



Gestational Diabetes Mellitus Can Be Prevented by Lifestyle Intervention: The Finnish Gestational Diabetes Prevention Study (RADIEL)

A Randomized Controlled Trial

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OBJECTIVE

To assess whether gestational diabetes mellitus (GDM) can be prevented by a moderate lifestyle intervention in pregnant women who are at high risk for the disease.

RESEARCH DESIGN AND METHODS

Two hundred ninety-three women with a history of GDM and/or a prepregnancy BMI of ≥ 30 kg/m² were enrolled in the study at < 20 weeks of gestation and were randomly allocated to the intervention group ($n = 155$) or the control group ($n = 138$). Each subject in the intervention group received individualized counseling on diet, physical activity, and weight control from trained study nurses, and had one group meeting with a dietitian. The control group received standard antenatal care. The diagnosis of GDM was based on a 75-g, 2-h oral glucose tolerance test at 24–28 weeks of gestation.

RESULTS

A total of 269 women were included in the analyses. The incidence of GDM was 13.9% in the intervention group and 21.6% in the control group ([95% CI 0.40–0.98%]; $P = 0.044$, after adjustment for age, prepregnancy BMI, previous GDM status, and the number of weeks of gestation). Gestational weight gain was lower in the intervention group (-0.58 kg [95% CI -1.12 to -0.04 kg]; adjusted $P = 0.037$). Women in the intervention group increased their leisure time physical activity more and improved their dietary quality compared with women in the control group.

CONCLUSIONS

A moderate individualized lifestyle intervention reduced the incidence of GDM by 39% in high-risk pregnant women. These findings may have major health consequences for both the mother and the child.

The prevalence of overweight and obesity are increasing worldwide (1). Obesity constitutes a major risk factor for type 2 diabetes (2), which it is estimated will affect almost half a billion people by 2030 (3,4). The global health care expenditure on diabetes is expected to total at least 490 billion U.S. dollars (5). In the U.S. and other developed countries, up to 60% of women of reproductive age are overweight or obese (1,6). Obesity is strongly associated with gestational diabetes mellitus (GDM), which affects 2–18% of all pregnancies globally (7–9). Regardless of the criteria used, the incidence of GDM is increasing (7–9). GDM is a heterogeneous disorder, resulting from an interaction between genetic and environmental risk factors (3). It is characterized by insulin resistance as well as impaired pancreatic β -cell function and is a well-known predictor of future diabetes (2). Type 2 diabetes is diagnosed in up to 10% of women with a history of GDM soon after delivery. During a 10-year follow-up, the risk can be as high as 70% (10).

GDM and obesity are both independently associated with adverse maternal and neonatal outcomes (11–13). Maternal overweight and GDM may also increase the offspring's predisposition to obesity, impaired glucose regulation, and GDM, creating a vicious cycle leading to an accumulating risk in the next generation (14–17). Thus, there is an urgent need for safe and effective interventions aimed at preventing GDM.

Findings in lifestyle intervention studies focusing on the prevention of type 2 diabetes have been encouraging, showing a risk reduction of 58% (18,19). No similar findings among high-risk women for GDM have been published. Adherence to a healthy lifestyle before pregnancy is, however, associated with reduced GDM risk (20). Several lifestyle intervention trials targeted at limiting gestational weight gain or preventing obesity-related perinatal complications, including GDM, have been performed (21–29). However, the results have been inconsistent; some studies (22,25,27,28) have been successful in reducing gestational weight gain, but the effect on GDM incidence has been minor (23–29).

The primary outcome of the Finnish Gestational Diabetes Prevention Study (RADIEL) was to examine the effect of combined moderate physical activity and diet intervention in high-risk

women on the incidence of GDM in a randomized controlled study setting.

RESEARCH DESIGN AND METHODS

The RADIEL

The RADIEL is a multicenter randomized controlled intervention study targeting women at high risk for GDM. The study was conducted between February 2008 and January 2014 in all three maternity hospitals of the Helsinki metropolitan area (Helsinki University Central Hospital, Department of Obstetrics and Gynecology; Kättilöopisto Maternity Hospital; Jorvi Hospital) and in the South-Karelia Central Hospital in Lappeenranta, in Finland.

