Chapter 6

Long-term effects of a preconception lifestyle intervention on cardiometabolic health of overweight and obese women

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Abstract

Background: The global prevalence of obesity in women keeps increasing. The preconception period may be a window of opportunity to improve lifestyle, reduce obesity and improve cardiometabolic health. This study assessed the effect of a preconception lifestyle intervention on long-term cardiometabolic health in two RCTs.

Methods: Participants of the LIFEstyle and RADIEL preconception lifestyle intervention studies with a baseline BMI ≥29 kg/m^2 were eligible for this follow-up study. Both studies randomised between a lifestyle intervention targeting physical activity, diet and behaviour modification, or usual care. We assessed cardiometabolic health six years after randomisation.

Results: In the LIFEstyle study (n=111) and RADIEL study (n=39), no statistically significant differences between the intervention and control groups were found for body composition, blood pressure, arterial stiffness, fasting glucose, HOMA-IR, HbA1c, lipids, and hs-CRP levels six years after randomisation. Participants of the LIFEstyle study who successfully lost ≥5% bodyweight or reached a BMI <29 kg/m^2 during the intervention (n=22, (44%)) had lower weight (-8.1 kg; 99% CI [-16.6 to -0.9]), BMI (-3.3 kg/m^2; [-6.5 to -0.8]), waist circumference (-8.2 cm; [-15.3 to -1.3]), fasting glucose (-0.5 mmol/L; [-1.1 to -0.0]), HbA1c (-4.1 mmol/mol; [-9.1 to -0.8]), and higher HDL cholesterol (0.3 mmol/L; [0.1 to 0.5]) compared to controls.

Conclusion: We found no evidence of improved cardiometabolic health six years after a preconception lifestyle intervention among overweight and obese women in two RCTs. Successful weight-loss during the intervention led to improved cardiometabolic health six years later, emphasising the importance of successful preconception lifestyle improvement.

Introduction

The prevalence of obesity continues to increase globally (1). Obesity is a major modifiable risk factor for cardiometabolic disease (2). Among women, obesity before and during pregnancy increases the risk of pregnancy complications which also increases the risk of cardiovascular disease (3).

Lifestyle interventions are the first step in the prevention and treatment of obesity and have the potential to lower the risks of pregnancy associated complications and cardiometabolic disease (4-7). Because women who are planning a pregnancy are more susceptible to lifestyle advice, the preconception period might be an optimal window of opportunity for a lifestyle intervention (8-10). Preconception lifestyle interventions can improve lifestyle, induce weight loss and improve spontaneous pregnancy rates and outcomes (11-13). We previously showed that a six-month preconception lifestyle intervention in obese infertile women improved cardiometabolic health, halved the odds for metabolic syndrome, and increased quality of life, during and directly after the intervention period (14).

Although these short-term effects are promising, previous studies have shown that permanent lifestyle changes are difficult to achieve and many people regain weight over time (15). Therefore, we aimed to assess the long term effects of a preconception lifestyle intervention on cardiometabolic health, based on the follow-up of the Dutch 'LIFEstyle' and Finnish 'RADIEL' preconception lifestyle intervention trials (16, 17).

Methods

The Randomised Controlled Trials (RCTs)

The protocols of the LIFEstyle (NTR 1530) and RADIEL (IDr: NCT01698385) studies have been published previously and had ethical approval (16, 17). Both studies were preconception lifestyle interventions among overweight or obese women. All participants provided written informed consent. Table 1 presents an overview of both lifestyle interventions.

The initial LIFEstyle study

The LIFEstyle study, a multi-centre RCT, was conducted in 23 medical centres in the Netherlands between 2009 and 2014. Infertile women between 18-39 years of age with a Body Mass Index (BMI) ≥29 kg/m² were eligible for inclusion. Infertility was defined as chronic anovulation or unsuccessful conception for over 12 months.

Women were randomly allocated (1:1) to a six-month lifestyle intervention preceding infertility treatment (intervention group) or prompt infertility treatment according the Dutch guidelines (control group) irrespective of BMI, stratified for trial centre and ovulatory status (18).

The LIFEstyle intervention led by trained intervention coaches consisted of six 30-minute face-to-face sessions at the outpatient clinics and four by telephone or e-mail, aiming at 5-10% weight reduction or a BMI < 29 kg/m² within six months. Women reaching this goal did not have to finish the six-month intervention, but could proceed with conventional infertility treatment. The intervention consisted of a dietary, physical activity and behavioural modification component (19). The dietary component was supported with an online diary and aimed at caloric reduction of 600 kcal with a minimum intake of 1200 kcal/day. The physical activity component aimed at moderate-intensity physical activity for at least two or three times a week and 10.000 steps a day, stimulated with the use of a pedometer. The behavioural modification part of the intervention was focused on creating awareness of lifestyle predisposing to obesity, and the goals were determined on individual basis. The intervention stopped in case of pregnancy, but was resumed after a miscarriage within six months after randomisation.

