THE HETEROGENEITY OF GESTATIONAL DIABETES AND LONG-TERM EFFECTS OF LIFESTYLE INTERVENTION AMONG HIGH-RISK WOMEN

Hanna Emilia Huvinen

ACADEMIC DISSERTATION

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Supervised by

Adjunct professor Saila Koivusalo, MD PhD
Department of Obstetrics and Gynecology
University of Helsinki and Helsinki University Hospital

Professor Johan Eriksson
Department of General Practice and Primary Health Care
University of Helsinki and Helsinki University Hospital
and Folkhälsan Research Center

Professor Aila Tiitinen
Department of Obstetrics and Gynecology
University of Helsinki and Helsinki University Hospital

Reviewed by

Associate professor Terhi Piltonen, MD PhD
Department of Obstetrics and Gynecology
PEDEGO Research Unit, Medical Research Center
Oulu University Hospital, University of Oulu

Adjunct professor Juha Saltevo, MD PhD
Central Finland Central Hospital, Jyväskylä
University of Eastern Finland

Official opponent

Professor Elisabeth Mathiesen
Center for Pregnant Women with Diabetes
Department of Endocrinology
Rigshospitalet, University of Copenhagen, Denmark

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To my family
ABSTRACT

Gestational diabetes (GDM) complicates around 18% of all pregnancies in Finland. It has negative effects on the pregnancy, affecting both the mother and the child. Additionally, GDM tells about the woman’s predisposition to diabetes later in life. Lifestyle interventions have proven effective in preventing type 2 diabetes, but there is only little evidence of the effects of a pregnancy and postpartum intervention focusing on women at high risk for GDM.

The pathophysiological background of type 2 diabetes is known to be heterogeneous, and that is probably also true for GDM. Women with GDM differ from each other in their insulin sensitivity and insulin secretion, body composition, and presence of diabetes-related autoantibodies. Only a few studies, however, have focused on the importance of the heterogeneity of GDM during pregnancy and its impact on the future metabolic health of the woman.

The aim of this study was to evaluate the effects of a lifestyle intervention during pregnancy on metabolic health after delivery and to assess the heterogeneity of GDM during pregnancy and its influence on metabolic health 5 years postpartum.

To answer these questions, this thesis uses data from the RADIEL GDM prevention trial (2008–2014) and the RADIEL 5-year follow-up study (2013–2017). Originally, 724 high-risk women with a BMI ≥ 30kg/m² and/or a history of GDM entered the study either before conception or in early pregnancy. They were allocated to either a lifestyle intervention or to a control group. Combined diet and exercise intervention was provided by trained study nurses every 3 months before and during pregnancy, and at 6 weeks and 6 and 12 months after delivery. Five years after delivery, participants and their children were invited to a follow-up visit.

Study I assessed the postpartum effects of the lifestyle intervention and included the 200 participants with a normal glucose tolerance at enrollment who entered the study in early pregnancy and attended at least one study visit during the first postpartum year. The RADIEL intervention significantly reduced the incidence of impaired glucose regulation defined as IFG, IGT, or diabetes; 13.3% of the participants in the control group and 2.7% in the intervention group [crude OR 0.18 (95% CI 0.05, 0.69)] had glycemic abnormalities during the first postpartum year. Although there were no differences in weight retention, physical activity, or diet at one year postpartum, the intervention group managed to maintain a better diet.
Study II focused on the clinical characteristics of the 269 women entering the study in early pregnancy with normal glucose tolerance at enrollment. By dividing the participants into four groups (A, B, C, and D) based on their parity, BMI, and previous history of GDM, we identified an interesting risk group. Non-obese women with a history of GDM had the highest occurrence of GDM, at 35.9% compared to the other groups (9.7–20.8%, p<0.001), despite having better metabolic health in the first trimester. Diabetes-related autoantibodies did not provide an explanation for this finding.

In study III, we tested two of the best-performing GDM risk scores among 510 RADIEL women with known glycemic status during pregnancy. Both scores underestimated the probability of GDM in the total study population, and when tested separately in groups A, B, C, and D, the lowest detection rate was seen among the non-obese women. We were unable to find any additional markers of GDM risk. Simply by using a BMI ≥ 30kg/m² or previous GDM as risk markers, we identified a group with a GDM incidence of 50%, a similar performance to many more complicated models.

Study IV assessed the metabolic health of the 333 high-risk women attending the RADIEL 5-year follow-up study. Overall prevalence of impaired glucose regulation (IFG, IGT, or diabetes) was 15%, and 3.6% had type 2 diabetes. The prevalence was lowest at 8% among the primiparous obese women and highest at 26% among the obese women with a previous history of GDM (p=0.021). Metabolic syndrome was diagnosed in 25–39% of the obese women and in 11% of the non-obese (p<0.001). Five years postpartum among the non-obese women with a previous history of GDM, the prevalence of obesity based on fat percentage was 58%, although based on BMI, the number was only 14%. This group faced metabolic disorders at a significantly lower BMI (p<0.001).

In conclusion, a lifestyle intervention during pregnancy and the first postpartum year was successful in reducing the incidence of glycemic abnormalities by 82% during the first postpartum year. This might have positive implications for the future health of the whole family considering the long-term metabolic risks of the mother and the intergenerational cycle of obesity and diabetes. There are clinically distinct groups among GDM women with differences in metabolic markers and body composition. The heterogeneity of GDM may as well influence the challenges in creating a GDM risk score. Non-obese women have largely been overlooked previously, but in our study, they were not only at high risk for GDM but also for metabolic derangements 5 years postpartum at a lower BMI. Despite having a fairly normal BMI, they had a high body fat percentage resembling a so-called normal weight obesity. To conclude, these results support the IADPSG recommendation for universal OGTT screening for GDM. Non-obese women require more attention as no identifiable risk markers exist so far, and they
clearly are at risk for metabolic complications both during pregnancy and postpartum.
TIIVISTELMÄ


Tämän väitöstutkimuksen tavoitteena oli selvittää raskauden aikaisen ja synnytyksen jälkeisen elintapaintervention vaikutuksia suuren diabetesriskin omaavien naisten terveyteen synnytyksen jälkeen. Lisäksi tavoitteena oli tutkia, miten raskausdiabeteksen heterogeenisyydsilmenee raskauden aikana ja miten se vaikuttaa naisten terveyteen viisi vuotta synnytyksen jälkeen.


Ensimmäinen osatyö (I) selvitti raskaudenaikaisen elintapaintervention vaikutuksia synnytyksen jälkeiseen terveyteen keskityen niihin naisiin, joilla oli alkuraskaudessa vielä normaali glukoosianeenvaihdunta (200 naista). RADIEL-interventio vähensi merkittävästi glukoosianeenvaihdunnan häiriöitä (kohonneet paastoglukoosi, heikentynyt sokerinsieto tai tyypin 2 diabetes); 13.3%lla kontrolliryhmästä ja 2.7%lla interventioryhmästä [OR 0.18 (95% CI 0.05, 0.69)] todettiin poikkeava sokeriaineenvaihdunta ensimmäisen synnytyksen jälkeisen vuoden aikana. Ryhmien välillä ei todettu eroja painossa, liikunta-aktiivisuudessa tai ruokavaliossa vuosi synnytyksen jälkeen.
Toinen osatyö (II) keskittyi raskausdiabeteksen heterogeneisyyden tarkasteluun raskausaikana. Jakamalla alkuraskaudessa glukoosiaineenvaihdunnaltaan terner veututut tavat neljään ryhmään (A, B, C ja D) painoindeksin, syynnyttäneisyysen sekä raskausdiabeteshistorian suhteen onnistuimme löytämään yllättävän riskiryhmän. Normaalipainoiset tai vain lievästi ylipainoiset (BMI<30kg/m²) naiset, joilla oli ollut aiempi raskausdiabetes (C-ryhmä), olivat suurimmassa riskissä sairastua raskausdiabetekseen keskiraskaudessa. Muihin ryhmiin verrattuna (9.7–20.8%) raskausdiabeteksen ilmaantuvuus oli heillä merkittävästi suurempi (35.9%, p<0.001), vaikka he olivat alkuraskaudessa terveimpiä. Diabetekseen liittyvät vasta-aineet eivät selittäneet tätä löydöstä.

Kolmas osatyö (III) selvitti kahden kansainvälistä parhaimmaksi arvioidun riskipisteytyksen toimivuutta RADIEL-aineistossa (510 naista). Molemmat kansainvälistä pisteytykset aliarvioivat raskausdiabeteksen esiintyvyyden, ja alaryhmmissä (A, B, C ja D) testaaminen osoitti, että huonon erotteluuky oli C-ryhmässä (BMI<30kg/m² ja aiempi raskausdiabetes). Toisaalta käyttämällä yksinkertaista mallia (BMI >30kg/m² ja tai aiempi raskausdiabetes), onnistuimme löytämään yli 35%:n, jossa raskausdiabeteksen ilmaantuvuus oli noin 50% - samaa luokkaa kuin monimutkaisempi riskipisteytysten tulos.

Neljäs osatyö (IV) selvitti 333 seurantatutkimukseen osallistuneen naisen terveyttä viisi vuotta synnytyksen jälkeen. Poikkeava glukoosiaineenvaihdunta (kohonnut paastoglukoosi, heikentynyt sokerinsieto tai tyyppin 2 diabetes) todettiin heistä 15,6%;lta, ja 3,6%;lta oli tyyppin 2 diabetes. Sokeriaineenvaihdunnan haitoja esiintyvyyttä oli matalin (8%) ylipainoisen ensisynnyttäjien joukossa ja korkein (26%) ylipainoisilla naisilla, joilla oli ollut raskausdiabetes jo ennen RADIEL-tutkimusta (p=0.021). Vaikkia aiemmin normaalipainoissten nasiten joukossa vain 14% oli painoindeksin perusteella lihaviiva 5 vuotta synnytyksen jälkeen, kehon rasvaprosentti oli korkea (58%;lla. Heillä aineenvaihdunnan haittoja (metabolinen oireyhtymä tai glukoosiaineenvaihdunnan häiriö) todettiin jo merkittävästi matalammalla painoindeksillä (p<0.001).

Yhteenvetona voidaankin todeta, että elintapainterventio raskauden ja ensimmäisen synnytyksen jälkeisen vuoden aikana vähensi glukoosiaineenvaihdunnan häiriöitä synnytyksen jälkeen 82%;lla. Tällä voi olla positiivisia vaikutuksia koko perheen terveyteen ajatellen aidin pitkäaikaisterveyttä sekä sukupolvien välistä lihavuuden ja diabetesen noidanhehää. Naiset, joilla todetaan raskausdiabetes, eroavat toisistaan niin aineenvaihdunnaltaan kuin kehon koostumuksestaan, ja tämä heterogeneisyyys voi osaltaan haastaa myös riskipisteytysten kehittämistä. Usein normaalipainoiset naiset jäävät huomiotta, mutta tämän tutkimuksen perusteella myös heillä on korkea riski sairastua niin seuraavassa raskaudessa kuin vielä viisi vuotta synnytyksen jälkeenkin. Lähis normaalista
painoindeksistä huolimatta heillä oli varsin korkea kehon rasvaprosentti, muistuttaen ns. "normaalipainoista lihavuutta". Nämä tulokset tukevat kansainvälistä suositusta, jonka mukaan sokerirasitus olisi tehtävä kaikille raskaana oleville painosta riippumatta, ja korostavat synnytyksen jälkeisen ajan kansanterveydellistä merkitystä.
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After ten colorful years put into this thesis, I am finally here writing these words of gratitude. This has been a long and educational journey, and through these years numerous people have contributed to the success of my work. The department of Obstetrics and Gynecology of Helsinki University Hospital provided the surroundings for my research and I want to thank the head of the department professor Seppo Heinonen, professor Juha Tapanainen, professor Oskari Heikinheimo, adjunct professor Mika Nuutila, adjunct professor Veli-Matti Ulander, adjunct professor Jari Sjöberg and adjunct professor Aydin Tekay for the academic environment for performing this study.

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### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
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<tr>
<td>CGM</td>
<td>Continuous Glucose Monitoring</td>
</tr>
<tr>
<td>DASH</td>
<td>Dietary Approach to Stop Hypertension</td>
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<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
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<tr>
<td>DOHaD</td>
<td>Developmental Origins of Health and Disease</td>
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<td>EASD</td>
<td>European Association for the Study of Diabetes</td>
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<tr>
<td>EBCOG</td>
<td>European Board and College of Obstetrics and Gynaecology</td>
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<tr>
<td>FIGO</td>
<td>International Federation of Gynaecology and Obstetrics</td>
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<tr>
<td>GADA</td>
<td>Glutamic acid decarboxylase antibody</td>
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<td>GCK</td>
<td>Glukokinase</td>
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<tr>
<td>GCT</td>
<td>Glucose Challenge Test</td>
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<td>GDM</td>
<td>Gestational Diabetes</td>
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<td>GI</td>
<td>Glycemic Index</td>
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<td>GWG</td>
<td>Gestational Weight Gain</td>
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<td>HAPO</td>
<td>Hyperglycemia and Adverse Pregnancy Outcome Study</td>
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<tr>
<td>HbA1c</td>
<td>Glycated Hemoglobin</td>
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<td>HOMA-β</td>
<td>Homeostatic Model Assessment (β-cell function)</td>
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<tr>
<td>HOMA-IR</td>
<td>Homeostatic Model Assessment (Insulin resistance)</td>
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<tr>
<td>IADPSG</td>
<td>International Association of the Diabetes and Pregnancy Study Groups</td>
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<td>ICA</td>
<td>Islet cell antibody</td>
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<tr>
<td>IFG</td>
<td>Impaired Fasting Glucose</td>
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<td>IGT</td>
<td>Impaired Glucose Tolerance</td>
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<td>IPD</td>
<td>Individual Participant Data analysis</td>
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<tr>
<td>LADA</td>
<td>Latent Autoimmune Diabetes in Adults</td>
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<td>LGA</td>
<td>Large for Gestational Age</td>
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<td>MetS</td>
<td>Metabolic Syndrome</td>
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<td>MODY</td>
<td>Maturity Onset Diabetes of the Young</td>
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<td>MTNR</td>
<td>Melatonin receptor</td>
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<td>NCEP/ATP III</td>
<td>National Cholesterol Education Program/Adult Treatment Panel III</td>
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<td>NPH</td>
<td>Neutral Protamine Hagedorn insulin</td>
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<td>NWO</td>
<td>Normal Weight Obesity</td>
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<td>OGGTT</td>
<td>Oral Glucose Tolerance Test</td>
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<td>PCOS</td>
<td>Polycystic Ovary Syndrome</td>
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<tr>
<td>RADIEL</td>
<td>The Finnish Gestational Diabetes Prevention study (Raskausdiabeteksen ennaltaehkäisy elintavoin)</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<tr>
<td>SGA</td>
<td>Small for Gestational Age</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1 INTRODUCTION

The prevalence of gestational diabetes (GDM) is increasing rapidly around the world (1), following the escalating epidemic of obesity and diabetes. In Finland in 2016, abnormal glucose tolerance complicated almost one out of five pregnancies (18%). Prevalence rates vary around the world, ranging from 25% in Singapore to less than 2% in Ireland (2). Ethnic background plays an important role but diagnostic criteria and screening strategies also vary highly between countries (3, 4).

The gold standard for GDM diagnosis is an oral glucose tolerance test (OGTT), which is usually performed in mid-pregnancy between 24 and 28 weeks of gestation (5). High-risk groups, such as women with a BMI ≥ 35 kg/m², early glucosuria in pregnancy, history of GDM, polycystic ovary syndrome (PCOS), or family history of diabetes should attend an OGTT screening already in the first trimester between 12 and 16 gestational weeks. According to Finnish National Guidelines, the thresholds in plasma glucose for diagnosis are 5.3, 10.0, and 8.6 mmol/l (for 0, 1, and 2 hours in the 75 g 2-hour OGTT). For the majority of women, modification of diet and an increase of exercise is sufficient to normalize glucose values, but 10–20% (6) of women need additional metformin and/or insulin treatment.

GDM has an extensive impact on both the mother and the child. Women with GDM are more prone to complications during pregnancy and labor; e.g., pre-eclampsia, birth trauma, and caesarean sections are more frequent among women with GDM (7). Children are at risk for, e.g., macrosomia, birth trauma, asphyxia, and neonatal hypoglycemia (8). Moreover, the influence of GDM extends from the pregnancy and childbirth onward. Women with a previous history of GDM are seven times more likely to develop diabetes later in life, and their children also have more obesity and diabetes (9, 10).

Fortunately, there is some evidence that lifestyle interventions could prevent GDM, although results are somewhat inconsistent (11). The RADIEL study succeeded in reducing GDM incidence by 39% (12), and unlike in other GDM prevention studies, the intervention continued during the first postpartum year. Concerning the prevention of type 2 diabetes by lifestyle intervention, studies have shown beneficial effects (13, 14). Focusing on a high-risk population and starting the intervention earlier could potentially improve the results. Nevertheless, there is only limited knowledge concerning the effects of a lifestyle intervention during pregnancy and the early postpartum period on future maternal health (15).
The pathophysiological background of type 2 diabetes is known to be heterogeneous (16, 17); a recent Scandinavian study identified five subgroups of diabetes with varying risks of complications and disease progression (17). Growing evidence suggests that this heterogeneity also concerns GDM (18–20). Although obesity is a major risk factor for GDM, not all GDM women are obese. In addition to body size, there is also heterogeneity in the glucose metabolism of GDM women. Half of them are mostly insulin resistant, and one third have mainly defective insulin secretion (20). This seems clinically significant; in a recent study, only insulin resistance was associated with macrosomia and higher caesarean section rates (20). There is, however, a lack of studies focusing on the heterogeneity of GDM during pregnancy and its effect on the future health of the mother.

