition Recommendations (NNR) were selected from the FFQ and included in the final evaluation. During the follow-up, intakes of fish ($P = 0.011$) and low-fat cheese ($P = 0.040$) increased in the intervention group compared with the control group.

The aim in study II was to investigate whether adiposity modifies the relationship between serum 25-hydroxyvitamin D (25(OH)D) concentrations and GDM in 219 pregnant women. The participants were stratified into four groups according to BMI in early pregnancy; <25, 25-29.9, 30.0-34.9 and ≥35 kg/m^2. Among severely obese women (BMI ≥35 kg/m^2), the increase in serum 25(OH)D concentrations was higher in those who did not develop GDM compared with those who did develop GDM (43.2 vs. 11.5%; $P < 0.001$). No relationships between 25(OH)D concentrations and GDM were found in women with a lower BMI.

The objective in study III was to examine the differences in food intake changes between the lifestyle intervention group and the control group. The study included 75 women who were followed from pre-pregnancy to early pregnancy. No differences were observed in between-group comparisons for changes in food intake when assessed by using the 12 foods or food groups based on the FFQ. Another aim in study III was to investigate the association between changes in food intake and GDM risk. Diagnosis of GDM was based on a 2-hour oral glucose tolerance test in early pregnancy. During the follow-up from pre-pregnancy to early pregnancy, low-fat cheese intake increased in women not developing GDM compared with women developing GDM (P = 0.028). No between-group differences were found for regular-fat cheese or other foods.

The aim of study IV was to evaluate whether diet quality based on the adherence to the NNR was related to HDL, LDL, and VLDL particle size and concentrations in 161 pregnant women. Diet quality was evaluated by using the Healthy Food Intake Index based on the adherence to the NNR. In early pregnancy, higher diet quality was associated with lower HDL particle concentrations. Further, improvements in diet quality were related to a reduction in VLDL particle size when followed from early to mid-pregnancy.

Though the current findings showed only modest improvements in maternal food intakes after lifestyle counselling in early pregnancy, antenatal clinics should continue providing dietary counselling to optimize diet quality in pregnant women. Further evidence is required to conclude whether lifestyle counselling should be initiated already when planning a pregnancy instead of during pregnancy to improve intervention efficiency in terms of dietary modifications. Furthermore, replacing high- and regular-fat cheese with low-fat cheese may help in lowering GDM risk among women at high risk. Though the relationship of diet quality with lipoprotein particle profile was limited, the current findings on improved diet quality and reduced size of VLDL particles during pregnancy may be suggestive of the role of dietary improvements in modifying triglyceride-rich lipoprotein particles to a less atherogenic form. Moreover, large controlled trials are needed to confirm whether severely obese pregnant women should have higher vitamin D status to improve glucose metabolism.

TIIVISTELMÄ

Raskausdiabeteksen yleisyys on kasvanut samanaikaisesti lihavuuden yleisyyden kanssa kaikkialla maailmassa. Raskausdiabetes lisää raskauskomplikaatioiden sekä tyypin 2 diabeteksen riskiä. Lihavilla naisilla sekä naisilla, jotka ovat sairastaneet raskausdiabetesta aiemmassa raskaudessa on suurentunut raskausdiabeteksen riski tulevissa raskauksissa. Lihavuuden lisäksi myös epäterveellinen ruokavalio saattaa lisätä raskausdiabeteksen riskiä. Vielä ei ole kuitenkaan tiedossa, millainen on optimaalinen ruokavalio raskausdiabeteksen ehkäisyssä.

Lihavuus ja raskausdiabetes saattavat molemmat lisätä sydän- ja verisuonisairauksien riskiä. Terveellisen ruokavalion tiedetään edistävän sydän- ja verisuoniterveyttä. Ruokavalion ja lipidien välistä yhteyttä käsittelevät tutkimukset usein keskittyvät vakiomittareihin lipidimäärityksessä kun taas vaihtoehtoiset lipidimittarit saattavat edesauttaa sydän- ja verisuonisairauksien riskinarviointia.

Tässä väitöskirjassa selvitettiin eroja ruoankäytön muutoksissa elämäntapainterventio- ja verrokkiryhmien välillä sekä ruokavalion ja lihavuuden yhteyttä raskaudenaikaiseen aineenvaihduntaan. Tutkimusaineisto koostuu Raskausdiabeteksen ehkäisy elämäntapamuutoksin (RADIEL)–tutkimukseen osallistuneista naisista, joilla on suurentunut raskausdiabeteksen riski; painoindeksi ≥30 kg/m² tai raskausdiabetes aiemmassa raskaudessa. RADIEL–tutkimus on satunnaistettu kontrolloitu ruokavalio- ja liikuntainterventiotutkimus.

Väitöskirjan osatyössä I tarkasteltiin eroja ruoankäytön muutoksissa interventio- ja verrokkiryhmien välillä raskaudenaikaisen elämäntapaintervention jälkeen. Tutkimuksessa seurattiin 242 raskaana olevan naisen ruoankäyttöä alkuraskaudesta raskauden keskivaiheeseen. Ruoankäytön arviointi perustui 48-kohtaiseen ruoankäytön frekvenssilomakkeeseen (FFQ), josta edelleen valittiin 12 ruokaa tai ruokaryhmää arviointia varten. Ruokien valinta perustui Pohjoismaisiin ravitsemussuosituksiin koskien ruoankäyttöä. Seurannan aikana kalan (P = 0.011) ja vähärasvaisten juustojen (P = 0.040) käyttö lisääntyivät interventionryhmässä verrattuna verrokkiryhmään.

Väitöskirjan osatyössä II tutkittiin selittääkö äidin raskaudenaikainen painoindeksi seerumin D-vitamiinipitoisuuden ja raskausdiabetesriskin yhteyttä. Kyseisessä osatyössä 219 raskaana olevaa naista seurattiin varhaisraskaudesta raskauden keskivaiheeseen. Osallistujat jaettiin neljään ryhmään perustuen varhaisraskauden painoindeksiin ; painoindeksi <25, 25-29.9, 30.0-34.9 ja ≥35 kg/m². D-vitamiinipitoisuusmittaus perustui seerumin 25-hydroksi-D-vitamiinipitoisuuteen (25(OH)D). Ryhmässä, jonka painoindeksi oli ≥35 kg/m², seerumin 25(OH)D-pitoisuuden prosentuaalinen nousu oli korkeampi naisilla, jotka eivät sairastuneet raskausdiabetekseen

verrattuna naisiin, jotka sairastuivat raskausdiabetekseen (43.2 vs. 11.5%; P < 0.001). Seerumin 25(OH)D-pitoisuuden ja raskausdiabeteksen välillä ei havaittu yhteyttä muissa painoindeksiryhmissä.

Osatyössä III tarkasteltiin eroja ruoankäytön muutoksissa interventio- ja verrokkiryhmien välillä raskauden suunnitteluvaiheesta varhaisraskauteen. Ruoankäytön muutokset arvioitiin FFQ:n avulla käyttäen edellä mainittuja 12:ta ruokaa tai ruokaryhmää. FFQ kerättiin seurannan alussa eli raskauden suunnitteluvaiheessa sekä varhaisraskaudessa. Ruoankäytön muutoksissa ei havaittu eroja interventio- ja verrokkiryhmien välillä seurannan aikana. Lisäksi osatyössä tutkittiin seurannan aikana havaittujen ruonkäytön muutosten yhteyttä raskausdiabeteksen riskiin. Raskausdiabeteksen diagnoosi perustui 2 tunnin glukoosirasitustestiin varhaisraskaudessa. Vähärasvaisten juustojen käyttö lisääntyi naisilla, jotka eivät sairastuneet raskausdiabetekseen verrattuna naisiin, jotka sairastuivat raskausdiabetekseen (P = 0.028). Rasvaisten juustojen käytössä ei havaittu ryhmienvälisiä eroja.

Osatyössä IV tutkittiin ruokavalion laadun ja seerumin lipoproteiinipartikkeleiden yhteyttä raskauden aikana. Ruokavalion laadun mittaus perustui terveellisen ruoankäytön indeksiin (engl. Healthy Food Intake Index, HFII), joka kehitettiin arvioimaan missä määrin raskausdiabeteksen riskiryhmään kuuluvat, raskaana olevat naiset noudattavat Pohjoismaisia ravitsemussuosituksia (engl. Nordic Nutrition Recommendations). Lipoproteiinipartikkeleista määritettiin seerumin LDL- , VLDL- , ja HDL- partikkeleiden koko ja pitoisuus. Parempi ruokavalion laatu varhaisraskaudessa oli yhteydessä matalampaan seerumin HDL-partikkeleiden pitoisuuteen. Sen sijaan parantunut ruokavalion laatu oli yhteydessä pienentyneeseen VLDL-partikkelikokoon varhais- ja keskiraskauden välisenä aikana.

Vaikka tässä väitöskirjassa havaitut ruoankäytön muutokset olivat vähäisiä raskaudenaikaisen elämäntapaintervention jälkeen, ravitsemusneuvontaa tulee jatkaa äitiysneuvolakäyntien yhteydessä terveellisen ruokavalion edistämiseksi. Lisätutkimukset ovat tarpeen arvioitaessa tulisiko elämäntapaneuvonta aloittaa alkuraskauden sijaan jo raskauden suunnitteluvaiheessa neuvonnan tehokkuuden parantamiseksi. Rasvaisten juustojen korvaaminen rasvattomilla ja vähärasvaisilla juustoilla saattaa pienentää raskausdiabeteksen riskiä. Lisäksi, parempi raskaudenaikainen ruokavalion laatu saattaa olla yhteydessä runsaasti triglyseridejä sisältävien lipoproteiinipartikkeleiden vähemmän aterogeeniseen muotoon. Satunnaistettuja kontrolloituja tutkimuksia tarvitaan, jotta voidaan osoittaa, hyötyvätkö vaikeasti ja sairaalloisesti lihavat naiset korkeammista D-vitamiinipitoisuuksista raskaudenaikaisen glukoosiaineenvaihdunnan parantamiseksi.

1 INTRODUCTION

Poor diet quality and obesity are both involved in metabolism during pregnancy and increase the risk of pregnancy complications, particularly the risk of gestational diabetes mellitus (GDM).

The prevalence of GDM is increasing worldwide simultaneously with that of obesity (Ferrara 2007). In Finland, the prevalence of GDM was 16% and that of obesity 14% among pregnant women in 2017 (National Institute for Health and Welfare. 2018). Overweight and obesity before pregnancy as well as GDM in previous pregnancies are major risk factors for future GDM (Chu et al. 2007, Schwartz et al. 2015). GDM elevates the risk of pregnancy complications and future type 2 diabetes (T2D) in the mother and the offspring (Damm 2009, Reece 2010, Schwartz et al. 2015). Additionally, GDM increases the risk of future obesity and metabolic syndrome in the offspring (Damm et al. 2016).

Modifiable factors have become an essential research focus to prevent GDM. According to observational data, dietary patterns characterized by high intakes of vegetables, fruits, fiber, and fish and low intakes of red and processed meat, sugar-sweetened beverages, high-fat dairy, sweets, and refined grains may reduce GDM risk (C. Zhang, Schulze et al. 2006, Tryggvadottir et al. 2015, Schoenaker et al. 2016, Donazar-Ezcurra et al. 2017). Furthermore, some clinical trials including combined dietary and physical activity advice have succeeded in lowering the risk of GDM (Petrella et al. 2014, Koivusalo et al. 2016, Bruno et al. 2017). Numerous studies have shown dietary improvements after maternal lifestyle and nutrition counselling (Piirainen et al. 2006, Kinnunen et al. 2007, Guelinckx et al. 2010, Jackson et al. 2011, Korpi-Hyövälti et al. 2012, Kinnunen et al. 2014). However, the studies are often heterogeneous by type and intensity of counselling, reporting of dietary outcomes, and population characteristics, which hinders the generalization of the findings. The possibilities of maternal nutrition advice in modifying dietary intakes towards nutrition guidelines as well as the potential of diets to optimize maternal glucose metabolism still require further investigation. Moreover, dietary interventions initiated already when planning a pregnancy may be more efficient in improving diets, yet the intervention studies conducted before conception have mainly focused on folic acid supplementation (Temel et al. 2014).

Both GDM and obesity are associated with increased risk of CVD in later life (Shah et al. 2008, Goueslard et al. 2016). Dietary patterns characterized by high intakes of vegetables, fruits, berries, fibre, low-fat dairy, whole-grain, and

unsaturated fat from vegetables, nuts, and fish, as well as low intakes of saturated fat, cholesterol, and red and processed meat are recommended to promote cardiovascular health (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2002, Nordic Council of Ministers 2014). Studies on diets and circulating lipids related to cardiovascular health have mostly reported on concentrations of triglycerides and total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol. One suggested alternative method in CVD risk prediction is the evaluation of lipoprotein particle concentration and size. Compared with evidence on diet and standard lipid associations, reports on the associations between diets and lipoprotein particle size and concentration are sparse (Damasceno et al. 2013, Hernaez et al. 2017). Moreover, no studies exist on such associations among pregnant women or in relation to a Nordic diet.

In addition to GDM risk, obesity also elevates the risk of low circulating 25(OH)D concentrations (Wortsman et al. 2000). Additionally, according to some observational data, low 25(OH)D concentrations during pregnancy may increase the risk of GDM, yet the findings remain inconsistent (Burris, Camargo 2014). When investigating circulating vitamin D-GDM associations, body mass index (BMI) has usually been used as a covariate only instead of a more detailed evaluation of the role of BMI.

Diet is an essential determinant of maternal metabolic milieu which undergoes alterations during pregnancy. These alterations may be exacerbated in pregnant women with pre-existing metabolic abnormalities such as obesity and previous GDM. The aim of this thesis was to describe the differences in dietary intakes after lifestyle intervention between the intervention and control groups and to investigate the role of dietary change and obesity in maternal metabolism among Finnish pregnant women affected by a history of GDM, obesity, or both. The hypothesis was that the lifestyle intervention group would improve their food intakes compared with the control group after lifestyle counselling and that dietary change and obesity would be related to markers of vitamin D, glucose, and lipoprotein metabolism (Figure 1).

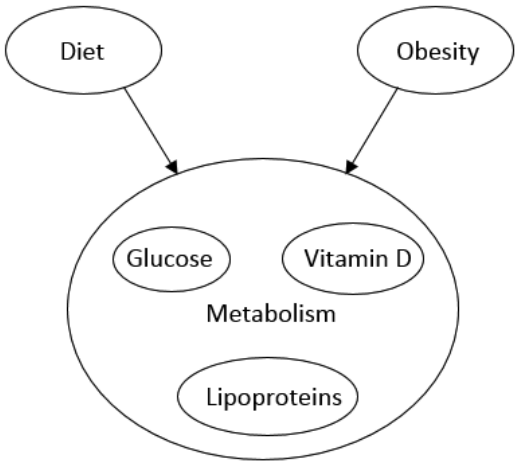

Figure 1. Description of the themes included in the current study.

2 REVIEW OF THE LITERATURE

2.1 GESTATIONAL DIABETES MELLITUS

2.1.1 DEFINITION AND DIAGNOSTIC CRITERIA

Gestational diabetes mellitus (GDM) is determined as impaired glucose tolerance with its onset or first notice in pregnancy that is not overt diabetes (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al. 2010).

Diabetes occurring only during pregnancy was first recognized by Duncan in 1881 (Drury 1984). In 1957, Carrington et al. proposed the word 'gestational diabetes' referring to a disorder which manifests only in pregnancy and has an adverse influence on fetal outcomes (Carrington et al. 1957). Later on, O'Sullivan et al. (1964) discovered that blood glucose concentrations during a 3-h 100-g oral glucose tolerance test (OGTT) in pregnancy were linked to the risk of diabetes after delivery suggesting that OGTT values during pregnancy may predict future risk of diabetes (O'Sullivan, Mahan 1964). In 1979, the National Diabetes Data Group proposed a modification to the cut-off values after the change from whole blood to plasma samples in glucose concentration assessment (National Diabetes Data Group 1979). Further, in 1982, the first diagnostic cut-off values for GDM set by O'Sullivan were further updated by Carpenter and Coustan (Carpenter, Coustan 1982) (Table 1).

Currently, the most commonly used diagnostic procedures are either one-phase 2-h 75-g OGTT or two-phase 3-h 100-g OGTT. In the two-phase procedure, the first phase includes a 50-g glucose challenge test, and those exceeding the cut-off value undergo the 3-h 100-g OGTT. In 2010, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) published recommendations based on the findings from the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study demonstrating a direct association between glucose concentrations in the 75 g OGTT and adverse pregnancy and neonatal outcomes. The recommendations by IADPSG are also supported by the American Diabetes Association (ADA) (2010) as well as the World Health Organization (WHO) (2013) (Table 1). Additionally, based on a recommendation of the IADPSG, ADA recommended a 75 g OGTT for all pregnant women at 24-28 gestational weeks in 2011. Currently, diagnostic criteria for GDM differ

between and within countries as there is no international consensus of uniform criteria (McIntyre et al. 2015).

Before 2008, GDM screening in Finland was based on existing risk factors: only mothers aged 40 years or higher or with glucosuria, a BMI ≥25 kg/m^2, macrosomic fetus in the current or previous pregnancy, a history of GDM, or diabetes in first-degree relatives were screened for GDM (Ellenberg et al. 2017). Since 2008, when the Finnish Medical Society Duodecim announced the national Current Care Guidelines for screening, diagnostic criteria, and treatment of GDM, the screening of GDM by using a 2-h 75-g OGTT has been recommended for most of the pregnant women between 24 and 28 gestational weeks in Finland. Only nulliparous women aged under 25 years, with a BMI between 18.5 and 25 kg/m^2, and with no diabetes among first- or second-degree family members, as well as parous women aged under 40 years, with a BMI <25 kg/m^2, and with no macrosomic child in previous pregnancies have been excluded from screening.

Table 1. Recommendations for diagnostic criteria for gestational diabetes mellitus.

Criteria	Procedure	Threshold glucose values† (mmol/L) Fasting	1-h	2-h	3-h
O'Sullivan, Mahan 1964	100-g, 3-h OGTT*; ≥2 pathologic values Whole blood	5.0	9.1	8.0	6.9
National Diabetes Data Group 1979	100-g, 3-h OGTT; ≥2 pathologic values Plasma	5.8	10.6	9.2	8.1
Carpenter, Coustan 1982	100-g, 3-h OGTT; ≥2 pathologic values Plasma, glucose oxidase	5.3	10.0	8.6	7.8
American Diabetes Association 2010	75-g, 2-h OGTT; ≥1 pathologic value Plasma	5.1	10.0	8.5	
International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al. 2010	75-g, 2-h OGTT; ≥1 pathologic value Plasma	5.1	10.0	8.5	
European Association for the Study of Diabetes[Δ] 1996	75-g, 2-h OGTT; ≥1 pathologic value Plasma	6.0	-	9.0	
World Health Organization 2013	75-g, 2-h OGTT; ≥1 pathologic value Plasma	5.1	10.0	8.5	
Finnish Current Care Guidelines[§] 2013	75-g, 2-h OGTT; ≥1 pathologic value Plasma	5.3	10.0	8.6	

OGTT, oral glucose tolerance test.
*Two-step approach; a 50-g non-fasting oral glucose challenge test; those exceeding the cut-off value of 7.8 mmol/L undergo a 100-g, 3-h OGTT.
†Greater or equal to reported value.
[Δ]Brown et al. 1996.
[§]Finnish Medical Society Duodecim et al. 2013.

2.1.2 RISK FACTORS

Numerous risk factors for GDM have been established (Table 2). GDM risk is increased remarkably with increasing maternal adiposity. For instance, obese women may have a four-fold and severely obese women an eight-fold risk for GDM compared with normal-weight women (Chu et al. 2007). In the National Health and Nutrition Examination Survey (NHANES), the estimated prevalence of obesity (BMI ≥30 kg/m^2) in women aged 20-39 years was 32% in 2011-2012 (Ogden et al. 2014). The prevalence of gestational obesity varies widely, between 1.8% to 25% worldwide (Guelinckx et al. 2008), whereas in American cohort studies, the range is between 18.5 and 38% (Galtier-Dereure et al. 2000). In Finland, the prevalence of obesity was 14% in pregnant women in 2017 (National Institute for Health and Welfare 2018).

In addition to maternal adiposity, a history of GDM is a well-known risk factor of future GDM. Approximately half of women with previous GDM develop GDM in the next pregnancy (N. Schwartz et al. 2015). Other potential factors contributing to development of GDM include diet and physical activity before and during pregnancy (C. Zhang et al. 2014), smoking (Solomon et al. 1997), genetic factors (C. Zhang et al. 2013), short stature (Laine et al. 2018), as well as maternal birth size (Seghieri et al. 2002).

Table 2. Risk factors for gestational diabetes mellitus

Excessive body weight before pregnancy (Chu et al. 2007)
GDM in previous pregnancies (N. Schwartz et al. 2015)
A family history of diabetes (American Diabetes Association 2004)
Higher maternal age (Lao et al. 2006)
Macrosomic child in previous labours (birth weight ≥4000 g) (McGuire et al. 1996)
Ethnicity (e.g., Hispanic and Asian) (Metzger et al. 1998)
History of impaired glucose tolerance (American Diabetes Association 2004)
Polycystic ovarian syndrome (Ben-Haroush et al. 2004)
Higher parity (Moses 1996)
Excessive gestational weight gain (Carreno et al. 2012)

2.1.3 PREVALENCE

GDM prevalence varies widely depending on the population characteristics and diagnostic protocol used (Ben-Haroush et al. 2004, Hollander et al. 2007, Reece et al. 2009). According to recent reports, GDM prevalence may vary between 1 and 24% (Farrar et al. 2015, Farrar et al. 2016). Furthermore, in the HAPO Study, the overall GDM prevalence was 18%, ranging from 9% in Israel to almost 26% in the USA when using IADPSG diagnostic criteria (Sacks et al. 2012). In 2017, GDM prevalence was 16% among pregnant women in Finland (National Institute for Health and Welfare. 2018).

