Student thesis

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Physical health and neurodevelopmental outcome in 7-year-old children whose mothers were at risk of gestational diabetes mellitus

Student thesis in Medicine
Supervisor: Kari Anne I. Evensen
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Abstract

Background: Children born to mothers with gestational diabetes mellitus (GDM) are at risk of metabolic disturbances such as diabetes mellitus and overweight. However, few have examined the outcome of children whose mothers were at risk of GDM. The aim of the study was to investigate how the mothers' risk of developing GDM affects the physical health and neurodevelopment of the child at 7 years of age.

Methods: A multicentre randomised controlled trial including 855 pregnant women was carried out at St. Olavs Hospital, Trondheim University Hospital, and Stavanger University Hospital in Norway from 2007-2009. From this study, we divided pregnant women into a risk (n=68) and a no risk group (n=189), where the risk group had one or more risk factors for GDM. At seven years of age, the children's height, weight and physical activity was reported by their parents, as well as neurodevelopmental outcomes using the Five-To-Fifteen questionnaire, including motor skills, executive functions, perception, memory, language, social skills and emotional or behavioural problems.

Results: Children in the risk group had higher birthweight and length at birth compared with the no risk group. At the follow-up at 7 years of age, children in the risk group had a higher weight and body mass index (BMI). The odds of being overweight (BMI $\geq$ 25 kg/m^2) was 3.31 (95% CI. 1.21-9.04), also adjusted for the children's birthweight, sex, age at follow up and maternal SES. There were no group differences in the children's physical activity. The children in the risk group had reduced social skills compared with the no risk group, but otherwise their neurodevelopmental outcomes were similar.

Conclusions: In this study, we have shown that the BMI and the social skills of the children were adversely impacted when born to mothers with risk factors for developing GDM. The modifiable risk factors for GDM should therefore be encouraged to be prevented.

Sammendrag

Bakgrunn: Det er dokumentert at svangerskapsdiabetes kan ha uheldige effekter på barnets helse både på kort og på lang sikt, deriblant økt risiko for utvikling av metabolske forstyrrelser som diabetes mellitus og overvekt. Det er likevel få som har undersøkt om mors risiko for svangerskapsdiabetes også kan påvirke barnet. Hensikten med studien vår var derfor å undersøke om mors risiko for å utvikle svangerskapsdiabetes har en effekt på barnets fysiske helse og utvikling ved 7 års alder.

Kunnskapsgrunnlag: En randomisert kontrollert studie som inkluderte 855 kvinner ble gjennomført ved St. Olavs Hospital i Trondheim og ved Stavanger Universitetssjukehus i perioden fra 2007-2009. Deltakerne i studien var friske gravide kvinner som ble invitert under sin rutineultralyd ved disse sykehusene. Vi delte disse kvinnene inn i en gruppe med risiko (n=68) og en gruppe uten risiko (n=189), der kvinnene i risikogruppen hadde en eller flere risikofaktorer for svangerskapsdiabetes. Vår oppfølgingsstudie baserte seg på foreldrenes selvrapportering av barnets høyde, vekt, grad av fysisk aktivitet og utvikling ved 7 års alder. I tillegg ble utviklingsmessige utfall rapportert ved hjelp av spørreskjemaet Fem til Femten. Dette inkluderer motoriske ferdigheter, eksekutive funksjoner, persepsjon, hukommelse, språkferdigheter, sosiale ferdigheter og emosjonelle eller atferdsmessige problemer.

Resultater: Barna i risikogruppen hadde høyere fødselsvekt og -lengde sammenlignet med gruppen uten risiko, og ved oppfølgingen ved 7 års alder hadde disse barna også høyere vekt og kroppsmasseindeks (KMI). Oddsen for å være overvektig (KMI $\geq$ 25 kg/m^2) var 3.31 (95% CI. 1.21-9.04) for barna i risikogruppen. Vi justerte for barnas fødselsvekt, kjønn, alder ved oppfølging og mors sosioøkonomiske status uten at resultatene endret seg. Det var ingen gruppeforskjeller i grad av fysisk aktivitet. Barna i risikogruppen hadde også reduserte sosiale ferdigheter, men ellers fant vi ingen utviklingsmessige problemer i de to gruppene.

Fortolkning: Denne studien viser at å ha én eller flere risikofaktorer for svangerskapsdiabetes har en negativ påvirkning på barnas KMI og sosiale ferdigheter. Det er derfor viktig å forebygge de modifiserbare risikofaktorene for utviklingen av svangerskapsdiabetes.

Content preface

We based our medical student thesis on a follow-up study of a multicentre randomised controlled trial (RCT) done in Trondheim and Stavanger named “Training in pregnancy” (TRIP). The aim of this study was to examine the effects of regular moderate intensity exercise during pregnancy. Supervising us in this thesis was Kari Anne Indredavik Evensen, employed as a professor at the Department of Clinical and Molecular Medicine at the Norwegian University of Science and Technology (NTNU). She is a physiotherapist specialised in children and adolescents and has a PhD in clinical medicine. Evensen has been responsible of the follow up of the children from the TRIP study. Physiotherapist and specialist in women’s health, Signe Nilssen Stafne, is the principal investigator of the TRIP study.

We would like to thank Kari Anne Indredavik Evensen for being a fantastic supervisor and for always helping us and improving our thesis with her knowledge and experience. We would also like to thank Signe Nilssen Stafne for giving us permission to use the TRIP data in our thesis and for letting us participate in this project.

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1 Introduction

Complications during pregnancy and childbirth can have a great influence on both the mother's health and the child's later development (1, 2). Gestational diabetes mellitus (GDM) is the most common metabolic complication during pregnancy and is defined as carbohydrate intolerance with the onset or first recognition during pregnancy (3-5). There are multiple well-documented risk factors for GDM, including advanced maternal age over 40 years, first degree relatives with history of diabetes, previous GDM, having a previous child with a birthweight ≥ 4500g or having a pre-pregnancy body mass index (BMI) ≥ 25 kg/m2 (6, 7), which is considered as overweight (8). Research has documented that overweight of the mother before pregnancy and increased weight during pregnancy are associated with pregnancy complications such as pre-eclampsia, hypertension, caesarean section, high baby birthweight and stillbirth, as well as increased risk of later child obesity (9-13).