Women in the control group were given written information about the negative effects of overweight/obesity on fertility, as part of the usual care.

The initial RADIEL study

The RADIEL study was a multi-centre RCT, conducted in four maternity hospitals in Finland, between 2008 and 2013. Women ≥ 18 years of age who were planning to become pregnant, with a BMI ≥ 30kg/m^2 and/or a previous history of gestational diabetes (GDM) were eligible for inclusion.

Women were randomly allocated to a lifestyle intervention (intervention group) or usual care (control group), stratified for trial centre and risk factors (history of GDM or preconception BMI≥30kg/m^2).

The intervention group received a structured lifestyle intervention consisting of a maximum of 11 face-to-face sessions and 3 group sessions, provided by trained study nurses. The individual sessions were scheduled every three months before pregnancy, once in each trimester of pregnancy, and 6 weeks, 6 and 12 months postpartum. The aim of the intervention was 5% weight reduction and no gestational weight gain in the first and second trimesters. Dietary advice was based on Nordic dietary recommendations encouraging use of vegetables, berries, and fish, and avoiding sugar-rich foods and saturated fat (20, 21). The recommendation for caloric intake was 1600 to 1800 kcal/day with 40-50% of total energy (E%) coming from carbohydrates, 30-40 E% from fats and 20-25 E% from protein. Participants also attended group sessions led by a dietitian at the enrolment, during the first trimester, and 6 and 12 months after delivery. Physical activity goal was 150 minutes of moderately strenuous exercise per week. The participants received pedometers and were encouraged to reach 10 000 steps per day. Lifestyle advice was personalised according to individual preferences and pregnancy status. Women in the control group received general information leaflets about diet and physical activity.

The follow-up studies

The LIFEstyle follow-up study

Women who participated in the original LIFEstyle study and who were not lost to follow-up were eligible for the follow-up study. A physical assessment after a 2-hour fast was performed minimally 6 months after pregnancy under standardised conditions inside of a mobile research vehicle close to the participants' homes. Blood samples were taken at home, during a separate visit by a research nurse, after an overnight fast. Biochemical analyses were performed by the AMC Clinical Chemistry Laboratory for the biochemical analyses (22).

The RADIEL follow-up study

Women who gave birth after participation in the original study and who had at least one study visit during pregnancy were approached for the follow-up study. The physical assessment took place at the Folkhälsan Research Center in Helsinki and in Lappeenranta at the South Karelian Central Hospital. Anthropometric measurements and fasting blood samples were taken during the study visit after a 10-12 hour overnight fast. Biochemical analyses were performed by the HUSLAB central laboratory in Helsinki and Central Hospital laboratory in Lappeenranta. The current study includes women who entered the RADIEL study prior to pregnancy with a BMI ≥ 29kg/m^2.

Outcomes

Assessments included weight, height, and waist and hip circumferences. BMI was calculated as (weight (kg) / length $(m)^2$). Systolic and diastolic blood pressure was measured in a sitting position using oscillometry (LIFEstyle: OMRON HBP-1300; RADIEL: OMRON M6W Intelli sense). We assessed fasting concentrations of triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and high sensitive C-reactive protein (hs-CRP), fasting glucose and insulin. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated (fasting insulin concentration (mU/l) x fasting glucose concentration (mmol/l))/22.5) (23).

Pulse wave velocity (PWV), a marker for the aortic elasticity, was measured between the carotid and femoral artery with mechanotransducer sensors using the Complior ® (ALAM Medical, France) at rest and in supine position. To calculate PWV the following equation was used: PWV=0.8x(direct distance between a. carotis and a. fermoralis measuring site / Δ time between upstroke of pressure waves). A scaling factor of 0.8 was used because direct distance leads to overestimation of real PWV (24).

Body fat percentage (BFP) was measured in the RADIEL study with multi-frequency bio-impedance measurement method using the InBody 3.0 (Biospace Co, Ltd, Seoul, Korea), and in the LIFEstyle study BFP was measured with arm-to-leg bioelectrical impedance analysis using the Bodystat 1500 (Bodystat Ltd, Isle of Man, UK) and the fat-free mass prediction equation by Kyle et al. (25).

All outcomes were measured two times. In the LIFEstyle study outcomes were measured a third time in case of substantial differences (>1 cm or > 10%) between the first two measurements. The mean of the measurements is used in the statistical analyses.