In addition to obesity, there are several other risk factors for GDM. A family history of diabetes, previous history of GDM, certain ethnicities such as Asian and Hispanic, advanced maternal age, and previous macrosomia are associated with a higher GDM risk. Several risk scores have been developed (21) to fight the increasing demands for early diagnosis and the simultaneously rising financial costs. These risk models usually take advantage of simple clinical data and aim at easy identification of women at high GDM risk. Similar risk equations have been successful in detecting people at risk for type 2 diabetes (22). According to a recent validation study (21), however, GDM scores have been performing only moderately. Hypothetically, the heterogeneity of GDM could be one underlying reason for the challenges in creating a successful GDM risk score.
2 REVIEW OF THE LITERATURE

2.1 BACKGROUND

2.1.1 HISTORY AND DEFINITION OF GESTATIONAL DIABETES

Gestational diabetes (GDM) is a disorder of glucose metabolism that is first detected during pregnancy. The first studies on women with diabetes during pregnancy date back to 1882, when maternal mortality among these women was as high as 60% and perinatal mortality was 47% (23). The main diagnostic method in those early days was the detection of glucose in the urine (24). The underlying causes of glucosuria were still unknown, but there were suggestions of pregnant women being “less tolerant” to glucose. Although most studies focused on overt diabetes during pregnancy, recurrent glucosuria also started to gain attention. In the early 1900s, Williams was the first to recognize this condition (25), which was later called gestational diabetes. He characterized women with recurrent glucosuria, which could manifest again in subsequent pregnancies. This condition (26), which might later develop into permanent diabetes, was also associated with macrosomia and a greater risk of toxemia, i.e., pre-eclampsia. Subsequently, blood glucose testing and glucose tolerance tests (GTT) became the methods for diagnosis. Discovery of insulin in 1921 revolutionized the treatment of diabetes during pregnancy, immensely improving maternal survival.

After the 1940s, several steps were taken toward modern screening and treatment of GDM. Studies showed (27, 28) that infants of mothers who later developed diabetes were at higher risk of macrosomia and perinatal mortality. The term GDM was first used in 1957 by Carrington (29), and the first prevalence study demonstrated a GDM rate of 3.4% (30). The first gold standard of GDM diagnostic criteria was based on a large follow-up study by Sullivan and Mahan (31), which focused on the severity of pregnancy hyperglycemia and its association with the future risk of type 2 diabetes. Short-term obstetric complications, however, did not receive any attention.

After the first international workshop on GDM in 1979, several modifications have been made to the diagnostic criteria, and the debate on the importance of mild hyperglycemia and the appropriate thresholds for diagnosis still continues. The most recent classification and diagnostic thresholds (5) came in 2010 from the International Association of Diabetes and Pregnancy Study Groups (IADPSG):
GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy that is not clearly overt diabetes.

2.1.2 PATHOPHYSIOLOGY OF GESTATIONAL DIABETES

Normal pregnancy induces hormone-regulated metabolic changes to ensure adequate transfer of nutrients to the fetus. Insulin resistance increases throughout the pregnancy, and hepatic gluconeogenesis aims at controlling adequate fasting glucose levels (32, 33). In general, by the end of the third trimester, insulin sensitivity decreases by 50%, hepatic glucose production increases by 30%, and insulin secretion by 200% (33). Pancreatic beta cells undergo changes leading to the enlargement of the beta cell pool and enhanced secretory capacity of insulin (34). These changes are mediated mainly through placental hormones and are related to the post-receptor insulin signalling cascade. Other hormones inducing pregnancy-related metabolic changes are estrogen, progesterone, cortisol, prolactin, and glucagon (35).

In gestational diabetes, the body is unable to meet the increasing demands for insulin due to increased insulin resistance and/or defective function of pancreatic beta cells. This results in hyperglycemia. The gradient between maternal and fetal glucose levels drives the passive transportation of maternal blood glucose to the fetus through the placenta (36). This, as presented by Jorgen Pedersen in the 1950s (37, 38), leads to fetal hyperinsulinemia, which in turn increases fat accumulation, metabolic changes, and accelerated fetal growth.

The mechanisms behind the increased insulin resistance are numerous. In addition to the placental hormones (human placental lactogen and placental growth hormone), adipose tissue also plays an important role. It is endocrinologically active (39) and further increases the inflammatory state of pregnancy (40). The adipose tissue insulin resistance results in the increased release of free fatty acids, and this lipolysis increases insulin resistance and hepatic glucose production, resulting in greater fuel transport to the fetus (41). Lower adiponectin and higher tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) concentrations are also associated with GDM (35). Together, placental hormones, low-grade inflammation, and excess lipolysis are central in the pathogenesis of insulin resistance in GDM.

Deficiencies in insulin secretion among GDM women are less well understood. Inherited monogenic forms of diabetes (42) or autoimmune destruction of the beta cells (43) can compromise beta cell function, but in numerous cases, the
underlying cause remains unclear. Hypothetically, previous stress of beta cells could offer one explanation, as every subsequent pregnancy increases the risk for GDM by threefold (44). An additional explanation for the decreased capacity of beta cells to secrete insulin might be through fetal programming (45). This association has been seen in both small-for-gestational-age (SGA) and large-for-gestational-age (LGA) growth patterns.

Figure 1. Pathophysiology of gestational diabetes

2.1.3 DIAGNOSING GESTATIONAL DIABETES

The first suggestion for screening all pregnant women for glucosuria dates back to the 1950s. Women with obesity, glucosuria, family history of diabetes, or poor obstetric history were additionally recommended to undergo a glucose tolerance test (GTT) (46). In 1964, Sullivan and Mahan created the first official criteria for GDM diagnosis (31) based on the association of hyperglycemia during pregnancy and future diabetes risk. In a 100g 3h-OGTT, the suggested thresholds were 5.0, 9.1, 8.0, and 6.9 mmol/l at 0, 1, 2, and 3 hours, respectively. Since that time, venous plasma has replaced whole venous blood as the source of glucose sampling. Table 1 presents the evolution of GDM diagnostic criteria.
In 2010, the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) study (7) induced the biggest change in GDM criteria in recent years. Instead of future diabetes risk, the main focus was on maternal and fetal pregnancy complications among the 23,000 participants. The results demonstrated increasing rates of high birth weight, cesarean sections, neonatal hypoglycemia, and cord blood c-peptide with increasing glucose categories starting below previous diagnostic thresholds. This encouraged the IADPSG to recommend new diagnostic thresholds (5), which were later endorsed by the WHO and the ADA (American Diabetes Association) as well. According to these criteria, GDM diagnosis results from meeting or exceeding one or more of the following values: 5.1, 10.0, and 8.5 mmol/l at 0, 1, and 2 hours in a 75 g 2h OGTT. These cut-offs are based on 1.75 higher odds of facing adverse pregnancy outcomes compared to mean glucose values.

Although the IADPSG recommends universal screening in the second trimester, screening strategies still vary globally. Many countries use a risk-factor–based screening or a two-step screening, where initial testing is a 50 g glucose challenge test (GCT) (47). Only women with a positive screening or certain risk factors will undergo an OGTT.

Finland has been following its own screening strategy (Current Care Guidelines), which was reviewed by local experts in 2013 (48). Thresholds in the 75 g 2h OGTT are 5.3, 10.0, and 8.6 mmol/l for 0, 1, and 2 hours, respectively. An OGTT is recommended for almost all pregnant women, with the exception of young women (under 25 years of age) with a BMI under 25 kg/m² and multiparous women (under 40 years of age) with a BMI under 25 kg/m² and no history of macrosomia or GDM. Early OGTT in the first trimester is recommended for women with a BMI over 35 kg/m², previous GDM, early glucosuria during pregnancy, PCOS, oral glucocorticoid treatment, or family history of diabetes.
Table 1. Diagnostic strategies for GDM.

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Glucose</th>
<th>Abnormal values</th>
<th>0-h</th>
<th>1-h</th>
<th>2-h</th>
<th>3-h</th>
<th>mmol/l</th>
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<td><strong>Two-step</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Sullivan and Mahan (31) 1964</td>
<td>50 g</td>
<td>≥ 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>100 g</td>
<td>≥ 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.0</td>
<td>9.1</td>
<td>8.0</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Carpenter and Coustan (49) 1982</td>
<td>50 g</td>
<td>≥ 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>100 g</td>
<td>≥ 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.3</td>
<td>10.0</td>
<td>8.6</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>ACOG 2018 (50) (or Carpenter-Coustan)</td>
<td>50 g</td>
<td>≥ 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>100 g</td>
<td>≥ 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.8</td>
<td>10.6</td>
<td>9.2</td>
<td>8.0</td>
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<tr>
<td><strong>One-step</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO (51) 1999</td>
<td>75 g</td>
<td>≥ 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.1</td>
<td>-</td>
<td>7.8</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>IADPSG (52) 2010</td>
<td>75 g</td>
<td>≥ 1&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>10.0</td>
<td>8.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ADA/EASD (53) 2010</td>
<td>75 g</td>
<td>≥ 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.1</td>
<td>10.0</td>
<td>8.5</td>
<td>-</td>
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</tr>
<tr>
<td>WHO (54) 2013</td>
<td>75 g</td>
<td>≥ 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.1</td>
<td>10.0</td>
<td>8.5</td>
<td>-</td>
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</tr>
<tr>
<td>Finnish Current Care Guidelines (48)2013</td>
<td>75 g</td>
<td>≥ 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.3</td>
<td>10.0</td>
<td>8.6</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Venous whole blood, <sup>b</sup>Venous serum, <sup>c</sup>Venous plasma

One important task is to differentiate GDM from pre-existing diabetes before pregnancy. Type 1 and type 2 diabetes are associated with more severe complications, such as congenital malformations that are related to early pregnancy hyperglycemia, and pre-existing diabetes requires more detailed follow-up and care. The current recommendation by the IADPSG (5) is to use a first-trimester fasting plasma glucose equal to or greater than 7.0 mmol/ml (126 mg/dl) or HbA1c equal to or greater than 6.5% (47.5 mmol/mol) to diagnose overt diabetes.
2.1.4 PREVALENCE

Along with obesity and type 2 diabetes, the prevalence rates of GDM are increasing epidemically. The overall frequency in 15 centers around the world collaborating with the HAPO study was 17.8% (55), and in Finland in 2016, it reached 18% (Figure 1). Comparing the rates in different countries is, however, rather difficult due to the varying screening strategies and diagnostic thresholds. Generally, the implementation of the lower cut-offs of the IADPSG criteria (2010) has led to a two- to fourfold increase in the prevalence rates (2, 56, 57).

In addition to ethnic differences, there are also other population characteristics that influence the diverging prevalence rates. Age is an important risk factor, and maternal age at the first childbirth varies among countries, from 18 years old in Chad and Bangladesh to 30 years old in Singapore and Switzerland, for example (58). The level of urbanization plays an additional role as there are studies showing that even among the same population, the GDM prevalence rates in cities can be up to 5 times higher (59) than in rural areas.

According to a recent review (2), the prevalence rates inside the WHO regions show high variations. The highest median regional rates were reported in the Middle East and North Africa at 12.9% (8.4–24.5%), as well as in Southeast Asia at 11.7% (8.1–18.3%) and the Western Pacific at 11.7% (4.5–25.1%). Europe had the lowest prevalence at 5.8% (1.8–22.3%).

Local screening policies and the uptake of screening affect these country-specific rates, which are presented in Table 2. For example, in Ireland, the country with the lowest prevalence (2), the uptake of screening is rather low and highly affected by the geographical region (60). On the other hand, another study reported the prevalence in Ireland to be 10% (61), demonstrating the difficulties in assessing the true prevalence rates of GDM around the world.
**Table 2.** Prevalence of GDM, adapted from Zhu et al 2016(2)

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>PREVALENCE OF GDM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGAPORE</td>
<td>25.1</td>
</tr>
<tr>
<td>UNITED ARAB EMIRATES</td>
<td>24.5</td>
</tr>
<tr>
<td>NORWAY</td>
<td>22.3</td>
</tr>
<tr>
<td>MALAYSIA</td>
<td>18.3</td>
</tr>
<tr>
<td>CUBA</td>
<td>16.6</td>
</tr>
<tr>
<td>QATAR</td>
<td>16.3</td>
</tr>
<tr>
<td>INDIA</td>
<td>13.6</td>
</tr>
<tr>
<td>BARBADOS</td>
<td>11.9</td>
</tr>
<tr>
<td>IRAN</td>
<td>8.4</td>
</tr>
<tr>
<td>CANADA</td>
<td>6.5</td>
</tr>
<tr>
<td>BRAZIL</td>
<td>5.7</td>
</tr>
<tr>
<td>JAPAN</td>
<td>4.5</td>
</tr>
<tr>
<td>IRELAND</td>
<td>1.8</td>
</tr>
</tbody>
</table>

**Figure 2.** Prevalence of GDM in Finland based on pathological OGTTs from year 2006 to 2016 (National Institute of Health and Welfare)
Figure 3. Pregnancies (%) where OGTT was performed from 2006 to 2016 (National Institute of Health and Welfare)

2.1.5 TREATMENT OF GESTATIONAL DIABETES

The goal of GDM treatment is to normalize maternal glycemic levels; an effective treatment is known to reduce the adverse pregnancy outcomes (62). The primary treatment strategy is generally lifestyle advice combining diet and exercise (63). Self-monitoring of blood glucose levels helps to achieve normoglycemia (64), and in Finland, the recommendation is to aim for a fasting glucose under 5.5 mmol/l, and one hour after a meal, it should be under 7.8 mmol/l.

In recent years, continuous glucose monitoring (CGM) has gained more and more interest. One Chinese study showed beneficial effects such as lowering cesarean section rates, and improving neonatal outcomes by CGM among women with GDM (65), and an RCT is ongoing (66). If these changes are not adequate, the initiation of medical treatment by insulin or oral antidiabetic medication should follow. Based on a recent Cochrane review (2017), lifestyle interventions in GDM women reduced the risk for LGA and macrosomia, postpartum weight retention, and postpartum depression, but had no effect on cesarean section rates, gestational hypertension, induction of labor, perineal trauma, or neonatal hypoglycemia (63).
2.1.5.1 Diet

Foods containing carbohydrates are the main sources affecting glucose levels. Both the type and the amount of carbohydrates are important for balance: Fiber and complex carbohydrates should be preferred over refined ones, simple glucose and fructose. The glycemic index (GI) is used to characterize the capability of food products to produce postprandial glucose elevation. Outside pregnancy, low-GI diets are proven effective in controlling glucose levels of patients with diabetes (67), but results concerning GDM are scarce (68).

Equal distribution of carbohydrates throughout the day and the addition of fiber to the diet are beneficial (69). If using refined carbohydrates, restriction to less than 45% of energy from carbohydrates might be beneficial (70), but if low-GI products are used, then up to 60% of energy can be derived from carbohydrates without compromising the treatment of GDM (71).

Fat consumption has an additional effect on glucose metabolism. Polyunsaturated fatty acids may protect from increased insulin resistance, whereas saturated fatty acids can increase glucose and insulin levels in GDM women (72).

The scientific evidence suggesting a specific diet is limited. A recent Cochrane review (73) summarized the effects of 10 different dietary approaches from 19 randomized controlled trials. There was no difference between diet types and the effect on incidence of pre-eclampsia, large-for-gestational-age newborns, perinatal deaths, type 2 diabetes development for the mother, and a composite outcome of neonatal mortality or morbidity. Dietary Approaches to Stop Hypertension (DASH) reduced the cesarean section rate, but the other types of diet had no effect. In the RADIEL study, adherence to the Nordic Nutritional Recommendations (NNR) was associated with lower post-glucose load values in the second trimester OGTT (74).

2.1.5.2 Exercise

Exercise is generally recommended for GDM women as part of lifestyle advice. In studies among people with type 2 diabetes, exercise improves insulin sensitivity in the skeletal muscle and is therefore considered beneficial for glycemic control (75). Physical activity increases the expression of several elements in the insulin signalling pathway, and it has other general effects facilitating glucose management: decreases hepatic gluconeogenesis, increases skeletal muscle blood flow (76), and reduces the insulin resistance induced by lipids (77).
Among GDM women, low- to moderate-intensity exercise, aerobic training, and resistance training influenced glucose levels and reduced the needed amount of insulin (78–81), also aiding in the restriction of gestational weight gain (GWG). There is, however, not adequate evidence on the safety and efficacy of specific exercise types or frequencies for GDM women. In the general pregnant population, exercise seems to be safe and does not increase fetal risks (82), but the current guidelines recommend avoiding the types of exercise that may cause a risk of trauma (83). Physical activity during pregnancy might potentially lead to sustainable positive lifestyle changes that are beneficial for long-term health.

2.1.5.3 Pharmaceutical therapy
Traditionally, medical treatment of GDM was based on insulin, but recent years have brought evidence of the safety and benefits of oral antidiabetic drugs such as metformin and glibenclamide.