GDM may cause adverse effects on the offspring's health, both short-term and long-term (5). Neonates are at risk of developing hyperinsulinism-caused foetal hypoglycaemia immediately after delivery, hypocalcaemia, respiratory distress and macrosomia (14). It is also found that intrauterine exposure to maternal hyperglycaemia, which occurs in GDM, increases the risk of the offspring developing impaired glucose tolerance in ages 5-9 years old and 10-16 years old (14). A Norwegian study from 2020 found an association between maternal pre-pregnancy obesity and higher BMI in offspring at birth, and between high gestational weight gain and a faster BMI growth from 6 months of age to 4-5 years (15).

Even though it is documented that GDM increases the risk of the offspring developing adverse health problems (14), it is still uncertain whether risk of GDM affects the children's neurodevelopment. Some studies have shown that there might be a correlation between GDM, motor development (16, 17) and attention span (17) during the children's school age, but the studies could not find any correlation between GDM and impaired cognitive function in the offspring (1). The purpose of our study was therefore to examine whether the mother's risk of developing GDM has an impact on the children's physical health and neurodevelopmental outcome.

2 Materials and methods

2.1 Study design

This is a prospective follow-up study of a randomised controlled trial (RCT) carried out in Trondheim and Stavanger called «Training in pregnancy» (TRIP) that examined whether training in pregnancy could prevent GDM (REC nr. 4.2007.81) (4). The participants in this trial were invited when booking appointments for their routine ultrasound scans during pregnancy at Stavanger University Hospital and St. Olavs Hospital, Trondheim University Hospital. A total of 875 of approximately 12 000 healthy women invited to the trial accepted the invitation and 855 of these participated from April 2007 to June 2009. The inclusion criteria were women of 18 years or older with a Caucasian race and with a singleton live foetus. Exclusion criteria were diseases that could interfere with the women's participation, high-risk pregnancies, and patients with a residence further than a 30-minute drive away from the hospitals. Participating women were randomised in blocks of 30 using a web based computerised procedure to an intervention group (n=429) and a control group (n=426). The intervention consisted of a 12-week long standardised exercise program between gestational weeks 20-36 and included moderate-intensity to high-intensity activity three or more days per week. The control group received standard Norwegian antenatal care. The participating women were examined at baseline (weeks 18-22 of pregnancy), at end of intervention (weeks 32-36 of pregnancy) and 3 and 18 months after delivery. Pregnancy outcome and newborn data were registered at time of delivery (4).

There were no differences in the prevalence of GDM between the intervention and control group in the original TRIP study. However, secondary analyses and follow-up studies have been performed to examine whether training in pregnancy would have an impact on the children's physical health and neurological development (18-20). In these studies, there were no differences between the children from mothers in the intervention group compared to the control group in length, weight or head circumference at birth (19), cognitive, language or motor skills, daily life functioning at 18 months (18), neurodevelopment outcome (19) or body mass index and physical activity at 7 years (20).

The present data collection was carried out from October 2014 to December 2016 using the software CHECKWARE (CheckWare AS, Trondheim, Norway) when the children were 7 years of age, during the autumn semester of their second year of primary school (19). The current follow-up study included assessment of physical health and neurodevelopment of

these children. In total 855 pregnant women were enrolled in the TRIP study, whereof 188 were excluded due to missing data on risk factors for GDM, such as BMI (n= 7), diabetes in family (n= 139) and previous GDM (n= 144). The remaining 667 participants were divided into a risk and a no risk group. The flow of the study participants is shown in Figure 1.

2.2 Risk group

The risk group included 193 women at enrolment, however, 125 women were missing from the follow-up due to missing address (n= 4) or no consent (n= 122) (Figure 1). We assessed the remaining 68 children whose mothers were at risk of developing GDM. The risk factors included mothers with an age older than 40 years at the start of pregnancy, first-degree relatives with history of diabetes, previous GDM, having a previous child with a birthweight ≥ 4500g or having a pre-pregnancy body mass index (BMI) of ≥ 25.

2.3 No risk group

In total, 474 women were enrolled in the no risk group. Due to missing address (n= 6) or no consent (n= 279), 285 women were missing from the follow-up (Figure 1). The no risk group included 189 children born to mothers without the above-mentioned risk factors.

2.4 Baseline variables

The women's age, BMI, height, parity and sessions of exercise per week were recorded at baseline. The women's BMIs were calculated by their weight (in kilograms) divided by the square of their height (in meters). To calculate the socio-economic status (SES) of the mothers, the Hollingshead Two-Factor Index of Social Position was utilised based on the education and occupation of the mother. Information about sex, birthweight, gestational age, length, head circumference, type of delivery and admittance to the intensive care unit (NICU) was retrieved from the children's medical charts after birth.

2.5 Outcome variables

At the 7-year follow-up, we used questions regarding height, weight, diseases and health problems from a questionnaire developed by the National Institute of Health for the Norwegian Mother and Child Cohort (MoBa) study (21, 22). The children's height was reported in cm and their weight in kg. We calculated the children's iso-BMI, i.e. BMI adjusted for sex and age, by using a weight calculator (23). Parents reported whether their

child had any of the following diseases or health problems; rheumatoid arthritis, cancer, diabetes, cerebral palsy, attention-deficit hyperactivity disorder, coeliac disease, bone fractures, epilepsy, mental retardation, autistic traits, Asperger's syndrome, chronic fatigue syndrome/myalgic encephalomyelitis, tonsillectomy, ear drainage or other conditions or congenital diseases (22).

The questions regarding physical activity (PA) were the same as used in a Norwegian cohort study in the county of Telemark (24, 25). Two of the questions were equal to questions from the WHO Health Behaviour in School-aged Children questionnaire (26), also used in the large Norwegian Young-HUNT study (27, 28). In order to assess whether the child met the recommendation from the Norwegian Directorate of Health (29) to perform one hour or more of daily moderate to vigorous PA (MVPA), parents reported total (including school, after-school program and leisure time) daily MVPA for their child as 1) less than 1 hour or 2) 1 hour or more (24). Frequency of leisure time MVPA, i.e., PA performed outside school and after-school programs where the child was out of breath or sweaty, was reported as the number of times per week (never/once a month or less/once a week/2 to 3 times a week/4 to 6 times a week/every day). Weekly leisure time MVPA was reported as approximate hours per week (none/1 hour/2 to 3 hours/4 to 6 hours/7 hours or more). Intensity of PA was reported as 1) takes it easy without getting out of breath and/or sweaty, 2) gets out of breath and/or sweaty, 3) gets almost exhausted (24). We also assessed time spent on TV, video, electronic devices, DVD or PC outside school, with response options 1) less than 1⁄2 hour, 2) 1⁄2 to 1 hour, 3) 2 to 3 hours a day (24). Finally, approximate hours of sleep at night on weekdays was reported (8 hours or less/9 hours/10 hours/11 hours/12 hours or more) (22).