Participants were identified with Metabolic Syndrome (MetS) based on the 2001 revised criteria of the National Cholesterol Education Program ATP III (26). Participants had to meet at least three of the following criteria: (1) plasma glucose ≥5.6 mmol/L or known drug treatment for elevated blood glucose; (2) HDL-C <1.3 mmol/L or known drug treatment for low HDL cholesterol; (3) triglycerides ≥1.7 mmol/L or known drug treatment for elevated triglycerides; (4) waist circumference ≥88 cm or (5) blood pressure ≥130/85 mmHg or known drug treatment for elevated blood pressure.

Statistical analyses

Participants were analysed in the treatment group in which they were randomised. For comparison of the baseline variables independent student t-tests or Mann-Whitney-U tests were performed for continuous variables and for binary or categorical variables Chi-Square tests were performed.

The continuous outcomes were analysed with linear regression, including 1500 bootstrap samples to calculate 99% bias-corrected and accelerated confidence intervals (99% BCa CI), because the normality assumption of linear regression appeared to be violated for some of the outcome variables (IBM SPSS version 24.0 (Armonk, NY, USA)). The regression models included the outcomes of interest as the dependent and the treatment group as independent factor. If available, baseline values of the outcomes of interests and potential confounders that differed between the treatment groups were incorporated as covariates. The difference between the groups was considered statistically significant if the confidence interval of the mean difference did not include zero.

Mixed effect logistic regression analyses including baseline and follow-up data were performed for binary outcomes (STATA version 15.0 (College Station, Texas, USA)). The intervention effect was assessed by the interaction between time and treatment group.

Subgroup analyses were performed to compare successful women with the control group. Women were identified as 'successful' if they had reduced their body weight more than 5% or lowered their BMI under 29 kg/m². Baseline differences in characteristics between the successful women and the control group were added as covariates to the adjusted model. Further explorative analyses were performed to assess (1) the interaction between treatment group and pregnancy status after randomisation as well as (2) between treatment group and PCOS status on the outcomes of interest (27). These explorative analyses were only performed in the LIFEstyle study population, since all included women of the RADIEL study gave birth after randomisation, and their PCOS status was not assessed.

Results

Participation

The flow charts of both studies are presented in Figure 1. Of the 577 women who participated in the LIFEstyle study, 111 (19.3%) were included in the current study, of whom 50 women were included in the intervention and 61 in the control group. Of the 234 women who were recruited before pregnancy in the RADIEL study, 121 women had a BMI of 29.0 and above. Of these eligible women 39 (32.2%) were included in the current study, of whom 22 women were included in the intervention and 17 in the control group. A total of 150 women of both studies were included in this follow-up study.

Characteristics of participants

Baseline and follow-up characteristics of the participating women in both studies are presented in table 2. A comparison of baseline characteristics of participants and non-participants are presented in Supplementary Table 1.

Outcomes

Primary analyses

In both studies, weight, BMI, waist and hip circumferences, blood pressure, fasting glucose, HOMA-IR, HbA1c, triglycerides, total cholesterol, LDL-C, HDL-C, hs-CRP, body fat percentage, and PWV were not statistically different between the intervention and control groups (Table 3).

Although the prevalence of MetS at follow-up was lower in the LIFEstyle intervention group compared to the control group (25.7% vs. 52.7%), adjustments for baseline prevalence showed no statistically significant difference between the intervention and control group (aOR: 1.11 95% CI 0.19-6.64). Also, no statistical significant difference in MetS prevalence at follow-up was found in the RADIEL study (aOR: 0.20 95% CI 0.01 – 2.8).

Subgroup analyses

Of the 50 women in the LIFEstyle intervention group, 22 women lost more than 5% body weight or reached a BMI below 29 kg/m² during the six month intervention period. These women had a lower BMI at baseline (34.2 ± 2.6 vs. 35.8 ± 3.2; P = 0.02), more often smoked (9 (40.9%) vs. 11 (18.0%); P = 0.03) and had been trying to conceive for a longer period of time (27 (IQR 19.5 – 40.25) vs. 16 (12.0 – 26.0); P = 0.04) compared to the control group. No other statistically significant differences were detected.

At follow-up, these successful women had lower weight (-8.1 kg; 99% BCa CI = -16.6 to -0.9), BMI (-3.3 kg/m^2; 99% BCa CI = --6.5 to -0.8), smaller waist circumference (-8.2 cm; 99% BCa CI = -15.3 to -1.3), lower fasting glucose (-0.5 mmol/L; 99% BCa CI = -1.1 to -0.0), lower HbA1c (-4.1 mmol/mol; 99% BCa CI = -6.4 to -0.3), and higher HDL-C (0.3 mmol/L; 99% BCa CI =0.1 to 0.5) compared to controls (Supplementary table 2). No subgroup analyses of successful intervention were performed for the RADIEL study, because only 4 of the RADIEL intervention women successfully reached the short-term weight goals.