Glibenclamide is a second-generation sulfonylurea, which did not seem to cross the placenta in early studies (84). This finding has since been questioned. In the first RCT (85) comparing glibenclamide with insulin, all outcomes were comparable. A systematic review, however, found that risks for neonatal hypoglycemia and macrosomia in the glibenclamide group were twofold (86). Metformin, on the other hand, crosses the placenta freely, but studies from PCOS women with long-term use of metformin have shown no teratogenic effects or adverse fetal outcomes (87). The biggest RCT Metformin in Gestational diabetes (MiG) (88), comparing metformin with insulin, reported less neonatal hypoglycemia but higher rates of preterm birth in the metformin group. A systematic review, on the other hand, showed no increase in preterm births (89). At the 2-year follow-up of the MiG trial, children exposed to metformin had more subcutaneous fat (90), and studies on women with PCOS have reported similar findings (91). The 7–9-year follow-up of the MiG trial just recently showed that children exposed to metformin were larger (e.g., weight, waist, skinfold, BMI), but there were no differences in metabolic markers or body composition (92).

When comparing metformin with glibenclamide, the failure rate in most studies is up to twofold higher, meaning that more women using metformin need additional insulin (93). However, in a recent BMJ review and meta-analysis comparing glibenclamide, metformin, and insulin, the metformin group presented with less GWG, macrosomia, and LGA babies compared to glibenclamide (86), and therefore, e.g., FIGO recommends (94) initiating the treatment with metformin. Oral antidiabetic medications are often preferred by the patients, although the gastrointestinal side effects, which are encountered by 5% of non-pregnant patients (95), can be an obstacle for sufficient dose increase of metformin. A Cochrane review in 2017 concluded
that so far, there is limited data to recommend one oral antidiabetic over another, and future studies are needed to fully estimate their long-term effects on both the mother and the offspring (96).

If adequate glucose levels are not achieved with metformin, additional insulin treatment should begin. Traditionally, neutral protamine hagedorn (NPH) insulin has been used in combination with short-acting insulin for meals, but there is growing evidence that insulin analogues lispro (97), aspart (98), detemir (99), and glargine (100, 101) are also safe. New insulin analogues often achieve better glycemic control with less risk of hypoglycemias and with similar pregnancy outcomes.

### 2.1.6 CONSEQUENCES

#### 2.1.6.1 Short-term consequences

**Mother**
Women with gestational diabetes are at increased risk for several complications during pregnancy and childbirth (7, 102). Many short-term consequences of gestational diabetes are associated with accelerated fetal growth. During labor, women with GDM are at increased risk for cesarean sections, third- and fourth-degree tears, shoulder dystocia, and operative vaginal deliveries. A higher cesarean section rate further increases complications during the early postpartum period and in the following pregnancy. Additionally, the rate of spontaneous preterm birth is associated with GDM independent of co-existing pregnancy complications (103). GDM also increases the risk for induction of labor among non-obese women by 1.2-fold and among obese by 1.8-fold (104), but the risk also depends on the cervical exam and parity (105).

The odds for pre-eclampsia are 2.3 times (106, 107) higher, and in Finland, about 20% of GDM women develop either gestational hypertension or pre-eclampsia (108). Pre-eclampsia is a pregnancy-specific heterogeneous disorder with hypertension, proteinuria, and various degrees of other symptoms leading to increased maternal and neonatal morbidity and mortality (109). GDM women also have higher odds for polyhydramnios (OR 6–7) (110), which can lead to preterm birth and discomfort of the mother.

The association between mental well-being and GDM still remains controversial. Some studies have shown a higher risk of prenatal and
postnatal depression among GDM women (111) while others indicate no connection (112). According to a systematic review, there is no consensus as to whether diabetes during pregnancy increases the mother’s risk for depression or if depression leads to a higher incidence of GDM (113). In the RADIEL study, depressive symptoms were more common among women at high risk for GDM compared to the normal pregnant population, but the difference disappeared after adjustment for BMI, income, and age (114).

Child
Fetal hyperinsulinemia and increased maternal supply of glucose, lipids and amino acids result in accelerated growth, macrosomia, and higher accumulation of adipose tissue (38, 115). The enhanced growth can be seen already between 20 to 28 gestational weeks, and it is further stimulated by maternal obesity (116). Even at a normal weight, fetuses from GDM pregnancies often have a higher fat percentage, which can be detected by ultrasound as early as 20 gestational weeks (117, 118). Macrosomia elevates the risk for birth injuries (119) and along the enhanced metabolic rate, oxygen consumption and the incidence of polycythemia also increases. This can lead to hyperbilirubinemia (8) and higher risk of asphyxia (119) during late pregnancy and childbirth. Hyperinsulinemia also increases the risk for neonatal hypoglycemia (120) and fetal cardiomyopathy (121) and impairs the synthesis of pulmonary surfactant (122), resulting in a higher risk of neonatal respiratory distress syndrome. According to a large cohort study (123), children of GDM mothers are at additional risk for preterm birth (OR 1.3) and cardiac malformations (OR 1.3).
2.1.6.2 Long-term consequences

Mother
Women with a history of GDM are seven times more likely to experience diabetes in the future (9). After pregnancy, insulin sensitivity and beta cell function decline over time independent of adiposity (124), and studies have also demonstrated an increased subclinical inflammation and a decreased vascular function (125, 126). After 10 years, it is estimated that 50% of women with GDM history have already been diagnosed with diabetes (127, 128). The rates vary between studies depending on the diagnostic criteria, screening strategy, and population. In a retrospective analysis of a multiethnic population 12 weeks postpartum, 24.4% had IFG or IGT, and 1.5% had diabetes (129). In another study applying the IADPSG criteria (130), the cumulative incidence of abnormal glucose tolerance 5 years postpartum was 26% among GDM women diagnosed. A Sri Lankan retrospective cohort study comparing GDM women to those with normal glucose tolerance during pregnancy (131), on the other hand, demonstrated as high as tenfold the risk for type 2 diabetes in a 10-year follow-up, emphasizing the effect of ethnicity.
The severity of glucose intolerance during pregnancy is associated with future diabetes risk, with an increasing risk for women with medically treated GDM (132) and higher glucose concentrations in the pregnancy OGTT (133) or HbA1c. Other factors related to diabetes risk are BMI, family history of diabetes, age, early diagnosis of GDM, multiparity, hypertensive disorders of pregnancy, PCOS, and preterm delivery (132).

Additionally, metabolic syndrome (MetS) is more common among women with a history of GDM (134, 135). In a Finnish follow-up study, 16% of women at high GDM risk (136) were diagnosed with MetS at 1 year postpartum. The risk of MetS seems to be associated with a severity of glucose intolerance during pregnancy (135), and it independently increases the predisposition to diabetes (137, 138). Both diabetes and MetS are further associated with cardiometabolic diseases and increased morbidity and mortality among women (139, 140).

Due to the high risk profile of women with previous GDM, the American Diabetes Association (ADA) (53) and the Finnish Current Care Guidelines (48) both recommend an early postpartum OGTT 6–12 weeks after delivery to diagnose persisting diabetes. Since then, screening intervals should be based on individual risk estimate, but should not exceed 3 years. Weight control and breastfeeding should be recommended to potentially prevent or delay diabetes diagnosis (141).

**Child**

Children born to GDM mothers have a higher risk of adiposity (142) independent of their birth weight (10), as well as obesity and higher risk of diabetes (10, 143, 144). Epigenetic mechanisms could be mediators of the adverse metabolic profile of offspring from GDM pregnancies. Neurodevelopmental consequences have also been studied, and it seems that these children are at higher risk for cognitive impairment (145) and poorer performance at school (146).
### Table 3. Consequences of GDM

<table>
<thead>
<tr>
<th>MOTHER</th>
<th>SHORT-TERM COMPLICATIONS</th>
<th>LONG-TERM COMPLICATIONS</th>
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<td>Pre-eclampsia</td>
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<tr>
<td>Adiposity</td>
<td></td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Birth injuries</td>
<td></td>
<td>Neurocognitive impairment</td>
</tr>
<tr>
<td>Polycythemia</td>
<td></td>
<td></td>
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<tr>
<td>Hyperbilirubinemia</td>
<td></td>
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<tr>
<td>Asphyxia</td>
<td></td>
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<tr>
<td>Neonatal hypoglycemia</td>
<td></td>
<td></td>
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<tr>
<td>Fetal cardiomyopathy</td>
<td></td>
<td></td>
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<tr>
<td>Neonatal respiratory distress syndrome</td>
<td></td>
<td></td>
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<tr>
<td>Preterm birth</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.2 POTENTIAL FOR PREVENTION

2.2.1 PREVENTION OF GESTATIONAL DIABETES

The rationale for GDM prevention by lifestyle interventions comes from studies focusing on the prevention of type 2 diabetes (13, 14). These studies have suggested that success lies in a comprehensive approach combining several small changes that can be maintained for a longer period (147).

Since 2000, there have been numerous studies evaluating intervention strategies for GDM prevention. Some have been based on exercise or diet alone, but most studies have provided combined lifestyle advice. In 2015, Bain (11) and colleagues reviewed contemporary GDM prevention studies and found no effect on the incidence of GDM. Since then, however, several intervention studies have been published, and in 2017, an updated Cochrane review including 23 studies (148) found a moderate effect on reducing GDM, preterm birth, and gestational weight gain (GWG). Another systematic review in 2017 by Song (149) included 29 trials and found similar effects on reducing GDM incidence. Recently, an Individual Participant Data (IPD) analysis combining data from 36 interventions (150) including 12,343 participants found an effect on GWG and cesarean section rate, but not on GDM incidence.

Individual GDM prevention studies have provided conflicting results; heterogeneous study populations, participants with different risk factor profiles, and various intervention intensities have probably influenced the overall results. Most of the studies have focused on overweight or obese populations, but despite reaching their goal of limiting GWG, many studies showed no effect on GDM incidence. The biggest trial, the Australian LIMIT (151), included 2152 overweight or obese women. The intervention did not influence maternal outcomes but it reduced the number of newborns weighing over 4000 g. Another big study, UPBEAT (The UK Pregnancies Better Eating and Activity Trial 2015), had 1555 obese participants (152) and demonstrated a modest effect on GWG, diet, and physical activity while reporting no effect on the incidence of GDM or LGA. One of the most recent studies was the European collaboration study DALI (Vitamin D and Lifestyle Intervention for GDM Prevention), which also included obese women (n=436) with a BMI over 29 kg/m² and compared the effect of diet, exercise, or combined lifestyle intervention (153). Diet intervention improved healthy eating, exercise intervention resulted in increased physical activity, and combined intervention in addition to improving lifestyle reduced GWG. In relation to GDM prevention, all arms were ineffective.

Lately, there have also been successful intervention trials (12, 154–156). One common feature between these is the early initiation of the intervention. Both
Jing (154) and Bruno (155) recruited overweight women before 12 gestational weeks, and they both recorded positive effects on GDM incidence. The RADIEL study in Finland (12) was one of the successful ones, showing a 36% decrease in GDM incidence. Its first study visit took place on average at 13 gestational weeks. The first study visit was at 14 weeks of gestation (mean) in LIMIT, at 15 weeks (mean) in DALI, and at 15–19 weeks in UPBEAT. However, not all the studies starting in early pregnancy were successful.

In addition to different study designs, GDM trials have also had different approaches concerning the target population. There are several studies focusing on risk populations, mostly based on obesity, and a few, including RADIEL, that also recruited women with other risk factors including a history of previous GDM (12, 157–159). There have also been numerous studies targeting the general population (154, 160–166). Two reviews and meta-analyses have aimed at clarifying the effects on different study populations: Interventions focusing on the normal weight, low-risk population showed no effect (167), but dietary interventions focusing on women with at least one risk factor reduced the incidence of GDM (168).

### 2.2.2 PREVENTION OF TYPE 2 DIABETES

Generally, type 2 diabetes prevention trials aim to influence known risk factors for diabetes, such as postpartum weight retention and a diet high in energy and saturated fat; it may also promote beneficial behavioral changes such as breastfeeding and exercise. Delivery of the intervention can be either through individual sessions, group sessions, or telephone or internet. The usual enrollment is a few weeks to many years after delivery, with only a few interventions starting during the pregnancy and continuing into the postpartum period (12, 15, 169, 170). A Taiwanese study focused on preventing weight retention: Compared to an intervention started only after delivery, starting an intervention during pregnancy and continuing during the postpartum year resulted in less weight retention (170). Other studies have also suggested that an intervention already starting during pregnancy and continuing during the postpartum period would be feasible and efficient (15).

#### 2.2.2.1 Interventions during pregnancy

Pregnancy is often considered to be a good period to improve lifestyle due to better motivation among the women (171), and there has been hope that the benefits could be maintained after delivery. The Danish LiP (Lifestyle in Pregnancy) study (172) focusing on obese women and aiming at weight control during pregnancy managed to reduce GWG, but there was no effect on the
postpartum weight retention 6 months after delivery (173). Similarly, the Norwegian Fit-for-Delivery study (160) managed to decrease GWG, but again showed no effect on postpartum weight (174). Two follow-ups of pregnancy interventions (175, 176), UPBEAT (152) and ROLO (177), demonstrated that the participants in the intervention group were able to improve their diet, and a few studies have demonstrated positive effects on weight retention 6 weeks to 12 months postpartum (176, 178, 179). By far the longest follow-up results come from the Finnish study Nelli (157), which focuses on women at high GDM risk. There were no effects on maternal metabolic outcomes 7 years after delivery, but the prenatal intervention was cost-effective as there were fewer absences due to sickness; the mean costs per person were 30.6% lower including the health care costs, and for example, loss of productivity due to absence on sick days. Among the group adherent to the intervention, children had significantly lower BMIs (180).

### 2.2.2.2 Interventions postpartum

Since the positive effects from the Diabetes Prevention Program (DPP) study (181), there have been numerous interventions targeting women with previous GDM aiming at type 2 diabetes prevention. There have also been positive results from pharmacological interventions (181, 182), but the focus here will be on lifestyle interventions.

Recently, there have been several reviews showing mostly beneficial effects on reducing type 2 diabetes risk (183, 184). Table 4 presents the randomized controlled lifestyle intervention trials on women with previous GDM.
### Table 4. Randomized lifestyle intervention studies among women with previous GDM

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Inclusion criteria</th>
<th>Initiation</th>
<th>Interventions</th>
<th>Primary focus</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wein 1999 (185)</td>
<td>200</td>
<td>Age &gt;25 years</td>
<td>Within 2 years after delivery</td>
<td>Diet and exercise</td>
<td>Type 2 diabetes</td>
<td>3 months</td>
<td>T2D RR 0.63, p=0.12</td>
</tr>
<tr>
<td>Ratner 2008 (181)</td>
<td>239</td>
<td>Age &gt;25 years and postpartum IGT</td>
<td>Age &gt;25</td>
<td>Diet and exercise</td>
<td>Type 2 diabetes</td>
<td>24 weeks</td>
<td>T2D RR 0.50, p=0.006</td>
</tr>
<tr>
<td>Ferrara 2011 (15)</td>
<td>197</td>
<td>Pregnancy, after GDM diagnosis</td>
<td>Diet, exercise, and breastfeeding</td>
<td>Weight</td>
<td>10 months</td>
<td></td>
<td>Weight goal 37.5 vs. 21.4%, p=0.07</td>
</tr>
<tr>
<td>Hu 2012 (186)</td>
<td>1180</td>
<td>Within 3 years after delivery</td>
<td>Diet and exercise</td>
<td>Weight</td>
<td>12 months</td>
<td></td>
<td>IFG/IGT/T2D 18.8% vs 30.1, p=0.018</td>
</tr>
<tr>
<td>Shyam 2013 (187)</td>
<td>77</td>
<td>20-40 years old, BMI postpartum&gt;23, or waist&gt;80cm, or IFG/IGT, of family history of T2D</td>
<td>20-40 years old</td>
<td>Low GI diet</td>
<td>Weight</td>
<td>3 months</td>
<td>Lower 2h glucose in 75g OGTT, p=0.025</td>
</tr>
<tr>
<td>Reference</td>
<td>N</td>
<td>Inclusion criteria</td>
<td>Initiation</td>
<td>Intervention</td>
<td>Primary focus</td>
<td>Duration</td>
<td>Results</td>
</tr>
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</tr>
<tr>
<td>Shek 2014 (188)</td>
<td>450</td>
<td>Postpartum IGT</td>
<td>Within 3 years after delivery</td>
<td>Diet and exercise</td>
<td>Type 2 diabetes</td>
<td>36 months</td>
<td>T2D RR 0.77 (95% CI 0.51-1.16)</td>
</tr>
<tr>
<td>Peacock 2015 (189)</td>
<td>31</td>
<td>BMI &gt;25</td>
<td>6 to 24 months after delivery</td>
<td>Diet and exercise</td>
<td>Type 2 diabetes</td>
<td>3 months</td>
<td>Weight change −2.5 (2.3) kg vs +0.2 (1.6) kg, p=0.009</td>
</tr>
<tr>
<td>Perez-Ferre 2015 (190)</td>
<td>260</td>
<td>Normal plasma fasting glucose</td>
<td>6 to 12 weeks after delivery</td>
<td>Mediterranean diet and exercise</td>
<td>Type 2 diabetes</td>
<td>3 years</td>
<td>IFG/IGT/T2D 42.8 vs 56.75%, p &lt; 0.05</td>
</tr>
<tr>
<td>O’ Reilly 2016 (191)</td>
<td>573</td>
<td>Age ≥18 years</td>
<td>3 months postpartum</td>
<td>Diet and exercise</td>
<td>Weight, waist, fasting glucose</td>
<td>12 months</td>
<td>Weight change difference −0.95 kg, 95% CI −1.87, −0.04, p = 0.04</td>
</tr>
<tr>
<td>Ferrara 2016 (169)</td>
<td>2280</td>
<td>Age ≥18 years</td>
<td>Within 2 weeks after GDM diagnosis</td>
<td>Diet and exercise</td>
<td>Weight</td>
<td>12 months</td>
<td>IFG/IGT/T2D 33.2 vs. 36.8%, HR 0.90 (95% CI 0.78, 1.04) Weight goals OR 1.28 (95% CI 1.10, 1.47)</td>
</tr>
</tbody>
</table>
2.3 HETEROGENEITY OF GESTATIONAL DIABETES

2.3.1 PREGNANCY

GDM is a heterogeneous entity with high variability in phenotypic and genotypic characteristics (19, 192). Diverse overlapping physiological mechanisms underlie the transient pregnancy hyperglycemia, but some specific forms of diabetes can also be first detected during pregnancy.