Eligible participants for the study were women aged ≥ 18 years, pregnant at < 20 weeks of gestation, with a history of GDM and/or a prepregnancy BMI of ≥ 30 kg/m². Exclusion criteria were type 1 or type 2 diabetes; use of medication that influences glucose metabolism, such as continuous therapy with oral corticosteroids or metformin; multiple pregnancy; physical disability; current substance abuse; severe psychiatric disorder; and significant difficulty in cooperating (e.g., inadequate Finnish language skills). In addition, participants with GDM before 20 weeks of gestation were excluded from this study.

Participants were recruited from obese women primarily in association with the first trimester screening ultrasound and women with prior GDM by personal invitation letters sent out based on data in the hospital registry. In addition, notices in newspapers, social media, and antenatal clinics were used. In the randomization process, we used randomly permuted blocks stratified by risk factors (BMI ≥ 30 kg/m², history of GDM). The randomization was performed by a study nurse and by dispensing the next sequentially numbered subject code and opening the corresponding code envelope, which included the intervention arm to be assigned to the subject.

Participants entered the study voluntarily, signed an informed consent form, and were allowed to discontinue the study at any time point. The study was performed in compliance with the Declaration of Helsinki, approved by the Ethics Committees of Helsinki University Central Hospital (14 September 2006, Dnro 300/E9/06) and South-Karelia Central Hospital (11 September 2008, Dnro M06/08), and registered at clinicaltrials.gov

(clinical trial reg. no. NCT01698385). Because of technical problems on the clinicaltrials.gov website, the initial date of the RADIEL was incorrectly changed to 11 September 2012 when the clinicaltrials.gov account for the RADIEL follow-up study was created. The original clinicaltrials.gov registration was performed in 2008, prior to the first patient being enrolled in the study.

A sample of ~ 280 pregnant women (140 in each group) was required to detect differences in the incidence of GDM between the intervention (20%) and control (35%) groups of 15% ($\alpha = 0.05$, power = 80%). We assumed a 40% drop-out rate.

Study Design

The intervention design and study methods have been published in detail elsewhere (30). This study focuses only on high-risk pregnant women at < 20 weeks of gestation.

The participants in the intervention group received lifestyle counseling from study nurses and dietitians who were specifically trained for their tasks. The participants visited the study nurse three times during pregnancy. These visits were structured, but the counseling was individualized according to the stage of the pregnancy. At the time of study enrollment, the participants attended one 2-h group counseling session led by a dietitian. The study visits took place at the following time: the baseline visit at 13.3 weeks of gestation (interquartile range [IQR] 12.0–14.6 weeks of gestation); the second visit at 23.1 weeks of gestation (IQR 22.4–24.1 weeks of gestation); and the third visit at 35.1 weeks of gestation (IQR 34.4–35.6 weeks of gestation). In addition, the participants visited antenatal clinics according to standard national practice.

For women with a prepregnancy BMI of ≥ 30 kg/m², the recommendation was no weight gain during the first two trimesters. The dietary advice was based on contemporary Nordic Nutrition Recommendations (2004) (31). The dietary counseling focused on optimizing participants' consumption of vegetables, fruits and berries, whole-grain products rich in fiber, low-fat dairy products, vegetable fats high in unsaturated fatty acids, fish, and low-fat meat products, and a lower intake of sugar-rich foods.

Regarding physical activity, the aim was to achieve a minimum of 150 min of moderate-intensity physical activity (32,33) per week and to adopt an overall

active lifestyle. The participants and the study nurses planned, and during the follow-up updated, an individual physical activity program. Participants had access, free of charge, to public swimming pools and/or guided exercise groups once a week provided by the municipalities.

In the control group, participants received general information leaflets on diet and physical activity usually provided by local antenatal clinics. Also, during pregnancy the control group participants visited the study nurse three times, to make measurements, obtain blood samples, and administer questionnaires, as well as antenatal clinics according to standard practice.