At 7 years of age, the parents of the participating children were asked to answer the Five-to-Fifteen (FTF) questionnaire to measure the neurodevelopmental outcome. It consists of 181 statements about the child's present functioning categorised into the following eight developmental domains: motor skills, executive functions, perception, memory, language, social skills and possible emotional or behavioural problems (19). The parents are asked to answer each statement by comparing their child to its peers on a three-point scale, from 0 defined as "does not apply", to 2 being "definitely applies" (19). Higher scores indicate more difficulties and scores ≥ 90th centile is cut-off for having more difficulties than children their age usually have (30). The FTF has been found to be valid as a screening instrument in 5-year-old children (30).

2.6 Statistical analyses

The IBM SPSS Statistics 27 was used for all analyses. Two-sided p values <0.05 were considered as statistically significant. Analysis of group differences was done by using chi-square statistics for categorical data, Student's T test for continuous data, Mann-Whitney U test for ordinal or continuous data with a non-normal distribution. To assess normality, we visually inspected histograms and Q-Q plots of the residuals. The child's anthropometric measurements were normally distributed. Odds ratio (OR) with 95% CI was used as an estimate of the relative risk of having a BMI $\geq$ 25 kg/m^2 and for having more difficulties than their peers (scores $\geq 90^{th}$ percentile) in the various FTF domains, both unadjusted and pre-specified adjusted for birthweight, sex, age at follow-up and maternal SES at baseline. In addition, we ran sensitivity analyses excluding preterm children and/or children who had been admitted to the NICU as well as children with reported diseases or health problems as these factors were thought to potentially influence physical health and neurodevelopmental outcome.

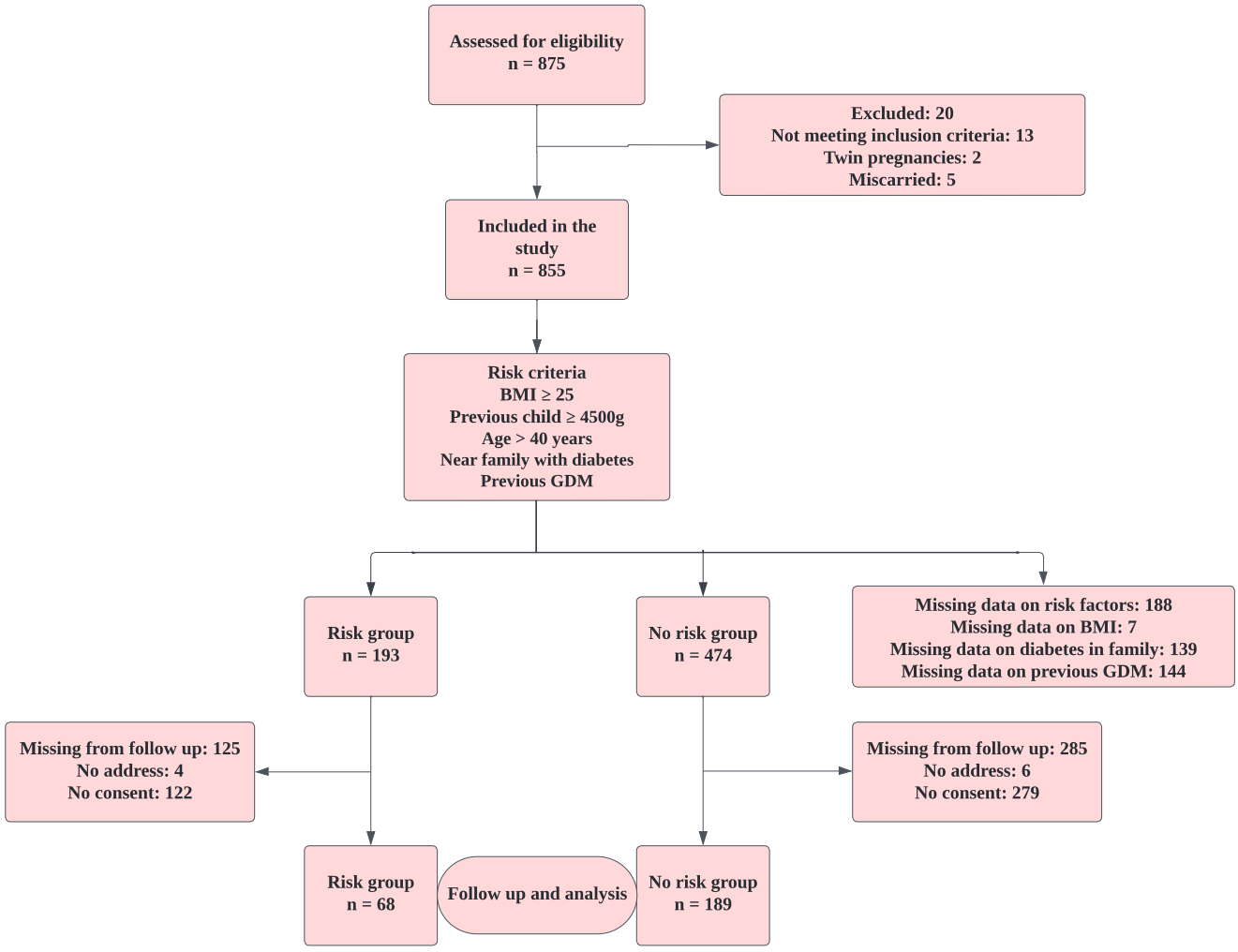

Figure 1. Flow of study participants.

3 Results

Baseline characteristics are shown in Table 1. As expected, maternal age, weight and BMI were higher in the risk group compared with the no risk group as these were selection criteria for the groups. There were no group differences in maternal SES, exercise sessions per week prior to pregnancy or parity. Children of mothers in the risk group had higher birthweight and length at birth. There were no group differences in head circumference, sex, type of delivery, prematurity, admittance to the NICU or the child's age at follow up.

