Development and Aging

Effects of maternal lifestyle interventions on child neurobehavioral development: Follow-up of randomized controlled trials

MALOU D. MENTING[1,2,3,4] CORNELIEKE VAN DE BEEK,[1,2] KRISTIINA RONO,[5] ANNEMIEKE HOEK,[6] HENK GROEN,[7] REBECCA C. PAINTER,[1,2] POLINA GIRCHENKO,[8] MARIUS LAHTI-PULKKINEN,[8,9] SAILA B. KOIVUSALO,[5] KATRI RÄIKKÖNEN,[8] JOHAN G. ERIKSSON,[10,11] TESSA J. ROSEBOOM[1,2,3,4] and KATI HEINONEN[8]

[1]*Department of Obstetrics and Gynecology, Amsterdam UMC, Amsterdam, the Netherlands*
[2]*Amsterdam Reproduction and Development Research Institute, Amsterdam UMC, Amsterdam, the Netherlands*
[3]*Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, Amsterdam, the Netherlands*
[4]*Amsterdam Public Health Research Institute, Amsterdam UMC, Amsterdam, the Netherlands*
[5]*Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[6]*University of Groningen, University Medical Centre Groningen, Department of Obstetrics and Gynecology, Groningen, the Netherlands*
[7]*University of Groningen, University Medical Centre Groningen, Department of Epidemiology, Groningen, the Netherlands*
[8]*Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland*
[9]*University/British Heart Foundation Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK*
[10]*Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[11]*Folkhälsan Research Center, Helsinki, Finland*

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Obesity is a major public health problem. Children of women who were obese before or during pregnancy are at increased risk for neurobehavioral developmental problems. Whether a maternal lifestyle intervention conducted before and during pregnancy in obese women affects child neurobehavioral development is unknown. This study reports on the follow-up of a subsample of two randomized controlled trials, the Finnish RADIEL (n = 216) and Dutch LIFEstyle (n = 305) trial. Women with a pre-pregnancy BMI ≥29 kg/m^2 wishing to conceive or who were already pregnant (<20 weeks) were allocated to a lifestyle intervention or to care as usual. Child neurodevelopment was measured with the Ages and Stages Questionnaire and child behavioral problems were measured with the Childhood Behavior Checklist (RADIEL) or the Strengths and Difficulties Questionnaire (LIFEstyle) at age 3-6 years. We used linear and binary logistic regression analyses to assess the effects of the lifestyle interventions on children's neurobehavioral developmental scores. Follow-up data was available from 161(38%) RADIEL and 96(32%) LIFEstyle children. Child neurodevelopmental scores did not differ significantly between children in the intervention and the control group (RADIEL:median = 275 vs. 280; LIFEstyle:median = 270 vs 267). Child behavioral problem scores did not differ significantly between children in the intervention and the control group (RADIEL:median = 22 vs. 21; LIFEstyle:median = 8 vs. 8). We did not observe considerable effects of the lifestyle interventions before or during pregnancy in obese women on child neurobehavioral development. With our sample sizes, we were not able to detect subtle differences in neurobehavioral development however.

Key words: Pregnancy, lifestyle intervention, obesity, behavioral problems, neurodevelopment.

Malou D. Menting, Amsterdam UMC, Department of Obstetrics and Gynecology, Room H4-260, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31205665794; e-mail: m.d.menting@amsterdamumc.nl

INTRODUCTION

Obesity is a major public health problem. The prevalence of obesity in women of reproductive age ranges from 7 to 25% in Western European countries while the prevalence is 30% in the United States (Poston, Caleyachetty, Cnattingius *et al*., 2016). Obesity before and during pregnancy is associated with pregnancy complications and adverse pregnancy outcomes (Marchi, Berg, Dencker, Olander & Begley, 2015). Importantly, it is also associated with long-term adverse consequences for the health of the future child, including neurobehavioral developmental problems (Alvarez-Bueno, Cavero-Redondo, Lucas-de la Cruz, Notario-Pacheco, & Martinez-Vizcaino, 2017; O'Reilly & Reynolds, 2013). For example, children whose mothers were obese before pregnancy have 58% higher odds of having a developmental delay and 42% higher odds of having emotional and behavioral problems relative to children born to mothers who were normal weight before pregnancy (Sanchez, Barry, Sabhlok *et al*., 2017).

Rodent studies have clarified several mechanisms, by which maternal obesity both before and during pregnancy may affect offspring's neurobehavioral development. For example, offspring of mothers who are obese before and during pregnancy are exposed to an excess of circulating nutrients (for example, fatty acids, glucose), an excess of metabolic hormones (for example, lipids) and higher levels of inflammatory cytokines in utero than offspring of mothers who have a normal weight (Rivera, Christiansen & Sullivan, 2015). These factors all change offspring's neuroendocrine regulation, neural pathways and brain structure, what consequently may lead to offspring neurobehavioral development problems (Rivera *et al*., 2015; Sullivan, Riper, Lockard & Valleau, 2015).

On the other hand, a healthy maternal diet and physical exercise ameliorates the functioning of the biological mechanisms that are affected by maternal obesity (Van Lieshout & Krzeczkowski, 2016). Improving these biological mechanisms in turn are expected to improve child development (Van Lieshout & Krzeczkowski, 2016). Therefore, improving the lifestyle of obese

women before and during pregnancy may be of great importance to reduce the potential negative impact of maternal obesity on child development (Alvarez-Bueno, Cavero-Redondo, Sanchez-Lopez, *et al*., 2017; Fernandez-Twinn, Gascoin, Musial *et al*., 2017; Van Lieshout & Krzeczkowski, 2016). Indeed, a recent study showed that a lifestyle intervention during pregnancy in obese women was effective in reducing infant adiposity (Patel, Godfrey, Pasupathy *et al*., 2017), but until now no studies have investigated whether maternal lifestyle interventions have beneficial effects on children's neurobehavioral development.