2.3.1.1 Autoimmune and monogenic diabetes during pregnancy

Latent Autoimmune Diabetes in Adults (LADA) is diagnosed in 5–10% of GDM women in Finland (48). Autoantibodies such as islet cell antibodies (ICA) and antibodies against glutamic acid decarboxylase (GAD-Ab), membrane tyrosine phosphatase IA2 (IA2-Ab), and insulin (IAA) can be detectable as a sign of humoral autoimmunity. In type 1 diabetes, these antibodies are responsible for the immune-mediated destruction of the pancreatic beta cells (193). Specific clinical characteristics are unable to differentiate this group from LADA during pregnancy, although some studies have demonstrated a higher degree of glucose intolerance (19). After pregnancy, women with diabetes-related autoantibodies are at increased risk for type 1 diabetes (43).

Another clinical entity, which is detected in Finland among approximately 5% of GDM women, is Maturity-Onset Diabetes of the Young (MODY). It is a group of autosomal dominantly inherited single-gene mutations leading to a disrupted function of beta cells. There are several known genes, but the most common mutations are in glucokinase (GCK), hepatic nuclear factor 1 alpha (HNF1A), hepatic nuclear factor 4 alpha (HNF4A), and hepatic nuclear factor 1 beta (HNF1B) (194, 195). GCK-MODY, the most common form in Finland (196), leads to an increased glucose threshold for insulin release, resulting in higher fasting glucose concentrations. During pregnancy, identification is important, as fetuses are at risk of macrosomia depending on their genotype (197, 198). These mothers require close follow-up and treatment with insulin if macrosomia develops, which is the case only in the absence of fetal GCK mutation (198). When both mother and fetus have GCK mutation, the growth pattern is normal. In cases where only the fetus has GCK mutation, it leads to fetal growth restriction. Clinical features indicating a risk of GCK-MODY are a BMI < 25 kg/m² and a fasting glucose of ≥ 5.5 mmol/l, with 68% sensitivity and 96% specificity (199, 200).
The other three most common types of MODY result in progressive beta cell failure and elevated postprandial glucose levels (195). They all have specific features linked to their underlying pathophysiology: HNF1A-MODY presents with glucosuria, HNF4A with fetal macrosomia and neonatal hypoglycemia, and HNF1B with developmental disorders of, e.g., the kidneys, liver, and intestines.

2.3.1.2 Insulin resistance and insulin secretion defects

There is also a large degree of heterogeneity underlying the hyperglycemia seen in “normal GDM women” (19). Already in the 1990s, Catalano described the different insulin secretion profiles of non-obese and obese GDM women (32, 33). Obese GDM women are typically more insulin resistant, whereas the non-obese have a lower acute insulin response hypothetically related to defective insulin secretion (201). There are suggestive findings that even placental insulin signaling is different between non-obese and obese women (202). Using a meal tolerance test, Cheney and colleagues (203) demonstrated how obese GDM women had higher fasting and postprandial insulin levels, but the levels of non-obese GDM women were even below those of normoglycemic pregnant women. A similar finding was detectable in the study by Damm and colleagues (204). A recent study estimated that 50% of GDM women are mainly insulin resistant, 30% have mainly defective insulin secretion and the rest have a combination (20). These features seem to vary greatly according to ethnicity (205).

Some studies have tried to assess the influence of different phenotypes of glucose metabolism. In a recent study by Powe (20), macrosomia and an elevated cesarean section rate were only associated with insulin resistance. A smaller study divided 22 women with GDM into hypoinsulinemic, normoinsulinemic, and hyperinsulinemic groups (206). Higher pre-pregnancy BMI was associated with hyperinsulinemia, but interestingly, LGA babies were only seen among hypo- and normoinsulinemic pregnancies, whereas gestational hypertensive disorders were more common among the hyperinsulinemic. Fasting glucose could offer one possible opportunity to differentiate between distinct metabolic profiles of GDM women (207). In a Polish study on 1025 women, high fasting glucose was associated with earlier diagnosis, higher pre-pregnancy BMI, higher HOMA-IR, and lower HOMA-beta indices. In another study, fasting glucose concentrations over 5.8 mmol/l increased the incidence of adverse perinatal outcomes (208). Abnormal fasting glucose concentrations are associated with higher BMI, hepatic insulin resistance, and lower basal insulin secretion, whereas pathological 1-h glucose in the OGTT depicts decreased stimulated insulin secretion (209).
2.3.1.3 Early-onset and late-onset gestational diabetes

The timing of GDM diagnosis can also potentially differentiate groups of GDM women. Although there is no consensus on the appropriate thresholds for first-trimester GDM screening, there have been attempts to characterize women diagnosed before 20 gestational weeks. In most studies, early GDM is associated with higher BMI, increased insulin resistance, higher fasting glucose, insulin treatment, and hypertensive disorders of pregnancy (210, 211), while some have additionally demonstrated higher risks for neonatal hypoglycemia and perinatal death among these women (212). Early insulin resistance possibly reflects pre-pregnancy insulin resistance, which is more common among obese individuals (33). Women diagnosed with GDM in the first trimester present a high-risk group needing early detection and close surveillance (212).

2.3.1.4 Genetic variations

Type 2 diabetes and GDM typically run in families, and GDM is often recurrent in subsequent pregnancies (213). This has been suggestive of a genetic and partly shared background between these two conditions. Genetic association studies have identified several variations in genes involved in insulin secretion, insulin sensitivity (214), and lipid and glucose metabolism.

A meta-analysis in 2013 by Zhang and colleagues identified nine single nucleotide polymorphisms (SNPs) in seven genes that were associated with GDM. Of these seven, transcription factor 7-like 2 (TCF7L2), glucokinase (GCK), potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11), CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1), insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2), and melatonin receptor 1B (MTNR1B) are related to beta cell function, and only insulin receptor substrate 1 (IRS1) is involved with insulin sensitivity. These genes are also associated with type 2 diabetes (215, 216).

The heterogeneity of the genetic background may influence the clinical presentation; genome-wide association studies (GWAS) have identified associations between certain genetic variants and specific metabolic traits. Particular genes are specifically related to higher fasting glucose, whereas others correlate with postprandial glucose or fasting C-peptide (217). In the pregnant population, MTNR1B has been associated with insulin resistance, early-phase insulin release, fasting proinsulin conversion to insulin, and increased fasting glucose (218), and in the non-pregnant population, it is associated with elevated fasting glucose, early defective insulin response, and insulin resistance (219, 220). In the RADIEL study, the MTNR1B risk allele G was associated with lower pre-pregnancy BMI and lower insulin concentrations and HOMA-IR, as well as a better lipid profile in the first
trimester. During pregnancy, it was associated with a higher occurrence of GDM (221).

Besides affecting the clinical manifestations, genetic background might also alter the susceptibility to treatment. Goni and colleagues demonstrated how MTNR1B polymorphism influenced the results of weight loss on a hypocaloric diet (222). In the RADIEL study, participants with a G allele of the MTNR1B were resistant to the lifestyle intervention (221) in contrast to the homozygous carriers of the C allele.

### 2.3.2 LONG-TERM METABOLIC HEALTH

In general, after a 5-year follow-up, 20–70% of women with previous GDM will develop type 2 diabetes (127). The screening strategy and diagnostic criteria for GDM influence the prevalence rates of type 2 diabetes, but additionally, different ethnicities have varying predispositions. There are also studies demonstrating a higher postpartum diabetes risk among early GDM women (223) and those with diabetes-related autoantibodies (43).

According to Damm and colleagues (204), the non-obese GDM women have a lower early insulin secretion profile during pregnancy, and this difference remains significant even 5 to 10 years postpartum, suggesting that there are differences in postpartum health as well. There is limited data, however, on the future risk of the heterogeneous subgroups, including the non-obese women with previous GDM.
2.4 PREDICTION OF GDM

2.4.1 RISK FACTORS

2.4.1.1 Maternal characteristics and lifestyle
The underlying detectable risk factors for GDM are generally related to either pre-existing insulin resistance, decreased secretory capacity of pancreatic beta cells, or enhanced insulin resistance and insulin requirements during pregnancy (224, 225). Genetic background has naturally overlapping effects.

The characteristics related to pre-pregnancy insulin resistance include obesity (226), higher maternal age (227, 228), and PCOS (229). Risk association with subfertility (230, 231) is probably partly related to PCOS as well. Interestingly, the amount of visceral adipose tissue (VAT) was inferior to pre-pregnancy BMI (232) in predicting insulin resistance and glucose intolerance in pregnancy, although in the general population, it has a good predictive value (233). Also, possibly partly related to pre-existing insulin resistance are the history of GDM (228) and a family history of diabetes (234), which might be additional signs of previous beta cell stress. Naturally, they also reflect genetic predisposition, as does ethnicity (192, 235); the risk for GDM is highest among people with Asian ancestry or Hispanic ethnicity and lowest among people of European ancestry. Among African American women, the risk is intermediate. Parity is also a risk factor independent of age (224) and is hypothetically associated with the previous burden of beta cells.

Characteristics intensifying insulin resistance during pregnancy include excessive gestational weight gain (236, 237) and multiple pregnancy (238), although results concerning higher gestations are somewhat conflicting (239). Another controversial risk factor is smoking, which has been associated with increased insulin resistance, altered glucose homeostasis, and hyperinsulinemia (240, 241), as well as type 2 diabetes risk (242). Results concerning GDM, however, have been inconsistent with both positive (234, 243) and negative associations (244).

Healthy lifestyle in the first trimester, on the other hand, can be protective (245). In addition to physical activity and specific diets, studies have assessed the effect of iron and vitamin D. Iron, with its capacity to induce oxidative stress and cellular damage, can decrease insulin secretion and increase insulin resistance by increased accumulation in the liver (246). Heme iron, derived from animal products, has been associated with type 2 diabetes risk (247), and rather consistent evidence links it with GDM as well (246, 248, 249). This is not true, however, for supplementary (250) and non-heme iron (246).
Vitamin D has receptors in most tissues of the body. In addition to calcium homeostasis and metabolism, it also plays an important role in glucose homeostasis by directly regulating the release of insulin (251, 252) and indirectly via calcium metabolism (253). Two meta-analyses have connected low serum vitamin D with higher risk of GDM (OR 1.38 and OR 1.49) (254, 255), but according to a recent Cochrane review, vitamin D supplements have no effect on GDM risk (256). Results from the RADIEL study suggested that adiposity might modify the association between vitamin D and GDM; in our study, only women with a BMI over 35 showed higher GDM risk with lower vitamin D concentrations (257).

Risk factors potentially supporting the Developmental Origins of Health and Disease (DOHaD) hypothesis include short stature (258, 259), low or high maternal birth weight (260), and parental smoking (261). Early timing of menarche is also associated with higher GDM risk (262), although the underlying physiology is not fully understood. Early menarche has been associated with insulin resistance and worse cardiometabolic health later in life, independent of childhood adiposity and adult lifestyle factors.

Although the most common risk factors such as obesity, family history of diabetes, GDM history, and higher age are fairly common, only half the women with GDM present one or more risk factors (263), and according to another study, the GDM detection rate when using maternal characteristics was only 61.6% (264). The GDM of low-risk women with a BMI < 25kg/m² and an age < 25 years resulted in similar adverse outcomes to GDM among other women (265), emphasizing the need for also diagnosing “low-risk women.”

### 2.4.1.2 Biochemical markers

Following the increasing GDM incidence, substantial effort has been invested in studying potential biochemical risk markers in early pregnancy. The focus has been on inflammatory markers, adipokines, and various measures of glucose and insulin metabolism. Although the inflammatory process is a part of GDM pathophysiology, these markers have not proven helpful in early prediction. TNF-α and hs-CRP brought no additional predictive value when combined with maternal characteristics (266). Among adipokines, adiponectin has been the most investigated (267). Studies on adiponectin and leptin showed an inverse relationship between first-trimester adiponectin and GDM risk, and the adiponectin/leptin ratio in combination with maternal characteristics resulted in a 77–80% detection rate (268). In a meta-analysis, however, the sensitivity of adiponectin alone was 60.3% and the specificity 81.3% (269). Other proteins of interest have been sex hormone binding protein (SHBG) (270), retinol-binding protein 4 (RBP-4) (271), and the hormone resistin and C-reactive protein (272), but results have not been convincing.
One of the most recently studied biomarkers has been glycated CD59, which showed a promising predictive value for GDM diagnosis (ROC 0.92) and for the risk of LGA (273).

Due to the time-consuming and costly nature of OGTT, researchers have attempted to identify other predictive markers of glucose metabolism. HbA\textsubscript{1c} in the second trimester was associated with a worse perinatal outcome, but it was not useful in GDM prediction in the first trimester (274, 275). Fasting glucose in early pregnancy, on the other hand, seems to perform better than BMI (276), but with a plasma glucose cut-off of ≥ 7.5 mmol/l, the sensitivity was only 0.70 and the specificity 0.90. There have also been evaluations of HOMA-\(\beta\) assessment in the first trimester, and a recent meta-analysis (277) reviewed current results; although HOMA-\(\beta\) is significantly lower among women with future GDM, due to the heterogeneity of the studies, it cannot be considered as a good diagnostic tool or prognostic marker.

### 2.4.2 GDM RISK SCORES

As single predictive markers have not produced sufficient accuracy, there have been efforts to form a risk score to enable finding high-risk individuals. These scores take advantage of simple clinical data and have been successfully created to detect type 2 diabetes (22). A recent review in the BMJ (21) assessed 12 published risk scores and evaluated them in a Dutch cohort of 3723 women (Table 5). The most common risk predictors were maternal age, body mass index, ethnicity, family history of diabetes, history of GDM, and history of macrosomia. Overall, performance of the scores was moderate. All scores performed differently among nulliparous women, some showing better predictive ability and some inferior in this subgroup. Two scores by Teede (278) and by Van Leeuwen (279) were identified as the best performing calculations based on their discrimination, calibration, and performance in the nulliparous subgroup.

The Australian GDM risk score by Teede and colleagues (278) was based on a retrospective study of 4276 women focusing on the first-trimester risk markers for GDM. Based on their data, they developed a risk calculation model, accounting for past history of GDM, age, BMI, ethnicity, and family history of diabetes, resulting in a score from 0 to 9. The suggested the cut-off was 4 points. This score had a sensitivity of 61.3% and a specificity of 71.4% in the original validation group, and in the external validation (21), the C-statistic was 0.77 (95% CI 0.73 to 0.81).

The risk calculation by Van Leeuwen (279) was created in a Dutch cohort of 995 women using a logistic regression model with clinical risk markers and
medical history. The probability of GDM could be calculated using the following formula: probability of GDM = 1/[1 + exp(−β)], in which β is calculated as [-6.1 + (0.83 × non-Caucasian ethnicity) + (0.57 × positive family history of diabetes mellitus) − (0.67 × multipara without history of GDM) + (0.5 × multipara with history of GDM) + (0.13 × BMI)]. In the original study, the C-statistic was 0.77 (95% CI 0.69–0.85), and in the external validation cohort, it was 0.74 (0.71–0.78) (21).

Since the BMJ review, an Australian group published a risk prediction model formed in a multi-ethnic group of 980 women. Variables at 11–13 gestational weeks included previous GDM, family history of diabetes, Southeast Asian ethnicity, parity, maternal age, and BMI, and this score reached a C-statistic of 0.88 (95% CI 0.85–0.92). The resulting prognostic model has not yet been externally validated.