2.1.4 CONSEQUENCES

GDM increases the future risk of type 2 diabetes (T2D) in the mother and the child (Damm 2009). Additionally, women with GDM are at increased risk of pre-eclampsia, induction of labour, and caesarean section in the current pregnancy (Reece 2010), as well as GDM in later pregnancies (Schwartz et al. 2015). Furthermore, women with GDM may be at increased risk for future cardiovascular disease (CVD) (Shah et al. 2008).

In relation to offspring health, GDM increases the risk for macrosomia, large for gestational age, obesity, and metabolic syndrome (Pettitt et al. 1991, Damm 2009, Reece et al. 2009, Reece 2010). Furthermore, babies of mothers with GDM may be at increased risk of neonatal hypoglycaemia, respiratory distress syndrome, and preterm birth (Reece et al. 2009, Reece 2010).

2.1.5 GLUCOSE-INSULIN METABOLISM IN NORMAL PREGNANCY AND GESTATIONAL DIABETES MELLITUS

During normal pregnancy, insulin resistance starts to increase in mid-pregnancy and continues to increase during the third trimester of pregnancy (Buchanan et al. 2007). With regard to glucose metabolism, insulin resistance is defined as impaired responsiveness of target tissues to the influence of insulin resulting in decreased glucose uptake in skeletal muscle and adipose tissue and reduced suppression of endogenous glucose production (Catalano et al. 2003). The pregnancy-induced insulin resistance may be a consequence of increased maternal adiposity and circulating free fatty acid (FFA) concentrations, as well as placental hormones which may attenuate insulin sensitivity in target tissues (Buchanan et al. 1990, Catalano et al. 1991, Buchanan et al. 2007). In the fetus, the increased insulin resistance promotes glucose transport across the placenta optimizing fetal development (Shepherd

et al. 2017). In response to progressive insulin resistance, insulin secretion from pancreatic β-cells is increased, which is a common characteristic also in obesity.

GDM may result when insulin secretion from pancreatic β-cells is insufficient in relation to increasing insulin resistance which eventually leads to hyperglycaemia (Figure 2) (Buchanan et al. 2007, Harlev, Wiznitzer 2010). One potential mechanism for inadequate pancreatic insulin secretion may be deterioration in pancreatic β-cell function (Buchanan et al. 2007, Harlev, Wiznitzer 2010). Cellular mechanisms underlying GDM development are still unclear. Potential mechanisms may include increased circulating concentrations of inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), and decreased concentrations of adiponectin observed in women with GDM compared with women without GDM (Kinalski et al. 2005, Ategbo et al. 2006, Lopez-Tinoco et al. 2012, Xu et al. 2014). TNF-α has been reported to impair insulin signaling pathways (Hotamisligil et al. 1994, Peraldi et al. 1996, Peraldi, Spiegelman 1998), whereas adiponectin promotes glucose uptake in skeletal muscle and hinders endogenous glucose production (Barbour et al. 2007).

After delivery, insulin resistance decreases rapidly in normal pregnancy. In contrast, in women with a history of GDM, insulin resistance continues after pregnancy and is further increased in the next pregnancy (Barbour et al. 2007, Buchanan et al. 2007).

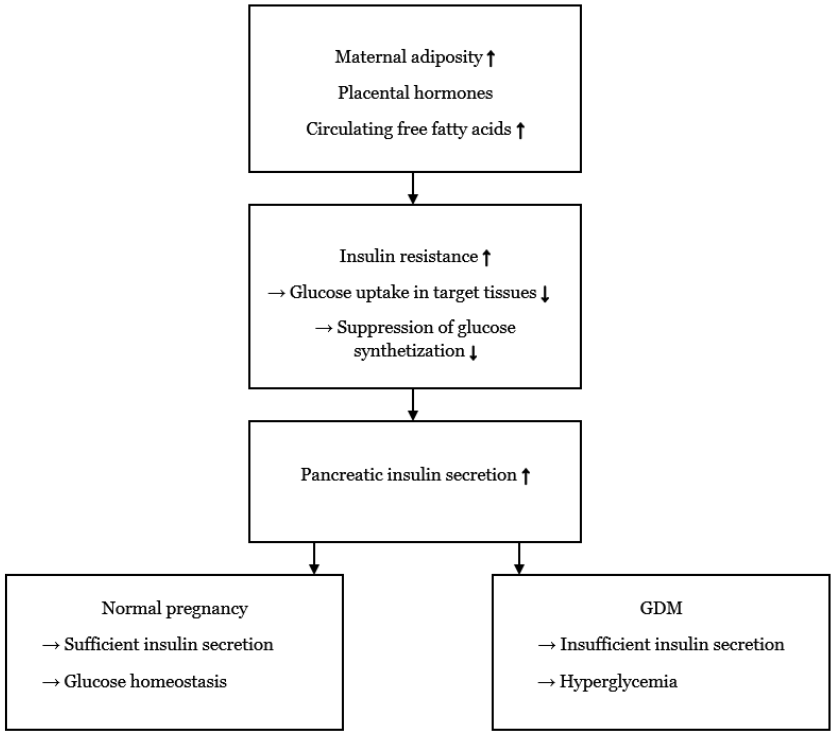

Figure 2. Glucose-insulin metabolism in normal pregnancy and in gestational diabetes mellitus (GDM).

2.1.6 TREATMENT OF GESTATIONAL DIABETES MELLITUS

Treatment of GDM reduces the risk of pregnancy and neonatal complications (Alwan et al. 2009). The primary treatment protocol consists of lifestyle modifications including diet and physical activity (American Diabetes Association 2017). However, additional pharmacological treatment is necessary in case women are unable to reach the glycaemic therapeutic goals with lifestyle modifications only. Insulin therapy is the standard pharmacological therapy as insulin crosses placenta only to a limited extent (American Diabetes Association 2017). Oral anti-diabetic drugs, such as metformin, may also be used (American Diabetes Association 2017). In Finland, the main aims of dietary treatment for GDM include regular meals, restriction of total carbohydrate intake (40-50% from total energy intake), as well as favoring carbohydrate sources high in fibre and fat sources high in mono- and polyunsaturated fatty acids (Finnish Medical Society Duodecim et al. 2013). Recommendations for physical activity are similar to those for the general population.

2.2 GESTATIONAL DIABETES MELLITUS AND DIET

2.2.1 OBSERVATIONAL DATA

Gestational diabetes mellitus and nutrients

Several nutrients have been related to GDM risk in observational studies (Table 3). Reports based on the NHS II data have demonstrated associations of higher pre-pregnancy intakes of heme iron, total fat, cholesterol, animal fat, and animal protein with increased GDM risk (Bowers et al. 2011, Bowers et al. 2012, Bao et al. 2013). In the same data, higher pre-pregnancy intakes of vegetable protein, as well as total, cereal, and fruit fiber were linked to reduced GDM risk (C. Zhang et al. 2006, Bao et al. 2013). Furthermore, higher intakes of cholesterol, heme iron, and total fat during pregnancy have been related to greater GDM risk (Saldana et al. 2004, Gonzalez-Clemente et al. 2007, Qiu, Zhang, et al. 2011). Moreover, lower concentrations of vitamin C and vitamin D in early pregnancy have been related to increased GDM risk (C. Zhang et al. 2004, C. Zhang et al. 2008).

Replacing carbohydrates with fat or animal fat before pregnancy has been associated with increased GDM risk (Saldana et al. 2004, Bowers et al. 2012). Similarly, substitution of animal fat with vegetable fat as well as the

substitution of animal protein with vegetable protein in pre-pregnancy have been related to lower GDM risk (Bowers et al. 2012, Bao et al. 2013).

Gestational diabetes mellitus and foods

Foods and food groups associated with GDM in observational studies are reported in Table 3. Observational data have frequently shown a positive relationship between intakes of red and processed meat before or during pregnancy and GDM risk (C. Zhang, Schulze, et al. 2006, Bao et al. 2013, Mari-Sanchis et al. 2018). Additionally, according to findings from the Alpha Study and the Omega Study, high egg consumption (≥7 eggs/week) may be related to higher GDM risk (Qiu, Frederick, et al. 2011). In a recent review (Schoenaker et al. 2016), the observational findings on other food intakes in relation to GDM risk were mostly non-significant whereas significant results were usually reported by only one study.

Karamanos et al. (2014), as well as Goshtasebi et al. (2018), reported on an inverse association between potato consumption and GDM risk (Karamanos et al. 2014, Goshtasebi et al. 2018). In contrast, in a prospective cohort study by Bao et al. (2016) using data from the NHS II, higher potato intake was associated with increased GDM risk (Bao et al. 2016). However, in the study by Bao et al. (2016), those with higher potato intake had less healthy lifestyles, higher prevalence of smoking, and higher BMI compared with those with lower potato intake. In addition to potato intake, findings on cereal intake and GDM risk have been inconsistent. Such discrepancy between the results on foods rich in carbohydrate and GDM risk may in part arise from various types of carbohydrates, such as fiber and sugar, in these foods. For instance, higher cereal fiber intake and diets with low glycaemic index and low glycaemic load have been associated with lower risk of GDM and TD2 (Schulze et al. 2004, Greenwood et al. 2013, Looman et al. 2018).

Gestational diabetes mellitus and dietary patterns

According to findings from observational studies with adjustments for potential confounders, higher adherence to dietary patterns rich in fruits, vegetables, whole grain, and fish and low in red and processed meat, high-fat dairy, refined grain products, and sugar-sweetened beverages may be related to reduced GDM risk (C. Zhang, Schulze et al. 2006, Tobias et al. 2012, Karamanos et al. 2014, Schoenaker et al. 2015, Shin et al. 2015, Tryggvadottir et al. 2015, Donazar-Ezcurra et al. 2017, Sedaghat et al. 2017, Zareei et al. 2018), yet some studies have reported no association (Fulay et al. 2018).

In the NHS II with over 13,000 participants, higher adherence to a low-carbohydrate diet before pregnancy was related to increased GDM risk whereas higher adherence to Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) diet, and alternate Healthy Dietary Index (aHEI) was related to lower GDM risk (Tobias et al. 2012, Bao et al. 2014). Further, data from the Australian Longitudinal Study on Women's Health showed that pre-pregnancy diet with rather low carbohydrate intake and high fat and protein intake was positively associated with GDM risk (Looman et al. 2018).

Table 3. Observational data on dietary factors and gestational diabetes mellitus

Nutrients	Foods and food groups	Dietary patterns
Increased GDM risk	*Increased GDM risk*	*Increased GDM risk*
Heme iron (Bowers et al. 2011, Qiu et al. 2011)	Total meat (Mari-Sanchis et al. 2018)	Western dietary pattern (Zhang, Schulze, et al. 2006; Donazar-Ezcurra et al. 2017, DU et al. 2017, Sedaghat et al. 2017)
Total iron (Helin et al. 2012)	Total red meat (Zhang, Schulze, et al. 2006; Bao et al. 2013, Marí-Sanchis et al. 2018)	Dietary glycaemic load (Zhang, Schulze et al. 2006)
Total fat (Saldana et al. 2004, Ley et al. 2011, Bowers et al. 2012)	Unprocessed red meat (Bao et al. 2013)	Low-carbohydrate dietary pattern (Bao et al. 2014, Looman et al. 2018)
Total cholesterol (Gonzales-Clemente et al. 2007, Qiu et al. 2011, Bowers et al. 2012)	Processed meat (Zhang, Schulze, et al. 2006; Bao et al. 2013, Marí-Sanchis et al. 2018)	Dietary Inflammatory Index (Shivappa et al. 2018)
Saturated fat (Bo et al. 2001, Park et al. 2013)	Fried foods (Bao et al. 2014)	
Animal protein (Bao et al. 2013)	Eggs (Qiu et al. 2011)	
Animal fat (Bowers et al. 2012)	Cheese (Karamanos et al. 2014)	
Monounsaturated fat (Bowers et al. 2012)	Bacon (Zhang, Schulze, et al. 2006)	
n-3 fatty acids (Radesky et al. 2008)	Hot dogs (Zhang, Schulze, et al. 2006)	
	Sugar-sweetened soft drinks (Chen et al. 2009, Donazar-Ezcurra et al. 2018)	
	Potatoes (Bao et al. 2016)	
	Cereal (Looman et al. 2018)	
Lower GDM risk	*Lower GDM risk*	*Lower GDM risk*
Carbohydrates (Saldana et al. 2004, Ley et al. 2011)	Nuts (Bao et al. 2013)	Prudent dietary pattern (Zhang, Schulze et al. 2006; Tryggvadottir et al. 2016)
Total fiber (Zhang, Liu, et al. 2006; Looman et al. 2018)	Cereal (Karamanos et al. 2014)	Mediterranean Diet Index (Karamanos et al. 2014)
Cereal fiber (Zhang, Liu, et al. 2006)	Potatoes (Karamanos et al. 2014, Goshtasebi et al. 2018)	alternate Mediterranean Diet (Tobias et al. 2012)
Fruit fiber (Zhang, Liu, et al. 2006)	Fruit juice (Looman et al. 2018)	Dietary Approaches to Stop Hypertension (Tobias et al. 2012)
Vegetable protein (Bao et al. 2013)	Fruit (Looman et al. 2018)	alternate Healthy Eating Index (Tobias et al. 2012, Gicevic et al. 2018)
Vitamin C (Zhang et al. 2004)		Healthy Eating Index (Tryggvadottir et al. 2016)
Vitamin D (Zhang et al. 2008)		Prime Diet Quality Score (Gicevic et al. 2018)
Non-heme iron (Darling et al. 2016)		

2.2.2 RANDOMIZED CONTROLLED TRIALS

Most of the randomized controlled trials including dietary intervention have reported no influence on GDM incidence after the intervention (Table 4). In contrast, Assaf-Balut et al. (2017) reported reduced incidence of GDM after a Mediterranean diet with additional extra virgin olive oil and pistachios (Assaf-Balut et al. 2017). Furthermore, also dietary supplementation with probiotics has been shown to lower the incidence of GDM (Luoto et al. 2010).

In a recent Cochrane Systematic Review, Tieu et al. (2017) assessed the influence of dietary interventions for preventing GDM and related adverse health outcomes (Table 4). Inclusion criteria were studies including dietary intervention only, randomized or quasi-randomized study design, any nutritional advice before GDM testing, available full-text manuscript, and no pre-existing type 1 or 2 diabetes among the participants. Based on the findings, the authors concluded that randomized clinical trials reporting on the influence of dietary intervention on GDM are at risk of numerous bias, and thus of very low quality (Tieu et al. 2017). Additionally, the authors conducted a meta-analysis including five trials and 1279 pregnant women receiving either dietary advice or standard antenatal care. The findings were non-significant, yet suggestive of a reduced GDM risk after the dietary intervention (RR 0.60, 95% CI 0.35 to 1.04; P = 0.07). Moreover, the authors observed no difference in GDM risk after nutritional counselling encouraging either a low-glycaemic index diet or a moderate-to high-glycaemic index diet (RR 0.91, 95% CI 0.63, 1.31). A detailed description of studies included in the meta-analyses of Tieu et al. (2017) is available in Table 4. Additionally, a description of a dietary intervention study (Assaf-Balut et al. 2017) published after the review by Tieu et al. (2017) is available in Table 4.

Moreover, numerous randomized controlled trials have reported on the incidence of GDM after combined diet and exercise intervention. Table 5 includes the description of 19 randomized controlled trials in the meta-analysis of Shepherd et al. (2017). Inclusion criteria for the studies in the meta-analysis were a randomized controlled or cluster-randomized controlled study design, comparison of combined dietary and exercise intervention with no intervention, and an outcome of GDM diagnosis. Based on the findings, Shepherd et al. (2017) concluded a possible reduction in GDM risk in the intervention group receiving diet and exercise advice compared with the standard care group, yet the results were non-significant (RR 0.85 95% CI 0.71 to 1.01; P = 0.07) (Shepherd et al. 2017). The included

studies were of moderate quality. Furthermore, in the lifestyle pilot for Vitamin D And Lifestyle Intervention for Gestational Diabetes Mellitus Prevention (DALI), Simmons et al. (2015) compared the influence of dietary advice with exercise advice on GDM incidence in pregnant women with a BMI ≥29 kg/m^2 (Simmons et al. 2015). Women receiving dietary counselling had a lower incidence of GDM in 35-37 weeks of gestation compared with those receiving exercise counselling (28% vs. 42%). The difference was non-significant, however (OR 0.67, 95% CI 0.25 to 1.75; P = 0.41).

A few controlled trials including combined dietary and physical activity intervention have succeeded to reduce the GDM risk (Koivusalo et al. 2016, Petrella et al. 2014, Bruno et al. 2017). In the study by Koivusalo et al. (2016) started in early pregnancy, 20 women (14%) in the intervention group and 27 (22%) women in the control group developed GDM (P = 0.097, unadjusted; P = 0.044, adjusted for age, BMI, a history of GDM, and gestational age during diagnostic OGTT) (Koivusalo et al. 2016). As for the dietary outcomes, changes in overall diet quality were assessed by the food-based Healthy Food Intake Index (HFII) developed for the RADIEL trial. Mean (95% CI) change in the HFII total score was 0.7 (95% CI 0.3 to 1.1) points in the intervention group and 0.3 (-0.01 to 0.7) points in the control group (P = 0.16, unadjusted; P = 0.037, adjusted for age, BMI, a history of GDM, gestational age, and baseline values).

When reporting the intervention effects in clinical trials, changes in diet should be described in more detail as dietary changes are usually variously or poorly reported (Shepherd et al. 2017). The characteristics of the participants and interventions may also vary significantly. Moreover, studies differ in criteria and tests to diagnose GDM, and several studies report primary outcomes other than GDM. Thus, the studies are not entirely comparable making the generalization of the results challenging. Therefore, more standardized reporting between the studies is required (Shepherd et al. 2017). Additionally, dietary advice provided already before pregnancy may be more beneficial regarding maternal and neonatal outcomes.

***Table 4**. Summary of dietary intervention trials reporting on the incidence of gestational diabetes mellitus in pregnant women (Tieu et al. 2017).*

Study	Country and study population*	Type and goals of intervention†	Criteria and time for GDM diagnosis as reported	Primary outcome	GDM incidence
Clapp 1998	USA; 20 women; 8 GW	LGI diet vs. HGI diet 35-45 kcal/kg of lean body mass; 55-60 % carbohydrate, 17-19% protein, 20-25% fat Carbohydrates from whole-grain, fruits, dairy products, etc. (LGI) Carbohydrates from highly processed grains, simple sugars, etc. (HGI)	OGTT; 28 GW	Pregnancy outcomes	HGI group 0% LGI group 0% *P* = NE
Moses et al. 2006	Australia; 70 women; age 21-40 y; 12-16 GW	5 counselling sessions with a Dietitian Low-sugar, high-fibre, moderate-to-high GI diet (HGI) vs. LGI diet	OGTT; 28 GW	Pregnancy outcomes	HGI group 3% LGI group 0% *P* = NS
Moses et al. 2014	Australia; 691 women; age ≥18 y; <20 GW	3 face-to-face sessions + 1 phone call session with a dietitian LGI vs. healthy eating (HE) diet Booklets with information on carbohydrate-rich foods (both groups) Suggested alternatives for relevant food choices (LGI group) General dietary counselling (HE group)	ADIPS+IADPSG	Pregnancy outcomes	HGI group 8% LGI group 8% *P* = NS
Quinlivan et al. 2011	Australia; 132 women; BMI ≥25 kg/m^2	Brief dietary counselling session with a food technologist at each antenatal visit	WHO‡	IGT+GDM	IGT+GDM: I group 6% C group 29% *P* = 0.043 (adjusted)

Continues.

Table 4 continued.

Thornton et al. 2009	USA; 257 women; BMI ≥30 kg/m²; 12-28 GW	≥1 counselling sessions with a dietitian; 18-24 kcal/kg; 40% carbohydrates, 30% protein, 30% fat from total energy intake	Medical records; after delivery	Perinatal outcomes	I group 10% C group 16% *P* = NS
Markovic et al. 2016	Australia; 147 women; age >18 y; ≥1 risk factors†; 12-20 GW	LGI diet vs. high-fibre, moderate GI diet 5 individual counselling sessions with a dietitian	ADIPS; at baseline and 26-28 GW	Pregnancy outcomes	LGI group 14% HF group 15% *P* = NS
Assaf-Balut et al. 2017	Spain; 1000 women; age ≥18 y; 12-14 GW	Mediterranean diet supplemented with EVOO and pistachios EVOO ≥40 ml/day Pistachios 20-30 g/day One group counselling session with a dietitian Walking ≥30min/day	IADPSG; 24-28 GW	GDM	I group 17% C group 23% *P* = 0.012 (unadjusted) *P* = 0.039 (adjusted)
Wolff et al. 2008	Denmark; 66 women; BMI ≥30 kg/m²; age 18-45 y	10 1-h counselling sessions 50-55% carbohydrate, 15-20% protein, 30% fat from total energy intake	50 g OGTT; FBG and 2-h glucose; cut-off values NR	GWG	I group 0% C group 10% *P* = NS
Laitinen et al. 2009	Finland; 256 women; <17 GW	3 counselling sessions with a dietitian; 3 diet groups: Diet with probiotics capsules Diet with placebo capsules Control diet	CC; 75 OGTT; FPG ≥4.8 mmol/L and 1-h glucose >10.0 mmol/L or 2-h glucose >8.7 mmol/L; only for women at GDM risk¶	Glucose metabolism	I group 36% C group 34% *P* = NS
Walsh et al. 2012	Ireland; age >18 y; <19 GW; previous macrosomic child	Two counselling sessions with a dietitian, booklets LGI diet; increased intake of LGI foods and decreased intake of HGI Foods	50 g OGTT; 1-h glucose ≥8.3 mmol/L; 100 g OGTT	Birth weight	I group 3% C group 5% *P* = NS

Continues.

Table 4 continued.

IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; FPG; fasting plasma glucose; FBG, fasting blood glucose; NR, not reported; ADIPS; Australasian Diabetes in Pregnancy Society; EVOO, extra-virgin olive oil; NE; not estimable; CC, Carpenter and Coustan criteria; LGI, low glycaemic index; HGI, high glycaemic index. *the number of randomized women and inclusion criteria. ‡2-h glucose >6.6 mmol/L for IGT and 2-h glucose >7.7 mmol/L for GDM in 75-g OGTT.†age >35 y, first-degree relative with type 2 diabetes, pre-pregnancy BMI ≥30 kg/m², history of GDM or glucose intolerance, a macrosomic child in a previous pregnancy, belonging to a high-risk ethnic group (Aboriginal or Torres Strait Islander, Polynesian, Middle Eastern, Indian, or Asian). ¶pre-pregnancy BMI >25 kg/m², age >40 y, previous GDM, a previous macrosomic child, detection of urinal glucose, or macrosomic fetus in the current pregnancy.

***Table 5**. A summary of combined diet and exercise intervention trials reporting on the incidence of gestational diabetes mellitus in pregnant women (Shepherd et al. 2017)*

Study	Country and study population*	Type and goals of intervention†	Criteria and timing for GDM diagnosis as reported	Primary outcome	GDM incidence
Bruno et al. 2017	Italy; 191 women; age >18 y; BMI ≥25 kg/m²; 9-12 GW	An individual counselling session with a dietitian Follow-up and feedback by a dietitian and a gynaecologist at 4 visits 1500 kcal/day 55% carbohydrates (80% LGI), 20% protein (50% animal, 50% vegetable), 25% fat (12 MUFA, 7% PUFA, 6% MUFA) from total energy intake Decreased consumption of foods with high GI and SFA content 30 min of moderate intensity exercise ≥3 times/wk	IADPSG criteria; 16-18 GW and 24-28 GW	GDM	I group 19% C group 37% *P* = 0.019 (unadjusted)
Dodd et al. 2014	Australia; 2012 women; BMI ≥25 kg/m²; 10-20 GW	Individual advise on diet, exercise, and behavioural change strategies provided by a research dietitian and trained research assistants at 3 face-to-face visits and 3 phone call sessions during pregnancy A balance of carbohydrate, protein, and fat; reduced intake of foods high in SFA and refined carbohydrates, increased intake of fibre; 2 servings of fruit, 5 servings of vegetables, and 3 servings of dairy per day An increased amount of walking and incidental activity	75-g OGTT; fasting glucose ≥5.5 mmol/L or 2-h glucose ≥7.8 mmol/L; timing NR	LGA	I group 14% C group 11% *P* = NS
Harrison et al. 2013	Australia; 228 women; BMI ≥25 kg/m²; BMI ≤23 kg/m² if high-risk ethnicity; women at high risk based on a validated prediction tool; 12-15 GW	Individual counselling on diet and exercise in 4 face-to-face sessions with an exercise physiologist Individual-specific goals for diet and exercise in 4 face-to-face sessions with an exercise physiologist Individual-specific goals for diet and exercise	ADIPS; IADPSG; at baseline and 28 GW	GWG	IADPSG criteria; I group 22% C group 33% *P* = NS

Continues.

Table 5 continued.

Herring et al. 2016	USA; 66 African American women; age >18 y; BMI 25-45 kg/m²; <20 GW	Technology-based dietary and exercise advice tailored through Facebook, phone, and text messages for low-income women Limited energy intake; limited use of sugar-sweetened beverages, 'junk' and high-fat foods, and limited portion sizes 5000 steps/day	Inpatient hospital records; after delivery	GWG	I group 4% C group 4% *P* = NS
A. Hui et al. 2012	Canada; 224 women; <26 GW	Exercise counselling provided in group sessions in community centres or by DVD at home 2 individually-tailored dietary counselling sessions with a dietitian Mild to moderate intensity exercise 3-5 times/wk	CDA; timing NR	GWG	I group 2% C group 3% *P* = NS
A. L. Hui et al. 2014	Canada; 113 women; <20 GW	Exercise counselling provided in group sessions in community centres or by DVD at home 2 individually-tailored dietary counselling sessions with a dietitian Mild to moderate exercise 3-5 times/wk	CDA; timing NR	GWG	BMI ≤24.9 kg/m²; I group 0% C group 0% *P* = NS BMI ≥25.0 kg/m²; I group 4% C group 10% *P* = NS
Jing et al. 2015	China; 262 women; age ≥18 y	Education manual and 2 individual counselling sessions with a trained graduate student Available support and feedback through telephone or instant messenger	NR	GDM, GWG	I group 23% C group 35% *P* = 0.043 (unadjusted)
Koivusalo et al. 2016	Finland; 492 women; age ≥18 y; previous GDM or BMI ≥30 kg/m²; <20 GW	One group counselling session with a dietitian 3 individual counselling sessions with a trained study nurse Increased intake of vegetables, fruits, berries, vegetable fats, whole grain, fish, low-fat meat, and low-fat dairy and reduced intake of sugar-rich foods Moderate intensity exercise ≥150 min/wk	75-g OGTT; FPG ≥5.3, 1-h glucose ≥10.0, and/or 2-h glucose ≥8.6 mmol/L; at baseline and 24-28 GW	GDM	I group 14% C group 22% *P* = 0.097 (unadjusted) *P* = 0.044 (adjusted)

Continues.

Table 5 continued.

Korpi-Hyövälti et al. 2012	Finland; 60 women; ≥1 risk factors: BMI >25 kg/m², previous GDM, previous macrosomic child, a family history of diabetes, fasting plasma glucose 4.8-5.5 mmol/L, 2-g OGTT glucose <7.8 mmol/L); 8-12 GW	6 individual dietary counselling sessions with a study nurse and 6 exercise counselling sessions with a physiotherapist Carbohydrate 50-55%, fat 30%, SFA <10%, and protein 15-20% of total energy intake, fibre 15 g/1000 kcal Diet rich in vegetables, berries, and fruits; use of low-fat dairy products, low-fat meat, soft margarine, vegetable oils, and whole-grain Products 30 or 45 min of daily exercise	75-g OGTT; FPG ≥5.6 and/or 2-g glucose ≥7.8 mmol/L; at baseline and 26-28 GW	Glucose tolerance	I group 11%, C group 4% *P* = NS
Luoto et al. 2011	Finland; 2271 women; ≥1 risk factors: BMI ≥25 kg/m², previous GDM or macrosomic child, age ≥40 y or family history of GDM; 8-12 GW	5 individual dietary and exercise counselling sessions with a study nurse ≤10% SFA, 5%–10% PUFA, 25%–30% fat, 10% saccharose of total energy intake and 25–35 g/d fiber ≥800 MET minutes/wk	75-g OGTT; FPG ≥5.3, 1-h glucose ≥10.0, and/or 2-h glucose ≥8.6 mmol/l; ; at baseline and 26-28 GW	GDM, LGA	I group 16% C group 12% *P* = 0.36 (unadjusted) *P* = 0.16 (adjusted)
Petrella et al. 2014	Italy; 63 women; age ≥18 y; BMI ≥25 kg/m²	2 counselling sessions with a dietitian and a gynaecologist Decreased consumption of high-glycaemic foods 1500 kcal/day; 55% carbohydrate (80% LGI), 20% protein (50% animal, 50% vegetable), 25% fat (12% MUFA, 7% PUFA, 6% SFA) from total energy intake 30 min of moderate intensity exercise ≥3 times/wk	ADA; 16-18 GW or 24-28 GW	GWG	I group 23% C group 57% *P* ≤0.01 (unadjusted) *P* = 0.014 (adjusted)
Phelan et al. 2011	USA; 401 women; age >18 y; BMI 19.8-40 kg/m²; 10-16 GW	One individual face-to-face counselling with an interventionist and 3 phone counselling sessions with a dietitian 20 kcal/kg, decreased intake of high-fat foods 30 min of walking in most days of the wk	Hospital records; after delivery	GWG	BMI 19.8-26.0 kg/m²: I group 9%, C group 8% *P* = NS

Continues.

Table 5 continued.

					BMI 26.1-40.0 kg/m²: I group 14% C group 8% *P* = NS
Polley et al. 2002	USA; 120 women; age ≥18 y; BMI ≥19.8 kg/m², <20 GW	Dietary and exercise counselling at standard clinical visits with masters or doctoral level personnel in nutrition or clinical physiology Bi-weekly education newsletters Decreased intake of high-fat foods, and substituting healthier alternatives, e.g., vegetables Increasing walking and developing a more active Lifestyle Monitoring via phone calls	NR	GWG	BMI 19.8-26.0 kg/m²: I group 0%, C group 6% *P* = NR BMI >26.1 kg/m²: I group 7%, C group 5% *P* = NR
Poston et al. 2013	UK; 183 women; BMI ≥30 kg/m²; 15-17 GW	One individual counselling session and 8 phone call sessions with a health trainer Low GI diet, reduced SFA intake by substituting with MUFA and PUFA Increased daily exercise, setting goals of incremental step counts	IADPSG criteria; 28 GW	Dietary and exercise changes	I group 28% C group 32% *P* = NS
Poston et al. 2015	UK; 1555 women; BMI ≥30 kg/m²; 15-18 GW	One individual counselling session and 8 phone call sessions with a health trainer Low GI diet, reduced SFA intake by substituting with MUFA and PUFA Increased daily exercise, setting goals of incremental step counts	IADPSG criteria; 27-28 GW	GDM, LGA	I group 25% C group 26% *P* = NS
Rauh et al. 2013	Germany; 356 women; age >18 y; BMI ≥18.5 kg/m²; <18 GW	2 individual dietary and exercise counselling sessions with a trained researcher Decreased intake of energy-dense and high-fat foods; increased intake of low-fat foods, vegetables, fruits, and whole-grain products; improved quality of dietary fat	German guidelines; 24-28 GW	GWG	GDM or IGT: I group 5% C group 12% *P* = NS

Continues.

Table 5 continued.

		30 min of moderate-intensity exercise in most days of the wk			
Sagedal et al. 2017	Norway; 606 women; age ≥18 y; BMI ≥19 kg/m²; ≤20 GW	Group exercise classes twice a week Moderate-intensity exercise 3 days/wk 2 dietary counselling sessions with a dietitian or graduate students Specific advice on portion sizes, regular meal patterns, limited use of snacks, and increased intake of fruits and vegetables	WHO criteria; 30 GW	GWG	I group 12% C group 9% *P* = NS
Vinter et al. 2011	Denmark; 360 women; age 18-40 y; BMI 30-45 kg/m²; 10-14 GW	4 individually-tailored dietary counselling sessions with a dietitian Free 6-month gym membership, weekly exercise classes with a physiotherapist, 4-6 group coaching sessions	75-g OGTT; 2-h glucose ≥9.0 mmol/L; at baseline, 28-30 GW and 34-36 GW	Obstetric and neonatal outcomes	I group 6% C group 5% *P* = NS
S. Wang et al. 2015	China; 299 women; ≥1 risk factors: age ≥35 y; BMI ≥25 kg/m², family history of diabetes; history of PCOS, previous GDM or macrosomic child	One group counselling session with a professional nutritional counsellor One group counselling session on exercise, and one on GWG with a physician	IADPSG; 24-28 GW	GDM	I group 17% C group 24% *P* = NS

BMI, body mass index; OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus; GW, gestational weeks; GWG, gestational weight gain; GI, glycaemic index; SFA, saturated fat; PUFA, polyunsaturated fat; not reported; I group, intervention group; C group, control group; NR, not reported; NS, non-significant; FPG, fasting plasma glucose; LGA, large-for-gestational-age; NW, normal weight; PCOS, polycystic ovary syndrome; MET, metabolic equivalent of task; IGT, impaired glucose tolerance; LGI, low glycaemic index; CDA, Canadian Diabetes Association criteria; IADPSG; International Association of Diabetes and Pregnancy Study Group; ADIPS, Australasian Diabetes in Pregnancy Society.
*the number of randomized women and inclusion criteria. ‡BMI before or during pregnancy; refers to each study. †control group received standard antenatal care in each study.

2.3 ROLE OF DIETARY COUNSELLING IN MODIFYING DIETS

Numerous clinical trials have found improvements in diets after maternal nutrition counselling, such as increased intakes of dietary fibre, fruits, and whole grains and decreased intakes of saturated fat, sugary food, and high-fat meat (Piirainen et al. 2006, Kinnunen et al. 2007, Guelinckx et al. 2010, Jackson et al. 2011, Korpi-Hyövälti et al. 2012, Kinnunen et al. 2014). However, more evidence is required of the possibilities of nutrition counselling to improve intervention effectiveness.

Evidence of dietary modification before pregnancy has mostly reported of the influence of interventions on folic acid supplementation (Temel et al. 2014). Weisman et al. (2011) studied the effect of pre- and interconceptional behavioural intervention on health-related outcomes in women living in low-income rural communities (Weisman et al. 2011). The authors observed increased use of multivitamin supplements containing folic acid, yet no influence on daily consumption of fruits and vegetables was found. Due to limited evidence, there is an urgent need for controlled trials investigating the influence of pre-pregnancy nutritional advice on dietary intakes other than folic acid to optimize the health of the mother and the child during pregnancy and later on.

Use of specific behaviour change techniques such as self-monitoring, setting goals, and providing feedback may help in modifying dietary habits (Michie et al. 2009, Dombrowski et al. 2010). However, the evaluation of the optimal form of counselling to improve diets is challenging due to the high variety in dietary intervention studies. A recent systematic review by Flynn et al. (2016) evaluated the content and delivery of 13 controlled trials to control weight gain and pregnancy outcomes in overweight and obese pregnant women (Flynn et al. 2016). The authors reported a wide variation in providers, intensity, and delivery type of the nutrition counselling as well as in reporting on the dietary outcomes making the comparison between the results difficult. In a systematic review by Greaves et al. (2011), the aim was to identify factors influencing the effectiveness of dietary and physical activity interventions in modifying diets and/or physical activity (Greaves et al. 2011). Combination of dietary and exercise counselling, use of clearly defined behaviour change techniques such as self-monitoring, and social support especially from family members increased the intervention effectiveness. Additionally, increased contact frequency was related to increased effectiveness. No relationship was found between the effectiveness and delivery mode, setting, or provider.

2.4 VITAMIN D STATUS, OBESITY, AND GLUCOSE METABOLISM

2.4.1 VITAMIN D METABOLISM

Vitamin D is a fat-soluble prohormone and vitamin originated from sunlight exposure, certain foods, and dietary supplements (Institute of Medicine et al. 2011). From the skin and intestine, vitamin D proceeds to circulation and is further transported to the liver by vitamin D binding protein (DBP). In the liver, vitamin D undergoes its first hydroxylation leading to the formation of the major circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D). Furthermore, 25(OH)D is transported from the liver to the kidney, and further hydroxylated to biologically active 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$) (calcitriol). Renal hydroxylation of 25(OH)D to $1,25(OH)_2D$ by 1α-hydroxylase (CYP27B1) is an essential phase in vitamin D metabolism and tightly regulated by concentrations of plasma parathyroid hormone, fibroblast growth factor 23, and serum calcium and phosphate. From the kidney, $1,25(OH)_2D$ passes to the circulation and is transported to target cells by DBP. In the cells, $1,25(OH)_2D$ binds to vitamin D receptor (VDR) activating an intracellular process in which vitamin D regulates the expression of vitamin D target genes via specific DNA sequences, vitamin D response elements (VDREs) (Institute of Medicine et al. 2011, Christakos et al. 2016).

Expression of 1α-hydroxylase (CYP27B1) and VDR has been recognized to occur also in extra-renal tissues and cells, such as in macrophages and osteoblasts (Adams et al. 2014, Turner et al. 2014) suggesting that $1,25(OH)_2D$ may influence several types of cells. However, in relation to overall $1,25(OH)_2D$ production, the contribution of extra-renal production is still unknown (Watson 2013).

2.4.2 GESTATIONAL VITAMIN D METABOLISM

Serum concentrations of $1,25(OH)_2D$ begin to increase in early pregnancy, and by the time of the third trimester, the concentrations are usually two to three times higher compared with non-pregnant women (Moller et al. 2013). Causes of the increased $1,25(OH)_2D$ concentrations are still poorly understood, however, according to some hypothesis, these may include increased renal production of 1α-hydroxylase (Kovacs, Kronenberg 1997). Contrary to $1,25(OH)_2D$, circulating 25(OH)D concentrations of the mother remain rather similar or fall slightly during pregnancy (Hillman et al. 1978, Ardawi et al. 1997). Sufficient maternal blood concentrations of 25(OH)D in pregnancy

ensure adequate 25(OH)D concentrations also in the fetus (Dror, Allen 2010). Maternal 25(OH)D passes placenta, and cord blood 25(OH)D concentrations have been reported to vary from 68 to 108% of maternal concentrations (Dror, Allen 2010). No evidence exists whether 25(OH)D concentrations should be higher in pregnant women compared with non-pregnant population.

2.4.3 VITAMIN D STATUS

Serum 25(OH)D concentrations are generally regarded as a marker of total vitamin D originated from cutaneous synthetization and dietary intake (Kabadi et al. 2012). The 25(OH)D concentrations are not tightly regulated, and the serum half-life of 25(OH)D is approximately three weeks whereas that of $1,25(OH)_2D$ is approximately 4 hours (Watson 2013). Criteria for vitamin D sufficiency, insufficiency, and deficiency vary as there is no consensus of the cut-off values, which are under debate. The Endocrine Society published the recommendations for cut-off values of 25(OH)D concentrations in 2011 for maximal musculoskeletal health; <50 nmol/L deficiency, 50 to 75 nmol/L insufficiency, and ≥75 nmol/L sufficiency (Holick et al. 2011). Additionally, the cut-off value of ≥75 nmol/L for sufficiency was also supported by the Endocrine Society's Practice Guidelines Committee after observing a reduced risk of falls at 25(OH)D concentrations of at least ≥75 nmol/L in a meta-analysis. In contrast, in an extensive review, Institute of Medicine (2011) reported a threshold of ≥50 nmol/L for vitamin D sufficiency for optimal bone health (Institute of Medicine et al. 2011).

Vitamin D deficiency and insufficiency is a global health concern (Holick 2017). In pregnant populations, the prevalence of vitamin D deficiency (defined as 25(OH)D concentrations <50 nmol/L) has been reported to range from 70 to 100% in Europe and from 27 to 91% in the USA (Holick 2017). Low 25(OH)D concentrations in pregnancy may increase the risk of several pregnancy and offspring complications, such as pre-eclampsia, caesarean section, and GDM in the mother as well as wheezing disorders, dental caries, and asthma in the children (Camargo et al. 2007, Erkkola et al. 2009, Merewood et al. 2009, Holick et al. 2011, Parlea et al. 2012, Hossein-Nezhad, Holick 2013, Ullah et al. 2013). Further, low serum 25(OH)D concentrations have been linked to several lifestyle-related and physiological factors, such as smoking, physical inactivity, obesity, ageing, pregnancy, dark skin pigmentation, avoidance of direct sun exposure, and living at high altitudes (Holick et al. 2011, Miettinen et al. 2014, Skaaby et al. 2016).

Few studies on maternal 25(OH)D concentrations conducted in Finland have reported the mean or median concentrations of <50 nmol/L (Kuoppala et al.

1986, Toriola et al. 2010, Munger et al. 2016). In these studies, however, blood samples were collected since 1983, after which vitamin D fortification for fluid dairy products and fat spreads started in 2003. The vitamin D fortification initiated in 2003 as well as doubling of the vitamin D fortification for these products since 2010 may have improved the maternal vitamin D status. For instance, Jääskeläinen et al. (2017) have demonstrated remarkable improvement in vitamin D status in the Finnish adult population when followed from 2000 to 2011 (Jääskeläinen et al. 2017). On the other hand, Viljakainen et al. (2010) observed mean 25(OH)D concentrations in early pregnancy of only 41.0 nmol/L among Finnish women (Viljakainen et al. 2010). However, in the study by Viljakainen et al. (2010), the blood samples were collected in 2007 which was before the doubling of vitamin D levels in fluid dairy products and fat spreads. With regard to maternal 25(OH)D concentrations in other European countries, a recent review reported highest mean 25(OH)D concentrations in Denmark (72 nmol/L) and lowest in the UK (15 nmol/L) (Saraf et al. 2016). However, studies differed widely in the year of implementation, design, and vitamin D definition methods.

2.4.4 VITAMIN D AND GLUCOSE-INSULIN METABOLISM

The best-known biological functions of vitamin D are to maintain bone health and calcium homeostasis. However, accumulating evidence exists of the role of vitamin D in non-skeletal health, such as in glucose-insulin metabolism (Parlea et al. 2012). In relation to T2D risk, results from two meta-analyses on longitudinal cohort studies have reported an inverse relationship between 25(OH)D concentrations and incident T2D (Song et al. 2013, Ye et al. 2015). Moreover, findings from cross-sectional data have mostly shown a positive relationship between serum 25(OH)D concentrations and insulin secretion and sensitivity (Orwoll et al. 1994, Boucher et al. 1995, Baynes et al. 1997, K. C. Chiu et al. 2004, Scragg et al. 2004, Kamycheva et al. 2007, Clifton-Bligh et al. 2008, Kayaniyil et al. 2010, Dutta et al. 2013, Heaney et al. 2013, Tepper et al. 2014). In the large NHANES study, an inverse relationship was observed between serum 25(OH)D concentrations and diabetes incidence and homeostatic model assessment of insulin resistance (HOMA-IR) (Scragg et al. 2004, Ford et al. 2005).

Studies on vitamin D supplementation in individuals with impaired fasting glucose, insulin resistance, and/or early diabetes have also reported improved pancreatic β-cell function and insulin sensitivity (von Hurst et al. 2010, Mitri et al. 2011, Naharci et al. 2012).