Exploratory analyses

No statistically significant interaction effects were found for treatment group with pregnancy status after randomisation or for treatment group with PCOS status on any of the continuous outcomes (all interaction $P \geq 0.05$).

Discussion

This is the first study reporting on the effects of preconception lifestyle interventions on long-term cardiometabolic health of overweight and obese women from two RCTs. Despite the positive short-term effects of the LIFEstyle preconception intervention, the six year follow-up of both the LIFEstyle and the RADIEL interventions did not show any effects on individual parameters of cardiometabolic health, nor on the prevalence of metabolic syndrome (14). However, positive long-term health effects were found among the women who successfully lost weight during the LIFEstyle intervention; they had smaller waist circumferences, lower weight, BMI, glucose, and HbA1c, as well as higher HDL cholesterol concentrations.

The absence of an overall effect of the interventions on long-term cardiometabolic health is in line with the only other study with a similar follow-up duration after a lifestyle intervention in pregnancy (28). Other post-conception lifestyle interventions in overweight and obese women reported inconsistent effects on adverse maternal outcomes during and directly after pregnancy, and did not yet report on the long-term health of these women (29-32).

Lifestyle is attained over time and is not easily changed without intrinsic motivation (33). The wish to have a child could be a strong motivator to improve lifestyle, but at the same time, the temporary nature of this motivator may explain the lack of long-term effects on cardiometabolic outcomes. After giving birth, mothers are exposed to the emotional post-partum period in which they adjust to their new

role and often prioritise parenthood over their own wellbeing (34). However, we found no evidence that women who had an ongoing pregnancy (>24 weeks) during the follow-up period had different long-term effects on cardiometabolic health compared to women who did not. The latter could be explained by the discouraging effect of persistent infertility on lifestyle improvement in this last group (35). In both scenario's, an individualised relapse prevention phase following the actual intervention could help women to adhere to their improved lifestyle (36).

The absence of long-term effects of the preconception lifestyle interventions on cardiometabolic health could also be explained by the high-risk profile of the study populations, who might need more intensive and prolonged lifestyle interventions for sustainable effects on cardiometabolic health. In the RADIEL study, 67% of the women included in the current follow-up study were diagnosed with GDM in their index pregnancy, leading to additional lifestyle advice and intensive follow-up from the health care system in both study groups. This regular care might have overshadowed the effect of the preconception lifestyle intervention, diminishing the potential differences between the intervention and control group

In the LIFEstyle study, 39% of the women were diagnosed with polycystic ovary syndrome (PCOS). Intrinsic insulin resistance, alteration in appetite regulation, and abdominal fat distribution can challenge weight management in women with PCOS (37, 38). However, the relatively high prevalence of women with PCOS in the LIFEstyle study could not explain the absence of long-term effects since no interaction effect was observed between treatment group and PCOS status on cardiometabolic outcomes.

Timing and duration of lifestyle interventions are possible determinants of successful lifestyle change, but in this study we found no such evidence (39). Scheduling the intervention solely before (LIFEstyle) compared to before, during, and after pregnancy (RADIEL) both failed to provide beneficial cardiometabolic effects in the long run.

Both studies had considerable attrition (80.7% in the LIFEstyle study and 67.8% in the RADIEL study), leading to limited statistical power to detect relevant differences and introduction of potential selection bias. To diminish potential confounding effects of selection on the outcome assessments, the regression analyses were adjusted for baseline values. Women of the LIFEstyle study follow-up were more likely to participate if they were Caucasian and younger at randomisation. Because cardiometabolic plasticity decreases with age, it is unlikely that our null-findings can be explained by the participation of younger women in the LIFEstyle study (40). Similar selection was not found for the RADIEL study (Supplementary

table 1). Because of the high percentage of Caucasian women in both studies, it should be noted that our findings should not be generalised to women of other ethnicities.

Short-term success is usually a good indicator for long-term effects (15, 35). Although we did not find overall effects, women who successfully lost weight during the LIFEstyle intervention, did have better cardiometabolic health six years after the intervention compared to control women. Future studies should therefore investigate determinants of a successful lifestyle intervention, in order to identify women who would benefit the most and to make tailored approaches more effective.

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Conflicts of Interest

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Table 1. Comparison of lifestyle interventions applied in the LIFEstyle and RADIEL study.