Furthermore, combining biochemical markers with maternal characteristics has produced still more complex risk models (280, 281). They have not been successful either, unfortunately. A biomarker panel study including adiponectin, apolipoproteins, SHBG, and RBP-4 (282) demonstrated varying risk marker profiles with different cut-offs among obese and non-obese women. The final model, however, had 75% sensitivity and 63% specificity, whereas separate models based on BMI did not improve the performance. The UPBEAT cohort has also been used for risk model development (283); their model combined clinical data with HbA1c, glucose, fructosamine, triglyceride, adiponectin, and sex hormone binding globulin (SHBG). This prognostic model for obese women had a C-statistic of 0.77, and 50% of score-positive women eventually developed GDM. Recently, a systematic review, meta-analysis, and IPD analysis of risk factor–based screening strategies concluded that their performance is poor, and a simple tool combining an age over 25 years and a BMI over 25 kg/m² performs equally in more complex models (284).
Table 5. GDM Risk scores, adapted from Lamain-de-Ruiter et al. (21)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Prediction model</th>
<th>C-statistic</th>
<th>C-statistic nulliparous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naylor 1997 (285)</td>
<td>$e^x/(1+e^x)$, where $X = \alpha + 0$ (age $\leq$ 30 yrs) + 0 (age 31-34 yrs) + 0.47 (age $\geq$ 35 yrs) + 0 (BMI $\leq$ 22.0 kg/m²) + 0.588 (BMI 22.1-25.0 kg/m²) + 1.163 (BMI $\geq$ 25.1 kg/m²) + 0 (if white race) + 0.357 (if black race) + 1.569 (if Asian race) + 0.47 (if other race)</td>
<td>0.72 (0.68 to 0.76)</td>
<td>0.71 (0.65 to 0.77)</td>
</tr>
<tr>
<td>Caliskan 2004 (286)</td>
<td>$X = 1$ (if adverse outcome (i.e. recurrent ($\geq$ 2) abortions &amp; previous IUFD)) + 1 (if age $\geq$ 25 yrs) + 1 (if BMI $\geq$ 25 kg/m²) + 1 (if parous with previous LGA above 90th percentile) + 0 (if age $\leq$ 24 yrs) + 0.512 (if age 25-29 yrs) + 1.515 (if age $\geq$ 30 yrs) + 0 (if BMI prepregnancy $\leq$ 24.9 kg/m²) + 0.513 (if BMI prepregnancy 25.0-29.9 kg/m²) + 0.892 (if BMI prepregnancy $\geq$ 30.0 kg/m²) + 0.842 (if family history of DM, first degree)</td>
<td>0.73 (0.69 to 0.76)</td>
<td>0.74 (0.68 to 0.80)</td>
</tr>
<tr>
<td>Shirazian 2009 (287)</td>
<td>$e^x/(1+e^x)$, where $X = \alpha + 0$ (if age $\leq$ 24 yrs) + 0.512 (if age 25-29 yrs) + 1.515 (if age $\geq$ 30 yrs) + 0 (if BMI prepregnancy $\leq$ 24.9 kg/m²) + 0.513 (if BMI prepregnancy 25.0-29.9 kg/m²) + 0.892 (if BMI prepregnancy $\geq$ 30.0 kg/m²) + 0.842 (if family history of DM, first degree)</td>
<td>0.71 (0.67 to 0.75)</td>
<td>0.73 (0.66 to 0.79)</td>
</tr>
<tr>
<td>Van Leeuwen 2010 (279)</td>
<td>$e^x/(1+e^x)$, where $X = -6.1 + 0.83$ (if non-Caucasian race) + 0.57 (if family history of DM, first degree) – 0.67 (if parous without history of GDM) + 0.5 (if parous with history of GDM) + 0.13 (BMI in kg/m² with BMI 30 transformed to 30)</td>
<td>0.74 (0.71 to 0.78)</td>
<td>0.74 (0.71 to 0.78)</td>
</tr>
<tr>
<td>Nanda 2011 (264)</td>
<td>$e^x/(1+e^x)$, where $X = \alpha + 0.058$ (age, yrs) + 0.113 (BMI, kg/m²) + 0 (if Caucasian ethnicity) + 0.888 (if Asian ethnicity) + 0 (nulliparous) + 3.723 (if parous with previous GDM) + 0.67 (parous with previous LGA above 90th percentile)</td>
<td>0.78 (0.74 to 0.82)</td>
<td>0.76 (0.70 to 0.83)</td>
</tr>
<tr>
<td>Syngelaki 2011 (288)</td>
<td>$e^x/(1+e^x)$, where $X = \alpha + 0.014$ (BMI, kg/m²) + 0.068 (age, yrs) + 0 (if Caucasian race) + 0.344 (if African race) + 1.050 (if Asian race) + 0.174 (if mixed race) + 0 (if spontaneous conception) + 0.432 (if conception with ovulation drugs) + 0.312 (if conception via IVF) + 0.020 (if smoking) – 0.010 (if chronic hypertension) + 0 (if nulliparous) – 0.211 (if parous without previous LGA above 95th percentile) + 0.663 (if parous with previous LGA above 95th percentile)</td>
<td>0.71 (0.66 to 0.75)</td>
<td>0.76 (0.70 to 0.82)</td>
</tr>
<tr>
<td>Reference</td>
<td>Prediction model</td>
<td>C statistic</td>
<td>C statistic nulliparous</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Teede 2011</td>
<td>$e^{Y/(1+e^X)}$, where $X = \alpha + 0 \text{ (if age &lt;25 yrs)} + 0.92 \text{ (if age 25-29 yrs)} + 1.22 \text{ (if age 30-34 yrs)} + 1.69 \text{ (if age 35-39 yrs)} + 1.95 \text{ (if age \geq 40 yrs)} + 0 \text{ (if BMI &lt;20 kg/m}^2\text{)} + 0.53 \text{ (if BMI }20.0-24.9 \text{ kg/m}^2\text{)} + 0.69 \text{ (if BMI }25.0-26.9 \text{ kg/m}^2\text{)} + 0.83 \text{ (if BMI }27.0-29.9 \text{ kg/m}^2\text{)} + 1.28 \text{ (if BMI }30.0-34.9 \text{ kg/m}^2\text{)} + 1.82 \text{ (if BMI }\geq35.0 \text{ kg/m}^2\text{)} + 1.31 \text{ (if Asian race)} + 0.06 \text{ (if African race)} + 0.37 \text{ (if other race)} + 0.53 \text{ (if family history of DM, first degree)} + 2.39 \text{ (if history of GDM)}$</td>
<td>0.77 (0.73 to 0.81)</td>
<td>0.75 (0.69 to 0.82)</td>
</tr>
<tr>
<td>Savona-Ventura 2013 (290)</td>
<td>$e^{Y/(1+e^X)}$, where $X = -4.144 + 3.142 \text{ (if glucose }&gt;5.0 \text{ mmol/L)} + 0.758 \text{ (if age }&gt;30 \text{ yrs)} + 0.543 \text{ (if diastolic blood pressure} \geq80 \text{ mmHg)}$</td>
<td>0.68 (0.64 to 0.72)</td>
<td>0.72 (0.65 to 0.78)</td>
</tr>
<tr>
<td>Tran 2013 (291)</td>
<td>$e^{Y/(1+e^X)}$, where $X = \alpha + 0.351 \text{ (age, yrs)} + 0.131 \text{ (BMI, kg/m}^2\text{)}$</td>
<td>0.67 (0.63 to 0.72)</td>
<td>0.69 (0.63 to 0.76)</td>
</tr>
<tr>
<td>Eleftheriadou 2014 (292)</td>
<td>$e^{Y/(1+e^X)}$, where $X = \alpha + 0.058 \text{ (weight, kg)} + 0.182 \text{ (age, yrs)}$</td>
<td>0.70 (0.65 to 0.74)</td>
<td>0.73 (0.66 to 0.79)</td>
</tr>
<tr>
<td>Gabbay-Benziv 2014 (293)</td>
<td>$1/(1+e^{-X})$, where $X = -11.569 + 0.064 \text{ (age, yrs)} + 0 \text{ (if white race)} + 2.026 \text{ (if Asian race)} + 0.083 \text{ (if African race)} + 1.661 \text{ (if other nonwhite race)} + 2.144 \text{ (history of GDM)} + 0.034 \text{ (systolic blood pressure, mmHg)} + 0.082 \text{ (BMI, kg/m}^2\text{)}$</td>
<td>0.75 (0.71 to 0.79)</td>
<td>0.72 (0.66 to 0.79)</td>
</tr>
</tbody>
</table>
| Pintaudi 2014 (294) | $e^{Y/(1+e^X)}$, where $X = \alpha + 0 \text{ (class 4)} + 1.361 \text{ (class 3)} + 1.856 \text{ (class 2)} + 3.091 \text{ (class 1)} + 1.281 \text{ (previous LGA with birth weight} \geq4500 \text{ gr)} + 0.588 \text{ (if family history of DM, first degree)}$  
Class 1: random glucose >5.1 mmol/L.  
Class 2: random glucose >4.4 ≤ 5.1 mmol/L & pre-pregnancy BMI >24.4 kg/m2  
Class 3: random glucose >4.4 ≤ 5.1 mmol/L & pre-pregnancy BMI ≤24.4 kg/m2  
Class 4: random glucose ≤4.4 mmol/L. | 0.72 (0.68 to 0.76) | 0.73 (0.67 to 0.79)   |
The overall aim of the thesis was to assess the heterogeneity of GDM and the long-term effects of a lifestyle intervention during pregnancy among high-risk women.

More specifically, the study objectives were:

I  To determine the long-term effects of a lifestyle intervention during pregnancy and the first postpartum year among high-risk women on their metabolic health during the first postpartum year

II To assess the heterogeneity of GDM and its importance during pregnancy

III To study the predictive value of GDM risk scores and the possible effects of heterogeneity of GDM on their performance

IV To evaluate the long-term risk of metabolic disturbances among heterogeneous groups of women at high GDM risk
4 MATERIALS AND METHODS

4.1 THE RADIEL STUDY (STUDIES I–III)

The RADIEL (Finnish Gestational Diabetes Prevention) study took place in Finland between 2008 and 2014 in three hospitals in the Helsinki metropolitan area (Women’s Hospital in the Helsinki University Hospital, Jorvi Hospital, and Kätilöopisto Maternity Hospital) and in Lappeenranta (South Karelian Central Hospital). It was a randomized controlled trial among women at high GDM risk assessing the possibilities of a lifestyle intervention to prevent GDM and additionally to improve postpartum glucose regulation.

4.1.1 PARTICIPANTS

We recruited 720 women at high GDM risk, defined as having a BMI ≥ 30kg/m² and/or a history of GDM. Of these, 228 entered the study before pregnancy and 492 in the first trimester before 20 gestational weeks. The additional requirements for inclusion were at least 18 years of age and communication skills in Finnish. Physical disabilities, diabetes before pregnancy, medication influencing glucose metabolism, severe psychiatric disorders, current substance abuse, and multiple pregnancy led to exclusion.

Study I included the 200 women entering the study in early pregnancy before 20 gestational weeks with normal glucose tolerance in the first trimester and attending at least one study visit during the first postpartum year. For the analysis of studies II and III assessing the heterogeneity of GDM, we divided the participants into groups A, B, C, and D according to their clinical characteristics (BMI, parity, and history of GDM) (Table 6). Study II focused on the 269 women who entered the study in early pregnancy before 20 gestational weeks with normal glucose tolerance in the first trimester. Study III included all 510 participants with known glycemic status during pregnancy.

All participants gave written informed consent and the Ethics Committees of the Helsinki University Hospital and South Karelia Central Hospital approved the study design.
Figure 5. Flow chart of the studies I-IV
Table 6. Group characteristics

<table>
<thead>
<tr>
<th>GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>BMI ≥ 30 KG/M²</td>
</tr>
<tr>
<td>PREVIOUS PREGNANCIES</td>
</tr>
<tr>
<td>PREVIOUS HISTORY OF GDM</td>
</tr>
</tbody>
</table>

4.1.2 STUDY DESIGN

Random allocation divided the participants to either an intervention or to a control group. Randomly permuted blocks were stratified according to risk factor (BMI or GDM history) as well as study site. The general intervention goals for all participants were increasing physical activity and improving diet quality. The recommendation for the overweight participants (BMI > 25kg/m²) was 5–10% weight loss before pregnancy and for the obese participants (BMI > 30kg/m²), the recommendation was also no additional weight gain during the first two trimesters of pregnancy. During the first postpartum year, the intervention encouraged breastfeeding and supported participants in returning to their pre-pregnancy weight. The specific goal for the overweight (BMI > 25kg/m²) participants was 5–10% weight loss.

Both groups visited the study nurse for anthropometric measurements and laboratory tests every three months before pregnancy, once during each trimester of pregnancy, and at 6 weeks and 6 and 12 months after delivery. The women in the control group received only general leaflets about the importance of healthy lifestyle similar to those usually provided by the local antenatal clinics. Study nurses providing the lifestyle intervention were specially trained midwives, and guidance was personalized according to the preferences of the participant.

Dietary advice was based on Nordic diet recommendations focusing on increasing the intake of vegetables, fruit, low-fat milk products, and whole grains, improving fat quality, and encouraging the intake of fish. The energy intake recommendation was 1600–1800 kcal/day and the “plate model” guided the amount of protein, carbohydrate, and vegetable portions of the meal. The suggested energy amount (E%) was 20–25% protein, 30–40% fats,
and 40–50% carbohydrates. Participants in the intervention group also attended a group session with a dietitian; the pre-pregnancy group at the beginning of the study, and all participants in the first trimester and at 6 and 12 months postpartum.

The physical activity recommendation was 150 minutes per week of moderately strenuous exercise, and study nurses supported the participants in finding a satisfying activity based on their preferences, taking into account the challenges due to pregnancy. They all received pedometers, and the recommended goal was 10 000 steps per day. Participants also received some free entrance tickets to sports activities organized by the city.

4.1.3 OUTCOMES
GDM incidence was the main outcome of Study II. Diagnosis of GDM was based on a 75 g 2-h oral glucose tolerance test (OGTT) with diagnostic thresholds of plasma glucose according to Finnish National Guidelines at 5.3, 10.0, and 8.6 mmol/L (0, 1, and 2 hours). The OGTT was performed at recruitment for the women entering the study before pregnancy and in the first trimester for all participants. If normal in the first trimester, it was repeated in the second trimester.

The main outcome of Study I was the incidence of glycemic disturbances during the first postpartum year. The OGTT at 6 weeks and 12 months after delivery provided the information for glucose tolerance postpartum. Fasting plasma glucose between 6.1 and 6.9 mmol/l resulted in the diagnosis of impaired fasting glucose (IFG), and impaired glucose tolerance was defined as a 2-hour plasma glucose between 7.8 and 11.0 mmol/l. Diabetes diagnosis followed if fasting plasma glucose exceeded 6.9 mmol/l or if the 2-h glucose exceeded 11.0 mmol/l. The definition for the composite outcome of impaired glucose regulation was having IFG, IGT, or diabetes.

4.1.3.1 Clinical measurements
Each study visit included anthropometric measurements, and blood pressure was measured from the right arm in the sitting position using an automatic sphygmomanometer. Among the pre-pregnancy group, the difference between the last visit before pregnancy and the weight in the second trimester represented the gestational weight gain. For the women recruited in early pregnancy, we used the self-reported pre-pregnancy weight from the antenatal card.
4.1.3.2 Laboratory tests

Laboratory tests included assessments of glucose metabolism (fasting glucose, fasting insulin, GHbA1c), lipids (cholesterol, low-density lipoprotein cholesterol, triglycerides), thyroid function (thyroid stimulating hormone, free thyroxine), inflammatory markers (high-sensitive C-reactive protein, adiponectin, interleukin-6, tumor necrosis factor alpha), and vitamin D. Diabetes-related autoantibodies GAD and ICA were analyzed in the first trimester from the 269 participants who entered the study in early pregnancy and had normal glucose tolerance in the first trimester (study II). The limit value for ICA positivity was 2.5 Juvenile Diabetes Foundation units (JDFU) and for GADA positivity it was 5.36 relative units (RU). The calculation for insulin resistance index (HOMA-IR) was $(\text{FPI} \text{ (mU/l)} \times \text{FPG (mmol/l)})/22.5$ and for the index for beta cell function (HOMA-b), it was $(20 \text{ FPI (mU/l)})/((\text{FPG (mmol/l)} \times 3.5)$.

The Helsinki University Hospital Laboratory (HUSLAB) performed the analyses of lipids, hs-CRP, thyroid function, insulin, and glucose measurements from venous blood taken into a serum gel tube and centrifuged at the survey sites. The following methods were used: for glucose enzymatic hexokinase assay (Roche Diagnostics, Gluco-quant, Modular analyzer), for GHbA1c immunoturbidimetric analyzer (Roche Diagnostics, Tina-quant Hemoglobin A1C Gen.2Integra800 analyzer), for insulin electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Insulin, Modular analyzer), for cholesterol enzymatic assay (Roche Diagnostics, Cholesterol CHOD-PAP, Modular analyzer), for HDL cholesterol enzymatic assay (Roche Diagnostics, HDL-C plus 3rd generation, Modular analyzer), for LDL cholesterol enzymatic assay (Roche Diagnostics, LDL-C plus 2nd generation, Modular analyzer), for triglycerides enzymatic assay (Roche Diagnostics TG Triglycerides GPO-PAP, Modular analyzer), and for hs-CRP High sensitive assay, Immunoturbidimetric latex-enhanced assay (Roche Diagnostics, CRPHS Tina-Quant Cardiac C-reactive protein [Latex] Modular analyzer).