Abundant evidence exists on mechanisms through which vitamin D may beneficially influence glucose-insulin metabolism. Vitamin D may improve pancreatic β-cell function via direct and indirect effects on insulin secretion (Pittas et al. 2007). Factors supporting the direct influence of vitamin D on insulin secretion are the presence of VDRs (Johnson, Kumar 1994) and the expression of 1α-hydroxylase (Bland et al. 2004) in pancreatic β-cells, VDRE found in the human insulin gene promoter (Maestro et al. 2003), and transcriptional activation of the human insulin resistance gene (Maestro et al. 2002). Additionally, findings on impaired insulin secretion in vitamin D-deficient rats (Norman et al. 1980, Kadowaki, Tanaka et al. 1984, Norman 1984, Bourlon et al. 1999) or VDR-knockout rats (Zeitz et al. 2003), as well as the normalization of insulin secretion after vitamin D supplementation in animal studies (Tanaka et al. 1984, Cade, Norman 1987, Bourlon et al. 1999) support the direct influence of vitamin D on insulin secretion. Vitamin D may also increase insulin secretion indirectly via regulation of extra- and intracellular calcium concentrations and calcium flux through the β-cell membrane (Takiishi et al. 2012). Moreover, in addition to insulin secretion, vitamin D may influence insulin action in target tissues directly via VDRs in muscle tissues (Simpson et al. 1985), increasing insulin responsiveness to glucose transport by stimulating the expression of insulin receptor protein (Maestro et al. 2000, Maestro et al. 2002), or by activating a transcription factor, peroxisome proliferator-activated receptor-δ, in muscle and adipose tissue (Takiishi et al. 2012). Indirect effects on insulin action may occur via regulation of extracellular calcium concentrations (Takiishi et al. 2012).

Vitamin D has been suggested to influence insulin resistance also by its immunoregulatory effects through interfering the production and action of pro-inflammatory cytokines which have been observed to impair insulin signaling pathways (Kadowaki, Norman 1984, Johnson, Kumar 1994, Watson 2013, Garbossa, Folli 2017). Additionally, vitamin D may enhance insulin secretion from β-cells by increasing the formation of insulin from proinsulin (Takiishi et al. 2012, Watson 2013), or by stimulating pancreatic β-cell replication and increasing the resistance of β-cells to apoptosis (Watson 2013).

2.4.5 VITAMIN D AND GESTATIONAL DIABETES MELLITUS

Observational data have shown significant differences in maternal 25(OH)D concentrations between women with and without GDM (Clifton-Bligh et al. 2008, Soheilykhah et al. 2010, Parlea et al. 2012, Poel et al. 2012, M. X. Zhang et al. 2015), yet some studies have reported no differences (Farrant et al. 2009, Makgoba et al. 2011). Differences in study characteristics, such as in population, vitamin D measurement methods, or criteria for GDM diagnosis,

may in part explain the discrepancies between the study results (Joergensen et al. 2014).

Several studies have reported the beneficial influence of vitamin D supplementation on glucose metabolism in pregnant women with GDM (Asemi et al. 2013, Yazdchi et al. 2016, Q. Zhang et al. 2016). However, intervention studies on GDM incidence are sparse. In a study by Wagner et al. (2013) combining data from two clinical trials, vitamin D supplementation of daily dosage of either 50 or 100 μg showed no significant influence on GDM incidence (Wagner et al. 2013). On the other hand, in a recent meta-analysis including 793 pregnant women from three controlled trials, the authors observed a significant reduction in GDM incidence after vitamin D supplementation (Corcoy et al. 2018).

2.4.6 VITAMIN D, GLUCOSE-INSULIN METABOLISM, AND OBESITY

The inverse relationship between serum 25(OH)D concentrations and obesity is well-known (Brock et al. 2010, Jorde et al. 2010, Pereira-Santos et al. 2015) and proposed to result from the higher storage of vitamin D in adipose tissue (Wortsman et al. 2000). Obesity may modify the relationship between vitamin D and insulin resistance. Cross-sectional studies in non-pregnant adult populations suggest a stronger relationship between circulating 25(OH)D concentrations and glucose-insulin metabolism in overweight and obese individuals compared with normal-weight individuals (Hyppönen, Power 2006, Lu et al. 2009, Ou et al. 2011). Additionally, in the NHANES 2001-2006 study, obese participants with insufficient 25(OH)D concentrations (defined as <50 nmol/L) had higher risk for insulin resistance than obese participants with sufficient 25(OH)D concentrations (≥50 nmol/L) when compared with the reference group; normal weight participants with sufficient 25(OH)D concentrations (Kabadi et al. 2012).

The possible interaction of obesity and vitamin D on insulin resistance may partly be explained by decreased bioavailability of vitamin D due to higher vitamin D storage in adipose tissue. Lower bioavailability may attenuate the possible influence of vitamin D on pancreatic β-cell function or the activation of VDRs, which may further result in impaired glycaemic control (Pittas et al. 2007). Thus, obesity may interact with vitamin D to impact the risk of insulin resistance and T2D (Kabadi et al. 2012).

A recent meta-analysis on vitamin D supplementation in overweight and obese adults reported improvements in 25(OH)D concentrations; however, no influence on glucose and insulin metabolism was observed (Jamka et al. 2015).

In relation to GDM, in studies reporting on the association between vitamin D and GDM, body size has usually been taken into account only by adjusting for BMI whereas detailed examination is lacking.

2.5 LIPOPROTEIN PARTICLES AND DIET IN PREGNANCY

2.5.1 LIPID METABOLISM IN PREGNANCY

Maternal metabolism is altered remarkably during pregnancy to ensure normal fetal development and growth (Lain, Catalano 2007). Alterations in lipid metabolism are characterized by both anabolic and catabolic stages eventually leading to a more atherogenic lipid profile (Herrera 2000). The anabolic stage occurring in early pregnancy includes aggregation of fat and increase in lipid stores (Herrera, Ortega-Senovilla 2014) which are likely promoted by increase in energy intake (Murphy, Abrams 1993), elevated insulin concentrations, as well as unchanged or increased insulin sensitivity during early gestation leading to enhanced fatty acid production in adipose tissue. Simultaneously, increased activity of lipoprotein lipase (LPL), which promotes lipid storage, and decreased lipolysis in adipose tissue stimulates hydrolysis of circulating triacylglycerols (TAG) carried by chylomicrons and very low-density lipoprotein (VLDL) particles.

In late pregnancy, accumulated lipid stores start to break down leading to hyperlipidaemia (Herrera, Ortega-Senovilla 2014). The breakdown of lipid stores may result from increased placental hormone concentrations and insulin resistance leading to increased lipolysis of TAG in adipose tissue. TAG content in VLDL particles is increased substantially in late pregnancy due to increased hepatic TAG production and reduced TAG uptake from circulation because of lower LPL activity occurring in late gestation. In addition to VLDL particles, TAG is also aggregated in LDL and high-density lipoprotein (HDL) particles, although in lesser quantities. Additionally, pregnancy induces a reduction in LDL particle size and elevation in LDL and VLDL particle concentrations (Sattar et al. 1997, Hubel et al. 1998).

2.5.2 LIPID METABOLISM IN OBESITY, GESTATIONAL DIABETES MELLITUS, AND CARDIOVASCULAR DISEASE

Normally, insulin suppresses lipolysis in adipose tissue inhibiting the concentrations of circulating free fatty acids, which are known to promote insulin resistance (Boden 2003). However, in obesity, the insulin-induced

suppression of lipolysis occurs to a lesser extent resulting in elevated circulating FFA concentrations. In addition to elevated FFA concentrations, obesity is characterized by increased concentrations of TGA and small LDL particles as well as decreased concentrations of HDL-cholesterol (Krauss 2005). During gestation, pregnancy-induced insulin resistance and risk of pregnancy complications are increased among obese women, who have pre-existing abnormalities in glucose and lipid metabolism, compared with non-obese women (Catalano 2007, American Dietetic Association et al. 2009).

Women with a history of GDM may have a more unfavourable lipid profile as well as an increased risk of CVD in later life (Meyers-Seifer, Vohr 1996, Shah et al. 2008). Numerous studies have reported on higher concentrations of circulating TAG, total cholesterol, and LDL-cholesterol and lower concentrations of HDL-cholesterol in women with GDM compared with women without GDM, though the overall evidence is still inconsistent (Herrera, Ortega-Senovilla 2010, Ryckman et al. 2015). In a meta-analysis by Ryckman et al. (2015), circulating TGA levels were found to be higher in women with GDM compared with women without GDM (Ryckman et al. 2015). Furthermore, pregnancy results in attenuation in insulin-dependent suppression of lipolysis, which is exacerbated in GDM causing elevated increases in circulating FFA concentrations (Sivan et al. 1999, Xiang et al. 1999, Catalano, Kirwan 2001). Moreover, higher TAG and FFA concentrations in the presence of GDM have been linked to higher offspring birth weight, body mass, and fat mass (Schaefer-Graf et al. 2008, Herrera, Ortega-Senovilla 2010, Ortega-Senovilla et al. 2013).

Cardiovascular health evaluation related to circulating lipids is usually based on concentrations of TGA, total cholesterol, LDL-cholesterol, and HDL-cholesterol. In addition to standard lipids, additional lipoprotein parameters may help to improve the CVD risk assessment (Mora et al. 2009). One alternative method suggested is evaluating the concentration and size of lipoprotein particles and their subfractions by nuclear magnetic resonance (NMR) spectroscopy, which is feasible to use also in large populations (Annuzzi et al. 2012). According to findings from observational studies, total LDL particle concentration may be a stronger predictor of CVD compared with LDL-cholesterol concentrations (Kuller et al. 2002, Otvos et al. 2006, Cromwell et al. 2007, Mora et al. 2007, Mora et al. 2009). Furthermore, small and dense LDL particles are known to be more atherogenic compared with larger LDL particles as the affinity with LDL-receptors is lower, and they are more susceptible to oxidation (Berneis, Krauss 2002, Musunuru et al. 2009, Mora et al. 2011). Further, numerous studies have demonstrated that elevated concentrations and smaller size of LDL particles, elevated concentrations and larger size of VLDL particles as well as lower concentrations and smaller size of HDL particles may be associated with increased insulin resistance and a

higher risk of T2D and CVD (Garvey et al. 2003, Festa et al. 2005, Mora et al. 2009) in non-pregnant populations. Similarly, with regard to lipoprotein subfractions, higher concentrations of large VLDL particles and small HDL particles have been related to a more atherogenic lipoprotein profile (Freedman et al. 2004). A larger size of VLDL particles is regarded as more atherogenic as larger particles bind to macrophages in the arterial wall and are further transformed to small LDL particles (Berneis, Krauss 2002). Furthermore, larger maternal VLDL particle size has been linked to recurrent preterm birth and lower gestational age at delivery (Thorp et al. 2013, Grace et al. 2017). With regard to HDL particles, the anti-atherogenic function may be diminished with a reduction in particle size (Pascot et al. 2001) probably resulting from reduced protection against LDL oxidation (Rosenson et al. 2002). Additionally, a smaller size of HDL particles may illustrate excessive production of VLDL particles (Rosenson et al. 2002).

2.5.3 LIPOPROTEIN PARTICLE METABOLISM

Circulating lipoprotein particles consist of TGA, phospholipids, cholesterol esters, and apolipoproteins (Lee et al. 2003). Lipoprotein particles carry cholesterol and triglycerides in the circulation. VLDL particles produced by the liver are rich in TGA and transport fatty acids for storage and energy source to target tissues, such as adipose tissue and skeletal muscle. The release of fatty acids from VLDL particles results in the formation of LDL particles rich in cholesterol esters, which are relevant cell membrane components in target tissues.

Oxidized LDL particles are characterized as the primary factor contributing to the development of atherosclerosis. LDL particles enter the arterial wall, undergo oxidation, and are further ingested by macrophages which again produce cholesterol-rich foam cells. Eventually, the foam cells accumulate into the arterial wall leading to atherosclerotic plaque formation. In contrast to LDL particles, HDL particles in the artery wall may prevent or reverse the formation of plaque, for instance, by inhibiting the LDL particle oxidation and removing cholesterol from the foam cells (Jeyarajah et al. 2006). The cholesterol carried by HDL particles is transported to the liver to be further metabolized.

2.5.4 DIET IN RELATION TO CHOLESTEROL CONTENT IN LIPOPROTEIN PARTICLES

Diet is one of the modifiable factors related to cardiovascular health (Lloyd-Jones et al. 2010). Diets rich in vegetables, low-fat dairy, and monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids derived

from vegetables and fish, and low in saturated fatty acids (SFA), cholesterol, and red and processed meat are recommended to optimize cardiovascular health (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2002, Nordic Council of Ministers 2014).

Studies reporting on the relationship between lipoproteins and dietary intake among non-pregnant populations have generally focused on the cholesterol content of circulating lipoproteins suggesting a benefit of replacing SFA with unsaturated fat. For instance, substitution of MUFA for SFA has been linked to decreased total cholesterol and LDL-cholesterol concentrations (Berglund et al. 2007) whereas replacing SFA with PUFA has been related to improved total to HDL-cholesterol ratio (Mensink et al. 2003). On the other hand, in contrast to findings from the Seven Countries Study showing a positive correlation between total fat intake and mortality from coronary heart disease, recent observational evidence suggests that diets with low total fat content may not be beneficial for cardiovascular health (Hooper et al. 2012).

Individuals with genetic susceptibility to higher proportions of small, dense LDL particles may have a greater decrease in LDL-cholesterol in response to a low-fat, high-carbohydrate diet compared with those with higher proportions of large and medium-size LDL particles (Krauss 2005). Moreover, in a recent meta-analysis, low-carbohydrate diet increased the concentrations of HDL-cholesterol whereas no influence on total or LDL-cholesterol was found (Huntriss et al. 2018). With regard to n-3 PUFA, a recent meta-analysis including clinical trials showed no influence on total, LDL-, or HDL-cholesterol concentrations after n-3 PUFA supplement intervention (Y. Y. Zhang et al. 2017).

In a pooled analysis of clinical trials on nut intake and circulating lipids, daily consumption of 67 g of nuts resulted in reduced total and LDL-cholesterol concentrations (Sabate et al. 2010). The highest beneficial effect was observed in individuals with high baseline LDL-cholesterol concentrations and a low BMI as well as in those adhering to a Western dietary pattern. Further, substantial evidence exists for cholesterol-lowering effects of foods enriched with plant sterol esters and plant stanol esters (Gylling, Miettinen 1994, Gylling et al. 1997, Hallikainen, Sarkkinen, Gylling, et al. 2000, Hallikainen, Sarkkinen, and Uusitupa 2000).

Findings on the whole diet approach in relation to lipoprotein cholesterol concentrations are controversial. Higher adherence to a healthy Nordic diet may improve lipoprotein profiles by reducing the concentrations of total and LDL-cholesterol, although a simultaneous reduction in HDL-cholesterol concentrations has been observed (Adamsson et al. 2011). Similarly, in a meta-

analysis including data from three Finnish cross-sectional studies, higher adherence to the healthy Nordic Diet was related to lower HDL-cholesterol concentrations in women (Kanerva et al. 2014). No association with the healthy Nordic Diet and total or LDL-cholesterol concentrations was found. On the contrary, adherence to a Mediterranean diet has been reported to increase HDL-cholesterol (Chrysohoou et al. 2004, Mantzoros et al. 2006, Tzima et al. 2007).

Clinical and longitudinal studies on Dietary Approach to Stop Hypertension (DASH) diet have shown a reduction in VLDL- and LDL-cholesterol concentrations, as well as reduced or elevated HDL-cholesterol concentrations (Asemi et al. 2014, S. Chiu et al. 2016, Maddock et al. 2018). In a meta-analysis by Siervo et al. (2015) including 20 controlled trials, DASH diet was found to lower the concentrations of total and LDL-cholesterol, but no influence on HDL-cholesterol was found (Siervo et al. 2015). Participants with higher baseline blood pressure and a higher baseline BMI benefited the most from the intervention.

Compared with the evidence in non-pregnant populations, studies reporting on circulating lipid-diet associations during pregnancy are sparse. In a randomized controlled trial among healthy pregnant women, cholesterol-lowering diet favouring fatty fish, vegetable oils, and nuts resulted in reduced total, LDL-, and HDL-cholesterol concentrations (Khoury et al. 2005). On the other hand, in another randomized controlled trial including two dietary intervention groups and a control group, dietary counselling aiming to improve maternal diets towards dietary recommendations had no effect on circulating lipids during pregnancy (Hoppu et al. 2014). However, lower concentrations of total cholesterol and LDL-cholesterol were observed 12 months postpartum in the two dietary intervention groups compared with the control group. In terms of dietary glycaemic load, a lower increase in total cholesterol concentrations but no influence on HDL- or LDL-cholesterol concentrations were observed after a low-glycaemic-load diet intervention compared with low-fat diet intervention in overweight and obese pregnant women (Rhodes et al. 2010). In a cross-sectional study including 513 pregnant women, the group with the highest DASH diet scores had the lowest TAG concentrations at 26 to 29 gestational weeks (Martin et al. 2016). Moreover, higher adherence to a Fast Food and Candy-dietary pattern was associated with higher TAG concentrations throughout pregnancy in a prospective cohort study by Eshriqui et al. (2017). Additionally, in the same study, women with higher adherence to a Vegetable and Dairy-dietary pattern had higher HDL-cholesterol concentrations in the third trimester of pregnancy.

2.5.5 DIET IN RELATION TO LIPOPROTEIN PARTICLE CONCENTRATION AND SIZE

Several intervention studies in non-pregnant populations have investigated the effect of dietary patterns on lipoprotein particle size and concentrations by using NMR spectroscopy. Most studies on Mediterranean dietary pattern and lipoprotein profile have demonstrated larger LDL particle size after the intervention. In the PREvención con DIeta MEDiterránea (PREDIMED) study which included individuals at increased CVD risk, adherence to a Mediterranean diet supplemented with nuts led to increased LDL particle size, elevated concentrations of large LDL particles, reduced concentrations of medium-small and very-small LDL particles, and decreased LDL particle number (Damasceno et al. 2013). In another study including individuals at high CVD risk, a traditional Mediterranean diet resulted in increased LDL particle size (Hernaez et al. 2017). Furthermore, a diet supplemented with pistachios significantly reduced small LDL particle concentrations and decreased HDL particle size when compared with a nut-free diet in pre-diabetic individuals (Hernandez-Alonso et al. 2015). A Mediterranean-style low-glycaemic-load diet supplemented with phytochemicals resulted in decreased concentrations of large VLDL and small LDL particles when compared to the same diet without supplementation in women with metabolic syndrome (Jones et al. 2012). On the other hand, in comparison with a Swedish dietary pattern, Mediterranean diet showed no influence on LDL particle size in healthy subjects, yet there was a reduction in LDL-cholesterol concentrations (Ambring et al. 2004). Similarly, no influence on lipoprotein particle concentrations or size after combined Mediterranean diet and physical exercise intervention was observed in women with a BMI between 30-40 kg/m^2 (Rodriguez-Garcia et al. 2018).

In a recent randomized controlled trial in healthy individuals, a high-fat DASH diet led to a reduction in large and medium VLDL particle concentrations and larger LDL particle size when compared with the DASH diet (S. Chiu et al. 2016). Furthermore, in an observational study in normal- and overweight school children, total fructose intake was related to smaller LDL particle size independent of adiposity (Aeberli et al. 2007).

No study in humans has reported on the relationship between overall diet quality and lipoprotein particle size and concentrations in pregnancy. Furthermore, studies on the relationship between a typical Nordic diet and lipoprotein particle profiles are warranted.

2.5.6 SUMMARY OF PREVIOUS LITERATURE

The type and intensity of counselling, reporting of dietary outcomes, and population characteristics vary widely between the controlled trials including dietary advice for pregnant women. Further evidence is required to recognize the optimal forms of counselling to help the participants to reach the dietary guidelines during pregnancy. Different subgroups of pregnant women, such as those at increased risk for GDM, should also be taken into account to provide more personalized counselling and to improve the intervention efficiency. Moreover, controlled trials to prevent GDM often lack a detailed description of dietary changes. In terms of optimal timing of counselling, dietary and lifestyle intervention studies initiated already before conception are urgently needed. According to observational studies, healthy dietary patterns before and during pregnancy may lower the risk of GDM. However, results from randomized controlled studies reporting on GDM incidence after dietary counselling have been inconsistent.

Obesity is a risk factor for both low vitamin D status and GDM; however, detailed examination of the role of maternal body size in circulating vitamin D-GDM associations is lacking.

Studies on the association between diet and lipid metabolism show rather diverse results with no association or association with lipoprotein factors related to either protective or adverse markers of cardiovascular health. Thus, the relationship between circulating lipid response to diet appears to be complex, and the role of confounding factors in lipid response, such as genetics and lifestyle, requires further investigation. Interestingly, no publications are reporting on the role of whole diet quality in lipoprotein particle concentration and size during pregnancy. Therefore, further research is required to gain a deeper understanding of the potential of dietary modulation of lipoprotein metabolism. Additionally, no evidence exists on the relationship between dietary patterns especially in Nordic countries and lipoprotein particle concentration and size.

3 AIMS OF THE STUDY

The overall aims of this thesis were to describe dietary changes after lifestyle intervention and to evaluate the role of diet and obesity in metabolic markers during pregnancy. This thesis tested the hypotheses that 1) dietary intakes are improved in the group receiving lifestyle counselling compared with the control group and that 2) dietary changes and body mass index (BMI) are related to vitamin D, glucose, and lipoprotein metabolism during pregnancy in women at increased risk for gestational diabetes mellitus (GDM).

Specific aims of the study were as follows:

1. To investigate the differences in food intake changes from early to mid-pregnancy between intervention and control groups.

2. To evaluate whether BMI modifies the relationship between maternal serum vitamin D concentrations and risk of GDM.

3. To examine the differences in food intake changes from pre-pregnancy to early pregnancy between intervention and control groups, and the relationship between changes in food intake and the risk of GDM.