In the present study, we conducted a planned follow-up (van de Beek, Hoek, Painter *et al*., 2018) of two randomized controlled trials (RCTs) of maternal lifestyle interventions before and during pregnancy in obese women on child neurobehavioral development at the age of 3 to 6 years. We hypothesized that the benefits of the lifestyle interventions were extended from the mothers (van Dammen, Wekker, van Oers *et al*., 2018; Koivusalo, Rono, Klemetti *et al*., 2016; Mutsaerts, van Oers, Groen *et al*., 2016) to the children.

METHODS

Study population

This study is a planned follow-up study (van de Beek *et al*., 2018) of two RCTs: the RADIEL study (NCT01698385) and the LIFEstyle study (NTR1530).

RADIEL. The RADIEL study was conducted between 2008 and 2014 in Finland (Fig. 1). The study has been described in detail elsewhere (Rono, Stach-Lempinen, Klemetti *et al*., 2014). Briefly, women aged ≥18 years and at high risk for gestational diabetes (a previous history of gestational diabetes (GDM) and/or pre-pregnancy body mass index (ppBMI) ≥ 30 kg/m^2) were recruited to the study either before pregnancy or during early pregnancy (<20 weeks). There were no exclusion criteria based on a maximum ppBMI. Women who were included in the RADIEL study had a mean ppBMI of 31.4 (SD: 6.0, range 17.8 to 52.9). The women who were included before pregnancy were recruited median 17.1 (interquartile range (IQR) 6.7 to 35.4) weeks before conception and the women included during early pregnancy were recruited at median of 13.0 (IQR 11.9 to 14.4) gestational weeks.

The women were randomized into an intervention group that received a lifestyle intervention and a control group that received usual care given at their local antenatal clinic. The lifestyle intervention consisted of individualized counseling on diet, physical activity, weight control, breastfeeding and infant nutrition from a trained study nurse and a dietitian before and during pregnancy as well as during the first post-partum year (Rono *et al*., 2014). The meetings with the study nurse took place every 3 months up to five visits. The group meetings with the dietitian took place once before pregnancy and once post-partum for the women recruited before pregnancy or once during the first half of pregnancy and once post-partum for the women recruited in early pregnancy. Hence, women who were recruited during pregnancy may only have missed one or two consults of the trained study nurse or dietitian.

The study was approved by Ethics Committees of Helsinki University Hospital (baseline: 14 September 2006, Dnro 300/E9/06, follow-up: 7811310310312011) and South Karelia Central Hospital (11 September 2008, Dnro M06/08). The following weight targets were set for the RADIEL intervention group: 5–10% weight loss before pregnancy and no weight gain during the first two trimesters of pregnancy for women with a ppBMI ≥ 30 kg/m^2 (Rono *et al*., 2014). In the present study, these targets were used as a definition of being successful in the lifestyle intervention for RADIEL participants, with the exception that the gestational weight gain (GWG) target in the first two trimesters was also applied in women with a ppBMI that equals 29 kg/m^2. Pre-pregnancy height and weight was measured at the first clinical visit. For those participants who were already pregnant at first visit, pre-pregnancy weight was self-reported.

The RADIEL study was effective in reducing GDM (primary outcome of the study) when the women with normal OGTT started the intervention in the early pregnancy (Koivusalo *et al*., 2016), but not before pregnancy (Rono, Stach-Lempinen, Eriksson *et al*., 2018). The intervention did not have any effect on reducing GDM, if those pregnant women with early GDM (pathologic OGTT already at inclusion) were included (Rono, Grotenfelt, Klemetti *et al*., 2018).

The RADIEL follow-up assessments were performed between 2015 and 2017. All singletons born to participating mothers with ppBMI of ≥29 kg/m^2 were eligible for the present study. This ppBMI cut-off was chosen in order to be able to include a population comparable to the LIFEstyle participants (see next subsection). Informed consent was obtained from at least one guardian of the child.

LIFEstyle. The LIFEstyle study was conducted in the Netherlands between 2009 and 2014 (Fig. 1). The study has been described in detail elsewhere (Mutsaerts, Groen, ter Bogt *et al*., 2010). Briefly, women aged between 18 and 39 years with a ppBMI ≥ 29 kg/m² were included. Women were eligible if they had infertility due to chronic anovulation, oligo- or amenorrhea or, in case of an ovulatory cycle, unsuccessful conception for at least 12 months. The participants were randomly allocated to a lifestyle intervention preceding infertility treatment or to prompt infertility care as usual. The lifestyle intervention consisted of individualized counseling on diet, physical activity and behavioral modification from a trained study nurse. The duration of the lifestyle intervention was 24 weeks with six face-to-face consultations and four telephone consultations.

The LIFEstyle program aimed at loss of 5–10% of the original body weight. Women in the intervention group could precede with fertility treatment before the end of the intervention if their weight loss was ≥ 5% or if they had reached a BMI below 29 kg/m^2 at any time point during the intervention (Mutsaerts *et al*., 2010, 2016). In the present study, this criterion was used as a definition of being successful in the lifestyle intervention for the LIFEstyle participants.