High molecular weight (HMW) adiponectin was determined by enzyme-linked immunosorbent assay (human HMW) Adiponectin ELISA (Millipore, Billerica, Massachusetts, USA). IL-6 and TNF alpha were measured by multiplex sandwich immunoassay (Milliplex High Sensitivity Human Cytokine kit, Millipore).
Materials and Methods

4.1.3.3 Questionnaires

Questionnaires covered educational attainment, chronic illnesses, medical history, and regular medications, obstetric history, socioeconomic background, diet, and physical activity. Leisure time physical activity was the self-reported time spent in moderately strenuous physical activity per week.

Dietary intake was assessed with a modified food frequency questionnaire (FFQ), and a three-day food diary assessed the diet quality. As a covariate in this study, we used the Healthy Food intake index (HFII), which was designed and validated especially for the RADIEL study based on the National Dietary Guidelines (74, 295). Altogether, 11 food components scored according to reported intake frequency indicate healthier diet quality with higher scores (score range 0–17).

4.1.4 GDM RISK CALCULATIONS (STUDY III)

The main objective of study III was to assess the performance of GDM risk calculations. We chose two of the best performing scores from a recent validation study in BMJ (21), where 3723 women served as the validation cohort for a total of 12 risk scores. In that review (21), the C-statistics values were 0.74 for the Van Leeuwen score and 0.77 for the Teede score.

The Belgian Van Leeuwen risk score calculates the probability of GDM by a mathematical formula combining clinical data. The probability of GDM = $1 / [1 + \exp(-\beta)]$, in which $\beta$ is calculated as $-6.1 + (0.83 \times \text{non-Caucasian ethnicity}) + (0.57 \times \text{positive family history of diabetes mellitus}) - (0.67 \times \text{multipara without history of GDM}) + (0.5 \times \text{multipara with history of GDM}) + (0.13 \times \text{BMI})$.

The Australian risk score by Teede takes into account similar clinical data resulting in a final score from 0 to 9. A score of 4 points or more was the proposed threshold for high GDM risk. Points derive from the following risk factors: age (<25 years 0 points, 25–34 years 1 point, 35 years or older 2 points), BMI (< 29 kg/m² 0 points, 30–34.9 kg/m² 1 point, 35 kg/m² or more 2 points), ethnicity (Anglo-Australian, European, or other 0 points; Polynesian, Maritime Southeast Asian, Chinese Asian, Southern Asian or African 1 point; Mainland Southeast Asian 2 points), family history of diabetes (1 point), and past history of GDM (2 points).
4.2 THE RADIEL 5-YEAR FOLLOW-UP STUDY (STUDY IV)

Between 2013 and 2017, all participants and their children were invited to a follow-up study focusing even in more detail on the metabolic health and long-term cardiovascular risk.

4.2.1 PARTICIPANTS AND STUDY DESIGN

In total, 348 women came to the study visit, which occurred according to their preference, either together or separately with their child. Inclusion criteria for study IV was information on the glucose tolerance at follow-up, i.e., either previously confirmed diagnosis of diabetes or OGGT at the 5-year follow-up. In this study, the 333 women with sufficient data on their glucose status served as a cohort of high-risk women without any attention to the prior division to intervention or control groups.

To assess the heterogeneity among high-risk women, we divided the participants similarly to studies II and III into groups A, B, C, and D (Table 6) according to their clinical characteristics (BMI, parity, and history of GDM before the RADIEL study). All participants gave written informed consent and the Ethics Committee of the Helsinki University Hospital approved the study protocol.

4.2.2 OUTCOMES

The main outcome of the study was the prevalence of abnormalities in glucose metabolism 5 years after delivery. Impaired fasting glucose (IFG) was diagnosed if plasma glucose was between 6.1 and 6.9 mmol/l and impaired glucose tolerance (IGT) was diagnosed if the 2-hour plasma glucose was between 7.8 and 11.0 mmol/l. Diabetes diagnosis was either previously confirmed by a physician, or it resulted from a fasting plasma glucose equal to or exceeding 7.0 mmol/l or a 2-h glucose exceeding 11.0 mmol/l. The definition for the composite outcome of impaired glucose regulation was having either IFG, IGT, or diabetes.

Another outcome was the presence of metabolic syndrome. We used the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria (296), which requires 3 out of the 5 following outcomes: waist circumference > 88 cm, fasting plasma glucose > 5.6 mmol/L, triglycerides > 1.7mm/L, HDL cholesterol < 1.29 mmol/L, and systolic blood pressure > 130mmHg or diastolic blood pressure > 85mmHg. Medication for hypertension or specific medication influencing HDL cholesterol or triglyceride levels were additional markers of metabolic risk. We also formed
a composite outcome of combined metabolic disturbances consisting of a
diagnosis of either IFG, IGT, diabetes, or metabolic syndrome.

4.2.2.1 Clinical measurements
The study nurses performed the anthropometric measurements at the visits
similarly to those in the main intervention study, and blood pressure was
measured from the right arm with a sphygmomanometer in a sitting position.
The final outcome was the mean of two consecutive measurements. The multi-
frequency bio-impedance measurement (InBody 3.0, Biospace Co, Ltd, Seoul,
Korea) was the method for measuring body composition (297). We followed
the American Council on Exercise in defining obesity based on a fat percentage
of 32% or over (298).

4.2.2.2 Laboratory tests
The laboratory tests included markers of glucose metabolism (GHbA1c, fasting
insulin), lipids (cholesterol, LDL cholesterol, HDL cholesterol, triglycerides),
thyroid function (TSH and fT4), alanine aminotransferase (ALAT), and highly-
sensitive C-reactive protein (hs-CRP). In the analysis of hs-CRP, we excluded
all values exceeding 10 mmol/L.

4.2.2.3 Questionnaires
Questionnaires provided self-reported information on the participants’ own
birth weight, socioeconomic background, chronic illnesses, and medication,
family history of diabetes, diet, and physical activity as well as health-related
behavior such as alcohol consumption and smoking.
### 4.3 STATISTICAL METHODS

The descriptive results for continuous variables are presented as means with standard deviation (SD) or medians with interquartile range (IQR). Frequency with percentages was used for categorical variables. The methods for statistical comparison between the groups were the analysis of variance (ANOVA), analysis of covariance (ANCOVA), and the Kruskal–Wallis test for continuous variables; Chi-squared tests for categorical variables or the Fisher-Freeman-Halton test, t-test, or permutation test were used when appropriate. Generalized estimating equations (GEE) models with appropriate distribution and link function were used to analyze repeated measures, for example, the incidence of GDM.

The p-values for pairwise group comparisons were adjusted for multiplicity using Hommel's multiple comparison procedure to identify significant differences in at least one of the two between-group comparisons (p=0.05). The p-values for pairwise group comparisons in the GDM outcome were adjusted for multiplicity using Hochberg’s multiple comparison procedure. Logistic regression was used to model the occurrence of GDM using second-trimester physical activity and dietary score, age, years of education, and family history of diabetes as covariates. Analysis of covariance (ANCOVA) was used to compare weight gain between groups while using physical activity and diet score in the second trimester and age, years of education, and family history of diabetes as covariates.

In the case of violation of the assumptions (e.g., non-normality), a bootstrap-type test (5000 replications) and confidence intervals estimation were used. The bootstrap method was used when the theoretical distribution of the test statistic was unknown or with a violation of the assumptions. The normality of the variables was tested by using the Shapiro-Wilk W test. The area under the curve (AUC) of the OGTT was calculated with the trapezoidal method. The STATA 14.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.
5 RESULTS

5.1 EFFECTS OF THE RADIEL LIFESTYLE INTERVENTION ONE YEAR POSTPARTUM (STUDY I)

In total, 200 women with normal glucose tolerance in early pregnancy attended at least one study visit during the first postpartum year. Table 7 presents baseline characteristics of the intervention and control groups at the first-trimester visit (mean 13 weeks of gestation). During the RADIEL pregnancy, 17 participants (15%) in the intervention group and 19 participants (21%) in the control group got a GDM diagnosis (p=0.30). The continuation rate was similar in both groups; 76% in the intervention and 72% in the control group continued in the study during the first postpartum year. The mean number of visits was 5.7 (4.0–6.0), and altogether, 75% of the participants attended all 6 visits.

Table 7. Baseline characteristics of Study I. Data are presented as means with SD, except for physical activity as median with IQR

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Intervention group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=90</td>
<td>n=110</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>32 (5)</td>
<td>32 (5)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>89 (17)</td>
<td>89 (18)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Prepregnancy BMI (kg/m²)</strong></td>
<td>32.2 (5.7)</td>
<td>31.9 (6.0)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Educational attainment (years)</strong></td>
<td>14.6 (1.8)</td>
<td>14.5 (2.1)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Previous deliveries, n (%)</strong></td>
<td>49 (54)</td>
<td>64 (58)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>History of GDM, n (%)</strong></td>
<td>27 (30)</td>
<td>40 (36)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systolic</strong></td>
<td>122 (14)</td>
<td>123 (12)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td>77 (9)</td>
<td>78 (9)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Total cholesterol (mmol/l)</strong></td>
<td>4.83 (0.82)</td>
<td>4.95 (0.91)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/l)</strong></td>
<td>1.74 (0.28)</td>
<td>1.73 (0.32)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Total triacylglycerol (mmol/l)</strong></td>
<td>1.36 (0.79)</td>
<td>1.33 (0.57)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Fasting plasma glucose (mmol/l)</strong></td>
<td>4.87 (0.25)</td>
<td>4.87 (0.24)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>2-h glucose in 75g OGTT (mmol/l)</strong></td>
<td>5.94 (1.10)</td>
<td>5.87 (1.00)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>5.20 (0.27)</td>
<td>5.23 (0.26)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>HbA1c (mmol/mol)</strong></td>
<td>33 (3)</td>
<td>34 (3)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Fasting plasma insulin (pmol/l)</strong></td>
<td>58.3 (32.3)</td>
<td>55.0 (29.2)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Physical activity (min/week)</strong></td>
<td>90 (30, 150)</td>
<td>60 (30, 130)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Dietary index at baseline</strong></td>
<td>9.8 (2.7)</td>
<td>10.2 (2.7)</td>
<td>0.32</td>
</tr>
</tbody>
</table>
5.1.1 POSTPARTUM GLUCOSE METABOLISM

Figure 6 presents the incidence of impaired glucose regulation at 6 weeks, 12 months, and cumulatively during the postpartum follow-up. The combined lifestyle intervention during pregnancy and the first postpartum year reduced the incidence of impaired glucose regulation (IFG, IGT, and type 2 diabetes) during the first postpartum year. After adjusting for age at 6 weeks postpartum, the OR was 0.11 (95% CI 0.01, 0.97), p=0.047, and at 12 months postpartum, the OR was 0.23 (95% CI 0.05, 1.14), p=0.07. During the postpartum follow-up, impaired glucose regulation was present among 13.3% in the control group and among 2.7% in the intervention group age-adjusted OR 0.18 (95% CI: 0.05–0.65, p=0.009). The AUC of the glucose values in the OGTT at 6 weeks (p=0.12) were not different between the groups, but at 12 months postpartum, they were significantly lower in the intervention group (p=0.04). One participant in the control group was diagnosed with type 2 diabetes.

Figure 6. Incidence (%) of impaired glucose regulation (IFG, IGT, or type 2 diabetes) during the first postpartum year in the intervention and control groups.
5.1.2 WEIGHT CHANGE AND METABOLIC PARAMETERS

There were no differences in weight change between the groups from pre-pregnancy to 12 months postpartum. When assessing the metabolic parameters at 12 months postpartum, there were no significant differences between the groups in blood pressure (p=0.83), total cholesterol (p=0.86), HbA1c (p=0.49), or fasting insulin (p=0.56).

5.1.3 LIFESTYLE CHANGES

At the 12-month postpartum visit, there were no significant differences in the self-reported physical activity in minutes per week [intervention group median 100 min (IQR 60, 180) and control group median 120 min (IQR 45, 180) p=0.94] or dietary index [intervention group 9.7 (SD 3.1) and control group 9.0 (SD 2.7) p=0.13]. The intervention group was able to maintain a slightly better diet [-0.3 (95% CI -1.0, 0.35) p=0.36], while in the control group it deteriorated from the first trimester to 12 months postpartum [-0.9 (95% CI -1.6, -0.3) p=0.011]. The change in physical activity was similar in both groups (p=0.28). The number of breastfeeding participants was comparable in both groups, and it decreased during the postpartum year. It was not associated with weight change from pre-pregnancy to one year postpartum, nor with the incidence of glycemic abnormalities after adjustment for pre-pregnancy BMI.

5.2 HETEROGENEITY OF GESTATIONAL DIABETES

The first trimester characteristics of the participants in studies II, III, and IV are presented in Table 8. The women in group C, the non-obese women with previous GDM, showed significantly better metabolic characteristics compared to the other groups at the first trimester (median 13.3 gestational weeks) study visit. Only a few women in each group presented with GAD (total n=5) or ICA (total n=11) antibodies, and there were no significant differences between the groups [GAD (p=0.75) or ICA (p=0.98)]. The prevalence of chronic diseases, most commonly asthma, was 25% (n=66) with no significant differences between the groups. The mother’s own birth weight was significantly lower in groups C and D (3416 g and 3433 g, respectively) compared to groups A and B (3620 g and 3536 g, respectively) (p=0.041).
Table 8. Baseline characteristics of Studies II, III, and IV. Dark grey = p<0.001, light grey = p<0.05. Group A= Primiparous obese women, B= Multiparous obese women, C= Multiparous non-obese women with previous GDM, D= Multiparous obese women with previous GDM

<table>
<thead>
<tr>
<th>Group</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A n=11; B n=68; C n=64; D n=24</td>
<td>A n=166; B n=97; C n=148; D n=99</td>
<td>A n=91; B n=63; C n=117; D n=62</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30 (5) 33 (5) 33 (4) 33 (5)</td>
<td>31 (5) 33 (5) 33 (4) 33 (5)</td>
<td>32 (5) 34 (4) 34 (4) 35 (5)</td>
</tr>
<tr>
<td>BMI (kg/m²) prepregnancy</td>
<td>34.2 (3.8) 34.2 (3.6) 23.6 (2.7) 34.7 (4.3)</td>
<td>35.3 (4.2) 34.9 (3.6) 24.9 (2.6) 34.9 (4.2)</td>
<td>34.3 (3.7) 34.2 (3.9) 24.4 (2.6) 34.3 (4.8)</td>
</tr>
<tr>
<td>Educational attainment (years)</td>
<td>14.1 (2.6) 13.6 (2.4) 14.8 (2.4) 13.1 (2.6)</td>
<td>14.4 (2.1) 14.2 (1.9) 14.9 (2.0) 13.7 (2.0)</td>
<td>14.9 (1.8) 14.2 (2.0) 15.0 (2.0) 14.2 (2.1)</td>
</tr>
<tr>
<td>Family history of diabetes, n (%)</td>
<td>24 (21) 11 (18) 15 (24) 7 (30)</td>
<td>42 (25) 20 (22) 51 (35) 37 (37)</td>
<td>27 (30) 14 (24) 43 (37) 21 (35)</td>
</tr>
<tr>
<td>Dietary score (HFII)</td>
<td>9.57 (2.60) 9.46 (2.85) 10.69 (2.74) 10.86 (2.71)</td>
<td>9.5 (2.7) 9.6 (2.9) 10.8 (2.7) 10.1 (2.9)</td>
<td>- - - -</td>
</tr>
<tr>
<td>Physical activity (min)</td>
<td>60 (30,125) 60 (30,140) 60 (45,150) 60 (0,180)</td>
<td>60 (30,120) 60 (30,120) 90 (30,150) 60 (30,125)</td>
<td>60 (30,120) 80 (30,140) 90 (30,135) 60 (30,150)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>4.85 (0.24) 4.89 (0.24) 4.89 (0.26) 4.92 (0.20)</td>
<td>5.08 (0.44) 4.95 (0.34) 5.06 (0.41) 5.23 (0.40)</td>
<td>4.99 (0.39) 4.96 (0.38) 5.10 (0.41) 5.30 (0.37)</td>
</tr>
<tr>
<td>Fasting insulin (mU/l)</td>
<td>10.39 (8.42) 8.82 (3.58) 5.01 (2.48) 7.90 (3.01)</td>
<td>11.13 (8.14) 9.28 (3.78) 5.75 (3.63) 9.83 (5.21)</td>
<td>10.61 (6.46) 8.25 (3.32) 5.52 (3.40) 9.81 (4.76)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.2 (0.25) 5.2 (0.31) 5.2 (0.27) 5.2 (0.27)</td>
<td>5.24 (0.30) 5.27 (0.31) 5.25 (0.28) 5.33 (0.35)</td>
<td>5.21 (0.29) 5.30 (0.31) 5.28 (0.27) 5.39 (0.31)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.27 (1.88) 1.87 (0.79) 1.09 (0.58) 1.74 (0.74)</td>
<td>4.78 (0.72) 5.02 (0.92) 4.74 (0.84) 5.01 (0.92)</td>
<td>4.74 (0.74) 4.99 (1.05) 4.72 (0.87) 5.06 (0.92)</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>124 (92,168) 129 (91,178) 63 (48,76) 103 (84,133)</td>
<td>478 (0.72) 5.02 (0.92) 4.74 (0.84) 5.01 (0.92)</td>
<td>4.74 (0.74) 4.99 (1.05) 4.72 (0.87) 5.06 (0.92)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.82 (0.73) 5.11 (0.94) 4.71 (0.91) 5.57 (0.96)</td>
<td>4.78 (0.72) 5.02 (0.92) 4.74 (0.84) 5.01 (0.92)</td>
<td>4.74 (0.74) 4.99 (1.05) 4.72 (0.87) 5.06 (0.92)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.73 (0.60) 3.00 (0.86) 2.60 (0.70) 3.22 (0.81)</td>
<td>2.72 (0.60) 2.91 (0.81) 2.65 (0.70) 2.86 (0.71)</td>
<td>2.67 (0.64) 2.98 (0.84) 2.66 (0.70) 2.91 (0.77)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.67 (0.31) 1.76 (0.31) 1.80 (0.33) 1.84 (0.30)</td>
<td>1.39 (0.54) 1.36 (0.51) 1.10 (0.37) 1.49 (0.81)</td>
<td>1.66 (0.32) 1.71 (0.30) 1.74 (0.33) 1.62 (0.33)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.38 (0.54) 1.35 (0.48) 1.11 (0.42) 1.81 (1.33)</td>
<td>9.55 (7.18) 8.53 (5.99) 4.29 (3.78) 11.18 (11.35)</td>
<td>8.0 (6.5) 8.7 (7.6) 4.5 (6.6) 9.4 (7.9)</td>
</tr>
<tr>
<td>hs-CRP (mmol/l)</td>
<td>9.0 (6.5) 8.0 (5.4) 4.0 (43) 13.7 (13.0)</td>
<td>13.9 (0.54) 13.6 (0.51) 1.10 (0.37) 1.49 (0.81)</td>
<td>1.31 (0.52) 1.33 (0.51) 1.13 (0.36) 1.45 (0.54)</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>11.5 (10.1) 11.0 (5.7) 12.7 (10.8) 10.8 (5.9)</td>
<td>11.5 (8.9) 10.9 (5.6) 12.1 (9.5) 10.8 (5.1)</td>
<td>11.5 (8.9) 10.9 (5.6) 12.1 (9.5) 10.8 (5.1)</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>6.2 (7.4) 5.5 (6.0) 9.5 (15.6) 5.9 (4.2)</td>
<td>6.18 (6.80) 5.07 (5.45) 9.27 (14.40) 5.20 (3.40)</td>
<td>6.18 (6.80) 5.07 (5.45) 9.27 (14.40) 5.20 (3.40)</td>
</tr>
<tr>
<td>Adiponectin (mg/ml)</td>
<td>16.9 (6.0) 16.8 (5.5) 19.9 (7.1) 16.5 (5.8)</td>
<td>15.8 (6.1) 16.2 (5.3) 18.3 (6.5) 15.2 (5.5)</td>
<td>15.8 (6.1) 16.2 (5.3) 18.3 (6.5) 15.2 (5.5)</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>123 (13) 123 (12) 115 (11) 132 (13)</td>
<td>122 (12) 122 (12) 114 (12) 123 (13)</td>
<td>79 (8) 78 (8) 72 (8) 77 (11)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79 (9) 78 (8) 72 (8) 82 (10)</td>
<td>79 (9) 78 (8) 72 (8) 82 (10)</td>
<td>79 (9) 78 (8) 72 (8) 77 (11)</td>
</tr>
</tbody>
</table>
Results