4. To determine the relationship between diet quality as assessed by the Healthy Food Intake Index and serum lipoprotein particle profiles during pregnancy.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN AND PARTICIPANTS

The studies included in this thesis were secondary analyses of the Finnish Gestational Diabetes Prevention Trial (RADIEL). The RADIEL trial was conducted between 2008 and 2014 in four maternity hospitals in Finland; Helsinki University Central Hospital, Kätilöopisto Maternity Hospital, Jorvi Hospital, and the South Karelia Central Hospital. Women aged 18 or above, and with a pre-pregnancy BMI ≥30 kg/m², or a history of GDM were recruited to the RADIEL trial either in early pregnancy (<20 gestational weeks) or when planning a pregnancy. Pregnant women were mainly recruited at the ultrasound screening visits in early pregnancy, and pre-pregnant women by personal invitation letters based on hospital registry of a history of GDM. Additional recruitment methods were announcements in newspapers, social media, and maternal clinics. Exclusion criteria included pre-existing diabetes, medication influencing glucose metabolism, multiple pregnancy, current substance abuse, severe psychiatric disorders, physical disability, or considerable communication difficulties such as limited Finnish language skills. Overall, 228 pre-pregnant women and 492 pregnant women were randomized into a control and an intervention group (Figure 3). Randomly permuted blocks were stratified by BMI ≥30 kg/m², a history of GDM, and center and used in the randomization.

In this thesis, baseline diagnosis of pre-existing T2D among pre-pregnant women was based on a pathologic value in both FPG (≥7.0 mmol/L) and glycated hemoglobin (HbA_{1c}) (≥48 mmol/mol) measurements, or a pathologic value in a 2-h OGTT (≥11.1 mmol/L). Data from both FPG and HbA_{1c} measurements were required to exclude possible T2D as only part of the T2D cases can be recognized based on either FPG or HbA_{1c} measurement alone (W. Wang et al. 2011). Further reasons for exclusion are reported in Figure 3.

Study I included only those women who entered the RADIEL study in early pregnancy and the study follow-up was conducted from early- to mid-pregnancy. Study III included only those women who entered the RADIEL study when planning a pregnancy and the participants were followed from pre-pregnancy to early pregnancy. Studies II and IV included women from both groups and were conducted between early and mid-pregnancy.

The study protocols were approved by the Ethics Committees of Helsinki University Central Hospital and the South-Karelia Central Hospital. The study was conducted according to the guidelines of the Declaration of Helsinki, and each procedure was approved by the Ethics Committees of Helsinki University Central Hospital and the South-Karelia Central Hospital. Written informed consent was received from all participants.

4.2 DIETARY AND PHYSICAL ACTIVITY INTERVENTION

The dietary intervention included two counselling sessions; one individual dietary and physical activity counselling session with a study nurse and one 2-h group counselling session with a dietitian. The pre-pregnancy study visits were conducted every three months before conception for women planning a pregnancy and in early, mid- and late pregnancy for all women. Dietary advice followed the contemporary Finnish Nutrition Recommendations (National Nutrition Council 2005) which were consistent with the NNR of that time (Nordic Council of Ministers 2004). The study nurse provided individual advice on gestational weight gain, physical activity, and healthy diets. When necessary, dietary changes were also discussed. After the first study visit in pre-pregnancy or early pregnancy, women participated in a dietitian-led, 2-h group session with six to eight participants. The group session consisted of general discussion about GWG, exercise, dietary glycaemic index, and healthy diets, as well examples of daily meals to reach the dietary aims. The aims of the dietary advice were to favor vegetables, fruits, berries, vegetable fats, whole grain, fish, and low-fat meat and dairy products, and to avoid sugar-rich foods.

In addition to dietary counselling, women in the intervention group also received individual counselling on physical activity at each study visit provided by a study nurse. The counselling session included discussion about the importance of physical activity in general and in preventing GDM, planning of individual exercise program by taking into account the possibilities of exercise in practice. For instance, in case the participant was severely obese, the lifestyle intervention focused more on dietary counselling with similar content as with the other participants. The aim of the physical activity intervention was at least 150 weekly minutes of exercise that makes one slightly out of breath or sweat. Additionally, daily exercise in any form of functional exercise was recommended, such as walking stairs or walking to a store.

The control group and the intervention group participated in the study visits at the same time points; before pregnancy and in early, mid-, and late pregnancy. The lifestyle counselling provided for women in the control group was similar to the standard antenatal counselling provided in the maternal clinics in Finland including general leaflets and discussion about healthy lifestyles.

In addition to study visits, the participants attended the standard visits at the maternal clinics.

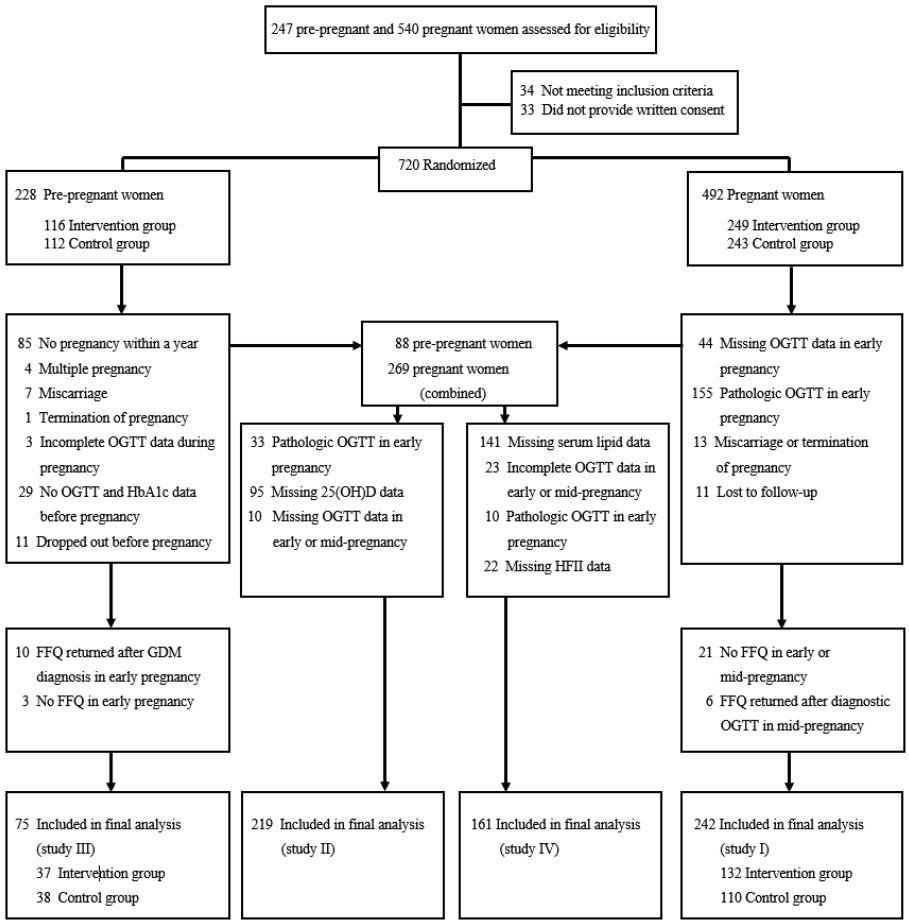

Figure 3. Flowchart of the participants in studies I-IV. OGTT, oral glucose tolerance test; 25(OH)D, 25-hydroxyvitamin D; HFII, Healthy Food Intake Index; FFQ, food frequency questionnaire; GDM, gestational diabetes mellitus.

4.3 MEASUREMENTS

Description of the data collection for dietary intakes and metabolic parameters in studies I-IV is available in Table 6.

Table 6. Dietary and metabolic data collection in studies I-IV.

	Study I	Study II	Study III	Study IV
Before pregnancy			FFQ Dietary record	
Early pregnancy	FFQ Dietary record	Serum 25(OH)D BMI	FFQ OGTT	FFQ Dietary record Lipoproteins
Mid-pregnancy	FFQ OGTT	Serum 25(OH)D OGTT		FFQ Lipoproteins
Primary Outcome	Change in food intake	GDM	Change in food intake GDM	Lipoproteins

FFQ, food frequency questionnaire; OGTT, oral glucose tolerance test; 25(OH)D; 25-hydroxyvitamin D; GDM, gestational diabetes mellitus; BMI, body mass index.
FFQ data in study IV were used in the development of the Healthy Food Intake Index.

4.3.1 DIETARY RECORD

Data obtained from 3-day dietary records were used in studies I, III, and IV. The dietary record data used in study I and IV were collected at early-pregnancy study visit whereas the data used in study III were collected at the first pre-pregnancy study visit. In study IV, dietary record data were used to report on energy and total fat intakes at baseline. The participants completed the dietary record and returned it at the study visit. Instructions on completing the dietary records were to provide a detailed description of the daily foods and drinks consumed for three consecutive days including two working days and one weekend day. Two nutritionists entered the dietary record data into the food calculation software AivoDiet (Aivo Ltd, Turku, Finland), which uses the Fineli Finnish Food Composition Database (National Institute for Health and Welfare, Nutrition Unit, Helsinki, Finland).

4.3.2 FOOD FREQUENCY QUESTIONNAIRE (FFQ)

Studies I, III, and IV included measurements based a non-validated, 48-item food frequency questionnaire (FFQ) which was formed to evaluate food intakes in the RADIEL study. The participants returned the completed questionnaire at each study visit. The food intakes were followed from early to mid-pregnancy in study I and IV (Table 6). In study III, changes in food intakes were followed from pre-pregnancy only until early pregnancy as most of the GDM cases (54%) were diagnosed already in early pregnancy, and lifestyle counselling received after GDM diagnosis may again influence food intakes.

In the FFQ, information on the current frequency of consumption of foods and food groups was requested, the options ranging from 'rarely or never' to '4 or more times/day'. Rarely referred to a frequency of consumption of less than once a week. The food components evaluated in this thesis were low-fat milk (≤1% fat), low-fat cheese (≤17% fat), whole grain cereals, fruits and berries, vegetables and legumes, fish, animal protein, sugar-sweetened beverages, snacks, and fast food. In addition to the FFQ evaluation, two fat scores were formed based on separate questions of the type of spreadable and cooking fats usually consumed. Further description of the foods and food groups based on the FFQ and scoring of the fat scores are available in Table 7, except for animal protein. Foods included in the category of animal protein were meat, poultry, egg, and organ meats.

4.3.3 HEALTHY FOOD INTAKE INDEX (HFII)

In study IV, the overall diet quality was assessed by the HFII. The HFII was developed to evaluate the overall diet quality based on the adherence to the NNR. In a previous study, higher scores in the HFII were associated with nutrient intakes closer to the nutrition recommendations indicating that the HFII is valid in ranking the participants according to their adherence to the NNR (Meinilä et al. 2016). Foods for the HFII were selected from the FFQ and further combined into 11 food groups which were relevant according to the NNR: low-fat milk, low-fat cheese, vegetables and legumes, fruits and berries, whole grain, fish, snacks, fast food, sugar-sweetened beverages, cooking fat, and spreadable fat (Table 7). The type of spreadable and cooking fats was evaluated based on separate questions in the questionnaire; "What type of fat do you normally use on bread/for cooking?" Relevance in the overall diet defined the maximum score of each food group. The points in the HFII score ranged between 0 and 17, and the higher total score reflected higher diet quality (Table 7).

4.3.4 25-HYDROXYVITAMIN D

In study II, serum 25(OH)D concentrations were evaluated in early and mid-pregnancy by using a chemiluminescence method with commercial IDS-iSYS 25-Hydroxy Vitamin D-assay (Immunodiagnostic Systems Ltd, UK, Boldon). The intra- and inter-assay coefficients for the measurement method of serum 25(OH)D concentrations were 5.8% and 7.9%, respectively. The method shows a 3% positive bias from all laboratory trimmed mean values and a 10% positive bias in comparison to standards of National Institute of Standards and Technology in international comparisons (Carter 2011).

4.3.5 LIPOPROTEIN PARTICLES

Measurements of circulating lipoprotein particles in study IV were conducted by using a high-throughput serum nuclear magnetic resonance (NMR) spectrometry. In terms of metabolic profiling, NMR is a quick, inexpensive, and reproducible technique based on molecule-specific signals (Soininen et al. 2015). NMR is suitable for lipoprotein quantification (Ala-Korpela et al. 1994, Mallol et al. 2013, Mihaleva et al. 2014) and has been used in several epidemiological studies (Kettunen et al. 2012, Wurtz et al. 2012, Kujala et al. 2013, Wurtz et al. 2014).

Twelve-hour fasting blood was drawn during the study visits by a study nurse. Blood samples were frozen for up to 2 hours in blood collection tubes and centrifuged afterwards with 2540 RCF (relative centrifugal force) for 15 minutes in 4°C. Before the analysis, serum samples were stored at −80 °C. Lipoprotein parameters included fasting serum concentrations and size of HDL, LDL, and VLDL particles.

Less atherogenic forms of HDL, LDL, and VLDL particles were defined as higher concentration and larger size of HDL particles, lower concentration and larger size of LDL particles, and lower concentration and smaller size of VLDL particles. Larger LDL particle size was considered favorable as small and medium LDL particles are more strongly associated with CVD risk (St-Pierre et al. 2005, Musunuru et al. 2009, Williams et al. 2014).

4.3.6 BACKGROUND CHARACTERISTICS AND CONFOUNDERS

Data on background characteristics including age, weeks of gestation, educational attainment, previous deliveries, a history of GDM, and parental history of diseases were collected by a self-administered questionnaire. Years

of education were based on the highest level of education. A study nurse performed anthropometric measurements at each study visit. Body weight was measured with scales while wearing light clothing and no shoes. Blood pressure from the right arm was measured by using a sphygmomanometer in a sitting position. BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2).

Evaluation of the amount of physical activity was self-reported and based on a single question in the questionnaire: 'How many minutes per week approximately do you exercise that makes you at least slightly out of breath and sweat?'

All laboratory measurements were performed in the Helsinki University Hospital laboratory (HUSLAB). The following methods were used; enzymatic hexokinase assay (Roche Diagnostics, Gluco-quant, Modular analyser) for fasting plasma glucose, electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Insulin, Modular analyser) for fasting insulin, a high sensitive assay with Immunoturbidimetric latex enhanced assay (Roche Diagnostics, CRPHS Tina-Quant Cardiac C-reactive protein (Latex) Modular analyser) for serum high-sensitivity C-reactive protein (hs-CRP), and immunoturbidimetric analyser (Roche Diagnostics, Tinaquant Hemoglobin A1C Gen.2 Integra800 analyser) for HbA1c. HOMA-IR was calculated as [fasting insulin (mU/l) × fasting glucose (mmol/l))/22.5].

Standard lipid measurements included concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. The measurement methods used were as follows: enzymatic assay (Roche Diagnostics, Cholesterol CHOD-PAP, Modular analyser) for total cholesterol, enzymatic assay (Roche Diagnostics, LDL-C plus 2nd generation, Modular analyser) for LDL cholesterol, enzymatic assay (Roche Diagnostics, HDL-C plus 3rd generation, Modular analyser) for HDL cholesterol, and enzymatic assay (Roche Diagnostics TG Triglycerides GPO-PAP, Modular analyser) for TGA.

Table 7. Description of the Healthy Food Intake Index (HFII) (Meinilä et al. 2016).

Food group	Cut-off values*	Scoring
Low-fat milk		0-2
	≤1% fat	2
	≤1% fat and >1% fat	1
	>1% fat or no milk	0
Low-fat cheese		0-1
	≤17% fat	1
	>17% fat or no cheese	0
Vegetables and legumes		0-2
	>2 times / day	2
	1-2 times / day	1
	Less than once / day	0
Fruits and berries		0-1
	Once or more / day	1
	Less than once / day	0
Whole grain		0-2
- Rye bread	≥3 times / day	2
- Porridge	1-2 times / day	1
- Brown rice and pasta	Less than once / day	0
Fish		0 or 2
	Once or more / week	2
	Less than once / week	0
Snacks		0-2
- Candy	≤4 times / week	2
- Chocolate	5-6 times / week	1
- Pastries	Once or more / day	0
- Chips		
- Ice cream		
Fast food		0-1
- Hamburger	Less than once / week	1
- Pizza	Once or more / week	0
Sugar-sweetened beverages		0-1
- Sugar-sweetened juice	Less than once / week	1
- Sugar-sweetened soft drink	Once or more / week	0

Continues.

Table 7 continued.

Cooking fat		0-1
	Vegetable oil, margarine, liquid margarine, or no cooking fat	1
	Butter, butter-oil mix, or baking margarine	0
Fat spread		0-2
	Margarine or low-fat margarine	2
	Sterol margarine	1
	Butter, butter-oil mix, or no spreadable fat	0

*Cut-off values are based on the numeric guidelines in the Nordic Nutrition Recommendations, Finnish Nutrition Recommendations, or decisions by Consensus Panel including four nutritionists. Cut-off values are reported as a frequency of daily or weekly consumption, except for milk and cheese based on fat content and cut-off values for cooking fat and fat spread based on the type of fat.

4.3.7 DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS

Fresh blood samples were used in GDM diagnosis. The diagnosis was based on at least one pathological glucose value in a 2-h 75 g OGTT. The following thresholds were applied; fasting glucose ≥5.3 mmol/l, 1-h glucose ≥10.0 mmol/l, and/or 2-h glucose ≥8.6 mmol/l (American Diabetes Association 2008). The OGTT was conducted in early pregnancy (5–20 wk in this thesis) and mid-pregnancy (22–30 wk).

4.3.8 STATISTICAL METHODS

Baseline characteristics in all studies (I-IV) are reported as mean (standard deviation, SD), the number of participants (n) with percentages, or median and interquartile range (IQR).

Studies I and III included assessment of differences in food intake changes between the intervention and control groups. Differences in baseline characteristics between the groups were evaluated by using Student's *t*-test for continuous variables and Pearson's chi-square test for categorical variables. Group comparisons for baseline-adjusted changes in food intakes were performed by using bootstrap-type analysis of covariance (ANCOVA) with 5000 replications. The bootstrap method is useful in the case of violation of the assumptions, such as non-normality, or when the theoretical distribution of the test statistic is unknown. Changes in food intakes were

adjusted by baseline values of each participant to exclude the possibility that the results would be affected by imbalance in individual baseline values. In study III, the intervention and control groups were further combined, and bootstrap-type ANCOVA was used to evaluate changes in food intakes according to GDM status. Adjustments included baseline food intakes, BMI, physical activity, duration of the follow-up, family history of diabetes, age, and the assignment group. No correction was performed for multiple comparisons in studies I or III. However, the information on multiple comparisons can be obtained by multiplying the actual *P* value by the number of comparisons made.

In study II, women were stratified into groups by early-pregnancy BMI; <25.0, 25.0–29.9, 30.0–34.9, and ≥35 kg/m². Statistical significance for hypotheses of linearity across BMI groups was generated by using analysis of variance (ANOVA) for continuous variables and Cochran–Armitage test for categorical variables. Percentage change in 25(OH)D concentrations from early to mid-pregnancy according to GDM status were evaluated by using ANCOVA and adjusted for baseline values, the assignment group, season, and change in overall diet quality based on the HFII, physical activity, and weight. Correlation coefficients between percentage change in 25(OH)D concentrations and area under the curve (AUC) of mid-pregnancy OGTT were calculated by the Pearson method. The total and incremental AUCs for OGTT (fasting, 1-h, and 2-h glucose concentrations) were generated by using the trapezoidal method. The bootstrap-type test was used if the assumptions were violated. All women in the BMI group <25.0 kg/m² (n = 43) and almost all women in the BMI group 25.0–29.9 kg/m² (*n* = 30, 88%) had a history of GDM. The adjustments for a history of GDM were thus performed only in the BMI groups 30.0–34.9 and ≥35 kg/m². In the BMI group 25.0–29.9 kg/m², four women had a BMI ≥30 kg/m² before pregnancy. However, these women lost weight until early pregnancy and were therefore included in the BMI group 25.0–29.9 kg/m².

In study IV, the women were stratified into groups by the early-pregnancy HFII score by using cut-off limits at ±1 standard deviation from the mean. The cut-off values for the three groups were as follows: 0-7, 8-12, 13-17. Residual change in the HFII and circulating lipoprotein particles from early to mid-pregnancy was calculated by regressing the mid-pregnancy values onto the early-pregnancy values. The residual change indicates the amount of change independent of the baseline value. Covariates based on previous literature were gestational age at blood sampling, BMI, years of education, age, and physical activity. Additional covariates were the allocation group, GWG, and the study group. The study group indicates whether the participants entered the RADIEL trial before or during pregnancy. The models used in the analyses

were as follows: unadjusted model (model 1); a model adjusted for age, BMI, gestational age, and years of education (model 2); a model adjusted for the covariates in model 2 and physical activity (model 3); and a model adjusted for the covariates in model 2, the allocation group, and the study group (model 4). When analyzing the change in the HFII and change in lipid parameters, gestational weight gain was added in model 4 as one of the covariates. Results for model 3 including adjustment for physical activity were reported separately as the data for physical activity was available only for 145 women at baseline. The normal distribution of the variables was tested by using the Shapiro–Wilk W-test. The bootstrap method was used in case of unknown theoretical distribution of the test statistics or violation of the assumptions such as non-normality. Effect size in study IV was estimated by using the method of Cohen in which correlation coefficient (r) = 0.1 is considered a small effect size, r = 0.3 a medium effect size, and r = 0.5 a large effect size (Cohen 1988).

All analyses were performed by using STATA versions 13.1, 14.0, and 14.1, StataCorp LP (College Station, TX, USA) statistical package, except for baseline analyses in study I in which Statistical Package for the Social Sciences (SPSS for Windows, release 22, IBM Corp., Armonk, NY, USA) was used. The level of significance was $P<0.05$ in all studies (I-IV).

5 RESULTS

5.1 CHANGES IN FOOD INTAKE FROM EARLY TO MID-PREGNANCY (STUDY I)

In study I, the objective was to describe the differences in food intake changes between the intervention and control groups from early to mid-pregnancy. Previously, Koivusalo et al. (2016) have reported on the differences in changes in the overall diet quality by using the HFII after lifestyle counselling initiated in early pregnancy in the RADIEL trial (Koivusalo et al. 2016). Total HFII score improved in the intervention group compared with the control group.

5.1.1 CHARACTERISTICS OF THE PARTICIPANTS

The participants consisted of 242 women who entered the RADIEL trial during pregnancy and who had available food intake data in early and mid-pregnancy. In total, 60 (25%) women had a pre-pregnancy BMI ≥30 kg/m^2, 162 (67%) women had a history of GDM, and 20 (8%) women had both risk factors. Characteristics of the participants included in the final analyses are presented in Table 8. There were no differences in demographic, metabolic, or dietary characteristics between the intervention (n = 132) and the control (n = 110) groups.