The LIFEstyle follow-up (called WOMB project (van de Beek *et al*., 2018)) was conducted in 2016 and 2017. All singletons conceived within the 24 months follow-up period after inclusion in the LIFEstyle study were eligible for follow-up. The baseline and the follow-up study were approved by the medical ethics

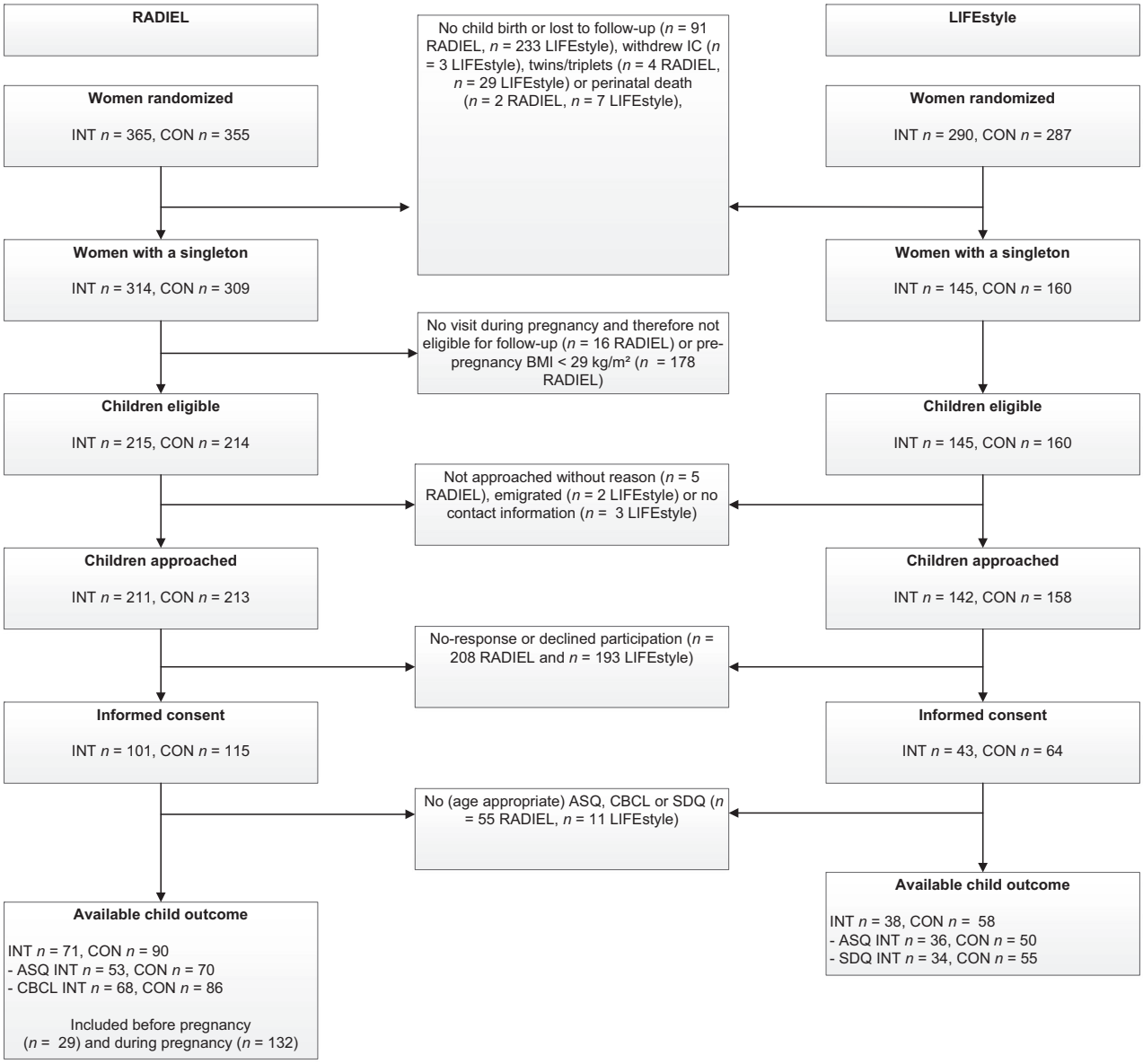

Fig. 1. Flowchart of the RADIEL and LIFEstyle follow-up. *Note*: The number of women with a ppBMI between 29 and 30 were for the RADIEL study: Among all women of the initial study with a child 21 women (8 intervention, 13 control) and among women included in our follow-up sample: 8 women (4 intervention, 4 control). For the LIFEstyle study: Among all women of the initial study with a child: 6 (2 intervention group, 4 control group) and among women included in our follow-up sample: 3 (1 intervention group, 2 control group).

committee of the University Medical Center Groningen in the Netherlands (NL24478.042.08). Both parents gave written informed consent.

Outcomes

In the RADIEL follow-up study parents completed the questionnaires when their child reached the age of 5 years. In the LIFEstyle follow-up study parents completed the questionnaires when their child was between the ages of 3 and 5 years.

Child neurodevelopment. The Ages and Stages Questionnaire, third edition (ASQ-3), having good validity (Squires, Twombly, Bricker & Potter, 2009) was used to assess child neurodevelopment. In the RADIEL study the Finnish 54 and 60 months versions were used and in the LIFEstyle study the Dutch 36, 42, 48, 54 or 60 months versions were used (Squires *et al*., 2009). The ASQ-3 addresses five developmental domains: communication, gross motor, fine motor, problem solving and personal-social skills. The total developmental score is the sum of the five developmental domains, ranging from 0 to 300. A higher score indicates a neurodevelopment that is closer to typical for the age of the child.

The total neurodevelopmental score was used as a continuous variable in the analyses. Because of the skewed distribution, the total neurodevelopmental score was rank transformed by using Blom's formula and then normalized. Developmental domain scores were dichotomized using the median score (<median versus ≥median) within the study population. A deviant neurodevelopmental score was based on the referral scores of American norms (Squires *et al*., 2009).

Child behavioral problems. In the RADIEL study, parents completed the Finnish version of the Child Behavior Checklist 1,5-5 (CBCL). This questionnaire has a good validity (Achenbach & Rescorla, 2000). The total behavioral problem score was used, ranging from 0 to 198. Additionally, three subscales of the CBCL were used: attention, internalizing and externalizing problems. In the LIFEstyle study, parents completed the Dutch version of the Strengths and Difficulties Questionnaire (SDQ). The 2-4 year version was used for 3 year old children and the 4–17 year version for the four or 5 year old children. The SDQ has been validated (Goodman & Scott, 1999; Theunissen, de Wolff, van Grieken & Mieloo, 2016). The total behavioral problem score (ranging from 0 to 50) and the subscales emotional, conduct and hyperactivity/inattention problems were used. A higher behavioral problem score indicates more behavioral problems.