	LIFEstyle study	RADIEL study
Inclusion criteria	• Age 18-39 years • BMI ≥ 29 kg/m^2 • Chronic anovulation or infertility > 1 year	• Age > 18 years • BMI ≥ 30 kg/m^2 and/or Prior Gestational Diabetes
Goal	• 5-10% weight reduction • BMI <29 kg/m^2	• 5% pre-pregnancy weight reduction • No gestational weight gain during first and second trimester of pregnancy
Amount of consultations	Max. 10 consultations in the 6 months before fertility treatment: • 6 outpatient clinic visits • 4 telephone consultations	Max. 14 consultations: • Every 3 months before pregnancy (max 5 visits) • 3 times in pregnancy (1/trimester) • 3 times after pregnancy (6 weeks, 6 months and 12 months postpartum) • 3 group sessions (baseline, 6 and 12 months postpartum)
Diet	• Reduction of caloric intake of 600 kcal, with a minimum intake of 1200 kcal/day using an online diary • Improve diet quality	• Reduction of caloric intake to 1600-1800 kcal/day. Using the plate model (40-50% carbohydrates, 30-40% fats and 20-25% proteins). • Improve diet quality
Physical activity	• Daily physical activity aimed at 10.000 steps per day using a pedometer • Moderate intensity physical activity for at least 30 minutes, 2-3 times a week	• Daily physical activity aimed at 10.000 steps per day, using a pedometer • Moderate intensity physical activity for 150 min/week
Motivational counselling	• Individualised motivational counselling: o Awareness of actual lifestyle leading to overweight or obesity o Awareness of healthy lifestyle in relation to infertility o Formulating individualised goals embedded in a "patient contract" • Motivation to change physical activity was monitored by the 'Physician-based Assessment and Counselling for Exercise' and counselling was adjusted accordingly	• Individualised motivational counselling based on personal preferences • Contact with local physical activity counsellor and entry tickets for local sport clubs • Goals were adapted to pregnancy on individual basis

Table 2. Baseline and follow-up characteristics of the study participants.

Baseline characteristics						
	LIFEstyle study			**RADIEL study**		
Variable	**Intervention N=50**	**Control N=61**	**P-value [a]**	**Intervention N=22**	**Control N=17**	**P-value [a]**
Age, years – mean (SD)	30.4 (4.0)	30.4 (4.2)	0.94	34.2 (3.3)	31.6 (5.3)	0.09
Weight, kg – mean (SD)	103.6 (13.0)	102.8 (11.4)	0.75	97.5 (15.0)	94.7 (16.4)	0.59
BMI, kg/m² – mean (SD)	35.5 (2.8)	35.7 (3.2)	0.64	35.2 (4.0)	34.0 (5.2)	0.44
Ethnicity – no. Caucasian (%)	48 (96)	57 (93.4)	0.69	22 (100)	17 (100)	n.a.
Education – no. (%)			0.95			0.41
Basic education	0 (0)	1 (1.7)		0 (0)	0 (0)	
Vocational education	11 (23.4)	12 (20.3)		4 (19.0)	2 (11.8)	
Secondary education	1(2.1)	1 (1.7)		1 (4.8)	4 (23.5)	
Vocational & Secondary education	24 (51.1)	28 (47.5)		9 (42.9)	7 (41.2)	
Higher education	11 (23.4)	17 (28.8)		7 (33.3)	4 (23.5)	
Alcohol use – no. (%)	19 (44.2)	19 (32.8)	0.24	11 (52.4)	12 (70.6)	0.25
Current smoker – no. (%)	14 (28.6)	11 (18.0)	0.19	1(4.5)	1(5.9)	1.00
Nulliparous – no. (%)	41 (82.0)	45 (73.8)	0.30	2 (9.1)	5 (29.4)	0.21
Ethnicity – no. Caucasian (%)	48 (96)	57 (93.4)	0.69	22 (100)	17 (100)	n.a.

Table 2. Continued

	Follow-up characteristics					
	LIFEstyle study			**RADIEL study**		
Age at follow-up, years – mean (SD)	36.3 (4.4)	36.5 (4.3)	0.83	40.6 (3.3)	38.0 (5.3)	0.08
Follow-up duration, months – median (IQR)	73.5 (61.3 – 80.4)	72.9 (65.4 – 80.4)	0.65	74.8 (71.0 – 82.2)	72.2 (69.8 – 82.2)	0.75
Pregnancy after randomisation, no. (%) [b]	35 (70)	47 (77)	0.40	22 (100)	17 (100)	n.a.

[a] P-values of continuous outcomes based on student t-test or Mann-Whitney-U test. P-values of dichotomous and categorical outcomes are based on the Pearson Chi-Square test, the Fisher's exact test or Fisher-Freeman-Halton exact test. b Number of women that had a pregnancy of more than 24 weeks of gestation.

Table 3. Cardiometabolic outcomes (change from baseline to 6-year follow-up and mean difference) in the intervention and control group of the LIFEstyle and RADIEL study.