5.1.2 BETWEEN-GROUP DIFFERENCES IN FOOD INTAKE

Baseline food intakes and change in food intakes in the intervention and control groups in study I are shown in Table 9. No differences in baseline food intakes were observed in between-group comparisons ($P > 0.05$ for all). The mean (range) follow-up for changes in food intake from early to mid-pregnancy was 10 (6 to 17) weeks; 10 (6 to 16) weeks in the control group and 10 (6 to 17) weeks in the intervention group ($P = 0.366$), respectively. During the follow-up, daily intake of low-fat cheese and weekly intake of fish increased in the intervention group compared with the control group when adjusted for baseline values (Table 9). In further analyses, no between-group difference in change in the regular-fat cheese intake was observed ($P = 0.306$) (Valkama et al. unpublished results).

Table 8. Characteristics of the participants in early pregnancy in study I.
(n = 242 unless otherwise stated)

	Intervention n = *132* Mean (SD)	Control n = *110* Mean (SD)	*P**
Pre-pregnancy weight, kg	87.0 (18.0)	88.7 (16.7)	0.468
Pre-pregnancy BMI, kg/m²	31.3 (5.8)	32.0 (5.6)	0.340
Age, years	32.4 (4.8)	32.6 (4.6)	0.732
Nutrient intake‡			
Energy, kcal/d	1885.5 (446.5)	1916.6 (447.3)	0.608
Protein, E%	17.7 (3.1)	18.0 (3.4)	0.480
Carbohydrates, E%	45.8 (6.2)	45.1 (5.7)	0.425
Total fat, E%	33.1 (6.1)	33.4 (5.9)	0.693
Saturated fat, E%	12.1 (3.1)	12.3 (3.0)	0.733
Sugar, E%	9.0 (3.7)	9.0 (4.1)	0.884
Fibre, g/MJ	2.9 (0.8)	2.9 (0.9)	0.926
Folic acid, µg/d	524.3 (268.8)	508.8 (238.2)	0.653
Vitamin D, µg/d	13.9 (7.9)	13.7 (6.9)	0.862
Calcium, mg/d	1216.2 (431.1)	1311.3 (354.1)	0.079
	n (%)	n (%)	*P**
A history of GDM			0.609
No	31 (24)	29 (26)	
Yes	45 (34)	31 (28)	
Nullipara	56 (42)	50 (46)	
Highest education†			0.226
Basic or secondary education	58 (44)	39 (36)	
Polytechnic education	33 (25)	38 (35)	
Academic education	40 (31)	32 (29)	
Parental history of diabetes§	29 (23)	24 (22)	0.937
Current smoker	5 (4)	3 (3)	0.366

GDM, gestational diabetes mellitus; BMI, body mass index; SD, standard deviation; E%, % of total energy; MJ, megajoule.

**P* for between-group difference generated by Student's t-test or Pearson's Chi-square.

‡Vitamins and minerals are reported as total intake. n = 121 in the intervention group and n = 100 in the control group.

†n = 131 in the intervention group and n = 109 in the control group.

§Type 1 or type 2 diabetes in one or both parents. n = 128 in the intervention group and 108 in the control group.

Table 9. Change in food intakes from early to mid-pregnancy in the control (n = 110) and intervention (n = 132) groups in study I.

Food/food group	Baseline*	Mean change (95% CI)	*P*‡
Low-fat milk, times/day			0.726
Intervention	1.27 (1.30)	0.10 (-0.07, 0.28)	
Control	1.26 (1.11)	0.14 (-0.02, 0.29)	
Low-fat cheese, times/day			0.040
Intervention	0.84 (0.97)	0.09 (0.07, 0.24)	
Control	0.93 (1.02)	-0.14 (-0.30, 0.01)	
Whole-grain cereals, times/day			0.182
Intervention	2.10 (1.41)	0.08 (-0.17, 0.33)	
Control	2.14 (1.29)	-0.13 (-0.33, 0.07)	
Fruits and berries, times/day			0.865
Intervention	1.45 (1.08)	-0.03 (-0.22, 0.15)	
Control	1.40 (1.03)	-0.03 (-0.20, 0.14)	
Vegetables and legumes, times/day			0.419
Intervention	1.49 (1.04)	-0.01 (-0.20, 0.18)	
Control	1.37 (1.11)	-0.02 (-0.21, 0.17)	
Fish, times/week			0.011
Intervention	1.55 (1.36)	0.28 (0.08, 0.49)	
Control	1.35 (1.50)	0.06 (-0.21, 0.34)	
Animal protein†, times/day			0.658
Intervention	1.18 (0.89)	-0.16 (-0.30, -0.02)	
Control	1.17 (0.75)	-0.18 (-0.30, -0.06)	
Snacks§, times/week			0.112
Intervention	6.37 (4.39)	0.21 (-0.57, 0.99)	
Control	6.62 (6.15)	0.94 (-0.03, 1.90)	
Sugar-sweetened beverages¶, times/week			0.750
Intervention	2.23 (3.91)	-0.64 (-1.18, -0.10)	
Control	2.50 (5.71)	-0.95 (-1.95, 0.05)	
Fast foodΔ, times/week			0.731
Intervention	0.85 (1.25)	-0.04 (-0.22, 0.13)	
Control	1.07 (1.42)	-0.21 (-0.41, -0.01)	
Cooking fat, score#			0.937
Intervention	0.88 (0.33)	0.02 (-0.03, 0.07)	
Control	0.83 (0.38)	0.05 (-0.00, 0.09)	
Spread fat, scoreω			0.103
Intervention	1.33 (0.92)	0.22 (0.11, 0.33)	
Control	1.15 (0.98)	0.15 (0.02, 0.30)	

CI, confidence interval.

Continues.

Table 9 continued.
*Mean (standard deviation).
‡P for between-group difference tested by bootstrap-type analysis of covariance adjusted for baseline value.
†Red meat, poultry, organ meats, and egg.
§Pastries, candy, ice cream, chocolate, and chips.
¶Sugar-sweetened soft drinks and juice.
ΔHamburger and pizza.
#Score range 0-1: cooking oil, regular margarine, bottled margarine, or no cooking fat 1 point; butter, butter-vegetable oil mixture, or hard margarine 0 points.
ωScore range 0-2: regular or low-fat margarine 2 points; sterol margarine 1 point; butter, butter-vegetable oil mixture, or no spread fat 0 points.

5.2 SERUM 25-HYDROXYVITAMIN D, BODY SIZE, AND RISK OF GESTATIONAL DIABETES MELLITUS (STUDY II)

5.2.1 CHARACTERISTICS OF THE PARTICIPANTS

Study II included 219 pregnant women followed from early to mid-pregnancy. Overall, 123 (56%) women had a pre-pregnancy BMI ≥30 kg/m², 73 (33%) women had a history of GDM, and 23 (11%) women had both risk factors. Characteristics in early pregnancy across the BMI groups are available in Table 10. BMI was positively associated with blood pressure, LDL-cholesterol, fasting insulin, HOMA-IR, hs-CRP, and the prevalence of vitamin D deficiency (serum 25(OH)D <50 nmol/l), and inversely associated with concentrations of HDL-cholesterol and serum 25(OH)D. Furthermore, women with a higher early-pregnancy BMI were less likely to have an academic degree, previous deliveries, and a history of GDM.

Table 10. Characteristics of the participants in study II according to body mass index (BMI) in early pregnancy.
(n = 219 unless otherwise stated)

	BMI (kg/m²)				
	<25.0	25.0-29.9	30.0-34.9	≥35.0	
	n = 43	n = 34	n = 84	n = 58	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*P**
Age, years	33.0 (3.9)	33.2 (3.6)	31.7 (4.7)	31.4 (4.3)	0.052
Gestational age, weeks	12.7 (1.7)	13.1 (2.1)	13.3 (1.7)	13.4 (2.1)	0.064
Blood pressure, mmHg (n 215)					
Systolic	115 (10)	118 (13)	123 (14)	127 (12)	<0.001
Diastolic	72 (8)	73 (7)	79 (9)	81 (8)	<0.001
Total cholesterol, mmol/l (n 201)	4.79 (0.80)	4.87 (1.06)	4.96 (0.90)	5.01 (0.76)	0.157
HDL-cholesterol, mmol/l (n 201)	1.89 (0.25)	1.68 (0.32)	1.75 (0.33)	1.67 (0.28)	0.002
LDL-cholesterol, mmol/l (n 201)	2.62 (0.68)	2.79 (0.88)	2.82 (0.83)	2.91 (0.58)	0.035
Total triglycerides, mmol/l (n 200)	1.02 (0.37)	1.30 (0.64)	1.38 (0.51)	1.51 (0.92)	<0.001
Fasting plasma glucose, mmol/l	4.79 (0.32)	4.97 (0.21)	4.85 (0.24)	4.90 (0.22)	0.559
1-h glucose, mmol/l	7.18 (1.55)	7.31 (1.53)	6.80 (1.34)	7.09 (1.07)	0.415
2-h glucose, mmol/l	5.90 (1.25)	5.78 (1.03)	5.76 (1.03)	5.90 (1.04)	0.600
HbA1c, % (n 190)	5.26 (0.23)	5.24 (0.24)	5.22 (0.32)	5.23 (0.23)	0.662
Fasting insulin, mU/l (n 200)	5.47 (4.46)	5.79 (2.74)	9.78 (9.41)	10.85 (4.46)	<0.001
HOMA-IR† (n 190)	1.19 (0.97)	1.26 (0.67)	2.10 (2.08)	2.38 (1.04)	<0.001
hs-CRP, mg/l (n 216)	4.09 (4.50)	5.33 (4.79)	6.82 (4.36)	10.26 (5.67)	<0.001
HFII score (n 193)	11.1 (2.7)	10.2 (3.0)	9.9 (2.6)	10.1 (2.9)	0.112
25(OH)D, nmol/l	74 (23)	73 (32)	64 (24)	57 (22)	<0.001

Continues.

Table 10 continued.

	n (%)	n (%)	n (%)	n (%)	*P**
Educational attainment (n 216)					0.027
No education/vocational school	14 (33)	13 (39)	34 (41)	27 (47)	
Vocational degree	11 (26)	7 (21)	27 (33)	19 (33)	
Academic degree	18 (42)	13 (39)	21 (26)	12 (21)	
Previous deliveries	43 (100)	32 (94)	42 (50)	24 (41)	<0.001
History of GDM	43 (100)	30 (88)	15 (18)	8 (14)	<0.001
Current smoking	1 (2)	2 (6)	1 (1)	3 (5)	0.723
Vitamin D deficiency, <50 nmol/l	5 (12)	9 (26)	26 (31)	25 (43)	0.001
Season of blood collection					0.455
Spring	12 (28)	8 (24)	23 (27)	16 (27)	
Summer	9 (21)	11 (32)	18 (21)	8 (14)	
Fall	14 (32)	7 (21)	19 (23)	19 (33)	
Winter	8 (19)	8 (23)	24 (29)	15 (26)	
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	*P**
Physical activity, min/week (n 200)	90 (45, 150)	85 (30, 130)	60 (30, 120)	60 (43, 120)	0.432

BMI, body mass index; GDM, gestational diabetes mellitus; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; 25(OH)D, 25-hydroxyvitamin D; HbA1c, glycated hemoglobin; IQR, interquartile range; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

**P* for linearity across BMI groups tested by analysis of variance or Cochran-Armitage test for trend.

†Calculated as [fasting insulin (mU/l) x fasting glucose (mmol/l)) / 22.5].

In the BMI group 25.0-29.9 kg/m², 12% (n = 4) of the women had a BMI ≥30 kg/m² before pregnancy and lost weight until early pregnancy. Thus, these women were included in the BMI group 25.0-29.9 kg/m².

5.2.2 SERUM 25-HYDROXYVITAMIN D, BODY SIZE, AND RISK OF GESTATIONAL DIABETES MELLITUS

Overall, 37 (17%) women developed GDM. Sixteen (36%) women in the BMI group <25 kg/m², 8 (24%) women in the BMI group 25.0-29.9 kg/m², 6 (7%) women in the BMI group 30.0-34.9 kg/m², and 7 (12%) women in the BMI group ≥35 kg/m² were diagnosed with GDM.

The mean (range) duration of follow-up between vitamin D measurements in early and mid-pregnancy was 10 (5 to 16) weeks. Serum 25(OH)D concentrations were elevated in each of the BMI groups. Mean (95% CI) percentage changes in serum 25(OH)D concentrations in the BMI groups were as follows; 31% (95% CI 17 to 45) in the BMI group <25 kg/m², 26% (95% CI 12 to 40) in the BMI group 25.0-29.9 kg/m², 31% (95% CI 21 to 41) in the BMI group 30.0-34.9 kg/m², and 39% (95% CI 30 to 49) in the BMI group ≥35 kg/m², respectively.

The relationship between change in serum 25(OH)D concentrations and GDM according to early-pregnancy BMI are shown in Figure 4. Elevation in serum 25(OH)D concentrations was higher in women not diagnosed with GDM compared with women diagnosed with GDM in the BMI group ≥35 kg/m² (43.2 vs. 11.5%, P <0.001). The results remained significant after adjusting for early-pregnancy 25(OH)D, the assignment group, season, and changes in diet quality, physical activity, and weight. No relationship between serum 25(OH)D change and GDM was observed in the other BMI groups.

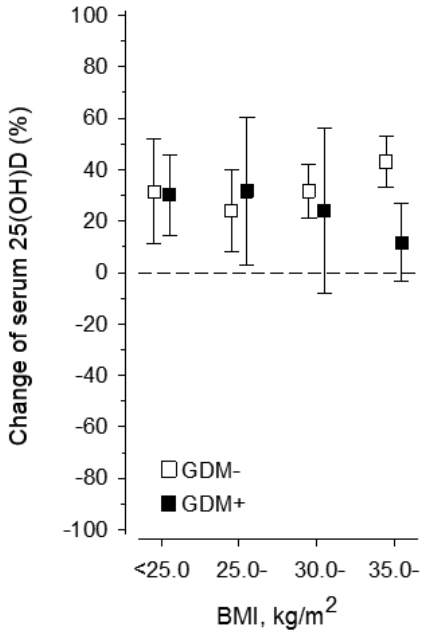

Figure 4. Percentage change in serum 25-hydroxyvitamin D concentrations from early to mid-pregnancy by early-pregnancy BMI. GDM- represents women who did not develop GDM and GDM+ represents women who developed GDM. Squares represent mean change and bars represent 95% confidence intervals. GDM, gestational diabetes mellitus; 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index.

The results for serum 25(OH)D change and GDM risk were further supported by the inverse correlation observed between serum 25(OH)D change from early to mid-pregnancy and AUC of the diagnostic $OGTT_{(0\text{-}2h)}$ in mid-pregnancy in the BMI group ≥35 kg/m² (Figure 5).

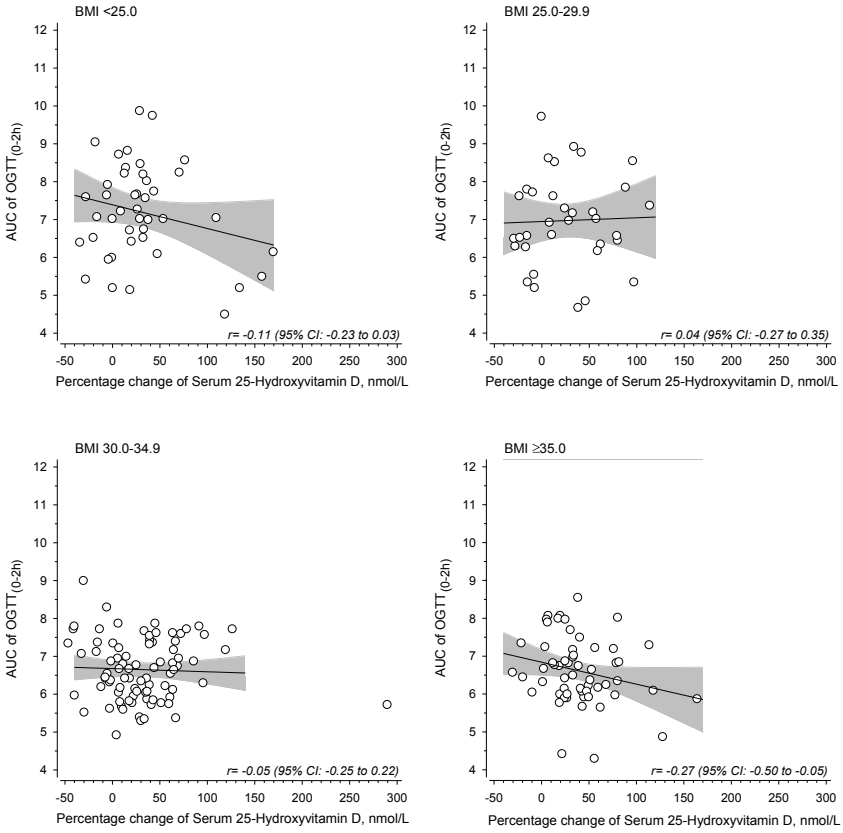

Figure 5. Percentage change in serum 25-hydroxyvitamin D concentrations from early to mid-pregnancy and area under the curve (AUC) for diagnostic oral glucose tolerance test ($OGTT_{(0-2h)}$) by early-pregnancy BMI (kg/m^2). The lines represent estimated linear regression with 95% confidence intervals. Correlation coefficients were generated by the Pearson method. CI, confidence intervals.

5.3 CHANGES IN FOOD INTAKE FROM PRE-PREGNANCY TO EARLY PREGNANCY AND RISK OF GESTATIONAL DIABETES MELLITUS (STUDY III)

5.3.1 CHARACTERISTICS OF THE PARTICIPANTS

Study III included only those women who entered the RADIEL trial when planning a pregnancy. Characteristics of the 75 women included are presented in Table 11.

Table 11. Characteristics of the participants before pregnancy in study III.
(n = 75 unless otherwise stated)

	Intervention n = 37 Mean (SD)	Control n = 38 Mean (SD)	*P**
Age, years	32.4 (4.1)	31.5 (3.9)	0.338
BMI, kg/m²	30.4 (6.1)	27.9 (5.8)	0.065
Waist circumference, cm	95.9 (14.0)	88.4 (12.5)	0.018
Education†, years	14.9 (2.0)	14.1 (1.8)	0.058
Physical activity§, min/week	82.9 (62.6)	97.9 (96.4)	0.439
Fasting plasma glucose, mmol/l	5.36 (0.37)	5.48 (0.44)	0.230
Total cholesterol, mmol/l	4.92 (0.76)	4.37 (0.65)	0.001
LDL-cholesterol, mmol/l	3.13 (0.69)	2.53(0.56)	<0.001
HDL-cholesterol, mmol/l	1.38 (0.30)	1.51 (0.35)	0.110
Total triglycerides, mmol/l	1.17 (0.62)	0.80 (0.31)	0.001
Systolic blood pressure, mmHg	122 (11)	119 (11)	0.309
Diastolic blood pressure, mmHg	80.4 (9.0)	78.9 (8.3)	0.452
Nutrient intake¶			
Energy intake, kcal/d	1908 (475)	1934 (445)	0.833
Protein, E%	18.5 (3.4)	18.2 (3.9)	0.823
Carbohydrates, E%	43.4 (8.3)	43.5 (8.0)	0.991
Total fat, E%	34.5 (6.8)	34.1 (6.8)	0.828
Saturated fat, E%	12.0 (3.3)	12.1 (3.2)	0.882
Sugar, E%	9.8 (4.8)	8.7 (3.7)	0.342
Fibre, g/MJ	2.8 (0.7)	2.5 (0.7)	0.168
Vitamin D, µg/d	10.7 (9.8)	12.0 (8.1)	0.579
Folic acid, µg/d	410 (262)	408 (163)	0.968
Calcium, mg/d	1273 (383)	1257 (387)	0.874
	n (%)	n (%)	*P**
History of GDM	28 (76)	32 (84)	0.356
Previous deliveries	35 (95)	33 (87)	0.249
Parental history of diabetes△	14 (40)	7 (19)	0.049

LDL, low-density lipoprotein; HDL, high-density lipoprotein; E%, % of total energy intake; GDM, gestational diabetes mellitus; BMI, body mass index; SD, standard deviation.

**P* for between-group difference generated by Student's t-test for continuous variables and Pearson's chi-squared test for categorical variables.

†n = 37 in the control group.

§n = 35 in the intervention group and n = 36 in the control group.

¶Vitamins and minerals are reported as total intake. n = 29 in the intervention group and n = 28 in the control group.

△Type 1 or type 2 diabetes of one or both parents. n = 35 in the intervention group and n = 37 in the control group.

The intervention group had higher concentrations of total cholesterol, LDL-cholesterol, and triglycerides, as well as larger waist circumference at baseline. Further, the intervention group was more likely to have parents with a history of diabetes compared with the control group. The prevalence of obesity (BMI ≥30 kg/m^2) was 57% in the intervention group and 32% in the control group (P = 0.028).

5.3.2 BETWEEN-GROUP DIFFERENCES IN FOOD INTAKE

The mean (range) follow-up time from the first pre-pregnancy visit to the early pregnancy visit was 6 (2-15) months amongst all women. With regard to the allocation group, the mean (range) follow-up time was 6 (2-14) months in the control group and 7 (2-15) months in the intervention group (P = 0.448). The mean (range) number of pre-pregnancy study visits was 2.0 (1 to 4) in the intervention group and 1.9 (1 to 4) in the control group (P = 0.578). Baseline food intakes and changes in food intakes from pre-pregnancy to early pregnancy in the intervention and control groups are presented in Table 12. In comparisons between the intervention and control groups, no differences in food intakes either at baseline or during the follow-up were observed (P >0.05 for all). As the prevalence of obesity was higher in the intervention group compared with the control group at baseline, further adjustments were made for pre-pregnancy BMI in study III. After the adjustments, the findings for between-group differences in food intake changes remained similar (P >0.05 for all).