Outcomes and Data Collection

The primary end point in the RADIEL was the incidence of GDM, which was defined as one or more pathological glucose values in a 75-g, 2-h oral glucose tolerance test (OGTT; run by a central laboratory) with the following diagnostic thresholds: fasting plasma glucose ≥ 5.3 mmol/L, 1-h value ≥ 10.0 mmol/L, and 2-h value ≥ 8.6 mmol/L (34). All participants underwent an OGTT at the time of study enrollment and again at ~ 24 – 28 weeks of gestation (second trimester) unless insulin or metformin treatment was initiated earlier. Blinded-study physicians reviewed participants' obstetric records and confirmed maternal and neonatal diagnoses. Fasting plasma glucose concentrations and weight change, incidence of preeclampsia and gestational hypertension, and mode of delivery were secondary outcomes. Preeclampsia was defined as a systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg occurring after 20 weeks of gestation in a previously normotensive woman combined with new-onset proteinuria of ≥ 0.3 g/24 h (35). Gestational hypertension was defined similarly but without the presence of proteinuria and essential hypertension as similar blood pressure levels occurring before 20 weeks of gestation.

At each visit, participants in both groups filled in questionnaires and underwent physical examinations that included anthropometric and blood pressure measurements and blood sampling. Antenatal clinic records served as a data source for prepregnancy weight.

A food frequency questionnaire designed for this study was filled in before each visit to the study nurse. To measure the general adherence to the recommended diet, a dietary index was

developed based on the food frequency questionnaire, with higher scores indicating better diet quality. The dietary index includes 11 components that represent each topic of the counseling and were scored based on reported intake frequency, as follows: snacks (0–2 points), sugar-sweetened beverages (0–1 point), vegetables (0–2 points), fruits and berries (0–1 point), low-fat cheese (0–1 point), cooking fat (0–1 point), spread fat (0–2 points), fast food (0–1 point), high-fiber bread and cereals (0–2 points), fish (0–2 points), and low-fat milk (0–2 points). The highest score (17 points) was set to reflect the highest adherence to the recommended intake of each score item.

Evaluation of leisure-time physical activity was based on the self-reported time spent weekly on physical activity that makes a participant at least slightly out of breath and sweaty. Prepregnancy physical activity was assessed at baseline in a similar way.

Statistics

The data are presented as means with SDs, as medians with IQRs, or as counts with percentages. The comparison between groups was made by using a *t* test, χ^2 test, or Mann-Whitney test. When using adjusted models, ANCOVA, a logistic regression model, or a median regression (least-absolute-value) model was applied. Repeated measures were analyzed using a generalized estimating equation (GEE) model with the unstructured correlation structure. GEEs were developed as an extension of the general linear model to analyze longitudinal and other correlated data. GEE models take into account the correlation between repeated measurements in the same subject; models do not require complete data and can be fitted even when individuals do not have observations at all time points. In the case of violation of the assumptions (e.g., nonnormality), a bootstrap-type test was used (10,000 replications). The normality of the variables was tested by using the Shapiro-Wilk *W* test. All statistical analyses are performed unadjusted and adjusted for age, prepregnancy BMI, previous GDM status, weeks of gestation, and baseline values. All analyses were performed using STATA software (version 13.1; StataCorp LP, College Station, TX).

RESULTS

In total, 540 women who were at high risk for GDM were recruited to the study. Of

these, 247 women did not meet the study inclusion criteria. The most common reason (28.7%) for not being included was a pathological OGTT result. The number of pregnant women included in the analysis was 269; 144 were allocated to the intervention group, and 125 were allocated to the control group (Fig. 1).

Demographic and clinical characteristics did not differ between the intervention group and the control group at baseline (Table 1). Of the participants, 25% ($n = 66$) reported a chronic disease, most commonly asthma, with no differences between the groups. Parental history of diabetes was present in 22% of the participants, with no group differences. Both study groups visited antenatal clinics four times before the second-trimester OGTT (intervention group mean 4.2 times, SD 1.20 times; control group mean 4.2 times, SD 1.69 times).