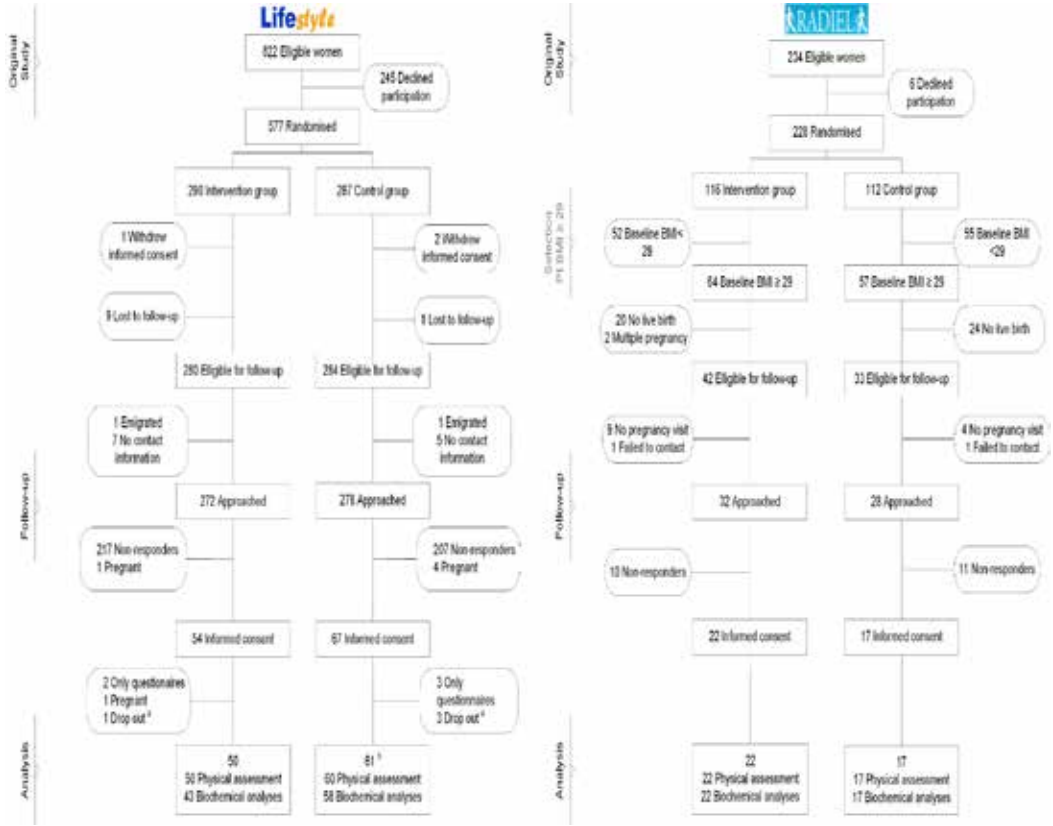
Cardiometabolic outcomes												
	LIFEstyle study						RADIEL study					
	N	Intervention Δ [a]	N	Control Δ [a]	MD [b]	BCa 99% C.I.	N	Intervention Δ [a]	N	Control Δ [a]	MD [b,c]	BCa 99% C.I.
Weight, kg – mean (SD)	50	-3.4 (14.2)	60	-1.5 (13.5)	-1.8	-8.8 – 4.7	22	2.9 (15.4)	17	-1.8 (9.3)	2.0	-10 – 11.8
BMI, kg/m^2 – mean (SD)	50	-0.5 (5.1)	60	0.0 (4.7)	-0.6	-2.7 – 1.6	22	1.1 (5.6)	17	-0.6 (3.2)	0.7	-3.5 – 4.2
Waist Circumference, cm – mean (SD)	48	-0.5 (12.5)	60	-0.3 (13.5)	-0.8	-6.1 – 4.6	21	7.1 (12.9)	17	8.1 (10.0)	-3.2	-14.3 – 8.0
Hip Circumference, cm – mean (SD)	49	-2.6 (9.9)	60	-2.5 (9.4)	-0.5	-5.0 – 3.6	21	2.9 (13.1)	17	-3.2 (6.6)	4.8	-4.6 – 13.8
Systolic Blood pressure, mmHg – mean (SD)	48	-3.9 (14.6)	60	-6.0 (15.3)	-0.2	-7.3 – 6.9	22	2.7 (11.1)	17	3.7 (15.0)	1.6	-11.2 – 17.5
Diastolic Blood pressure, mmHg – mean (SD)	48	1.6 (10.2)	60	0.5 (9.4)	-0.5	-5.1 – 4.4	22	-0.8 (8.4)	17	-2.8 (11.0)	4.1	-4.1 – 12.4
Fasting glucose, mmol/L –mean (SD)	36	0.0 (0.6)	52	0.0 (1.1)	-0.3	-0.7 – 0.2	22	-0.1 (0.7)	17	0.0 (0.5)	-0.2	-0.7 – 0.4
HOMA-IR – mean (SD)	35	-0.1 (2.3)	50	0 (2.6)	-0.4	-1.6 – 0.9	18	1.4 (2.8)	16	0.8 (2.2)	0.3	-2.3 – 2.6