For comparison of the SDQ and CBCL scores, (sub)scales were used that have previously shown to measure similar constructs and which are highly correlated (Goodman & Scott, 1999): CBCL attention with SDQ hyperactivity/inattention problems ($r = 0.71$); CBCL internalizing problems and SDQ emotional problems ($r = 0.74$); CBCL externalizing problems and SDQ conduct problems ($r = 0.84$) and CBCL total behavioral problem and SDQ total behavioral problem score ($r = 0.87$).

The total behavioral problem score was used as a continuous variable in the analyses. Because of the skewed distribution, the CBCL and SDQ total behavioral problem scores were square root transformed and then normalized. Subscale scores were dichotomized using the median score (≤median and >median). A deviant behavioral problem score was a score ≥ borderline cut-off based on norms scores appropriate for the Finnish population for the CBCL (Achenbach & Rescorla, 2010) and based on Dutch norms for the SDQ (Theunissen *et al*., 2016) (only for attention/hyperactivity SDQ subscale the British norms were used because the Dutch norms were not available for this subscale (Youthinmind, 2014)).

Covariates

Group differences in baseline and other characteristics were tested: maternal age, maternal ethnicity, maternal educational attainment, mode of conception, parity, gestational diabetes, maternal anxiety and depression score (RADIEL:Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown & Steer, 1988) and the Center for Epidemiologic Studies Depression (CES-D) Scale (Radloff, 1977); LIFEstyle : Hospital Anxiety and Depression Scale (HADS) (Spinhoven, Ormel, Sloekers *et al*., 1997), child sex, birth weight, gestational age, age and BMI at follow-up.

Statistical analysis

Group differences in participant characteristics were assessed with chi squared tests and independent sample T-tests. Primary analyses were performed using linear regression analyses with the total neurodevelopmental and the total behavioral problem score as the dependent variable and intervention/control group as the independent variable. Secondary analyses were performed using binary logistic regression analysis with the dichotomized neurodevelopmental subdomains and behavioral problem subscales as dependent variable and intervention/control group as the independent variable. In subgroup analyses, children of women in the intervention group who were successful in changing the lifestyle were compared with children of the control group.

Initial analyses were performed without any adjustment; with adjustment for sex and age of the child (model 1) and with additional adjustment for baseline and other characteristics that differed significantly between the intervention and control group (model 2). The studies were analyzed separately. Further explorative analyses were performed by repeating the primary analyses with: (1) inclusion of the interaction effect of maternal intervention group with child sex; (2) exclusion of children of mothers with GDM; (3) a wider range of success definition for RADIEL (e.g., a maximum of 5% GWG); and (4) pooling data of both studies.

A p-value of < 0.05 was considered statistically significant. For the secondary analyses, the Bonferroni correction was applied: a p-value of < 0.01 and < 0.02 was considered significant for the developmental subdomains and the behavioral problem subscales respectively.

RESULTS

Study group

Of the 216 RADIEL children and 300 LIFEstyle children who were eligible and contacted for follow-up, 161 (38%) RADIEL children and 96 LIFEstyle (32%) children had data on the ASQ and/or SDQ or CBCL (Fig. 1). In the RADIEL study, participating mothers were more highly educated ($p < 0.05$) and were more often nulliparous (47% vs. 31%, $p < 0.05$) than mothers whose child did not participate in the follow-up (participants who were eligible and approached for follow-up but were not included in the present analyses). In the LIFEstyle study, participating mothers were more often Caucasian (97% vs. 86%, $p < 0.01$) than mothers who did not participate with their child in the follow-up. Other participant characteristics did not differ between the non-participants and participants in either study (Table S1 in the online Supporting Information).

There were no differences in maternal characteristics between the intervention and control group in the RADIEL study (Table 1). There were no other differences in characteristics between the intervention and control group in the LIFEstyle study, than that more children in the intervention group were conceived naturally ($p < 0.01$) than in the control group (Table 1). The total neurodevelopmental and behavioral problem score did not depend on mode of conception (natural or fertility treatment) (Table S2).

In the RADIEL study, women started the intervention either before pregnancy or during pregnancy. However, the exact timing of the start of the intervention varied: before pregnancy, Median = 126 days before conception, IQR = 80–220, N = 29; During pregnancy, Median = 92 days gestation, IQR = 87–102, N = 132. All women of the LIFEstyle study started the intervention before pregnancy. The time of the conception varied and thus also the time between the start of the intervention and date of conception varied among women included in the LIFEstyle trial (Median = 209 days before conception,