5.3.3 FOOD INTAKE AND RISK FOR GESTATIONAL DIABETES MELLITUS

The intervention and control groups were combined to evaluate the relationship between changes in food intakes from pre-pregnancy to early pregnancy and GDM. Figure 6 illustrates the changes in food intake among women who developed and women who did not develop GDM during the study follow-up. Consumption of low-fat cheese increased significantly in women without GDM diagnosis compared with those with GDM diagnosis (P = 0.028). No other differences were observed in between-group comparisons for changes in food intake. To assess whether the significant relationship was related to the fat content in cheese, further analyses were performed for regular-fat cheese. In the analyses, no between-group differences were found for change in the regular-fat cheese intake (P >0.05).

Table 12. Changes in food intake from pre-pregnancy to early pregnancy in the control and intervention groups in study III (n = 75).

	Baseline		Change		
	Intervention	Control			
	n = 37	n = 38	Intervention	Control	
Food groups[‡]	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)	*P*[*]
Low-fat milk, times/d	1.10 (1.29)	1.30 (1.15)	0.34 (0.02 , 0.73)	0.21 (-0.22, 0.65)	0.88
Low-fat cheese, times/d	0.86 (0.99)	0.86 (0.88)	0.38 (0.01 , 0.77)	0.26 (0.05 , 0.49)	0.57
Whole grain, times/d	2.12 (1.23)	1.94 (1.22)	0.08 (-0.44 , 0.59)	0.45 (0.04 , 0.90)	0.39
Vegetables and legumes, times/d	1.35 (1.04)	1.46 (1.07)	0.36 (0.06 , 0.67)	0.10 (-0.28 , 0.44)	0.32
Fruits and berries, times/d	0.96 (0.80)	1.14 (0.77)	0.40 (0.08 , 0.81)	0.31 (0.03 , 0.64)	0.94
Fish, times/wk	1.49 (1.19)	1.42 (1.39)	0.14 (-0.28 , 0.57)	0.12 (-0.29 , 0.53)	0.79
Animal protein[†], times/d	1.29 (0.71)	1.25 (1.00)	0.00 (-0.31 , 0.42)	-0.22 (-0.54 , 0.05)	0.24
Snacks[§], times/wk	9.91 (14.04)	8.42 (5.54)	-4.93 (-10.7 , -2.17)	-2.25 (-3.71 , -0.64)	0.15
Fast food[¶], times/wk	0.55 (1.05)	0.70 (1.07)	-0.10 (-0.50 , 0.31)	0.08 (-0.32 , 0.47)	0.16
Sugar-sweetened beverages[Δ], times/wk	1.20 (2.60)	0.92 (2.13)	0.67 (-0.55 , 1.90)	1.26 (0.37 , 2.47)	0.59
Cooking fat, score[#]	0.86 (0.35)	0.89 (0.31)	0.03 (-0.07 , 0.13)	0.08 (-0.03 , 0.19)	0.21
Spread fat, score[ω]	0.70 (0.97)	0.62 (0.89)	0.92 (0.57 , 1.25)	0.65 (0.33 , 1.00)	0.084

SD, standard deviation; CI, confidence intervals.
[*]*P* for between-group differences in baseline-adjusted changes in food intake tested by bootstrap-type analysis of covariance.
[†]Red meat, poultry, organ meats, and egg.
[§]Pastries, candy, ice cream, chocolate, and chips.
[¶]Hamburger and pizza.
[Δ]Sugar-sweetened juice and soft drinks.
[#]Score range 0-1: cooking oil, regular margarine, bottled margarine, or no cooking fat 1 point; butter, butter-vegetable oil mixture, or hard margarine 0 points.
[ω]Score range 0-2: regular or low-fat margarine 2 points; sterol margarine 1 point; butter, butter-vegetable oil mixture, or no spread fat 0 points.

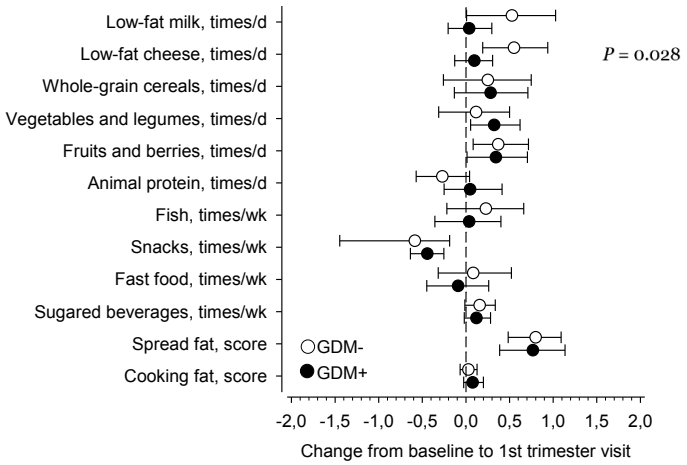

Figure 6. Changes in food intake according to GDM status. Between-group differences in food intake changes were generated by bootstrap-type analysis of covariance with 5000 replications. Changes in food intakes were adjusted for baseline value, physical activity, age, assignment group, BMI, parental history of diabetes, and follow-up time. Circles represent mean change and bars represent 95% confidence intervals. GDM, gestational diabetes mellitus.

5.4 DIET QUALITY AND LIPOPROTEIN PARTICLES IN PREGNANCY (STUDY IV)

5.4.1 CHARACTERISTICS OF THE PARTICIPANTS

Study IV included 161 pregnant women followed from early to mid-pregnancy. In total, 54 (34%) women had a history of GDM, 92 (57%) women had a pre-pregnancy BMI ≥30 kg/m^2, and 15 (9%) women had both risk factors for GDM. Characteristics of the participants according to total HFII score in early pregnancy are shown in Table 13. Higher total HFII score at baseline was related to higher prevalence of a history of GDM, higher level of education, and lower total fat intake (reported as % from total energy intake).

Table 13. Participant characteristics by the Healthy Food Intake Index (HFII) score in early pregnancy in study IV.

		HFII score						
		0-7		8-12		13-17		
		n = 35		n = 77		n = 49		
	n	Mean	SD	Mean	SD	Mean	SD	*P**
HFII score	161	5.86	1.44	9.57	1.11	13.37	1.20	<0.001
Age, years	161	30.8	4.5	32.0	4.7	32.1	4.4	0.181
Weight, kg	161	86.5	14.7	87.1	16.6	81.9	20.1	0.225
BMI, kg/m²	161	31.6	4.3	31.4	5.7	29.6	6.0	0.074
Gestational age, weeks	161	12.5	2.0	13.4	1.4	13.2	1.6	0.079
Years of education	161	13.7	1.9	14.4	2.2	14.6	2.1	0.045
Diastolic blood pressure, mmHg	159	74.9	7.7	76.5	9.2	77.8	9.9	0.131
Systolic blood pressure, mmHg	159	121	11	122	14	123	13	0.357
Triglycerides, mmol/l	161	1.30	0.49	1.30	0.56	1.17	0.41	0.175
Fasting insulin, mU/l	160	8.56	4.2	7.93	4.1	7.36	5.51	0.253
OGTT, mmol/l								
Fasting	161	4.90	0.23	4.89	0.24	4.88	0.21	0.580
1-h	161	6.88	1.54	7.20	1.33	6.77	1.39	0.740
2-h	161	5.70	1.01	6.02	1.07	5.56	1.28	0.576
Total energy intake, kcal/d	142	1885	445	1944	441	1896	420	0.919
Total fat intake, E%	142	35.6	5.8	33.7	5.8	32.4	5.8	0.028
		n	%	n	%	n	%	*P**
Intervention group	161	19	54	39	51	30	61	0.461
History of GDM	161	11	31	30	39	28	57	0.015

Continues.

Table 13 continued.

Previous deliveries (yes/no)	161	21	60	45	58	37	76	0.108
Parental history of diabetes	159	7	21	13	17	12	25	0.546
Parental history of CVD	159	15	44	41	53	25	52	0.525
Parental history of hypertension	159	14	41	38	49	22	46	0.741
Current smoker	161	3	9	2	3	2	4	0.387
		Median	IQR	Median	IQR	Median	IQR	*P*[1]
Physical activity, minutes/week	145	60	25, 135	60	30, 120	90	45, 145	0.332

OGTT, oral glucose tolerance test; IQR, interquartile range; E%, % from total energy intake; GDM, gestational diabetes mellitus; CVD, cardiovascular disease.

[*]*P* for linearity across the Healthy Food Intake Index groups generated by analysis of variance for continuous variables and Cochran-Armitage test for trend for categorical variables.

5.4.2 DIET QUALITY AND LIPOPROTEIN PARTICLES

Linearity for lipoprotein parameters across the HFII groups in early pregnancy is reported in Table 14. Total HFII score was inversely related to HDL particle concentrations. No other relationships between the HFII and lipoprotein parameters were observed in early pregnancy.

Mean (range) follow-up time from early to mid-pregnancy was 10 (6-17) weeks among all women. Mean (95% CI) crude change in the HFII score was 0.22 (95% CI -0.13 to 0.56) points in the total study population. Correlations between residual change in the HFII and residual change in lipoprotein particle concentration and size are shown in Figure 7. An increase in the HFII score correlated with reduced VLDL particle size. The significant correlation remained in all adjusted models except for a slightly attenuated correlation after further adjusting for the allocation group and the study group (r = -0.15, 95% CI -0.30 to 0.00). No significant correlation were observed between change in the HFII and change in other lipoprotein parameters or standard lipid parameters.

Table 14. Lipoprotein particle profiles based on nuclear magnetic resonance (NMR) technique across the Healthy Food Intake Index (HFII) groups in early pregnancy in study IV (n = 161).
(Means and standard deviations)

	HFII score									
	0-7 (n = 35)		8-12 (n = 77)		13-17 (n = 49)					
	Mean	SD	Mean	SD	Mean	SD	$P_{\text{for trend}}$*	$P_{for\ trend}$†	$P_{for\ trend}$‡	$P_{for\ trend}$§
Lipoprotein particle profile										
Size, nm										
VLDL	36.2	1.1	36.1	1.2	35.9	1.0	0.247	0.745	0.892	0.805
LDL	23.6	0.1	23.6	0.1	23.6	0.1	0.382	0.499	0.293	0.626
HDL	10.2	0.2	10.2	0.2	10.2	0.2	0.986	0.329	0.272	0.330
Concentration										
VLDL, nmol/l	79.9	24.5	80.2	26.5	77.0	24.4	0.590	0.627	0.947	0.705
LDL, nmol/l	546	131	538	131	563	152	0.585	0.977	0.878	0.968
HDL, µmol/l	10.1	1.1	9.72	0.97	9.49	0.97	0.010	<0.001	0.002	0.002

VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

*†‡§Linearity across the Healthy Food Intake Index groups was tested by using analysis of variance (ANOVA) and covariance (ANCOVA).

*Model 1: Unadjusted.

†Model 2: Adjusted for age, body mass index, years of education, and gestational age.

‡Model 3: Adjusted for age, body mass index, years of education, gestational age, and physical activity (n = 145).

§Model 4: Adjusted for age, body mass index, years of education, gestational age, the allocation group, and the study group (time when the participant entered the RADIEL trial; before or during pregnancy).

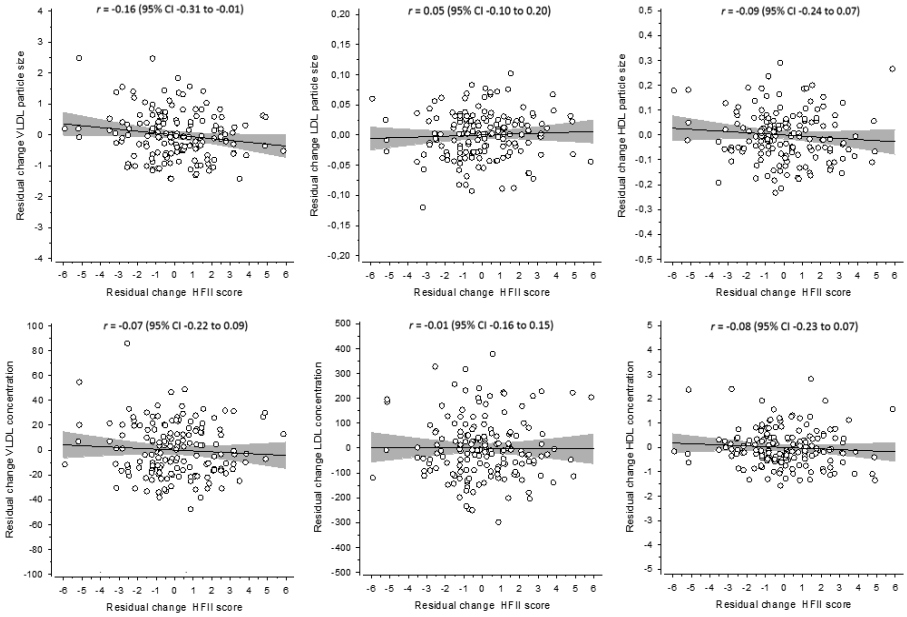

Figure 7. Correlations between residual changes in the Healthy Food Intake Index (HFII) score and residual changes in serum lipoprotein particle concentration and size. The lines indicate estimated linear regression with 95% confidence intervals. Correlation coefficients were generated by the Pearson method. LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; CI; confidence intervals.

6 DISCUSSION

6.1 MAIN FINDINGS

In study I, the aim was to investigate the differences in food intake changes from early to mid-pregnancy between the intervention and control groups. Out of the 12 foods and food groups included in the analyses, daily intakes of low-fat cheese and weekly intakes of fish increased significantly in the intervention group compared with the control group. In study II, the objective was to evaluate whether maternal body size modifies the relationship between changes in serum 25(OH)D concentrations and risk of GDM. The higher increase in serum 25(OH)D concentrations during pregnancy was associated with lower risk of GDM in women with a BMI ≥35 kg/m^2 whereas no relationship between serum 25(OH)D concentrations and GDM was observed in women with a BMI <35 kg/m^2. The objective of study III was to investigate the differences in food intake changes from pre-pregnancy to early pregnancy between the intervention and control groups. After the follow-up, no between-group differences were observed in the changes in food intakes. Moreover, increased low-fat cheese intake was associated with lower GDM risk whereas, in additional analyses, no association between regular-fat cheese intake and GDM was observed. In study IV, the aim was to assess the relationship of overall diet quality as assessed by adherence to the NNR based on the HFII score with lipoprotein particle concentration and size during pregnancy. The higher HFII score was associated with lower HDL particle concentrations in early pregnancy whereas improved HFII score was related to decreased VLDL particle size during the follow-up from early to mid-pregnancy.

6.2. INTERPRETATION OF THE RESULTS

6.2.1 CHANGES IN FOOD INTAKE FROM EARLY TO MID-PREGNANCY (STUDY I)

After dietary and physical activity advice including one individual counselling session with a study nurse and one group counselling session with a dietitian in early pregnancy, the intakes of low-fat cheese and fish increased in the intervention group compared with the control group. Low-fat cheese instead of regular- and high-fat cheese as well as different types of fish twice or three times per week are recommended by the Finnish Nutrition Recommendations which are further based on the NNR. Improved adherence to the recommendation for replacing high- and regular-fat cheese with low-fat

cheese was not supported by the current analyses as no simultaneous reduction in regular-fat cheese intake was observed in the intervention group. However, low-fat cheese is high in protein and calcium, and the increased consumption may indicate a lowered total fat content in the diet as well as improvements in other health-related behaviours. Fish is rich in protein, PUFA, and vitamin D. The increased fish intake towards the dietary recommendations may reflect substitution of fish for other foods such as red meat or poultry.

Several randomized controlled trials have reported dietary improvements after receiving dietary intervention (Piirainen et al. 2006, Kinnunen et al. 2007, Guelinckx et al. 2010, Jackson et al. 2011, Korpi-Hyövälti et al. 2012, Kinnunen et al. 2014). For instance, in a Finnish trial including 105 mainly normal-weight pregnant primiparae, combined dietary and physical activity intervention resulted in a greater increase in number of daily portions of vegetables, fruits, and berries and a lower decrease in high-fibre bread intake (reported as % of total bread) (Kinnunen et al. 2007). In study I, changes in the frequency of daily consumption of vegetables and legumes, fruits and berries, and whole-grain products including high-fibre bread were similar in between-group comparisons. Another Finnish trial by Kinnunen et al. (2014) including 399 pregnant women at increased risk for GDM reported improvements in intakes of several foods after dietary counselling. Among other improvements, the proportion of low-fat cheese from total cheese and the intake of snacks remained similar in the intervention group whereas in the control group, the proportion of low-fat cheese decreased and the intake of snacks increased. Further, the authors also reported an increased frequency of weekly fish consumption in the intervention group compared with the control group, which is in line with the findings in study I for improved fish intake. In a trial by Guelinckx et al. (2010) conducted in Belgium among 122 obese pregnant women, both of the groups receiving either an informative brochure about diet and physical activity or additional face-to-face group counselling improved their vegetable intake whereas no difference in fruit intake was observed in comparison to the control group with standard prenatal care (Guelinckx et al. 2010). In the RADIEL trial, the control group received leaflets about healthy lifestyles as the group in the trial by Guelinckx et al. (2010) and additional counselling in standard antenatal clinics due to their high risk for GDM. Thus, the lifestyle counselling provided in the control group may have reduced the between-group differences in food intake changes in study I.

Contradictory findings on the effect of dietary interventions on food intakes may in part arise from numerous differences between the studies such as in dietary measurement methods, the number and type of foods included, reporting of dietary intakes (e.g. crude intakes or proportions of total intake), type and delivery of counselling, participant characteristics, and follow-up time.

Study I included two dietary counselling sessions. A higher number of counselling visits could have resulted in greater differences in food intakes between the intervention and control groups. As suggested by previous studies, a higher number of contacts may improve the intervention effectiveness in modifying diets (Greaves et al. 2011). Additionally, a lower number of intervention visits has been shown to explain intervention effectiveness related to weight loss and improved glucose tolerance (Rautio et al. 2013). Moreover, individual lifestyle counselling was provided by a study nurse in the RADIEL trial to make the counselling applicable in primary health care. Individual dietary counselling led by a dietitian may have, however, resulted in greater improvements in food intakes in the intervention group. Dietary counselling in the RADIEL trial consisted of both individual and group counselling sessions. According to other randomized controlled trials, studies including either individual, group, or both types of intervention have shown similar effectiveness in terms of dietary and/or physical activity change (Greaves et al. 2011).

Though the intervention showed improvements in intakes of foods related to healthy diets in study I, no between-group difference was observed in intakes of foods rich in sugar and saturated fat such as fast food and snacks. High energy and saturated fat intakes have been associated with elevated GDM risk (Park et al. 2013), and thus a reduction in the consumption of these food groups may have been relevant in preventing the development of GDM. In our previous publication of women in the present study, we reported a reduction in GDM risk by dietary and physical activity advice initiated in early pregnancy (Koivusalo et al. 2016). In the same study, dietary changes were evaluated by total HFII score reflecting the change in overall diet quality (Koivusalo et al. 2016).

Instead of assessing overall diet quality based on a dietary index, study I focused on evaluating the actual changes in food intakes. The significant differences in food intake changes observed in study I may have contributed to the reduced GDM risk. The literature of the role of fish and low-fat dairy intake in GDM development is yet limited. In a cohort study by Bao et al. (2013) on dietary protein sources, substitution of red meat with fish was associated with reduced GDM risk (Bao et al. 2013). Moreover, increased intakes of both low-fat cheese and fish may also reflect improvements in other health behaviours which again may promote glucose regulation.

6.2.2 SERUM 25-HYDROXYVITAMIN D, BODY SIZE, AND RISK OF GESTATIONAL DIABETES MELLITUS (STUDY II)

In study II, higher increase in serum 25(OH)D concentrations during pregnancy was related to a lower risk of GDM in severely and morbidly obese women but not in women with a BMI <35 kg/m². Additionally, changes in serum 25(OH)D concentrations were inversely correlated with AUC of the diagnostic OGTT only amongst women with a BMI ≥35 kg/m². Observational studies in non-pregnant populations have reported similar results suggesting that 25(OH)D may play a more critical role in glucose-insulin metabolism among overweight and obese populations compared with normal-weight populations (Hyppönen, Power 2006, Ou et al. 2011). This may in part be a consequence of lower baseline 25(OH)D concentrations and higher prevalence of vitamin D deficiency observed in overweight and obese individuals. Additionally, in study II, women with a BMI ≥35 kg/m² were the most insulin resistant according to baseline HOMA-IR, and they also had a more atherogenic lipid profile at baseline compared with women with a BMI <35 kg/m². Thus, in terms of glucose-insulin metabolism, severely and morbidly obese individuals with a more adverse metabolic profile and lower baseline 25(OH)D concentrations might benefit more from the increase in 25(OH)D concentrations than normal-weight individuals with lower metabolic risk status and higher 25(OH)D concentrations.

In study II, the highest incidence of GDM was observed in normal-weight women with the most favorable baseline metabolic profile. This is likely due to the inclusion criteria in the RADIEL trial; BMI ≥30 kg/m², a history of GDM, or both. Therefore, all women with a BMI <25 kg/m² and only 8 (14%) women with a BMI ≥35 kg/m² had a history of GDM which is a well-known risk factor for GDM in future pregnancies and has been associated with reduced insulin secretion (Dornhorst et al. 1990). In the current data, lean women with a history of GDM seemed to be at higher risk of GDM compared with obese women without a history of GDM, which may in part explain the non-significant results between serum 25(OH)D concentrations and GDM among lean women. Additionally, normal-weight women with a history of GDM may develop GDM by different mechanisms compared with obese women without a history of GDM (Huvinen et al. 2016).

As suggested by Mitri and coworkers (2011), higher 25(OH)D concentrations may indicate higher consumption of foods which are high in vitamin D, such as salmon, but also contain other ingredients with beneficial effects on glycaemic control (Mitri et al. 2011). Moreover, lower GDM risk may result from substituting foods high in vitamin D for foods associated with increased GDM risk, e.g., fatty fish for red meat.