Table 1. Baseline characteristics of mothers and children in the risk group and the no risk group.

	n	Risk group Mean (SD)		n	No risk group Mean (SD)		*P* value
Maternal characteristics at baseline							
Age, years	68	31.6	(4.4)	189	30.2	(3.5)	0.021
Weight, kg	68	77.7	(10.9)	189	66.6	(6.8)	<0.001
Height, cm	68	168.9	(0.1)	189	168.7	(0.1)	0.746
BMI, kg/m^2	68	27.2	(3.5)	189	23.4	(1.9)	<0.001
SES	68	4.0	(0.7)	189	4.1	(0.8)	0.643
Exercise sessions per week	68	1.7	(1.5)	189	2.0	(1.4)	0.256
Parity, n (%)	68			189			
0		33	(48.5)		116	(61.4)	
1		25	(36.8)		55	(29.1)	0.165
2 or more		10	(14.7)		18	(9.5)	
Child characteristics at birth							
Gestational age, weeks	68	40.3	(1.2)	189	40.0	(1.3)	0.133
Birthweight, g	68	3715.7	(574.7)	189	3481.0	(450.9)	0.003
Length at birth, cm	68	50.7	(2.3)	179	49.8	(1.9)	0.002
Head circumference at birth, cm	68	35.3	(1.7)	188	35.0	(1.4)	0.248
Male sex, n (%)	68	36	(52.9)	189	98	(51.9)	0.877
Older siblings, n (%)	68	35	(51.5)	189	73	(38.6)	0.066
Vaginal delivery, n (%)	68	58	(85.3)	189	171	(90.5)	0.240
Prematurity, n (%)	68	1	(1.5)	189	5	(2.6)	1.000
Admitted to NICU, n (%)	66	1	(1.5)	186	3	(1.6)	1.000

Child's age at follow-up, years	68	7.3	(0.3)	189	7.4	(0.3)	0.203

P-values based on Student's T test for the continuous data, Chi-square statistics for dichotomous data, Mann-Whitney U test for ordinal data (i. e. SES, parity).
BMI= Body mass index, SD= standard deviation, SES= Socio-economic status.

3.1 Body mass index and physical health

Table 2 shows the children's BMI and physical activity at the 7-year follow-up. The children's weight and BMI were higher in the risk group compared with the no risk group. There were significantly more overweight children in the risk group (Table 2 and Table S1). The odds ratio of being overweight was 3.31 (95% CI. 1.21-9.04) for the risk group compared with the no risk group. The odds did not change when we adjusted for the children's birthweight, sex, age at follow up or maternal SES (Table S1).

There were no significant group differences in times or hours per week of MVPA or intensity of PA per week, use of electronical devices per day or hours of sleep. Although not statistically significant, 72.1% of the risk group children met the recommendation of one or more hours per day of MVPA compared with 60.4% of the no risk group children. When we excluded children born preterm and children admitted to the NICU (n=4 in the risk group and n=10 in the no risk group) the results were essentially the same. When excluding children with diseases or health problems at the 7-year follow up (n=14 in the risk group and n=38 in the no risk group), the results did not change (data not shown).

Table 2. Parent-reported weight, height, BMI and physical activity at the 7-year follow up in the risk group and the no risk group.

	Risk group			**No risk group**			***P* value**
	n	**Mean**	**(SD)**	**n**	**Mean**	**(SD)**	
Weight, kg	58	26.9	(5.8)	153	24.7	(3.8)	0.008
Height, cm	66	128.2	(6.0)	176	126.8	(5.9)	0.090

BMI	58	16.2	(3.3)	152	15.3	(1.6)	0.050
Iso-BMI	58	20.2	(3.9)	152	19.1	(2.4)	0.056
Iso-BMI ≥ 25 kg/m^2, n (%)	58	9	(15.5)	152	8	(5.3)	0.022
		n	**(%)**		**n**	**(%)**	
Times per week of MVPA	68			189			
Every day		0	0		4	(2.1)	
4-6 times		9	(13.2)		29	(15.3)	
2-3 times		39	(57.4)		105	(55.6)	0.482
Once a week		18	(26.5)		45	(23.8)	
Once a month or less		2	(2.9)		6	(3.2)	
Hours per week of MVPA	68			189			
7 hours or more		2	(2.9)		4	(2.1)	
4-6 hours		9	(13.2)		29	(15.3)	
2-3 hours		34	(50.0)		91	(48.1)	0.921
1 hour		22	(32.4)		57	(30.2)	
None		1	(1.5)		8	(4.2)	
Intensity of PA	68			188			
Easy		7	(10.3)		25	(13.3)	
Out of breath		60	(88.2)		154	(81.9)	1.000
Almost exhausted		1	(1.5)		9	(4.8)	
MVPA	67			188			
≥ 1 hour per day		49	(72.1)		113	(60.4)	0.106
Electronical devices	67			189			
Less than ½ hours a day		4	(6.0)		16	(8.5)	
½-1 hours a day		44	(65.7)		131	(69.3)	0.271
2-3 hours a day		19	(28.4)		42	(22.2)	
Hours of sleep	67			189			
12 hours or more		1	(1.5)		2	(1.1)	
11 hours		19	(28.4)		60	(31.7)	
10 hours		38	(56.7)		110	(58.2)	0.439
9 hours		7	(10.4)		15	(7.9)	
8 hours or less		2	(3.0)		2	(1.1)	

P-values based on Student's T test for continuous data, Chi-square statistics for dichotomous data, Mann-Whitney U test for ordinal data (i. e. hours per week of MVPA, intensity of PA). BMI= Body Mass Index, MVPA= moderate to vigorous PA, PA= physical activity, SD= standard deviation.

3.2 Neurodevelopmental outcome

Table 3 shows the FTF-scores in the domains motor skills, executive functions, perception, memory, language, social skills and emotional or behavioural problems. The children in the risk group had more reported difficulties in their social skills than the no risk group. There were no other group differences in mean scores. The proportions of children with scores ≥90th centile ranged from 4.7% in language to 17.2% in emotional or behavioural problems in the risk group, and from 8.0% in social skills to 12.0% in social skills in the no risk group (Table S2). Odds ratios for having more difficulties than their peers were not significantly increased in the risk group compared with the no risk group. Adjustment for sex, age at follow up or maternal SES did not change the results (Table S2). When we excluded children born preterm and children admitted to the NICU (n=4 in the risk group and n=10 in the no risk group) and children with diseases or health problems at the 7-year follow up (n=14 in the risk group and n=38 in the no risk group), the results did not change (data not shown).