Table 1. *Participants characteristics*

Characteristic	Intervention group		Control group		Total
	Mean (SD)/Median (IQR)/*n* (%)	*n*	Mean (SD)/Median (IQR)/*n* (%)	*n*	*n*
Maternal age (years, mean (SD))					
RADIEL study	33 (4)	71	32 (5)	90	161
LIFEstyle study	30 (4)	38	30 (4)	58	96
Maternal ethnicity (Caucasian, *n*, %)					
RADIEL study	71 (100)	71	90 (100)	90	161
LIFEstyle study	37 (97)	38	56 (97)	58	96
Maternal education level (*n*, %)					
RADIEL study		71		90	161
Basic education only	1 (1)		1 (1)		
Vocational education	21 (30)		20 (22)		
Secondary school	3 (4)		8 (9)		
Secondary school and vocational education	29 (41)		36 (40)		
Higher education	17 (24)		25 (28)		
LIFEstyle study		36		58	94
No education/primary school	1 (3)		0 (0)		
Secondary education	8 (22)		15 (26)		
Intermediate vocational training	21 (58)		32 (55)		
Higher vocational education and university	6 (17)		11 (19)		
Maternal pre-pregnancy Body Mass Index (mean (SD))					
RADIEL study	35 (4)	71	34 (4)	90	161
LIFEstyle study	36 (3)	38	36 (3)	58	96
Maternal mental health at follow-up (Median (IQR))					
RADIEL study					
CES-D score	12 (10-16)	66	12 (10–14)	85	151
BAI score	24 (22-27)	64	25 (22–30)	85	149
LIFEstyle study (HADS score)	14 (11-18)	36	14 (12–20)	55	91
Parity (nulliparous (*n*, %))					
RADIEL study	31 (44)	71	44 (49)	90	161
LIFEstyle study	29 (76)	38	44 (76)	58	96
Method of conception (naturally (*n*, %))					
RADIEL study	49 (91)	54	72 (92)	78	132
LIFEstyle study	22 (58)*	38	14 (24)*	58	96
Gestational diabetes (yes (*n*, %))					
RADIEL study	30 (42)	71	38 (44)	86	157
LIFEstyle study	4 (11)	38	11 (19)	58	96
Breastfeeding (ever, yes (*n*, %))					
RADIEL study	62 (97)	64	76 (94)	81	145
LIFEstyle study	17 (46)	37	28 (52)	54	91
Child gestational age at birth (weeks, mean (SD))					
RADIEL study	40 (2)	71	40 (1)	90	161
LIFEstyle study	39 (2)	38	39 (2)	58	96
Child birth weight (gram, mean (SD))					
RADIEL study	3637 (554)	71	3671 (541)	90	161
LIFEstyle study	3405 (531)	38	3545 (492)	58	96
Child sex (male, (*n*,%)					
RADIEL study	37 (52)	71	44 (49)	90	161
LIFEstyle study	16 (42)	38	32 (55)	58	96
Child age[a] (months, mean (SD))					
RADIEL study	60 (4)	71	60 (4)	90	161
LIFEstyle study	49 (9)	38	52 (11)	58	96
Child Body Mass Index at follow-up (mean (SD))					
RADIEL study	16 (2)	71	17 (2)	90	161
LIFEstyle study	16 (1)	33	16 (2)	54	87

Notes: *Significant different between intervention and control group: $p = 0.001$.
[a]Age at assessment of SDQ/CBCL. When SDQ/CBCL was not available: age at assessment of ASQ.

IQR = 97–422 days, N = 96). There were 22 (31%) mothers in RADIEL intervention group who lost ≥5% of weight before pregnancy or, if having ppBMI ppBMI ≥ 30 kg/m^2, gained no weight during the first two trimesters of pregnancy, and twenty (53%) mothers in LIFEstyle intervention group who lost ≥5% of the original body weight or achieved BMI below 29 kg/m^2 at any time point during the intervention. These women were considered as being successful. Seventeen women were "successful" in the RADIEL and three in LIFEstyle control groups respectively.

Child neurodevelopment

Table 2 shows the median and IQR of the ASQ scores as well as the number of children classified as having a deviant neurodevelopmental score. In both RADIEL and LIFEstyle follow-up, there were no differences in total (Table 3) and subdomain (Table 4) neurodevelopmental scores between the intervention and control group or between the successful participants of the intervention group and the control group in either unadjusted or adjusted analyses.

Child behavioral problems

Table 5 shows the median and IQR of the CBCL and SDQ scores as well as the number of children classified as having a deviant behavioral problem score. In both RADIEL and LIFEstyle follow-up, there were no differences in total (Table 6) and subscale (Table 7) behavioral problem scores between the intervention and control group or between the successful participants of the intervention group and the control group in either unadjusted or adjusted analyses.

Explorative analyses

Explorative analyses with: (1) the interaction effect of maternal intervention group with sex of the child; (2) exclusion of children of mothers with GDM; (3) a wider range of success definition for RADIEL; and (4) pooling of the data of both cohorts did not show different results.

DISCUSSION

With this follow-up study of two RCTs, we were not able to detect an effect of maternal lifestyle interventions before and/or during pregnancy on children's neurobehavioral development at the age of 3 to 6 years. With our small sample sizes we were unable to detect subtle differences between the groups and due to potential selective participation possible bias may have been introduced which does not allow us to draw firm conclusions. These findings are novel as no previous study has investigated the effect of lifestyle interventions before and during pregnancy in obese women on child neurobehavioral development in a RCT design.

In previous observational studies, associations between maternal pre-pregnancy obesity and child higher risk of neurobehavioral developmental problems were based on comparisons between children of obese mothers and children of normal weight mothers (Sanchez *et al*., 2017). The present study sample consisted of mothers with a ppBMI of $\geq$ 29 kg/m^2 only.

Table 2. *Median and interquartile range (IQR) scores of the Ages and Stages Questionnaire*

	Intervention group				Control group			
	Median	IQR	*n* (%) deviant score	*n*	Median	IQR	*n* (%) deviant score	*n*
RADIEL study								
Total development	275	253–290	0 (0)[a]	52[a]	280	255–290	4 (6)	70
Communication	55	45–60	0 (0)	53	58	53–60	1 (1)	70
Fine motor	55	45–60	0 (0)	53	55	50–60	3 (4)	70
Gross motor	60	55–60	2 (4)	52	60	55–60	4 (6)	70
Personal-social	55	50-60	1 (2)	53	55	50–60	1 (1)	70
Problem-solving	60	50-60	0 (0)	53	60	55–60	1 (1)	70
LIFEstyle study								
Total development	270	255–285	1 (3)	36	267	244–281	0 (0)[a]	47
Communication	55	50–60	0 (0)	36	55	50–60	2 (4)	50
Fine motor	50	45–55	2 (6)	36	50	40–55	1 (2)	48
Gross motor	55	50–60	0 (0)	36	55	50–60	0 (0)	48
Personal-social	55	50–60	0 (0)	36	55	50–60	0 (0)	50
Problem-solving	55	50–60	2 (6)	36	55	50–60	0 (0)	50

Note: [a]Children with missing scores on developmental subdomains were excluded for the assessment of having a deviant score on the total developmental score (RADIEL intervention group n = 1, LIFEstyle control group n = 3).