GDM

GDM was diagnosed in 20 participants (13.9% [95% CI 8.7–20.6%]) in the intervention group and in 27 participants (21.6% [95% CI 14.7–29.8%]) in the control group ($P = 0.097$, unadjusted; $P = 0.044$, after adjustment for age, prepregnancy BMI, previous GDM status, and number of weeks of gestation at the time of the diagnostic OGTT). The crude relative risk for GDM was 0.64 (95% CI 0.38–1.09) in the intervention group. Women belonging to the intervention group had a crude reduction in fasting plasma glucose concentration of -0.18 mmol/L (95% CI -0.24 to -0.12 mmol/L) from baseline to the third trimester compared with -0.07 mmol/L (95% CI -0.13 to -0.02 mmol/L) in the control group ($P = 0.026$, unadjusted; $P = 0.011$, after adjustment for age, prepregnancy BMI, previous GDM status, the number of weeks of gestation, and baseline glucose concentration). In the intervention group, the 2-h glucose value increased from baseline to second trimester by 0.54 mmol/L (95% CI 0.35–0.72 mmol/L), and in the control group by 0.55 mmol/L ([95% CI 0.33–0.78 mmol/L]; $P = 0.92$, unadjusted; $P = 0.42$, after adjustment for age, prepregnancy BMI, previous GDM status, the number of weeks of gestation, and baseline glucose concentration).

Weight Change

There was a difference in gestational weight gain between the intervention group (2.5 kg [95% CI 2.1–3.0]) and the control group (3.1 kg [95% CI 2.7–3.5])

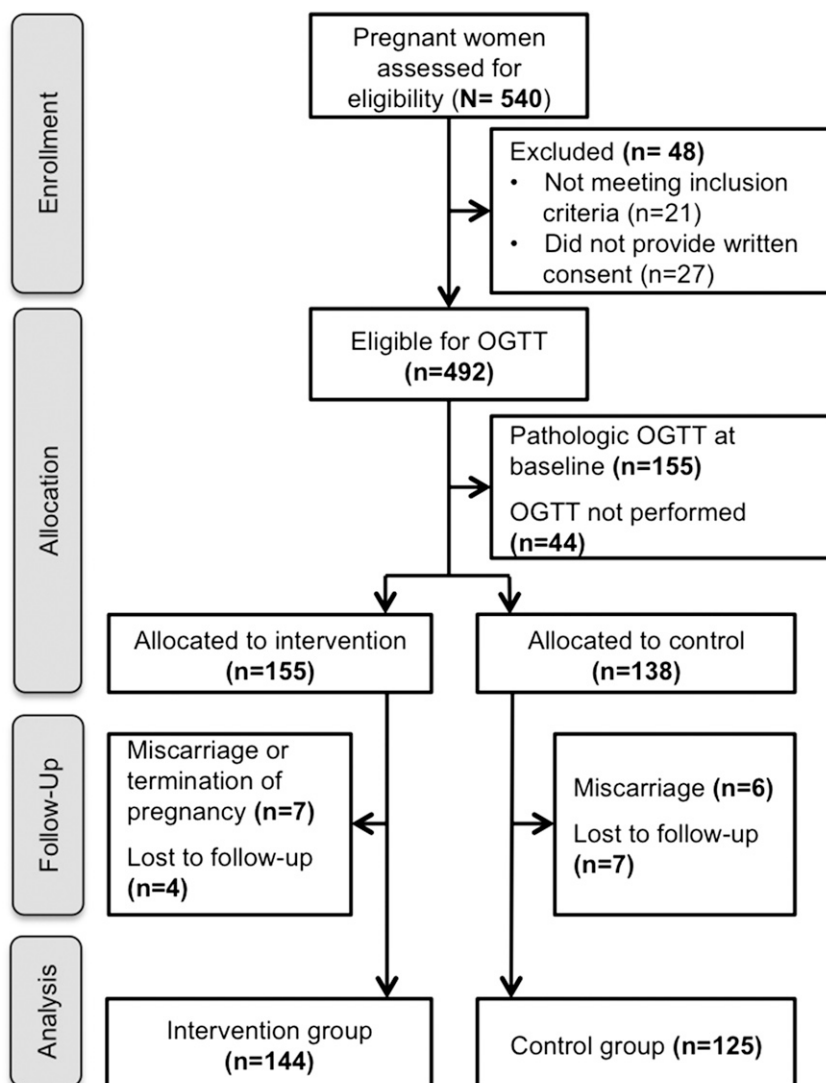


Figure 1—Flowchart of the RADIEL study.

from baseline to the second trimester (at the time of the OGTT at week 23.4 on average), and the mean difference was -0.5 kg [95% CI -1.1 to 0.05]; $P = 0.072$, unadjusted; $P = 0.039$, after adjustment for age, previous GDM status, the number of weeks of gestation, and baseline weight).