Table 3. Five-to-Fifteen scores in the various domains and subdomains at the 7-year follow-up in the risk group and the no risk group.

	Risk group			**No risk group**			
	n	**Mean**	**(SD)**	**n**	**Mean**	**(SD)**	***P* value**
Motor skills	65	0.17	(0.19)	184	0.17	(0.22)	0.486
Gross motor skills	65	0.12	(0.25)	185	0.16	(0.30)	0.233
Fine motor skills	65	0.20	(0.19)	186	0.18	(0.24)	0.078
Executive functions	63	0.33	(0.29)	181	0.27	(0.26)	0.139
Attention	65	0.41	(0.41)	184	0.32	(0.36)	0.113
Hyperactive/impulsive	65	0.28	(0.32)	186	0.25	(0.32)	0.364
Hypoactive	65	0.28	(0.39)	189	0.24	(0.34)	0.551
Planning and organizing	64	0.26	(0.33)	184	0.25	(0.37)	0.464
Perception	64	0.15	(0.13)	181	0.14	(0.16)	0.390
Relation in space	64	0.09	(0.16)	182	0.09	(0.16)	0.861

Time concepts	67	0.33	(0.39)	186	0.37	(0.44)	0.771
Body perception	65	0.15	(0.21)	184	0.11	(0.19)	0.282
Visual perception	67	0.01	(0.07)	187	0.03	(0.10)	0.383
Memory	64	0.21	(0.22)	184	0.20	(0.27)	0.246
Language	64	0.08	(0.12)	179	0.10	(0.18)	0.759
Comprehension	65	0.12	(0.21)	183	0.14	(0.26)	0.908
Expressive language skills	64	0.06	(0.10)	182	0.07	(0.18)	0.794
Communication	66	0.12	(0.27)	185	0.12	(0.26)	0.663
Social skills	64	0.09	(0.15)	182	0.06	(0.10)	0.047
Emotional/behavioural problems	64	0.11	(0.16)	183	0.08	(0.09)	0.362
Internalizing	66	0.10	(0.13)	184	0.08	(0.12)	0.550
Externalizing	64	0.16	(0.24)	187	0.13	(0.16)	0.836
Obsessive-compulsive	65	0.08	(0.23)	184	0.05	(0.10)	0.385

P-values based on Mann-Whitney U test.

SD=standard deviation.

3.3 Non-respondents

The proportion of non-respondents was 64.7% (n= 125) in the risk group and 60.1% (n= 285) in the no risk group (p= 0.264). When comparing data from respondents and non-respondents, there were no significant differences between the groups in baseline maternal or child characteristics (Table S3).

4 Discussion

4.1 Main findings

In this study, we found that children in the risk group had higher weight and BMI at the 7-year follow up. Further, they had higher odds for being overweight, which remained when we adjusted for the children's birthweight, sex, age at follow up or maternal SES. There were no significant group differences in parent-reported PA. Regarding neurodevelopmental outcome, children in the risk group had poorer social skills compared with children in the no risk group.

4.2 Strengths and limitations

A strength of the initial RCT was the large number of participating women. The included women were motivated to participate in an exercise study during their pregnancy. This could have introduced selection bias to our study, in favour of healthier participants than the general population. Given the nature of the study, women with risk factors for GDM with less motivation for exercise would possibly not participate in the study but would still fulfil our criteria and contribute to the findings. These factors could have affected the generalisation of our results. However, the BMI and PA of the participating women where comparable to the participants in the MoBa Study (n= 34 508) (21). Both studies included women within the normal range of BMI and who exercised regularly, indicating a representative selection of Norwegian women in our study (4).

Another limitation to our study is the low follow-up rate (38.5%) and the missing data on GDM risk factors for 188 women. However, the follow-up rate was similar in the two groups and there were few differences between the groups at baseline other than the selection criteria. The selection criteria consisted of the well-established risk factors for developing GDM, which are maternal age ≥ 40 years, first-degree relatives with history of diabetes, previous GDM, having a previous child with a birthweight ≥ 4500g or having a pre-pregnancy BMI ≥ 25 kg/m^2 (6, 7). As these variables were the only selection criteria, it is less likely that the results could have been affected by misclassification or selection bias.

The 7-year follow-up was based on parent-reported data from standardised questionnaires that was collected electronically. A strength of this survey is the parents' unique access to knowledge about their children's lives and day-to-day activities. There is a likelihood that the respondent's scorings could have been affected by misinterpretations, exaggerations, social desirability bias or lack of insights in their child's actual weight, PA levels and neurodevelopment. Cultural and language differences could also affect the results. For the questions regarding height and weight, we used a questionnaire developed by the Norwegian National Institute of Health for the MoBa study (21, 22). It is unknown whether the parents in our study estimated or precisely measured the child's height and weight. A Belgian study (n=297) concluded that parents' estimations of their child's weight and height, and subsequently the calculation of their BMI, were less accurate than measurements (31). On a group level, however, there were no important differences between the measured and

estimated reports in that study (31). Furthermore, the BMI of the children in our study were comparable to the data from the MoBa study (22). The questions regarding the frequency and duration of the PA of the children are shown to be valid and reliable (27), and are used in other Norwegian and international studies (24-27). It is, however, shown that parents under-report their children's PA when compared to measurements with accelerometers (32), which could affect the validity of our results. The FTF-questionnaire is a reliable and valid screening instrument for developmental disorders (30, 33), although it is shown that parents may report concerns related to their children's development even though there are no significant clinical implications of such problems (30). We cannot dismiss that these factors may have influenced the results of this study. However, it is unlikely that these factors would have affected the two groups differently.