Table 3. *Effects of a maternal lifestyle intervention on child total score of the Ages and Stages Questionnaire*

	Unadjusted			Model 1[a]			Model 2[b]		
	B	95% CI	*p*	*B*	95% CI	*p*	*B*	95% CI	*p*
RADIEL INT versus CON	−0.18	−0.54–0.18	0.32	−0.17	−0.51–0.16	0.31	n/a	n/a	n/a
Successful INT versus CON	−0.13	−0.71–0.45	0.66	−0.11	−0.66–0.44	0.70	n/a	n/a	n/a
LIFEstyle INT versus CON	0.12	−0.32–0.56	0.59	0.08	−0.34–0.50	0.70	0.06	−0.38–0.51	0.77
Successful INT versus CON	0.26	−0.29–0.81	0.35	0.21	−0.32–0.74	0.43	0.19	−0.35–0.73	0.48

Notes: Regression coefficients (*B*) of standardized ranked scores using Blom's formula of the total problem score of the Ages and Stages Questionnaire for the intervention group (INT) versus control group (CON). A higher score indicates a development that is closer to typical.
[a]Adjusted for child's age and sex.
[b]Adjusted for child's age, sex and conception method.

Table 4. *Effects of a maternal lifestyle intervention on child Ages and Stages Questionnaire subdomains*

	Unadjusted			Model 1[a]			Model 2[b]		
	OR	99% CI	*p*	OR	99% CI	*p*	OR	99% CI	*p*
Communication									
RADIEL INT versus CON	0.49	0.18 to 1.31	0.06	0.47	0.16 to 1.33	0.06	n/a	n/a	n/a
Successful INT versus CON	0.48	0.11 to 2.09	0.20	0.64	0.13 to 3.22	0.48	n/a	n/a	n/a
LIFEstyle INT versus CON	0.96	0.30 to 3.06	0.93	1.00	0.31 to 3.23	1.00	1.02	0.30 to 3.53	0.96
Successful INT versus CON	1.05	0.25 to 4.42	0.93	1.10	0.25 to 4.78	0.87	1.13	0.26 to 4.98	0.84
Fine motor									
RADIEL INT versus CON	0.83	0.32 to 2.12	0.60	0.82	0.30 to 2.25	0.62	n/a	n/a	n/a
Successful INT versus CON	1.33	0.31 to 5.75	0.62	1.59	0.32 to 7.95	0.46	n/a	n/a	n/a
LIFEstyle INT versus CON	0.82	0.26 to 2.59	0.66	0.82	0.24 to 2.74	0.67	0.72	0.20 to 2.54	0.50
Successful INT versus CON	1.12	0.26 to 4.75	0.84	1.14	0.25 to 5.10	0.83	1.03	0.22 to 4.82	0.96
Gross Motor									
RADIEL INT versus CON	1.29	0.46 to 3.57	0.52	1.27	0.46 to 3.56	0.54	n/a	n/a	n/a
Successful INT versus CON	0.60	0.14 to 2.63	0.37	0.57	0.13 to 2.56	0.33	n/a	n/a	n/a
LIFEstyle INT versus CON	1.56	0.46 to 5.33	0.35	1.47	0.42 to 5.16	0.43	1.93	0.50 to 7.47	0.21
Successful INT versus CON	2.25	0.44 to 11.60	0.20	2.13	0.40 to 11.33	0.24	2.55	0.45 to 14.60	0.17
Personal-social									
RADIEL INT versus CON	1.42	0.54 to 3.73	0.35	1.47	0.54 to 4.04	0.33	n/a	n/a	n/a
Successful INT versus CON	1.33	0.31 to 5.75	0.62	1.25	0.25 to 6.11	0.72	n/a	n/a	n/a
LIFEstyle INT versus CON	1.52	0.46 to 4.99	0.37	1.69	0.44 to 6.44	0.32	1.79	0.45 to 7.12	0.28
Successful INT versus CON	3.56	0.60 to 21.15	0.07	4.85	0.64 to 36.90	0.05	4.79	0.63 to 36.64	0.05
Problem-solving									
RADIEL INT versus CON	0.89	0.35 to 2.28	0.75	0.89	0.34 to 2.35	0.75	n/a	n/a	n/a
Successful INT versus CON	1.02	0.24 to 4.31	0.97	1.02	0.23 to 4.59	0.98	n/a	n/a	n/a
LIFEstyle INT versus CON	1.45	0.45 to 4.68	0.42	1.33	0.40 to 4.41	0.54	1.05	0.30 to 3.74	0.92
Successful INT versus CON	1.24	0.30 to 5.19	0.70	1.10	0.25 to 4.78	0.87	1.01	0.23 to 4.53	0.98

Notes: Odds ratio (OR) for scoring ≥ the median (indicating a development that is closer to typical) on the Ages and Stages Questionnaire for the intervention group (INT) versus control group (CON).
[a]Adjusted for child's age and sex.
[b]Adjusted for child's age, sex, conception method.