Table 3. Continued

	Cardiometabolic outcomes											
	LIFEstyle study						RADIEL study					
	N	Intervention Δ [a]	N	Control Δ [a]	MD [b]	BCa 99% C.I.	N	Intervention Δ [a]	N	Control Δ [a]	MD [b,c]	BCa 99% C.I.
Total Cholesterol, mmol/L – mean (SD)	36	-0.1 (1.0)	52	0.0 (0.8)	0.0	-0.5 – 0.5	22	-0.1 (0.7)	16	-0.1 (0.6)	-0.1	-0.6 – 0.5
LDL Cholesterol, mmol/L – mean (SD)	36	-0.2 (1.0)	52	-0.2 (0.7)	0.0	-0.4 – 0.4	22	0.0 (0.7)	16	0.2 (0.5)	-0.2	-0.8 – 0.4
HDL Cholesterol, mmol/L – mean (SD)	36	0.2 (0.3)	52	0.1 (0.3)	0.1	-0.0 – 0.3	22	0.1 (0.4)	16	0.0 (0.4)	0.1	-0.2 – 0.5
Triglycerides, mmol/L – mean (SD)	36	-0.3 (1.6)	52	-0.1 (0.6)	-0.3	-0.7 – 0.3	22	-0.1 (0.7)	16	0.1 (0.6)	-0.1	-0.6 – 0.4
HS-CRP, mg/l – mean (SD)	36	0.1 (4.5)	52	1.8 (5.6)	-1.6	-4.4 – 1.2	22	-0.5 (6.3)	17	-0.1 (2.5)	0.6	-3.5 – 5.9
HbA1c, mmol/mol – mean (SD) [d]	42	n.a.	52	n.a.	-1.7	-5.2 – 1.2	18	1.6 (4.7)	11	-0.3 (5.7)	1.2	-3.3 – 7.1
Fat percentage, % [e]	50	n.a.	60	n.a.	-0.5	-2.7 – 1.3	17	n.a.	16	n.a.	-1.1	-8.5 – 5.8
Pulse wave velocity, m/s [f]	37	n.a.	49	n.a.	0.1	-1.2 – 1.1	19	n.a.	16	n.a.	0.4	-0.8 – 1.7

[a] Change between baseline and follow-up. [b] Mean differences between intervention and control group at follow-up based on linear regression models adjusted for baseline values, unless stated otherwise. [c] Adjusted for age at baseline. [d] No baseline value in LIFEstyle study, mean difference is unadjusted. [e] No baseline value, mean difference is adjusted for BMI at baseline. [f] No baseline value, mean difference is adjusted for pulse pressure at baseline.

Figure 1. Flow-chart of study participants.



[a] One women in the intervention and three women in the control group had given informed consent but canceled the physical measurement visit. [b] One women only attended the blood sample collection, but cancelled the physical measurement.

Supplementary Table 1. Comparison of baseline characteristics between non-participants and participants of the LIFEstyle and RADIEL study.

Baseline characteristics						
	LIFEstyle study			RADIEL study		
Variable	**Non participants N=463**	**Participants N=111**	**P-value [a]**	**Non participants N=82**	**Participants N=39**	**P-value [a]**
Age, years – mean (SD)	29.6 (4.6)	30.4 (4.1)	0.07	32.2 (4.6)	33.1 (4.4)	0.30
Weight, kg – mean (SD)	103.3 (13.3)	103.2 (12.1)	0.96	95.2 (13.5)	96.3 (15.5)	0.69
BMI, kg/m^2 – mean (SD)	36.1 (3.5)	35.7 (3.0)	0.19	34.5 (3.8)	34.7 (4.5)	0.79
Ethnicity – no. Caucasian (%)	397 (85.7)	105 (94.6)	0.01	86 (100)	39 (100)	n.a.
Education – no. (%)			0.23			0.34
Basic education	26 (5.9)	1 (0.9)		5 (6.1)	0 (0)	
Vocational education	96 (21.7)	23 (21.7)		22 (26.8)	6 (15.8)	
Secondary education	10 (2.3)	2 (1.9)		8 (9.8)	5 (13.2)	
Vocational & Secondary education	214 (48.3)	52 (49.1)		29 (35.4)	16 (42.1)	
Higher education	97 (21.9)	28 (26.4)		18 (22.0)	11 (28.9)	
Alcohol use – no. (%)	139 (37.0)	38 (37.6)	0.90	44 (55.7)	23 (60.5)	0.62
Current smoker – no. (%)	111 (24.2)	25 (22.7)	0.75	10 (12.2%)	2 (5.1)	0.33
Nulliparous – no. (%)[b]	355 (76.8)	86 (77.5)	0.89	20 (24.4)	7 (17.9)	0.43

[a] P-values of continuous outcomes based on student t-test or Mann-Whitney-U test. P-values of dichotomous and categorical outcomes are based on the Pearson Chi-Square test, the Fisher's exact test or Fisher-Freeman-Halton exact test.