The gestational weight gain was 7.6 kg (95% CI 6.7 – 8.3 kg) in the intervention group and 7.7 kg (95% CI 7.1 – 8.4 kg) in the control group from baseline to the third trimester, and the mean difference was -0.2 kg [95% CI -1.1 to 0.8]; $P = 0.74$, unadjusted; $P = 0.37$, after adjustment for age, previous GDM status, the number of weeks of gestation, and baseline weight).

Dietary Quality and Physical Activity
The dietary index score improved more among women in the intervention group (0.7 [95% CI 0.3 – 1.1]) compared

with those in the control group (0.3 [95% CI -0.1 to 0.7]), and the mean difference was 0.4 ([95% CI -0.1 to 1.0]; $P = 0.16$, unadjusted; $P = 0.037$, after adjustment for age, prepregnancy BMI, previous GDM status, the number of weeks of gestation, and baseline values).

Women in the intervention group increased their median weekly leisure time physical activity by 15 min (95% CI 1 – 29 min), while the physical activities of women in the control group remained unchanged ($P = 0.17$, unadjusted; $P = 0.029$, after adjustment for age, prepregnancy BMI, previous GDM status, the number of weeks of gestation, and baseline values). Of the women in the intervention group and the control group, 26% and 23%, respectively, met the physical activity goal of

150 min/week in the second trimester, with no significant differences between the groups.

Other Maternal Pregnancy and Birth Outcomes

There were no differences in the other maternal pregnancy or birth outcomes assessed between the intervention and the control group (Table 2).

CONCLUSIONS

This is, to our knowledge, the first randomized controlled lifestyle intervention trial that has succeeded in reducing the overall incidence of GDM among high-risk pregnant women. As a result of the combined moderate physical activity and diet intervention, the overall incidence of GDM was reduced by 39%. The participants in the intervention group increased their physical activity and improved their dietary quality during pregnancy, indicating a real effort to change their overall lifestyle in a healthier direction. By contrast, the control group participants did not increase their physical activity or improve the dietary quality in a significant manner. Average weight gain during pregnancy was modest in both groups. Other maternal and neonatal outcomes, including birth size, were similar in both groups.

The results of this lifestyle intervention study in pregnant women who are at high risk of GDM are encouraging and are similar to findings from major type 2 diabetes prevention studies (18,19). It is worth keeping in mind that since the women participating in the RADIEL were women who were at high risk for GDM, the women in the control group also received general health advice, for example, in weight control at antenatal clinics. Therefore, the control group is more of a mini-intervention group than a pure control group. We believe that in an unselected high-risk population the impact of this kind of lifestyle intervention could be even more pronounced.

Previous type 2 diabetes prevention studies, including the Finnish Diabetes Prevention Study (18) and the Diabetes Prevention Program (19), have shown that the prevention of type 2 diabetes is possible and feasible by lifestyle intervention. However, these studies have been criticized for being too labor intensive and therefore not directly applicable to a primary health care setting (36). The RADIEL protocol and design were much less resource and labor

Table 1—Baseline demographic and clinical characteristics of the participants in the intervention and control groups