Table 5. *Median and interquartile range (IQR) of the Childhood Behavior Checklist (RADIEL study) and the Strengths and Difficulties Questionnaire (LIFEstyle study)*

	Intervention group				Control group			
	Median	IQR	*n* (%) deviant score	*n*	Median	IQR	*n* (%) deviant score	*n*
RADIEL study								
Total behavioral problems	24	11–34	3 (4)	68	22	12–32	5 (6)	86
Attention/hyperactivity	1	1–3	0 (0)	68	1	0–2	2 (2)	86
Internalizing/emotional	6	3–9	4 (6)	68	4	2–8	8 (9)	86
Externalizing/conduct	10	3–13	8 (12)	68	8	5–13	4 (5)	86
LIFEstyle study								
Total behavioral problems	8	5–11	11 (32)	34	8	7–11	21 (38)	55
Attention/hyperactivity	4	2–5	6 (18)	34	4	2–6	15 (27)	55
Internalizing/emotional	1	0–2	7 (21)	34	1	0–3	14 (26)	55
Externalizing/conduct	1	0–2	4 (12)	34	1	1–2	9 (16)	55

The effect of the lifestyle interventions on losing weight in the obese women may have been too modest (Koivusalo *et al*., 2016; Mutsaerts *et al*., 2016) to induce any difference in children's neurobehavioral development between the intervention and the control group. Although we can hypothesize that more rigorous weight loss may have led to differences in children's neurobehavioral development, a weight change of comparable size is observed in other lifestyle intervention programs in obese women (Hill, Skouteris & Fuller-Tyszkiewicz, 2013; Mutsaerts, Kuchenbecker, Mol, Land & Hoek, 2013) and thus may be the most feasible in practice. Moreover, too rigorous a weight loss can have adverse effects for the child as well (Galazis, Docheva, Simillis & Nicolaides, 2014).

Nevertheless, it is possible that the lifestyle interventions had a subtle effect on children's neurobehavioral development, but that we were unable to detect this subtle effect with our study sample sizes. With our sample sizes, intervention effects could be detected if they were considerable.

Table 6. *Effects of a maternal lifestyle intervention on child total developmental problem score of the Childhood Behavior Checklist (RADIEL study) and of the Strengths and Difficulties Questionnaire (LIFEstyle study)*

	Unadjusted			Model 1[a]			Model 2[b]		
	B	95% CI	*p*	*B*	95% CI	*p*	*B*	95% CI	*p*
RADIEL INT versus CON	−0.06	−0.38 to 0.27	0.73	−0.07	−0.39 to 0.25	0.68	n/a	n/a	n/a
Successful INT versus CON	−0.11	−0.60 to 0.37	0.64	−0.10	−0.59 to 0.38	0.68	n/a	n/a	n/a
LIFEstyle INT versus CON	−0.07	−0.50 to 0.37	0.77	−0.06	−0.51 to 0.39	0.78	0.01	−0.47 to 0.48	0.98
Successful INT versus CON	−0.31	−0.86 to 0.24	0.26	−0.33	−0.90 to 0.25	0.26	−0.28	−0.86 to 0.31	0.34

Notes: Regression coefficients (*B*) of standardized square root transformed scores of the total behavioral score for the intervention group (INT) versus control group (CON).
A higher score indicates more behavioral problems.
[a]Adjusted for child's age and sex.
[b]Adjusted for child's age, sex and conception method.

Table 7. *Effects of a maternal lifestyle intervention on child Childhood Behavioral Checklist (RADIEL study) and Strengths and Difficulties Questionnaire (LIFEstyle study) subdomains*

	Unadjusted			Model 1[a]			Model 2[b]		
	OR	98% CI	*p*	OR	98% CI	*P*	OR	98% CI	*p*
Attention/hyperactivity									
RADIEL INT versus CON	1.16	0.54 to 2.49	0.64	1.13	0.53 to 2.44	0.70	n/a	n/a	n/a
Successful INT versus CON	1.26	0.41 to 3.93	0.63	1.21	0.38 to 3.81	0.71	n/a	n/a	n/a
LIFEstyle INT versus CON	0.93	0.33 to 2.63	0.87	1.02	0.35 to 2.95	0.97	1.30	0.42 to 4.10	0.59
Successful INT versus CON	0.58	0.15 to 2.30	0.35	0.69	0.17 to 2.88	0.55	0.78	0.18 to 3.37	0.70
Internalizing/emotion									
RADIEL INT versus CON	1.41	0.66 to 3.01	0.29	1.40	0.65 to 3.02	0.30	n/a	n/a	n/a
Successful INT versus CON	1.70	0.53 to 5.43	0.29	1.65	0.51 to 5.35	0.32	n/a	n/a	n/a
LIFEstyle INT versus CON	0.88	0.32 to 2.44	0.77	0.96	0.34 to 2.74	0.93	1.16	0.38 to 3.53	0.76
Successful INT versus CON	0.89	0.25 to 3.18	0.84	0.96	0.26 to 3.60	0.95	1.12	0.28 to 4.37	0.84
Externalizing/conduct									
RADIEL INT versus CON	1.16	0.55 to 2.48	0.64	1.14	0.53 to 2.44	0.70	n/a	n/a	n/a
Successful INT versus CON	1.21	0.39 to 3.75	0.70	1.18	0.37 to 3.76	0.73	n/a	n/a	n/a
LIFEstyle INT versus CON	1.50	0.53 to 4.23	0.37	1.56	0.52 to 4.64	0.34	1.49	0.48 to 4.63	0.41
Successful INT versus CON	0.95	0.25 to 3.61	0.93	0.99	0.23 to 4.15	0.98	1.03	0.24 to 4.42	0.96

Notes: Odds ratio (OR) for scoring > median (indicating more behavioral problems) on the Childhood Behavioral Checklist or the Strengths and Difficulties Questionnaire for the intervention group (INT) versus control group (CON).
[a]Adjusted for child's age and sex.
[b]Adjusted for child's age, sex and conception method.