Supplementary Table 2. Cardiometabolic outcomes (change from baseline to six year follow-up and mean difference) of 22 participants that lost ≥ 5% body weight or lowered BMI <29 during the LIFEstyle intervention and the control group.

	LIFEstyle study				Model 1		Model 2	
Cardiometabolic outcome	**N**	**Successful Intervention Δ [a]**	**N**	**Control Δ [a]**	**MD [b]**	**BCa 99% C.I.**	**MD [f]**	**BCa 99% C.I.**
Weight, kg – mean (SD)	22	-7.6 (13.1)	60	-1.5 (13.5)	-7.2	-15.9 – 0.2	-8.1	-16.6 – -0.9
BMI, kg/m² – mean (SD)	22	-2.1 (4.7)	60	0.0 (4.7)	-3.0	-5.9 – -0.3	-3.3	-6.5 – -0.8
Waist Circumference, cm – mean (SD)	22	-4.2 (11.5)	60	-0.3 (13.5)	-7.1	-13.4 – -0.8	-8.2 [g]	-15.3 – -1.3
Hip Circumference, cm – mean (SD)	21	-4.6 (10.2)	60	-2.5 (9.4)	-4.1	-9.6 – 1.7	-4.3 [g]	-10.7 – 2.5
Systolic Blood pressure, mmHg – mean (SD)	22	-7.1 (12.9)	60	-6.0 (15.3)	-2.4	-11.8 – 6.3	-3.5	-12.7 – 6.3
Diastolic Blood pressure, mmHg – mean (SD)	22	-0.0 (10.0)	60	0.5 (9.4)	-2.0	-7.6 – 4.8	-2.5	-8.5 – 3.1
Fasting glucose, mmol/L – mean (SD)	16	-0.3 (0.4)	52	0.0 (1.1)	-0.5	-0.9 – -0.0	-0.5	-1.1 – -0.0
HOMA-IR – mean (SD)	16	-0.5 (1.7)	50	0.0 (2.6)	-0.9	-2.2 – 0.8	-0.8	-2.1 – 0.7
Total Cholesterol, mmol/L – mean (SD)	16	0.0 (1.0)	52	0.0 (0.8)	0.1	-0.7 – 0.8	0.1	-0.7 – 0.7
LDL Cholesterol, mmol/L – mean (SD)	16	0.0 (1.1)	52	-0.2 (0.7)	0.1	-0.5 – 0.8	0.0	-0.6 – 0.7
HDL Cholesterol, mmol/L – mean (SD)	16	0.3 (0.3)	52	0.1 (0.3)	0.2	0.0 – 0.4	0.3	0.1 – 0.5
Total Triglycerides, mmol/L – mean (SD)	16	-0.7 (2.3)	52	-0.1 (0.6)	-0.5	-0.9 – 0.2	-0.5	-1.0 – 0.1
HS-CRP, mg/l – mean (SD)	16	1.0 (3.9)	52	1.8 (5.6)	-0.8	-4.0 – 2.4	-0.5	-5.0 – 3.2

Supplementary Table 2 Continued

		LIFEstyle study			Model 1		Model 2	
Cardiometabolic outcome	**N**	**Successful Intervention Δ [a]**	**N**	**Control Δ [a]**	**MD [b]**	**BCa 99% C.I.**	**MD [f]**	**BCa 99% C.I.**
HbA1c, mmol/mol [c]	19	n.a.	52	n.a.	-3.0 [c]	-6.4 – -0.3	-4.1	-9.1 – -0.8
Fat percentage, % [d]	22	n.a.	60	n.a.	-2.0 [d]	-4.6 – 0.5	-1.6	-4.5 – 0.9
Pulse wave velocity, m/s [e]	18	n.a.	49	n.a.	0.3 [e]	-1.2 – 1.7	0.6	-1.0 – 2.1

[a] Change between baseline and follow-up. [b] Mean differences between intervention and control group based on linear regression models adjusted for baseline values (model 1), unless stated otherwise. [c] No baseline HbA1c, unadjusted. [d] No baseline fat percentage, adjusted for BMI at baseline. [e] No baseline pulse wave velocity, adjusted for pulse pressure at baseline. [f] Mean differences between intervention and control group based on linear regression models. In model 2, BMI, smoking status and duration of infertility at baseline are added as covariates to model 1, unless stated otherwise. [g] BMI at baseline was not added as covariate to model 2.