	Intervention group (n = 144)	Control group (n = 125)	P value
Age (years)	32.3 (4.9)	32.6 (4.5)	0.60
Body weight (kg)			
Prepregnancy	87.4 (18.1)	88.3 (16.4)	0.67
At baseline	89.2 (17.9)	89.3 (15.9)	0.98
Height (m)	1.66 (0.07)	1.66 (0.06)	0.81
BMI (kg/m ²)			
Prepregnancy	31.5 (6.0)	32.0 (5.5)	0.54
At baseline	32.2 (5.9)	32.3 (5.4)	0.84
Gestational age at baseline (weeks)	13.2 (12.3–14.8)	13.3 (11.9–14.4)	
Educational status at baseline, n (%)			0.60
Basic education only	4 (3)	3 (2)	
Vocational education	38 (26)	26 (21)	
Upper secondary school	13 (9)	8 (7)	
Upper secondary school and vocational education	46 (32)	50 (41)	
Higher education	43 (30)	35 (29)	
Previous deliveries, n (%)			0.99
None	61 (42)	52 (42)	
1	42 (29)	38 (30)	
2	29 (20)	24 (19)	
3+	12 (8)	11 (9)	
Prior GDM, n (%)	50 (35)	38 (30)	0.45
Blood pressure			
Systolic (mmHg)	123 (13)	121 (14)	0.21
Diastolic (mmHg)	78 (9)	77 (9)	0.28
Total cholesterol (mmol/L)	4.94 (0.91)	4.92 (0.86)	0.88
HDL cholesterol (mmol/L)	1.73 (0.33)	1.75 (0.30)	0.61
Total triglycerides (mmol/L)	1.31 (0.52)	1.38 (0.75)	0.37
Fasting glucose (mmol/L)	4.87 (0.24)	4.89 (0.24)	0.45
2-h glucose (mmol/L)	5.78 (1.05)	5.98 (1.09)	0.13
HbA _{1c}			
%	5.2 (0.3)	5.2 (0.3)	0.47
mmol/mol	33.5 (3.0)	33.2 (3.0)	0.53
Insulin (mU/L)	8.48 (4.56)	8.44 (4.56)	0.98
HOMA-IR	1.74 (0.94)	1.79 (0.90)	0.67
Smoking, n (%)	6 (4)	4 (3)	0.68
No alcohol use, n (%)	139 (97)	114 (94)	0.37
Dietary index at baseline	10.1 (2.9)	9.7 (2.5)	0.30
Physical activity at baseline (min/week)	60 (30–130)	60 (30–150)	0.92

Data are mean (SD) or median (IQR), unless otherwise indicated. HbA_{1c}, hemoglobin A_{1c}; HOMA-IR, HOMA for insulin resistance.

intensive, including only three visits to the study nurse and one group visit to the dietitian during pregnancy.

Why was the RADIEL successful? One possible explanation is the high-risk status of the women recruited to the study. In several previous GDM and other lifestyle intervention studies during pregnancy (21–24,26,28,29), the women recruited were only at a modest risk for the development of GDM. This kind of study setting would need a bigger sample size to reveal the effect of a lifestyle intervention. In the RADIEL, the intervention was targeted at high-risk pregnant women with a history

of GDM and/or a BMI of ≥ 30 kg/m². One indication of the participants' high GDM risk was the high prevalence of pathological OGTT results already existing at the beginning of the pregnancy. It is known that the largest effect of a lifestyle intervention is observed in high-risk individuals (18,19).

Our nutrition and physical activity counseling was also individualized and comprehensive. At baseline, the study nurses identified possible lifestyle factors that needed attention, and the counseling was tailored and focused. We also considered personal preferences of the

participant in counseling (e.g., when choosing the type of physical activity). This probably helped the participants to engage in activities according to personal preferences. The intervention started early in gestation, allowing for a longer intervention period. This may have influenced physical activity levels positively. Taking into account that pregnancy is an exceptional time to make lifestyle changes, the counseling was modified during pregnancy; that is, if antenatal contractions occurred, and the participant was unable to exercise, the counseling focused more on dietary aspects.