5.2.1 PREGNANCY (STUDIES II AND III)

5.2.1.1 Incidence of Gestational Diabetes
When analyzing all the participants (n=510) in study III with known glycemic status during pregnancy, our results demonstrated a high incidence of GDM in the first trimester; 37.4% (95% CI: 33.2–41.8) were diagnosed with early GDM, and the total cumulative incidence of GDM was 49.4% (45.0–53.8).

Pre-pregnancy BMI was higher (mean 32.4 kg/m$^2$) among women with early diagnosis compared to standard GDM women (28.9 kg/m$^2$) and those with normal glucose tolerance during pregnancy (31.7 kg/m$^2$) (p < 0.001). Women with early GDM also had a family history of diabetes (41%) more often than standard GDM (28%) and normoglycemic women (21%), but the difference was not statistically significant (p=0.069).

Figure 7. Cumulative incidence of GDM (%) in the first and second trimester in groups A, B, C, and D.

A high incidence of early GDM was especially seen among women with previous GDM. The first-trimester OGTT was pathological among 38% of non-obese women (group C) and 63% of obese women (group D) with a previous
history of GDM (Figure 7). The risk of GDM was similar in groups A and B [OR 0.87 (95% CI 0.51–1.48)]. Compared to group A, it was markedly higher in groups C [OR 2.52 (95% CI 1.60–3.97)] and D [OR 4.96 (95% CI 2.87–8.58)], both of which had a history of GDM.

When analyzing only the 269 participants in study II, the women recruited in early pregnancy with a normal OGTT in the first trimester, the occurrence of GDM was significantly higher among the non-obese women with previous GDM: In group A, it was 9.7%, in group B 11.8%, in group C 35.9%, and in group D 20.8% (p<0.001, adjusted for second-trimester physical activity and dietary score, age, educational attainment, and family history of diabetes).

5.2.1.2 Gestational Weight Gain (Study II)

The weight change from pre-pregnancy to the second-trimester study visit was highest in group C, both in absolute values (p<0.001) and percentages of body weight (p<0.001). Gestational weight gain (GWG) was fairly low in all groups: 3.7 kg, 3.1 kg, 6.3 kg, and 4.5 kg (in groups A, B, C, and D). GWG, however, was not associated with GDM incidence (interaction p=0.88).

5.2.1.3 Lifestyle factors (Study II)

Diet score measured at baseline was similar in all the groups (Table 8), with the only statistically significant difference seen between groups A and C. In the first trimester, the amount of physical activity in minutes per week was similar in all groups.

5.2.2 FIVE YEARS POSTPARTUM (STUDY IV)

Among the women attending the 5-year follow-up visit, GDM was diagnosed in the index pregnancy in 33% of the women in group A, 25% in group B, 60% in group C, and in 66% in group D, respectively. Five years after delivery, the non-obese women with a previous history of GDM before the RADIEL study (group C) were still metabolically healthier than the obese participants when considering anthropometric measurements, insulin, lipids, and blood pressure (Table 9).
Results

Table 9. Metabolic characteristics of the participants 5 years after delivery. Data are presented as means with SD, except for physical activity as median with IQR.

<table>
<thead>
<tr>
<th></th>
<th>A n=91</th>
<th>B n=63</th>
<th>C n=117</th>
<th>D n=62</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>35.4 (5.0)</td>
<td>35.1 (5.8)</td>
<td>25.5 (3.7)</td>
<td>35.4 (5.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>113 (14)</td>
<td>112 (15)</td>
<td>91 (11)</td>
<td>113 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total triglycerides (mmol/l)</td>
<td>1.1 (0.55)</td>
<td>1.00 (0.42)</td>
<td>0.89 (0.53)</td>
<td>1.13 (0.66)</td>
<td>0.021</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.86 (0.68)</td>
<td>3.12 (0.91)</td>
<td>2.97(0.73)</td>
<td>3.03 (0.73)</td>
<td>0.20</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.37 (0.34)</td>
<td>1.44 (0.32)</td>
<td>1.62 (0.34)</td>
<td>1.41 (0.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP (mmol/l)</td>
<td>2.50 (2.07)</td>
<td>2.61 (2.26)</td>
<td>1.19 (1.40)</td>
<td>2.20 (1.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>5.32 (0.28)</td>
<td>5.43 (0.33)</td>
<td>5.41 (0.30)</td>
<td>5.63 (0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.07 (0.48)</td>
<td>5.07 (0.49)</td>
<td>5.30 (0.53)</td>
<td>5.67 (1.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma insulin (mU/l)</td>
<td>13.52 (8.55)</td>
<td>12.67 (7.11)</td>
<td>8.14 (5.31)</td>
<td>13.69 (8.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>127 (13)</td>
<td>127 (13)</td>
<td>117 (11)</td>
<td>127 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>80 (10)</td>
<td>80 (9)</td>
<td>74 (8)</td>
<td>81 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical activity (min/week)</td>
<td>60 (30, 180)</td>
<td>60 (30, 120)</td>
<td>85 (50, 160)</td>
<td>110 (30, 180)</td>
<td>0.56</td>
</tr>
<tr>
<td>Medication for hypertension, n (%)</td>
<td>6 (7)</td>
<td>2 (3)</td>
<td>3 (3)</td>
<td>6 (10)</td>
<td>0.16</td>
</tr>
<tr>
<td>Medication for dyslipidemia, n (%)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

5.2.2.1 Prevalence of impaired glucose regulation

At the five-year follow-up, 3.6% were diagnosed with diabetes, and among all participants, there was a high prevalence (18%) of impaired glucose regulation (IFG, IGT, or diabetes). It was highest among group D (26%) and lowest among group A participants (8%) (p=0.021) (Figure 8).

Glucose values in the OGTT were higher among women with GDM in the index pregnancy in all groups. This was also true for HbA₁c values, and there was no interaction between a history of GDM and ABCD grouping (p=0.14 - 0.89).
5.2.2.2 Prevalence of metabolic syndrome

Metabolic syndrome according to NCEP/ATP III criteria was diagnosed in 32% of the participants in group A, 25% in group B, 11% in group C, and in 39% in group D (p<0.001).

When analyzing the prevalence of pathological components of metabolic syndrome separately, group C differed from the other groups. Waist circumference, HDL cholesterol, and blood pressure were normal more often in group C compared to the obese groups. Still, waist circumference exceeded the recommended cut-off among 58% of the women in group C, who were non-obese before the RADIEL pregnancy.
5.2.2.3 Prevalence of metabolic derangements

The prevalence of the composite metabolic outcome (IFG, IGT, diabetes, or metabolic syndrome) was similar in all groups (p=0.24, adjusted for age). BMI was associated with a higher prevalence of metabolic derangements in all groups. Group C, the previously non-obese women, showed metabolic derangements at a lower BMI compared to the other groups (p<0.001).

There were differences between the groups when assessing the metabolic parameters at follow-up. Group C had better metabolic health when considering waist circumference, HDL cholesterol, hs-CRP, fasting insulin, and blood pressure (Table 9). Time spent on leisure time physical activity per week was similar in all groups (p=0.56). There were only a few women in each group using medication for hypertension or dyslipidemia, and no differences were detectable between the groups (for hypertension p=0.16 and hyperlipidemia p=0.41).

5.2.2.4 Body composition

Body fat percentage was higher among participants with metabolic syndrome in all groups (p<0.001), and this difference was most clearly seen in group C. The prevalence of obesity based on fat percentage was over 90% within the obese groups, and 58% in group C, who were non-obese before the RADIEL pregnancy. According to BMI, the prevalence of obesity was 14% in group C.
5.3 RISK SCORES FOR GESTATIONAL DIABETES (STUDY III)

5.3.1 RISK SCORE PERFORMANCE

5.3.1.1 Total study population
Van Leeuwen’s risk score calculated the estimated probability of GDM to be 19%, although the true GDM incidence in this study population was 49%. When using the Teede score, the risk identification succeeded in 61% of cases. High numbers of participants fell below the suggested 4-point cut-off limit.

5.3.1.2 According to ABCD groups
When tested in the ABCD groups separately, the Van Leeuwen score underestimated the incidence of GDM in all groups (Table 10). The detection rate was lowest in group C.

The Teede risk calculation performed best in group B, the multiparous obese women without a history of GDM, and worst among the non-obese women in group C.

Table 10. Performance of GDM Risk scores in ABCD groups

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>True incidence of GDM</td>
<td>36%</td>
<td>33%</td>
<td>59%</td>
<td>74%</td>
</tr>
<tr>
<td>Van Leeuwen score</td>
<td>21%</td>
<td>11%</td>
<td>11%</td>
<td>31%</td>
</tr>
<tr>
<td>Estimated probability of GDM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teede score</td>
<td>66%</td>
<td>69%</td>
<td>52%</td>
<td>57%</td>
</tr>
<tr>
<td>Agreement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.3.2 OTHER POTENTIAL RISK MARKERS

Following the weak performance of the previously created risk calculations, we chose the most commonly used metabolic markers from the first trimester and tested their predictive value in groups A, B, C, and D separately (Table 11). The only predictive marker for GDM found was fasting plasma glucose in group A [OR 3.76 (95% CI: 1.48–9.53)].

Table 11. Performance of common risk markers in A, B, C, and D groups. *** p<0.01

<table>
<thead>
<tr>
<th>Marker</th>
<th>Group A OR (95% CI)</th>
<th>Group B OR (95% CI)</th>
<th>Group C OR (95% CI)</th>
<th>Group D OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.08 (0.91, 1.27)</td>
<td>1.07 (0.88, 1.29)</td>
<td>0.99 (0.86, 1.15)</td>
<td>0.91 (0.72, 1.15)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>1.02 (0.18, 5.71)</td>
<td>0.77 (0.09, 6.90)</td>
<td>1.33 (0.40, 4.37)</td>
<td>5.08 (0.27, 96.30)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>3.76 *** (1.48, 9.53)</td>
<td>0.62 (0.17, 2.35)</td>
<td>1.31 (0.66, 2.57)</td>
<td>0.58 (0.04, 8.64)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.64 (0.82, 3.30)</td>
<td>1.66 (0.71, 3.88)</td>
<td>1.37 (0.64, 2.90)</td>
<td>0.95 (0.27, 3.28)</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.57 (0.27, 1.24)</td>
<td>0.84 (0.33, 2.18)</td>
<td>0.62 (0.32, 1.22)</td>
<td>0.70 (0.18, 2.73)</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.61 (0.24, 1.58)</td>
<td>0.93 (0.27, 3.15)</td>
<td>0.71 (0.24, 2.09)</td>
<td>0.49 (0.12, 2.01)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>2.00 (0.76, 5.26)</td>
<td>0.67 (0.32, 1.42)</td>
<td>1.05 (0.56, 1.97)</td>
<td>1.99 (0.60, 6.60)</td>
</tr>
</tbody>
</table>
6 DISCUSSION

6.1 MAIN FINDINGS

In the RADIEL study, a lifestyle intervention during pregnancy and the first postpartum year among high-risk women managed to reduce the incidence of GDM by 36%. This study additionally demonstrated the positive effects on postpartum health in high-risk women: During the first postpartum year, women from the intervention group had 82% less glycemic abnormalities than those in the control group. Although there were no differences in weight or metabolic characteristics assessed at 12 months postpartum, the intervention group managed to maintain a healthier diet, while in the control group the diet index declined.

GDM is a heterogeneous disorder, and this study highlighted that there are also high-risk women among the non-obese. In our high-risk group of women with a BMI $\geq 30$ kg/m$^2$ and/or previous history of GDM, 37% had already received a GDM diagnosis in the first trimester, and the cumulative incidence in the second trimester was 49%. The “early GDM” women presented with a higher BMI and a somewhat stronger family history of diabetes. When analyzing the high-risk women with normal glucose tolerance in the first trimester, the highest GDM incidence in the second trimester was 36.4% among the non-obese women with a history of previous GDM. This was despite the fact that they were metabolically healthier in the first trimester. Diabetes-related autoantibodies or family history of diabetes did not provide any explanation for the increased GDM risk. Furthermore, there was no association between GWG and GDM incidence.

The heterogeneity of GDM also challenges the development of prognostic risk calculations. These risk models have been developed to enable better-focused GDM screening, but their performance has been only moderate. In our study, we tested two of the best-performing risk scores and both underestimated the incidence of GDM. When tested in subgroups based on clinical characteristics, the score performance was poorest in the non-obese group; the Van Leeuwen score predicted GDM incidence to be 11%, whereas in reality, it was 59%. Teede’s score succeeded in risk identification in 52% of cases. When searching for risk markers among these subgroups, only fasting glucose among the obese primiparous women was an indicator of GDM risk. The other groups showed no identifiable risk markers.

The RADIEL follow-up study provided important information on the metabolic risk profiles of high-risk women 5 years postpartum. Interestingly, the previously non-obese women were still at high risk for glycemic
disturbances, although they were metabolically healthier based on other markers such as lipids and blood pressure. The overall prevalence of diabetes and pre-diabetes was 15%, with the highest prevalence, 26%, among the obese women with GDM history and the lowest prevalence, 8%, among primiparous obese women. Metabolic syndrome was common among the obese participants as approximately one-third were diagnosed with MetS; non-obese women with a high fat percentage were also at risk. Of the participants who were non-obese before the RADIEL study, 14% were obese at the follow-up based on BMI, but 58% had a high fat percentage (>32%), indicating obesity. This resembles the condition called normal weight obesity (NWO). In all groups, BMI was associated with metabolic derangements, but this previously non-obese group faced them at a lower BMI compared to the other groups.

6.2 STRENGTHS AND LIMITATIONS OF THE STUDY

The strengths of this study lie in the unique study design. This is one of the few studies providing a lifestyle intervention starting during pregnancy and continuing during the first postpartum year. The participation rate in the intervention was good; 75% of women in Study I attended all 6 visits, and the mean number of study visits was 5.7. Another strength was performing an additional OGTT in the first trimester. This has enabled the identification of “early GDM” women and the analysis of the intervention effects among the population where GDM still could be prevented.