Our results are in line with one previous study showing no effect of a maternal lifestyle intervention during pregnancy in women with overweight or obesity on children's developmental level at the age of 6 months (Dodd, McPhee, Deussen *et al*., 2018). No other similar follow-up studies have been published about the development of older children or about children's behavior and therefore we have no basis for comparison of these findings. Two lifestyle interventions during pregnancy in obese women that examined offspring anthropometrics, showed that the intervention reduced neonatal adiposity (van Poppel, Simmons, Devlieger *et al*., 2019) and infant adiposity (Patel *et al*., 2017). Conversely, other studies of prenatal lifestyle interventions showed no intervention effects on child anthropometrics or other early life metabolic risk factors (Ronnberg, Hanson & Nilsson, 2017; Tanvig, Vinter, Jorgensen *et al*., 2015). Animal experiments do show that exercise interventions (Fernandez-Twinn *et al*., 2017; Moser, McDaniel, Woolard, Phillips, Franklin & Gordon, 2017; Vega, Reyes-Castro, Bautista, Larrea, Nathanielsz & Zambrano, 2015) and dietary interventions (Zambrano, Martinez-Samayoa, Rodriguez-Gonzalez & Nathanielsz, 2010) during pregnancy in obese animals can prevent adverse physical health outcomes (Fernandez-Twinn *et al*., 2017; Vega *et al*., 2015; Zambrano *et al*., 2010) and learning abilities (Moser *et al*., 2017) in the offspring, without affecting offspring memory performance (Moser *et al*., 2017) and social behavior (Moser *et al*., 2017). To the best of our knowledge other measures of neurobehavioral development has not been assessed in animal experiments yet.

Strengths and limitations

A major strength of our study is that it builds on lifestyle interventions in two RCT settings, eliminating selection bias which observational studies on this topic are prone to. Another strength is that we were able to assess the consistency of our results in two populations. We were also able to use the well

validated questionnaires of neurobehavioral development of children aged 3–6 years (Achenbach & Rescorla, 2000; Squires *et al*., 2009; Theunissen *et al*., 2016).

Limitations also exist. The present analysis was planned beforehand (van de Beek *et al*., 2018). Unfortunately, we experienced considerable loss to follow-up, despite our efforts to maximize participation rates (participation rates: RADIEL 38%, LIFEstyle 32%, and RADIEL and LIFEstyle combined 35%). First, this loss to follow-up reduced our power and therefore increased the risk of type 2 error. Second, the loss to follow-up may have led to selection bias and impact the generalizability of the results. Attrition analyses showed that compared to those who had dropped up from the current analyses, the participating women in RADIEL had higher educational level and were more often nulliparous, and women in LIFEstyle were more often Caucasian. However, those included in the current study did not differ in any other characteristics.

A limitation of the present study is also the limited effectiveness of lifestyle intervention in terms of women's weight, diet and physical activity compared to control group receiving care as usual. As an example, also in the control group 17 and three women were "successful" in the RADIEL and LIFEstyle control groups, respectively. Further, our additional analyses did not find significant differences between the changes in diet quality and physical activity between the intervention and control groups in RADIEL (measured with the changes in the Healthy Food Intake Index and weekly self-reported leisure time physical activity (Rono, Stach-Lempinen, Klemetti *et al*., 2018) from start of the intervention till 3rd trimester) or in LIFEstyle (measured with changes in diet intake variables and leisure time physical activity between the start of the intervention and last measured before conception (Van Elten, Van Poppel, Gemke *et al*., 2018)) - study. Some women in the intervention groups changed their lifestyle, while others did not. Therefore, the contrast between the intervention and control group may have been limited. For this reason, we also investigated whether women in the intervention group who successfully changed their lifestyle had children with different development outcomes than those in the control group. These additional comparisons showed no consistent trends towards differences in children's neurobehavioral development.

Participants of the RADIEL study who were pregnant already during the first clinical visit self-reported their pre-pregnancy weight. Women are suggested to underreport their weight (Merrill & Richardson, 2009). However, as women were randomly allocated to the intervention and control group, potential underreporting of weight has unlikely affected the outcomes of this study. As only children of mothers with ppBMI $\geq$ 29 kg/m2 were eligible for the present study, underreporting of weight may have led to an incorrect exclusion of some participants. This exclusion could have led to reduced statistical power to detect significant effects.

The women of the LIFEstyle study may not fully represent the general population of women with obesity. The infertile women of the LIFEstyle study may have been more eager to start fertility treatment than to start with a lifestyle intervention, which could have reduced the effectiveness of the lifestyle intervention in our LIFEstyle study group. Nevertheless, still 20 women (53%) were successful in the intervention and almost all of them (nineteen women) were already successful before the end of the lifestyle intervention. Another concern about the generalizability of the LIFEstyle population is that within this infertile population, many women (N = 43, 45%) were diagnosed with polycystic ovary syndrome (PCOS), and PCOS in turn may negatively affect child's neurobehavioral development (Bell, Sundaram, Mumford *et al*., 2018; Berni, Morgan, Berni & Rees, 2018). Because we randomized women, the numbers of women with PCOS in each arm were equally distributed and it is therefore unlikely that PCOS has affected our conclusion about effects of the intervention on child development. Also, we performed an additional analysis that showed us that the presence of PCOS was not a confounding factor in our data. The number of women with PCOS in the intervention group (N = 17, 45%) was not different from the amount of women with PCOS in the control group (N = 26, 45%) and also, adding PCOS as a covariate to our primary analysis did not change our conclusions.

Finally, recent studies (Hanson *et al*., 2017) have suggested that lifestyle interventions starting before pregnancy compared to those interventions starting during pregnancy may have different effects on the offspring's health. It has also been suggested that interventions starting before pregnancy may have greater impact as women may be healthier when they enter their pregnancy (Hanson *et al*., 2017). In our study, neither the intervention that started before pregnancy nor the intervention that started during pregnancy had an effect on children's neurobehavioral development. Our analyses were, however, limited by the relatively small sample sizes combined with the considerable time spans of the start of the lifestyle interventions. Larger intervention studies are needed to inform us whether timings of the maternal lifestyle intervention is important for the child's neurobehavioral development.

In conclusion, we did not observe considerable effects of the lifestyle interventions before or during pregnancy in obese women on child's neurobehavioral development. More follow-up studies assessing this topic are needed, especially since the rate of maternal obesity is increasing and maternal obesity has been associated with adverse consequences for children's neurobehavioral development.

CONFLICTS OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web site:

Table S1. Participant characteristics of participants versus non-participants.

Table S2. Correlations between mother and child characteristics and child neurobehavioral development.