Table 2—Maternal pregnancy and neonatal outcomes in the intervention and control groups

	Intervention group (n = 144)	Control group (n = 125)	P value
Maternal pregnancy outcomes			
Hypertension (essential), n (%)	12 (8.3)	6 (4.8)	0.25
Pregnancy-induced hypertension, n (%)	7 (4.9)	6 (4.5)	0.98
Preeclampsia, n (%)	7 (4.9)	3 (2.4)	0.29
Cesarean delivery, n (%)	31 (21.5)	30 (24.0)	0.63
Neonatal outcomes			
Birth weight (g), mean (SD)	3,626 (562)	3,680 (549)	0.43
Birth weight SD score, mean (SD)	0.15 (1.02)	0.26 (1.05)	0.38
Birth weight >4,500 g, n (%)	6 (4.2)	5 (4.0)	0.95
Crown-heel length, mean (SD)	50.3 (2.6)	50.7 (2.4)	0.19
Gestational age at birth (weeks), mean (SD)	40.0 (1.8)	40.0 (1.6)	0.83
Respiratory distress or transient tachypnea of newborn, n (%)	7 (4.9)	7 (5.6)	0.79
Congenital malformation, n (%)	1 (0.7)	3 (2.4)	0.34

The study nurses in RADIEL were midwives with strong expertise in counseling pregnant women; this probably increased the participants' confidence in the study protocol. The lifestyle advice provided was designed to be easily implemented and applicable to everyday life.

The dietary score applied in the study showed a significant but small improvement in the adherence to dietary recommendations in the intervention group. This kind of holistic approach has proven fruitful in the prevention and management of type 2 diabetes (37). Even a small change in dietary choices can be important when applied at a population level (38). The intervention group also increased their leisure time physical activity level and gained less weight than the women in the control group from baseline to the second trimester when the GDM diagnosis was set. Despite the fact that only a small proportion of the women in the intervention group reached the physical activity goals, and the difference in weight gain was modest between the groups, it is obvious that the individual changes in lifestyle do not need to be large, but together they have a beneficial effect on the reduction of the incidence of GDM.

Since the RADIEL was performed in a white population, the validity of generalizing the results needs to be discussed. However, we suggest that it is possible to generalize the results, at least to some extent, since the study protocol was simple and modifiable, and thus easy to implement in the different societies and ethnic groups.

Focusing on a selected group of women with a high risk for the development of GDM may be considered a potential weakness, since, for example, overweight women at the population level may form a greater proportion of women in whom GDM will develop than the obese population alone. On the other hand, if overweight women or women with previous macrosomia had been recruited to the trial, the heterogeneity of the study group would have been increased markedly. This could also have had effects on the intervention results (24,26,28,29). We believe that in the RADIEL we have been able to identify a real high-risk group that is also the most likely to benefit from a lifestyle intervention during pregnancy. Our study findings show that modest changes in several lifestyle-associated factors have a large overall effect on GDM risk. However, a larger sample size would probably have been needed to see an effect on other maternal or neonatal outcomes.

We have shown that GDM can be prevented in a high-risk population by simple, easily applicable lifestyle interventions. Our findings suggest that individualized lifestyle intervention should be initiated in early pregnancy in high-risk women and continued throughout pregnancy. These results are unique and highly promising. Preventing GDM may have major short- and long-term health consequences for both the mother and the child.

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Author Contributions. S.B.K. initiated, participated in the design of, and coordinated the study and helped in the drafting and editing of the article. K.R. participated in the implementation of the study, prepared the database, performed the statistical analyses, and participated in the drafting of the article. M.M.K. participated in the design and implementation of the study and the drafting of the article. R.P.R. participated in the implementation of the study and the drafting of the article. J.L., M.E., A.V., and J.M. participated in the implementation and statistical analyses of the nutrition aspects of the study and the drafting of the article. R.J.K., M.P.-A., A.T., S.A., and H.L. participated in the design of the study and the drafting of the article. E.H. participated in the implementation of the study and the drafting of the article. H.K. is the statistician for the study and performed the statistical analyses. J.G.E. is the principal investigator of the study and participated in the implementation of the study and advised on editing of the article. B.S.-L. participated in the design of the study, coordinated the study in Lappeenranta, and helped with the statistical analyses and drafting of the article. All authors have read and approved the final version of the manuscript. S.B.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Prior Presentation.** The main results of the trial were reported in a short oral presentation at the international course "Pre- and Perinatal Determinants of Health in Child- and Adulthood," Tartu, Estonia, 23–24 April 2015.

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