4.3 Interpretations

Consistency with literature

We found no other studies that examined outcomes of children with mothers at risk of developing GDM, but multiple studies have reported on anthropometric measurements in children of mothers diagnosed with GDM. As macrosomia is a known consequence of GDM, our findings regarding birthweight and length at birth in the risk group complies well with what has been found in multiple other studies (14, 34-36). However, not that many studies have found associations between GDM and overweight in childhood. A systematic review and meta-analysis included nine studies with anthropometric measurements of offspring of mothers with GDM or diabetes mellitus (37, 38). Three of these studies (39-41) studied children aged 6–14 years old and found that the GDM exposed children had a higher BMI than the control children. However, they found that the children's BMIs were strongly associated with maternal pre-pregnancy BMI. Unlike these studies, Krishnaveni et al. (42) studied 9-year-old children and found that those exposed to GDM had a higher BMI than the control children even after adjusting for the mothers' BMIs. As maternal overweight was one of the selection criteria for the groups in our study, we did not adjust for the mothers' pre-pregnancy BMIs. The remaining studies studied children in younger age groups and of mothers with type 1 or 2 diabetes mellitus. A Norwegian cohort study followed 734 mother-offspring pairs to examine whether there was an association between GDM and the offspring's BMIs up to preschool age (15). Children of mothers with pre-pregnant obesity had a persistently higher BMI from birth, and the authors concluded that maternal overweight

prior to pregnancy therefore seems to be an independent risk factor for development of overweight in the offspring (15).

We did not find any significant group differences in PA. Both children in our risk and no risk group seemed to be less physically active than the general population (43, 44). The current recommendation from the Norwegian Directorate of Health for children in this age group is one or more hours per day of MVPA (45). A national Norwegian comprehensive survey from 2018 (43, 44) studied PA in 6-, 9- and 15-year-old children by using an accelerometer. Amongst the 6-year-olds 94% of the boys and 87% of the girls met this recommendation, and amongst the 9-year-olds this applied for 81% of the boys and 64% of the girls (44), compared with 72.1% in our risk group and 60.4% in our no risk group. This difference could be explained by the different methods used, as it is shown that parents tend to underreport their children's PA compared with measurements done by accelerometers (32).

In this study, we found that children in the risk group had more parent-reported problems regarding their social skills compared with the children in the no risk group. There are few studies on long-term neurodevelopmental outcome of children born to women with risk factors for GDM during pregnancy. However, some studies have examined outcomes in younger children of mothers diagnosed with GDM, such as a Japanese study that included 81705 mothers and their children at age 6 months to 4 years old (46). This study showed that mothers with GDM had children with reduced social skills and fine motor skills compared with children of mothers without GDM (46). These results comply well with ours, as the children in our risk group also had a tendency towards more problems in fine motor skills ($p= 0.078$). Some studies have examined neurodevelopment of infants of women with and without GDM, such as a Serbian study that included 203 mother-child pairs (16). This study showed that the children of mothers with GDM had lower motor scores at both 3 and 6 months of age. Ghassabian et al. found that children exposed to maternal diabetes, gestational or pre-gestational diabetes, achieved motor milestones, such as sitting without support and walking, at a later age than the non-exposed (47). An Israeli study compared neurodevelopment of 57 children born to diabetic women with 56 children of non-diabetic women (17). They found that early school aged children born to the diabetic women had more neurological soft signs and lower gross and fine motor scores compared to the control group. However, most of these differences diminished in the group of 9–12-year-olds compared to the 5–6-year-olds (17). In comparison to these studies, we had less findings on neurodevelopmental outcomes. The

reason for this might be that, in contrast to our study, the women included in these studies were diagnosed with diabetes mellitus or GDM.

Biological credibility

Our main findings regarding the children's physical health suggests that the mothers' risk of developing GDM has an influence on the children's weight and BMI. Looking at the intrauterine environment in diabetic mothers, the changes in the nutrient supply to the foetus can cause metabolic modifications which can increase the risk of overweight later in life (38). One study claims that intrauterine metabolic programming due to hyperglycaemia and oxidative stress is one of the links between GDM and metabolic disease in the offspring (48). Others have found that GDM can affect the gene regulation of lipid metabolism and endocrine signalling pathways, which also could explain the increased risk of the offspring developing diabetes and obesity (5).

There is not plentiful literature on why GDM and diabetes in pregnancy can affect the neurodevelopment of the children. Some authors have speculated that hyperketonaemia, which may occur in GDM, can have a teratogenic effect on the foetus and that this could be the explanation to why GDM can influence neurodevelopment (47). This could also explain why the children in our study only had modest neurodevelopmental outcomes, as they were not exposed to this in the same degree as children of mothers with GDM or diabetes. These teratogenic effects and complications could also be the explanation to why the children in our study also had reduced social skills.

Clinical implications

Our finding of increased risk of overweight in children born to mothers with risk factors for GDM may have implications for the children's future health. An American study from the state of Louisiana showed that over three quarters (77%) of the overweight children remained obese as adults (49). Overweight before the start of puberty is associated with significantly increased risk of mortality and morbidity later in life, especially type 2 diabetes mellitus and cardiovascular disease (50). Reducing body weight into normal range before adulthood may reduce these risks significantly (50, 51), especially if done before puberty. Childhood obesity also has great economic and social costs, including increased burdens on health care systems

as well as reduced economic productivity later in life (52). Thus, measures to avoid childhood obesity should be encouraged.

The reduced social skills of children in the risk group may have an impact on their present and future well-being. Having reduced social skills is shown to increase the risk of depression and loneliness (53, 54) as well as low self-esteem, anxiety and shyness (55) in childhood, but also later in life. Reduced social skills is associated with difficulties when establishing and maintaining satisfying relationships with other people (54). It is shown that people with poor social skills are not as resilient to the impact of stress and have less feeling of psychological well-being compared to those with effective social skills (56). Poor social skills is also a risk factor for getting bullied (55).

Overweight and reduced social skills found in our study may be interrelated. A German study found reduced social skills in a group of 2-3 year old boys with higher BMI compared to boys with lower BMI (57). Overweight might be a risk factor for other unfavourable childhood outcomes such as bullying (58, 59). Other studies have compared friendships of overweight with normal weighted children and adolescents, and have found that those overweight are less socially accepted and have fewer friends compared to their non-overweight peers (60) and that there were significant differences in the quality of these social relationships and their social-emotional aspects (61). In addition, obese and overweight children and adolescents are more likely to suffer from psychological comorbidities, such as depression (62), anxiety and low self-esteem than their normal weighted peers (52). It is possible that these factors could affect the social skills of the children in our study, given that they were more overweight than the no risk group. We speculate that poor social skills could have adverse impacts on the quality of life of the children and could be worsened by overweight. As having risk factors of GDM can impact the weight status and social skills of the children and has multiple effects on both the mother and child, it should continue to be prevented by eliminating the modifiable risk factors before pregnancy.