6.2.3 CHANGES IN FOOD INTAKE FROM PRE-PREGNANCY TO EARLY PREGNANCY AND RISK OF GESTATIONAL DIABETES MELLITUS (STUDY III)

In study III, no differences in food intake changes between the intervention and control groups were observed during the follow-up from pre-pregnancy to early pregnancy. With regard to pre-pregnancy counselling, studies reporting on the effects on dietary intakes are sparse. Similar findings on between-group differences in food intakes as in study III were reported in a controlled trial by Weisman et al. (2011) evaluating the long-term influence of behavioural intervention based on telephone interviews in pre- and interconceptional women (Weisman et al. 2011). On the other hand, in the study by Weisman et al. (2011), the evaluation of dietary intake included daily fruit and vegetable consumption only. Furthermore, the follow-up was long including two follow-up points, at 6 and 12 months. Similarly, during the mean follow-up period of 6 months in study III, differences in food intake changes between the intervention and control groups may have required more intensive lifestyle intervention. Furthermore, in a study by Hammiche et al. (2011) including mostly subfertile couples planning a pregnancy, all of the participants received tailored preconception dietary and lifestyle counselling once or twice after which higher adherence to the food-based Dutch dietary guidelines was observed (Hammiche et al. 2011). However, the study was observational by design and did not include a control group.

Findings for changes in food intake in study III are in line with the findings for changes in overall diet quality observed after pre-pregnancy lifestyle intervention in the RADIEL trial (Rönö et al. 2018). The follow-up in the study by Rönö et al. (2018) was conducted as in study III; from pre-pregnancy to early pregnancy. After the intervention, the authors observed no effect on GDM risk, overall diet quality based on the total HFII score, or the amount of physical activity.

Furthermore, an increased intake of low-fat cheese but not regular-fat cheese was inversely associated with GDM. Certain nutrients in cheese and other dairy products, e.g., calcium and magnesium, may improve glucose-insulin metabolism (Paolisso et al. 1990, Sanchez et al. 1997). For instance, in two recent systematic reviews (Simental-Mendia et al. 2016, Morais et al. 2017) including also a meta-analysis (Simental-Mendia et al. 2016), the authors concluded that magnesium supplementation might improve insulin sensitivity and reduce glucose concentrations. Furthermore, calcium supplementation for eight weeks resulted in increased insulin sensitivity in hypertensive participants (Sanchez et al. 1997). On the other hand, the beneficial effect of

other nutrients might attenuate when the fat content in foods is higher (Aune et al. 2013). Further, cheese is one of the major sources of saturated fat among the Finnish population (Helldan et al. 2013). Thus, the increased intake of low-fat cheese may indicate a reduction in saturated fat intake, which again could play a role in the lowered risk for GDM, as diets high in saturated fat are associated with higher GDM risk (Bo et al. 2001, Park et al. 2013).

Evidence of the association between cheese intake alone and GDM risk is limited. In an observational study by Karamanos et al. (2014), women who developed GDM during the follow-up reported higher intakes of cheese compared to women who did not develop GDM (Karamanos et al. 2014). However, the fat content of the cheese was not taken into account so the results may have been different for regular-fat cheese and low-fat cheese. Studies on the association between dairy products and GDM are limited. In a recent meta-analysis including cross-sectional and prospective observational studies, Schoenaker et al. (2016) concluded that high consumption of low-fat dairy being a part of a healthy diet might help to lower GDM risk (Schoenaker et al. 2016). Compared with GDM, T2D-dairy intake associations have been studied more frequently. T2D and GDM partly share similar risk factors, such as obesity. Thus, dietary factors related to T2D may, at least theoretically, be related to GDM risk as well. A meta-analysis including 17 cohort studies showed that high intakes of low-fat dairy and cheese were associated with lower T2D risk whereas no association was found for high intakes of high-fat dairy when compared with low intakes of these foods (Aune et al. 2013). In the analyses, however, no division into low-fat and regular-fat cheese was performed. The current results for regular-fat and low-fat cheese intakes in relation to GDM are parallel to those observed for high-fat and low-fat dairy in relation to T2D in the meta-analysis. Such results for low-fat cheese versus regular-fat cheese and GDM may be suggestive of that higher intakes of low-fat but not regular-fat dairy may help in improving glucose metabolism.

On the other hand, increased low-fat cheese intake may reflect improvements in overall diets or lifestyle in general or replacement of other foods related to higher GDM risk, which again may contribute to lower risk of GDM. One potential confounding factor is reduced intake of red and processed meat as higher consumption has been associated with elevated risk (C. Zhang, Schulze, et al. 2006, Bao et al. 2013). In study III, red meat was included in the group of animal protein together with poultry, egg, and organ meats, which showed no association with GDM.

Regarding the study population in study III, the prevalence of a history of GDM was high, and most of the women with GDM were diagnosed already in early pregnancy. The high GDM risk status among the participants may have

weakened the role of dietary changes in GDM development and thus in part explain the mainly non-significant findings between changes in food intake and GDM. Finally, the dietary changes may have been too small to show a significant association with GDM.

6.2.4 LIPOPROTEINS AND HEALTHY FOOD INTAKE INDEX (STUDY IV)

At baseline, a higher HFII score was inversely yet weakly related to lower HDL particle concentrations. Furthermore, an increase in the HFII score from early to mid-pregnancy was related to reduced VLDL particle size. To our knowledge, this is the first study focusing on the relationship between Nordic dietary patterns and lipoprotein particle size and concentration in pregnant women.

Metabolomics during pregnancy has been previously studied (Houttu et al. 2017, Jacob et al. 2017, Röytiö et al. 2017, White et al. 2017). In terms of lipoprotein particle profiles, Houttu et al. (2017) have reported higher concentrations of several lipid parameters in VLDL particles and lower concentrations of lipid parameters in HDL particles in obese pregnant women compared with overweight pregnant women (Houttu et al. 2017). Further, Röytiö et al. (2017) recently reported on the associations between dietary fat and fiber intakes, gut microbiota richness, and lipoprotein particle parameters in overweight pregnant women (Röytiö et al. 2017).

Generally, studies on the relationship between dietary patterns and circulating lipid parameters have focused on cholesterol and triglyceride concentration in lipoprotein particles. Some of these studies have shown similar results for HDL-cholesterol concentration as in the current study for total HDL particle concentration. For instance, in a meta-analysis including three Finnish studies with a cross-sectional design, higher adherence to a healthy Nordic diet was associated with lower HDL-cholesterol concentration (Kanerva et al. 2014). Parallel findings have been observed in dietary intervention studies. A healthy Nordic diet for six weeks resulted in a 5% reduction in plasma HDL-cholesterol concentration compared with a control diet in hypercholesterolemic individuals (Adamsson et al. 2011). Furthermore, the DASH diet for three weeks led to reduced concentrations of HDL-cholesterol amongst healthy men and women, although there was no influence on HDL particle concentrations (S. Chiu et al. 2016). The inverse relationship between dietary patterns and HDL particle parameters may be a consequence of lower total fat intake, which was also supported by the findings in study IV on the inverse association between the HFII score and total fat intake in early pregnancy.

During the follow-up in study IV, an elevated HFII score was significantly yet weakly related to a reduction in VLDL particle size. The relationship was only slightly attenuated after further adjustment for the allocation group and the study group. According to some evidence, higher fish intake may modify VLDL particle size. A diet with 60% of total protein from lean-seafood sources for four weeks resulted in a reduced size of VLDL particles compared with a diet with 60% of protein from non-seafood sources in non-pregnant, healthy subjects (Aadland et al. 2015). Further, an observational study in Alaska Eskimos at increased risk for CVD reported inverse associations of n-3 PUFA intake with large VLDL particle concentration and total VLDL particle size (Annuzzi et al. 2012). Moreover, in a cross-sectional study in healthy Finnish twins, higher fish intake and a higher proportion of docosahexaenoic acid (DHA) from total serum fatty acids were linked to reduced VLDL particle size whereas higher intake of foods related to unhealthy diets such as salty snacks and sweets was related to increased VLDL particle size (Bogl et al. 2013).

The current data is unable to demonstrate the underlying mechanisms through which diet could modify lipoprotein particle profile. However, according to some suggestions, dietary n-3 PUFA may modify VLDL particle size through increased expression of LPL. The enhanced LPL expression stimulates the removal of triglycerides from the VLDL particles and the resulting conversion first to smaller VLDL particles and eventually to LDL particles (Annuzzi et al. 2012, Dias et al. 2017). However, change in the HFII score was not related to change in LDL particle concentrations in study IV.

A major factor likely affecting the rather weak and also non-significant findings between HFII and lipoprotein particles is pregnancy. Despite diet and lifestyle, atherogenic alterations in lipid metabolism are necessary to confirm normal development and growth of the fetus (Lain, Catalano 2007). Thus, other factors, such as hormones and increased insulin resistance, may play a more significant role than diet in lipoprotein particle profile during gestation compared with non-pregnant state.

All women in the current study were at increased risk for GDM due to obesity, a history of GDM, or both. Both of the conditions are characterized by increased insulin resistance also outside pregnancy. Insulin resistance may attenuate the lipid response to diet, which again may have attenuated the relationship between diet and lipid parameters. Furthermore, genetic variation may contribute to the differing lipid response to diet between individuals (Ordovas 2001). For instance, studies on genetic polymorphism in apolipoprotein E (ApoE) have reported different results based on genotype. A carbohydrate-rich diet replaced with MUFA-rich diet led to an opposite effect on LDL particle size in healthy young adults with different genotypes of ApoE (Moreno et al. 2004). Further, depending on ApoE genotype, higher intake of

SFA was associated with either smaller or larger size of LDL particles in a Costa Rican population (Campos et al. 2001). Finally, stronger relationships between changes in lipoprotein particles and changes in diet quality may have required greater dietary changes.

6.3 METHODOLOGICAL CONSIDERATIONS

This thesis only included secondary analyses of the RADIEL trial due to which power calculations were not performed. Therefore, it is unclear whether the power of the sample size was sufficient to detect statistical significance for the differences and relationships evaluated in this thesis. In terms of between-group comparison of dietary intakes in study I and III, the sample size in other similar studies conducted among high-risk pregnant women in Finland has ranged between 54 to 399 (Korpi-Hyövälti et al. 2012, Kinnunen et al. 2014). No study has previously examined the relationship between maternal BMI, serum 25(OH)D, and risk of GDM. However, compared with the sample size of 219 in study II, observational studies reporting on the relationship between serum 25(OH)D, obesity, and glucose-insulin metabolism in non-pregnant populations have mostly been larger (Hyppönen et al. 2008, Lu et al. 2009). This may indicate that the study groups in study II may have been insufficiently powered. Similarly, observational studies reporting on diet-standard lipid associations in pregnancy have usually included a larger sample size compared with the sample size of 161 in study IV.

Further, the participants consisted of a high-risk group affected by obesity, a history of GDM, or both. Therefore, also women in the control group received lifestyle counselling at the standard maternal clinics, which may in part explain the mainly non-significant differences in food intake changes between the intervention and control groups in studies I and III. Furthermore, as data on the number of standard clinic visits were not collected in the RADIEL trial, the intervention and control groups may have varied in the number of visits, which again may have resulted in measurement bias. Especially, a higher number of clinic visits in the control group compared with the intervention group may have attenuated the between-group differences in food intakes in study I and III. Additionally, the Hawthorne effect indicating a behavioural change in response to participating in an experiment (D. Schwartz et al. 2013) may have hindered the differences in food intake changes between the intervention and control groups. Therefore, the participants may have over-reported the intakes of foods considered as healthy and, in contrast, under-reported the intakes of foods considered as unhealthy. The study population consisted of Caucasian women only. Thus, the observed findings may be

different in pregnant women with different ethnic and genetic background and dietary culture.

Diet record data during pregnancy were available in early pregnancy only as the data collection was not performed in mid-pregnancy in the RADIEL trial. In addition to the evaluation of food intakes, changes in nutrient intakes would have been relevant to provide more detailed information about the dietary changes. Moreover, dietary records were not checked by the study personnel afterwards whereas reviewing the dietary records may have improved the quality of dietary intake data.

Data on vitamin D supplements were not reported in study II as the information on usage and dosage of vitamin D supplements was not properly collected in the questionnaire. This information would have been relevant as the use of vitamin D supplements as well as vitamin D intake from supplements may have partly explained the relationship between elevated serum 25(OH)D and lower GDM risk among women with a BMI ≥35 kg/m^2.

Furthermore, the amount of leisure time physical activity was self-reported which may have caused measurement bias. Use of accelerometers or pedometers instead of questionnaires would have increased the objectiveness and accuracy of the results. In a systematic review by Prince et al. (2008), the measures of physical activity based on self-reporting were either lower or higher compared with those based on direct methods such as accelerometers.

The strength in studies I and III was the randomized controlled study design which is the most optimal study design to evaluate causality. Studies II and IV were observational studies with two measurement points enabling usage of longitudinal data.

In study I, the potential influence of GDM diagnosis on food intakes was prevented by excluding the women with GDM diagnosed already in early pregnancy and women who returned their FFQ after the diagnostic OGTT in mid-pregnancy, and by following the women only until mid-pregnancy, during which GDM diagnosis is usually received (14-26 weeks of gestation).

In study II, the two consecutive measurements of serum 25(OH)D concentrations enabled the assessment of the changes in 25(OH)D concentrations. Most of the observational studies in pregnant women have mainly included a single measurement only (Moon et al. 2015). Additionally, the prospective design enabled the exclusion of women with GDM diagnosis already at baseline. Analyses were performed in groups stratified by BMI whereas in many other studies this variable has only been used for adjustments. However, the adjustment may not be enough to eliminate the

overlapping effect that vitamin D and BMI may have on GDM (Kovacs 2012). Additionally, instead of using specific cut-off points, the 25(OH)D concentration was evaluated as a continuous variable in study II. Cut-off values for the definition of vitamin D insufficiency or deficiency differ between studies which may partly explain inconsistent results in previous studies. In terms of limitations, the causes of change in 25(OH)D concentrations during pregnancy were not demonstrated which may have been relevant when exploring the association with GDM.

In study III, the strength was the follow-up starting already when planning a pregnancy. However, the study does not provide information whether changes in food intakes before pregnancy are more important compared with changes in food intakes during pregnancy in relation to the development of GDM, which may be relevant when investigating the diet-GDM associations. On the other hand, dietary changes from pre-pregnancy to pregnancy may be rather small (Crozier et al. 2009). Thus, changes in most of the food intakes in study III may have been too minor to show statistically significant between-group differences. Dietary record data were available only for 45 out of 75 participants due to which the data was not included in study III. Further, the recruitment of the participants planning a pregnancy, especially the nulliparae, appeared to be challenging due to which the women were mainly recruited based on the hospital registries of a history of GDM. This again resulted in a high prevalence of a history of GDM in study III.

In study IV, the use of alternative lipoprotein parameters in CVD risk prediction provides a new perspective in the literature on maternal diet-lipid associations. The NMR spectrometry is a rapid, highly reproducible, and non-invasive technique which enables the repeated usage of the samples (Mika et al. 2017). However, the use of mass spectrometry measurements together with the NMR measurements has been proposed to improve the reliability of the NMR-based results (Mika et al. 2017). Further, the evaluation of whole diet quality instead of individual foods and nutrients enabled more extensive approach by taking into account the interactions and synergy of multiple nutrients and foods (Hu 2002).

In study I, II, and IV including a follow-up from early to mid-pregnancy, all women with GDM diagnosis in early pregnancy were excluded. Thus, the participants included in these studies represent a group of women being more insulin sensitive and at lower risk for future T2D compared with women with early GDM diagnosis.

In this thesis, the nutrient intake data was based on a 3-day diet record, and the food intake data on the 48-item FFQ developed for the RADIEL trial. Diet record is not based on memory and enables the recording of detailed information on meals such as portion sizes and recipe ingredients during one

or a few days (Willett 2013). However, factors which may reduce the accuracy when completing a diet record include memory limitations if the recording is delayed after the meal, time-consuming method, under-reporting especially in intakes of energy and foods related to unhealthy diet and especially among overweight and obese individuals (Prentice et al. 1986, Livingstone et al. 1990, Rennie et al. 2007, Willett 2013). Additionally, dietary modifications during the recording days are general in which case the information provided does not represent the usual dietary intakes (Willett 2013).

In contrast to the diet record, the FFQ provides information on long-term dietary intakes by asking frequency of food consumption. As the FFQ enables dietary intake evaluation in daily or even annual level, the FFQ is the most used method to collect dietary intake data in epidemiological studies, although the degree of the information is more crude compared with that derived from the diet record (Willett 2013). The ability of the FFQ to measure the dietary factors it is supposed to measure (validity) as well as the consistency in responses at different time points (reproducibility) are essential quality measures of the FFQ (Willett 2013). The 12 foods and food groups used in the analyses in study I and III may not have been sufficient to recognize other relevant foods and their intakes. Further, the FFQ used in this thesis may have been too crude and inaccurate as a measure of dietary change. Additionally, some food groups presented in the current FFQ may have included several types of foods which in turn could have been interpreted variously by the participants. For instance, low-fat cheese may refer to various types of cheese such as slice cheese as well as processed and soft cheeses and cheese used in food preparation. Further, change in one dietary factor usually means a change in another. Thus, the increased intake of low-fat cheese observed in the intervention group in study I may reflect a change in the intakes of some other food or foods. Similarly, the significant relationship observed between increased low-fat cheese intake and lower GDM risk may be a consequence of a change in the intake of another food, e.g., lowered red or processed meat intake.

The FFQ used in this thesis has not been validated whereas the validity and reproducibility of the HFII, which is based on this FFQ, has been evaluated previously (Meinilä et al. 2016). The reproducibility of the HFII was found to be moderate, and the HFII was reported to be able to rank the participants according to the adherence to the NNR in early pregnancy. However, the ability of the HFII to capture dietary changes during pregnancy has not been validated, and thus the HFII changes may not reflect all the dietary changes made during the follow-up in study IV.

7 CONCLUSIONS AND FUTURE IMPLICATIONS

The current thesis consisted of secondary analyses of the RADIEL trial. The aims were to evaluate the differences in food intake changes between the intervention and control groups as well as the relationships of dietary change and adiposity with vitamin D, glucose, and lipoprotein metabolism in pregnancy.

Dietary and physical activity intervention including two counselling sessions in early pregnancy may result in modest dietary improvements in women at increased GDM risk. Moderate dietary changes could be expected after such low-intensity counselling. A similar phenomenon has been observed in studies to prevent T2D (Rautio et al. 2013). Despite the modest dietary improvements observed in this thesis, the standard nutrition counselling should be continued at the antenatal clinics to improve dietary intakes of pregnant women and probably those of their family members as well. By contrast, lifestyle counselling provided when planning a pregnancy was not successful in this study. Large controlled trials are needed to confirm whether lifestyle advice initiated already before pregnancy is superior to that initiated during pregnancy in terms of the dietary modification. Moreover, investigating the efficiency of different types, contents, and amount of nutrition counselling and taking into account different subgroups of pregnant women would help in individualizing the counselling.

Substituting low-fat cheese for regular-fat cheese may help to lower GDM risk and improve maternal glucose metabolism in high-risk women. This supports the dietary recommendations for replacing high- and regular-fat dairy with low-fat dairy and should be emphasized when providing nutritional advice at the antenatal visits as well as when planning dietary intervention studies to improve glucose metabolism among high-risk women. Furthermore, as GDM is a heterogeneous condition, future studies should pay more attention to subgroups of women with various risk factors when examining diet-GDM associations.

This thesis provides novel findings of how maternal adiposity modifies the relationship of circulating 25(OH)D with GDM risk. Improvements in vitamin D status may help in lowering GDM risk and improving glucose metabolism in severely and morbidly obese pregnant women with an abnormal metabolic milieu. This would have great importance in public health with regard to vitamin D supplementation and its recommendations. However, large controlled trials with proper adjustments are required to conclude whether

improved vitamin D status has a clinical impact on GDM risk and maternal glucose metabolism particularly in severely and morbidly obese women. Moreover, future studies are required to confirm whether circulating vitamin D independently contributes to the development of GDM and glucose homeostasis or if it is rather an indicator of general health status.

The findings of this thesis suggest that improvements in diet quality based on the adherence to the NNR may, to some extent, help in modifying circulating lipoprotein particles to a less atherogenic form through a reduction in triglyceride-rich lipoprotein particle size. The possibilities of dietary modification in improving maternal lipoprotein particle profiles need to be confirmed in large controlled trials. This thesis investigating the alternative lipid parameters provides new insight into diet-lipid associations during pregnancy. Further evidence on the relationship between lipoprotein particle parameters related to CVD risk and dietary intakes in pregnancy is warranted. Additionally, maternal metabolic environment during gestation affects offspring health in later life. Thus, evaluation of diet in relation to alternative lipid parameters in pregnancy may add knowledge of the possibilities of maternal diets to promote future health of the child. In addition to total concentration and mean size of lipoprotein particles estimated in this thesis, the lipoprotein subfractions based on the particle size, namely the small, medium, and large size particles, are also considered as parameters in CVD risk prediction. These subfractions should be investigated in detail in future studies on diet-lipid associations during pregnancy.

Both obesity and GDM are associated with increased risk for future CVD and T2D. Thus, improvements in maternal glucose and lipid metabolism are essential in obese women and also in those who have had GDM in previous pregnancies. Diet is one of the modifiable factors that influence glucose and lipid metabolism. Overall, lifestyle advice in early pregnancy may result in modest dietary improvements, and dietary modifications may help to improve maternal glucose and lipoprotein metabolism among women at increased GDM risk. Further, as metabolic milieu during pregnancy affects the future health of the offspring, improvements occurring in glucose and lipid metabolism during fetal development may provide a more favourable basis for later metabolic health of the child. Future studies should investigate in more detail the factors that influence the individuals' response to nutrition and lifestyle counselling and the glucose and lipid response to dietary intakes during pregnancy. Moreover, further evidence from controlled trials is required to conclude whether severely and morbidly pregnant women benefit from higher vitamin D status and if additional vitamin D supplementation should be recommended when instructing these women on GDM prevention.

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