Furthermore, the inclusion of non-obese women at risk has provided an exceptional possibility to evaluate the risk profiles of the heterogeneous groups of high-risk women. The various questionnaires and metabolic assessments at several time points during pregnancy and the first postpartum year are also a strength of the study, allowing us to follow longitudinal changes and assess the health of the participants from several aspects. The participation rate at follow-up was also good compared to many other studies; in total, 57% of the women attended the follow-up visit at 5 years postpartum. The more comprehensive analysis of metabolic health including the assessment of body composition is a further strength of the study.

However, this study included only Caucasian women, and they were quite highly educated, which can limit the generalizability of these findings. Moreover, the number of women in different subgroups was rather small, and this can be considered an additional weakness.
Like in most intervention studies, the control group received some kind of “mini-intervention.” Although they did not get any special advice, they still attended study visits for measurements and filled in questionnaires and food diaries. This might have affected our findings, but in this case, the results concerning the intervention effect might be even more pronounced if comparing to the general population. There might also be a selection bias toward more motivated participants, as this was a long study with several follow-up visits. In the drop-out analysis, however, we did not see any differences in the characteristics of the participants. Unfortunately, we are also missing a normal weight control group without a history of GDM to enable a better characterization of the non-obese risk group.

Although the measurements and collected data were quite comprehensive, there is a paucity of some outcomes that might have further assisted in answering our research questions. At the follow-up study, we measured body composition, but unfortunately, we lack detailed information on the distribution of adipose tissue between visceral and peripheral tissues. Additionally, there is a deficiency of more sophisticated measurements of the insulin secretion profile to further analyze the pathophysiological background of these heterogeneous subgroups. Only the subgroup of 269 women with normal glucose tolerance in the first trimester provided samples for the analysis of diabetes-related autoantibodies, ruling out the higher-risk groups such as “early GDM” women and restricting the possible conclusions. Moreover, there are some missing data from the outcomes we assessed; especially the OGTT was considered burdensome, and some participants refused to undergo it.

6.3 LIFESTYLE INTERVENTIONS

Our findings from the RADIEL study are in accordance with previous evidence showing that lifestyle interventions are effective in preventing diabetes among women with a history of GDM (149). Women in the intervention group had 82% less glycemic abnormalities during the first postpartum year, although there were no differences in metabolic markers such as HbA1c, insulin, lipids, and blood pressure at the 12-month postpartum visit. They were, however, able to maintain a healthier diet, and this might have positive implications for the future health of the mother and possibly the whole family. Similar small changes were detectable during the pregnancy period of the RADIEL study, leading to less GDM incidence (12).

The overall incidence of glycemic abnormalities during the first postpartum year was low compared to other studies. This might be partly due to the study
Design and the “mini-intervention” that possibly affected the control group. Furthermore, pathological OGTT in the first trimester led to exclusion in this study (Study I), which also potentially influenced the incidence of glycemic abnormalities postpartum. From previous studies, we know that early diagnosis of GDM, severity of glucose intolerance during pregnancy, and medical treatment of GDM are associated with an increased diabetes risk in the future (132, 133).

One special feature of the RADIEL study was initiating the intervention during pregnancy and continuing during the first postpartum year, additionally aiming at the prevention of type 2 diabetes (15, 169, 170). There are some suggestions that starting the postpartum intervention during pregnancy might improve the results compared to starting only after delivery (170). Unfortunately, the effect seen in our study declined over the first postpartum year, similarly to the GEM study (169). The difference between the intervention and control groups was most remarkable at 6 weeks after delivery. One can speculate that this early OGTT might be a good marker of the beta cells’ ability to recover from pregnancy-related stress. If this is true, these results might have long-term consequences on future diabetes risk.

Some follow-up studies of pregnancy interventions have demonstrated effects on weight retention and/or diet 3–12 months postpartum (175, 176, 178, 179), but there is no effect on glycemic outcomes. Our study, however, indicated no differences in body weight but showed apparent effects on glycemic outcomes. One explanation might be the differences in study populations and the lack of a consistent association of BMI and diabetes risk. Most other studies have focused on obese populations, with a potentially lower risk of diabetes compared to women with a history of GDM recruited in our study. Also, the effect on weight loss might be more achievable among obese women than among women of normal weight. In our study, we also included non-obese women at high diabetes risk, and among them, diet has hypothetically more effect than weight loss as their diabetes risk is assumingly based on deficient insulin secretion rather than on adiposity and insulin resistance.

Breastfeeding is associated with improved insulin sensitivity and lower type 2 diabetes risk (299–301), and it also facilitates weight loss after pregnancy (173). It is also beneficial for the child in lowering the risk for obesity and diabetes (302). The RADIEL intervention emphasized breastfeeding, but there were no differences in the number of breastfeeding women between the intervention and the control groups. The total number of breastfeeding women was high, similar to Finnish standards, but glucose tolerance was not associated with breastfeeding.
6.4 HETEROGENEITY OF GDM

6.4.1 IMPORTANCE DURING PREGNANCY

The heterogeneity of type 2 diabetes is rather well-established and we know that it results from several overlapping features that are further modified by the environment (16, 17). The heterogeneity of GDM has gained less attention, and our study results demonstrate that there are also high-risk women among the non-obese, highlighting the need for further studies.

In our high-risk population with a BMI $\geq 30$ kg/m² and/or previous GDM, the incidence of “early GDM” was 37.4%. This was markedly higher than the reported incidence of 14% in a previous Finnish intervention study targeting women at high GDM risk (158). That study, however, included not only obese but also overweight women without GDM history, thus lowering the overall risk of GDM. Currently, there is debate on the appropriate screening strategy and definition for “early GDM,” but studies have shown that it is associated with increased insulin resistance, higher fasting glucose, higher BMI, hypertensive disorders of pregnancy, insulin treatment (210, 211), and even higher neonatal risks (212). This might be suggestive of pre-existing insulin resistance even before pregnancy (33).

Women with a history of GDM presented with the highest risk for GDM. Previous studies have also demonstrated a notable protective effect of multiparity without previous GDM (303). Similarly, in our study, women without GDM history, both primiparous and multiparous, had lower GDM incidence, and the prevalence of postpartum glycemic abnormalities was lower among those women.

According to our findings, there are women at high GDM risk within the normal weight population. The non-obese women with a history of GDM had a high GDM risk in the RADIEL pregnancy. During pregnancy, they had a 60% cumulative incidence and 38% were already diagnosed in the first trimester. In a sub-study of women with normal glucose tolerance in the first trimester, this subgroup of normal weight women was metabolically healthier in the first trimester despite having the highest GDM incidence. There were no signs of subclinical inflammation, and the prevalence of diabetes-related autoantibodies was low. During pregnancy, non-obese women tend to have more insulin secretory problems as opposed to the obese, who have a more pronounced insulin resistance (20, 32, 33). The present results support these findings. The non-obese women had lower HOMA-β, indicating a secretory defect, whereas the obese women already had higher HOMA-IR in the first trimester, indicating insulin resistance.
BMI and weight-related factors such as GWG are generally considered major risk factors for GDM (226, 237, 304), while genetic and autoimmune factors play an additional role (19). Previous studies have shown that diabetes-related autoantibodies are often present among women with lower BMI and those who are less insulin resistant (18), but this was not the case in our study. The diabetes-related autoantibodies were only analyzed in the sub-study of women with normal glucose tolerance in early pregnancy (Study II), and therefore the exclusion of women with “early GDM” might have influenced the overall findings. Previous reports have emphasized the connection between GWG and GDM incidence (236, 237). In the RADIEL study, however, there was no such association. The non-obese women had higher GWG, both in absolute values and as body weight percentages, but this was not associated with GDM incidence.

The observed heterogeneity of GDM might have influenced previous GDM prevention trials as well. If the intervention aims at reducing insulin resistance, it might have a minor or non-existing effect on those with deficient insulin secretion (20). Studies on the genetic background of GDM have also highlighted the heterogeneity. MTNR1B polymorphism seems to affect the responsiveness to lifestyle intervention and also weight loss (221, 222). Hypothetically, there could also be other gene-environment interactions that influence the effect of the intervention.

6.4.2 LONG-TERM HEALTH

Five years postpartum, glycemic abnormalities were detectable among 15% of the total study population. Among women with GDM in the RADIEL study, the prevalence of IFG, IGT, or type 2 diabetes was 23% compared to 8.5% in women with normoglycemic pregnancy. In previous studies, the incidence of diabetes after a GDM pregnancy varied between 8% and 26% depending on the diagnostic criteria of GDM, population, and duration of the follow-up. In a 5-year follow-up of women with GDM (IADPSG-defined), the prevalence of prediabetes or diabetes was 26%, very similar to our study. On the other hand, in a Swedish study where the cut-offs for GDM diagnosis are markedly higher, the prevalence rate 5 years after delivery for any form of glycemic abnormality was 51% (305). A history of GDM before the RADIEL study was a much stronger predictor of postpartum glycemic abnormalities than adiposity.

In total, 18% of the previously non-obese women were diagnosed with either diabetes or pre-diabetes (IFG or IGT) 5 years after delivery, but they were still metabolically healthy concerning their lipids and blood pressure levels. Previously, type 2 diabetes risk has been associated with defects in insulin secretion. According to the studies by Damm and colleagues, non-obese GDM women have a delayed and lower insulin secretion profile, and this difference lasted 5–10 years postpartum, possibly contributing to the high prevalence of
glycemic abnormalities (204). Although obesity is an important risk factor for diabetes, the Nurses’ Health Study (NHS) (306) also showed an increasing risk at normal BMI levels.

Women with GDM are also at higher risk for metabolic syndrome, which is associated with the severity of glucose intolerance during pregnancy (135, 136). In accordance with previous studies, metabolic syndrome was common among the obese participants in the RADIEL follow-up. In another Finnish GDM prevention study, the prevalence at the 1-year follow-up was 16% (136), which is considerably lower than the total prevalence of 25% in the RADIEL study. This is an important finding because early metabolic derangements are associated with future diabetes (138). Both metabolic syndrome and glycemic disturbances were associated with adiposity, and previous studies have also demonstrated this among the normal weight population (307).

There was also a high prevalence of normal weight obesity (NWO) among this non-obese subgroup. Five years postpartum, 14% were obese based on BMI, but 58% had a high fat percentage (≥32%), indicating obesity. Earlier studies have identified this condition (308), but the consensus on the definition is still lacking. Generally, it includes people with normal BMI (<25kg/m²) and high body fat percentage, with metabolic consequences usually associated with obesity (309). It has been associated with a higher risk of dyslipidemia, insulin resistance, high blood pressure, type 2 diabetes, and cardiovascular disease (310, 311). Unfortunately in our study, we lack precise measurements of the fat distribution, but the overall body fat percentage correlated strongly with waist circumference. We can therefore only hypothesize on the amount of visceral fat, which is acknowledged as metabolically disadvantageous (307).

The highest risk of metabolic derangements both during pregnancy and 5 years postpartum was observable among the women with previous GDM, both among obese and non-obese women. Interestingly, women belonging to these subgroups had significantly lower birth weights compared to groups without a previous history of GDM before the RADIEL study. Hypothetically, fetal programming might have influenced the greater metabolic risk of these women. According to the DOHaD (Developmental Origins of Health and Disease) hypothesis, intrauterine conditions shape our health and disease for generations onward (312, 313). Maternal diet, hyperglycemia, physical activity, stress, and obesity can affect fetal size, body composition, and future risk of diabetes and other non-communicable diseases (314–316). Other plausible explanations for the high risk among the non-obese women could be a genetic predisposition or other mechanisms, including alterations in the gut microbiota.
6.5 GDM RISK SCORES

Previously generated risk scores for detecting individuals at high diabetes risk have been successful (22). A similar intention has yielded several risk calculations for assessing GDM risk, but their performance has been only moderate (21). In our high-risk population, two of the best-performing GDM risk scores (278, 279) underestimated the incidence of GDM, even when tested in phenotypically distinct subgroups. The poorest performance was among the non-obese women with previous GDM. This varying performance in heterogeneous subgroups was also detectable in the validation study, which showed different performance among nulliparous women (21). Many scores emphasize ethnic background, and as our study population included only Caucasian women, this might have influenced the results. Moreover, the diagnostic criteria for GDM were different in not only the original cohorts where the risk scores were developed but also in the validation cohort. This can have an additional effect as our thresholds for diagnosis are lower, also diagnosing milder forms of GDM. However, current IADPSG recommendations are even lower (52) than the current Finnish cut-off levels (48), and therefore this level of identification should be the target.

The heterogeneity of GDM might have partly influenced the moderate performance of GDM risk scores (21). Risk score models based on biochemical parameters have shown different markers and levels among obese and non-obese women (282). Most probably, there are even more distinct subgroups. The high prevalence of “early GDM” among high-risk populations challenges the risk identification even further.

Individual risk markers have not been successful either. Adiponectin has been frequently studied (267, 269, 317), but in our study (e.g., in the high-risk group of non-obese women), it was low in the first trimester but high among the obese women. When analyzing individual risk predictors in the subgroups separately, only fasting glucose proved to be of any value among obese primiparous women. Other groups showed no identifiable predictive markers. Random fasting plasma glucose or HbA1c in the first trimester have been the focus in previous studies as well, but the performance has not been fully satisfying (274–276).

The development of more complex models has not added much to risk identification (280, 281, 318). The risk model derived from the UPBEAT study (283), for example, performed similarly to our very simple model: by choosing a group of women with a BMI $\geq 30$ and/or previous GDM, the GDM incidence in our study was 50%.
A recent review highlighted the poor performance of risk-based screening (284). Hypothetically, it might be impossible to create one universal risk score due to the heterogeneity of GDM. Instead, the focus should be on universal screening, as otherwise, the high-risk non-obese women of Caucasian origin are easily missed.

### 6.6 FUTURE PERSPECTIVES

Heterogeneity of the pathophysiological background is true not only for type 2 diabetes but also for GDM. Differences in the pathophysiology of the non-obese GDM women require more focus, and the genetic influence needs detailed assessment. In the time of personalized medicine, this heterogeneity should be taken into account when planning GDM prevention, treatment, and follow-up studies. Already, treatment of type 2 diabetes is tailored according to the pathophysiology, and maybe it should be the case when treating women with GDM as well.

GDM prevention interventions have yielded conflicting results, and the heterogeneity of GDM might be one underlying reason. Future studies should consider this and aim at assessing different prevention strategies in phenotypically distinct groups. Interventions targeting insulin resistance might not be a correct way to prevent GDM among women who are mainly deficient in their insulin production.

Women with previous GDM are at high risk for metabolic derangements after delivery, and this is also true for non-obese women. Therefore, considering our positive results from the first postpartum year, we should acknowledge the importance of the postpartum period in identifying these women at high risk for diabetes and metabolic syndrome. Furthermore, screening strategies for type 2 diabetes after GDM should not overlook non-obese women.
7 CONCLUSIONS

This thesis focused on the postpartum effects of a lifestyle intervention during pregnancy and the first postpartum year, and on the heterogeneity of GDM with an additional focus on metabolic health 5 years postpartum. The RADIEL and its follow-up study recruiting women at high GDM risk provided the data for this study. Overall, among this high-risk cohort of women with previous GDM and/or a BMI $\geq 30\text{kg/m}^2$, 37% were diagnosed in the first trimester, and the cumulative GDM incidence was 49%. Especially among the women with previous GDM, the incidence of early diagnosis was notably high, and this should be taken into account when planning future interventions and screening strategies.

Later in life, GDM women are at a sevenfold higher risk for diabetes. Our results after following a lifestyle intervention during pregnancy and the first postpartum year are encouraging, showing an 82% reduction in glycemic abnormalities. The effect of the intervention seemed to decline over the first year after delivery, but the intervention group managed to maintain a healthier diet. Hypothetically, this could have a positive impact on their future health.

This study also demonstrated an important risk group: When analyzing women with normal OGTT in early pregnancy, the highest GDM incidence was seen among the non-obese women with a history of GDM, despite their better metabolic health in the first trimester. Gestational weight gain or diabetes-related autoantibodies were not associated with greater risk for GDM in this study population.

When analyzing the risk profiles of the different subgroups of high-risk women, we found no identifiable risk markers. Two previously evaluated risk scores by Van Leeuwen and Teede underestimated the incidence of GDM in both the total study population and in the separately analyzed phenotypically distinct groups. The poor performance is in line with the current knowledge of risk factor–based screening: In our study, it was most deficient among the non-obese women, which highlights the need for universal screening, as there are also high-risk women among the non-obese, and the risk calculations are unable to detect them.

The non-obese group is also at high risk for future metabolic derangements. The prevalence of pre-diabetes or of diabetes 5 years after delivery was 18% among the non-obese and 26% among the obese women with GDM before the RADIEL study. BMI was associated with metabolic derangements, but the previously non-obese women were already diagnosed at a lower BMI. There was also a high prevalence of normal weight obesity (NWO) in this group, as
only 14% were obese at the 5-year follow-up based on BMI, but that number increased to 58% based on fat percentage. This represents a metabolically different high-risk group not identifiable by BMI.

Our results, in line with FIGO recommendations, emphasize the need for universal GDM screening and the importance of the postpartum period in finding women at risk and promoting a healthy lifestyle. We should not overlook the non-obese women with previous GDM as they are clearly at risk for both recurrent GDM and diabetes later in life. The postpartum period is a great opportunity to improve the lifestyle of the whole family and support better metabolic health later in their life course.
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