5 Conclusions

In this prospective follow-up study of women included in a randomised controlled trial during pregnancy, we have reported on physical health and neurodevelopmental outcome of children born to mothers with risk factors for GDM. We found that the children of the mothers with

one or more risk factors for GDM had higher BMI than the no risk group and an increased risk of being overweight at 7 years old. The children in the risk group also had reduced social skills. As our results indicate that there are adverse impacts on the children of mothers at risk of developing GDM, the modifiable risk factors for GDM should be encouraged to be prevented.

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Supplementary material

Table S1 shows crude and adjusted odds ratio (OR) with 95% confidence intervals (CIs) as an estimate of the relative risk of having higher iso-BMI than their peers (scores ≥ 25 kg/mg^2) at the 7-year follow up in the risk group compared with the no risk group. The odds did not change when we adjusted for the children's birthweight, sex, age at 7-year follow up or maternal SES. When we excluded children born preterm and children admitted to the NICU (n=4 in the risk group and n=10 in the no risk group) and children with diseases or health problems at the 7-year follow-up (n=14 in the risk group and n=38 in the no risk group) the results did not change (data not shown).

Table S1. Supplementary table 1, crude and adjusted odds ratio (OR) with 95% confidence intervals (CIs) as an estimate of the relative risk of having higher iso-BMI than their peers (scores ≥ 25 kg/mg^2) at the 7-year follow up in the risk group compared with the no risk group.

	n	Risk group		n	No risk group		Crude OR (95% CI)	Adj. OR[a] (95% CI)	Adj. OR[b] (95% CI)	Adj. OR[c] (95% CI)	Adj. OR[d] (95% CI)
		n	(%)		n	(%)					
Iso-BMI ≥ 25	58	9	(15.5)	152	8	(5.3)	3.31 (1.21-9.04)	3.64 (1.31-10.17)	3.38 (1.23-9.30)	3.64 (1.30-10.15)	3.27 (1.19-8.95)

Logistic regression with iso-BMI ≥ 25 kg/mg^2 as dependent variable and group as independent variable. Additionally adjusted for birthweight, sex, age at follow up and maternal SES entered separately as independent variables.

CI= confidence intervals, OR= odds ratio.

[a] Adjusted for the child's birthweight

[b] Adjusted for the child's sex

[c] Adjusted for the child's age at follow up

[d] Adjusted for maternal SES at baseline

Table S2 shows crude and adjusted odds ratio (OR) with 95% confidence intervals (CIs) as an estimate of the relative risk of having more difficulties than their peers (≥ 90th centile) in the various Five-to-Fifteen domains in the risk group compared with the no risk group at 7 years of age. There were no significant group differences, and adjustment for sex, age at 7-year follow up or maternal SES did not change the results. When we excluded children born preterm and children admitted to the NICU (n=4 in the risk group and n=10 in the no risk group) and children with diseases or health problems at the 7-year follow-up (n=14 in the risk group and n=38 in the no risk group) the results did not change (data not shown).

Table S2. Supplementary table 2, crude and adjusted odds ratio (OR) with 95% confidence intervals (CIs) as an estimate of the relative risk of having more difficulties than their peers (≥ 90th centile) at the 7-year follow up in the various Five-to-Fifteen domains in the risk group compared with the no risk group.

	n	Risk group	n	No risk group	Crude	Adj. [a]	Adj.[b]	Adj.c

							OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
		n	**(%)**		**n**	**(%)**				
Motor skills	65	5	(7.7)	184	22	(12.0)	0.61 (0.22-1.70)	0.60 (0.22-1.67)	0.59 (0.21-1.64)	0.62 (0.23-1.72)
Executive functions	63	8	(12.7)	181	20	(11.0)	1.17 (0.49-2.81)	1.15 (0.48-2.78)	1.08 (0.44-2.61)	1.16 (0.48-2.80)
Perception	64	8	(12.5)	181	21	(11.6)	1.09 (0.46-2.60)	1.09 (0.45-2.59)	1.11 (0.46-2.66)	1.09 (0.46-2.61)
Memory	64	5	(7.8)	184	17	(9.2)	0.83 (0.29-2.36)	0.82 (0.29-2.35)	0.82 (0.29-2.32)	0.86 (0.30-2.45)
Language	64	3	(4.7)	179	17	(9.5)	0.47 (0.13-1.66)	0.46 (0.13-1.65)	0.44 (0.12-1.56)	0.47 (0.13-1.65)
Social skills	60	8	(13.3)	176	14	(8.0)	1.78 (0.70-4.48)	1.81 (0.71-4.56)	1.74 (0.69-4.41)	1.80 (0.71-4.53)
Emotional/ behavioural problems	64	11	(17.2)	183	20	(10.9)	1.69 (0.76-3.76)	1.69 (0.76-3.77)	1.70 (0.76-3.78)	1.72 (0.77-3.84)

Logistic regression with FTF-domains as dependent variables and group as independent variable. Additionally adjusted for sex, age at follow up and maternal SES entered separately as independent variables.

CI= confidence intervals, OR= odds ratio.

[a] Adjusted for the child's sex

[b] Adjusted for the child's age at follow up

[c] Adjusted for maternal SES at baseline

Table S3 shows the differences in baseline variables compared between respondents and non-respondents. There were no group differences between the non-respondents and respondents in either the risk group or the no risk group.

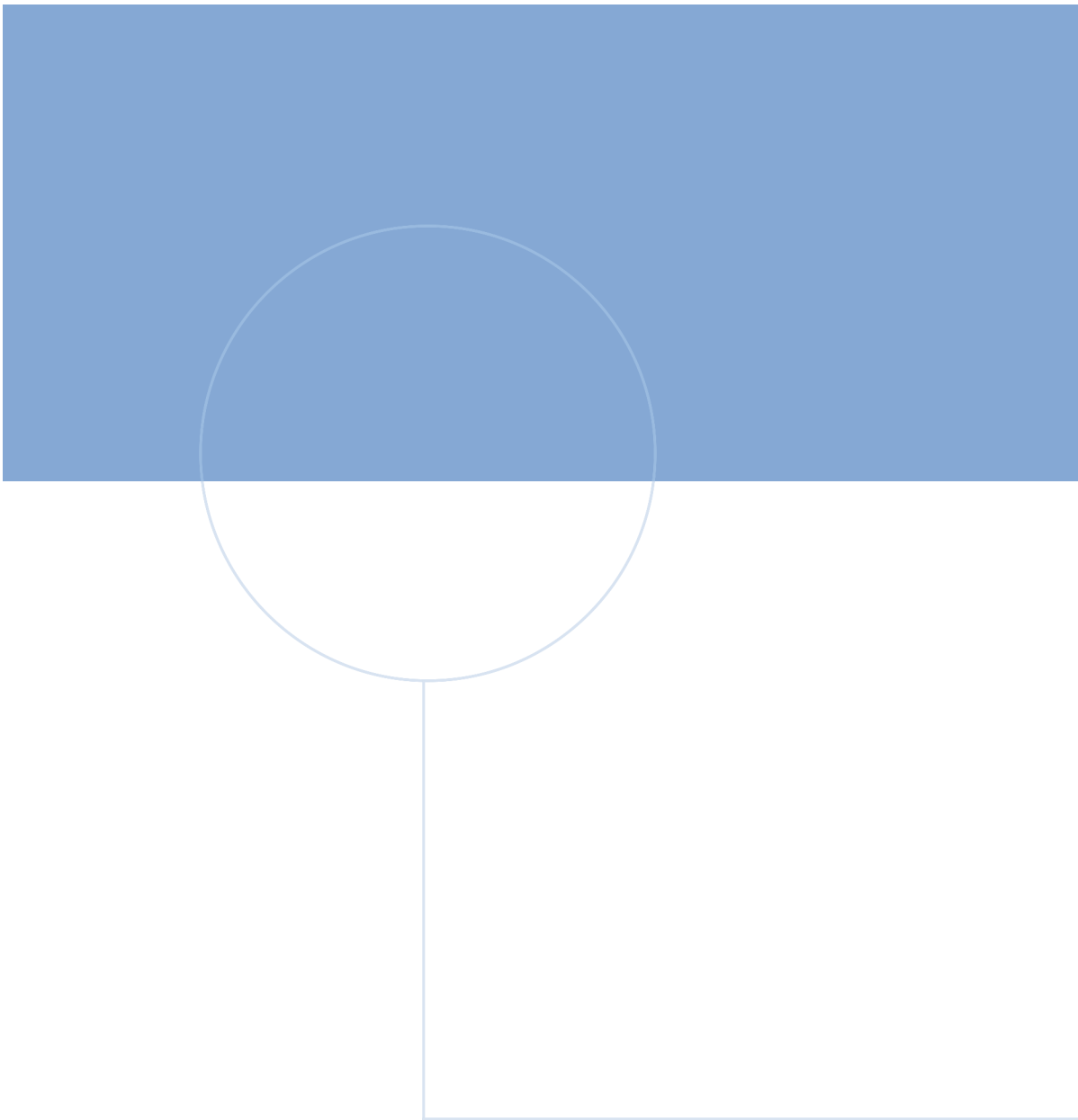
Table S3. Supplementary table 3, baseline variables compared between respondents and non-respondents.

	Risk group					**No risk group**				
	Respondent		Non-respondent			Respondent		Non-respondent		
	n	Mean (SD)	n	Mean (SD)	*P* value	n	Mean (SD)	n	Mean (SD)	*P* value
Maternal characteristics at baseline										
Age, years	68	31.6 (4.4)	125	31.3 (5.2)	0.691	189	30.2 (3.5)	285	30.3 (3.8)	0.684
Weight, kg	68	77.7 (10.9)	125	78.2 (10.2)	0.754	189	66.6 (6.8)	283	67.4 (6.7)	0.193
Height, cm	68	168.9 (0.1)	125	167.7 (0.1)	0.167	189	168.7 (0.1)	285	169.1 (0.1)	0.411
BMI, kg/m^2	68	27.2 (3.5)	125	27.8 (3.3)	0.258	189	23.4 (1.9)	284	23.6 (1.9)	0.342
SES	68	4.0 (0.7)	125	3.7 (1.0)	0.066	189	4.1 (0.8)	285	3.9 (0.9)	0.122
Exercise sessions per week	68	1.7 (1.5)	125	1.8 (1.5)	0.639	189	2.0 (1.4)	285	1.7 (1.3)	0.075
Parity, n (%)										
0	68	33 (48.5)	125	72 (57.6)		189	116 (61.4)	285	170 (59.6)	
1	68	25 (36.8)	125	31 (24.8)	0.428	189	55 (29.1)	285	77 (27.0)	0.521

2 or more	68	10 (14.7)	125	22 (17.6)		189	18 (9.5)	285	38 (13.3)	
Child characteristics at birth										
Gestational age, weeks	68	40.3 (1.2)	125	40.3 (1.3)	0.776	189	40.0 (1.3)	285	40.1 (1.3)	0.238
Birth-weight, g	68	3715.7 (574.7)	125	3657.3 (462.5)	0.443	189	3481.0 (451.0)	285	3514.3 (461.4)	0.438
Length at birth, cm	68	50.7 (2.3)	121	50.5 (2.1)	0.675	179	49.8 (1.9)	280	49.9 (2.2)	0.499
Head circum-ference at birth, cm	68	35.3 (1.7)	125	35.4 (1.4)	0.853	188	35.0 (1.4)	279	35.1 (1.4)	0.487
Male sex, n (%)	68	36 (52.9)	125	71 (56.8)	0.606	189	98 (51.9)	285	146 (51.2)	0.894
Older siblings, n (%)	68	35 (51.5)	125	53 (42.4)	0.227	189	73 (38.6)	285	115 (40.4)	0.707
Vaginal delivery, n (%)	68	58 (85.3)	125	109 (87.2)	0.711	189	171 (90.5)	284	266 (93.7)	0.201
Prematurity, n (%)	68	1 (1.5)	125	4 (3.2)	0.658	189	5 (2.6)	285	8 (2.8)	0.916
Admitted to NICU, n (%)	66	1 (1.5)	125	5 (4.0)	0.666	186	3 (1.6)	282	10 (3.5)	0.213

Chi-square statistics for dichotomous data, Mann-Whitney U test for ordinal data (i. e. SES, exercise per week), Student's T test for the continuous data.

BMI= Body mass index, SD= standard deviation, SES= Socio-economic status.



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