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Ascending growth is associated with offspring adiposity in pregnancies complicated with obesity or gestational diabetes

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Conflict of interest

The authors declare that there are no conflicts of interest associated with this manuscript.

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Abbreviations:

GDM = gestational diabetes

PI = ponderal index

PA = physical activity

LCMM = latent class mixed model

HUH = Helsinki university hospital

SKCH = South Karelia central hospital

OGTT = oral glucose tolerance test

FFQ = food frequency questionnaires

HFII = healthy food intake index

MVPA = moderate-to-vigorous physical activity

IQR = interquartile range

SD = standard deviation

GWG = gestational weight gain

Abstract

Context

Early growth associates with childhood adiposity, but the influence of lifestyle remains unknown.

Objective

To investigate the association of growth profiles from high-risk pregnancies with adiposity at 5 years of age, taking into account lifestyle and several antenatal/postnatal exposures.

Design

Prospective cohort study

Patients

609 children born during the Finnish Gestational Diabetes Prevention Study (RADIEL), recruiting women with BMI≥30 and/or prior GDM (2008-2013). Altogether 332 children attended the 5-year follow-up (2014-2017).

Main Outcome Measures

Growth profiles based on ponderal index (PI=weight/height^3), investigated using latent class mixed models. Adiposity was assessed with anthropometrics and body composition(InBody720).

Results

We identified three growth profiles: ascending (n=82), intermediate (n=351), and descending (n=149). Children with ascending growth had a higher body fat percentage, ISO-BMI, and waist circumference ($p<0.05$) at 5 years of age. Ascending (B 4.09,CI 1.60-6.58) and intermediate (B 2.27,CI 0.50-4.03) profiles were associated with higher fat percentage, even after adjustment with age, sex, gestational age, diet, physical activity, education, and pre-pregnancy BMI. Similar associations existed with ISO-BMI. After adjusting with age and education, ascending growth was associated with pre-pregnancy BMI (OR 1.06,CI 1.01-1.12), primiparity (OR 3.07,CI 1.68-5.62), cesarean section (OR 2.23,CI 1.18-4.21), and lifestyle intervention (OR 2.56,CI 1.44–4.57). However, meeting the intervention goals and exclusive breastfeeding for ≥3 months were associated with lower odds of ascending growth.

Conclusions: Accelerated early growth was associated with higher adiposity in 5-year-old children from high-risk pregnancies, even when adjusted with lifestyle. Reducing cesarean sections and promoting breastfeeding may be beneficial for postnatal growth.

Key words: early growth, childhood obesity, gestational diabetes, body composition, lifestyle, fetal programming

1. Introduction

Childhood obesity is one of the greatest public health challenges of the 21st century, with far-reaching effects[1]. Not only does it cause poorer health in childhood and adolescence, but also predicts metabolic morbidity in adulthood [2]. Epidemiological studies have demonstrated that offspring from pregnancies complicated by obesity and/or gestational diabetes are at increased risk of obesity and diabetes themselves[3-5]. Although genetics and postnatal lifestyle play an important role, part of this effect may be mediated through fetal programming [6].

For long, birth weight has been the proxy for fetal programming, describing e.g. the level of under or over nutrition during pregnancy. Recently more focus has been on early growth and its connection to the future risk of metabolic morbidity[7]. Various studies have associated accelerated early weight gain with childhood obesity[8], as well as morbidity and obesity in adolescence and adulthood [9]. Most studies, however, have growth data only from few time points during childhood, or assess limited variables such as adiposity rebound or BMI at adiposity peak[5].

Latent class mixed modelling (LCMM) is a method allowing assessment of individual non-linear growth profiles and combination of data from numerous time points. Recent studies on unselected populations using LCMM have identified 3-5 distinct BMI trajectories in childhood - including at least an ascending, a descending, and an intermediate profile. Early ascending growth profiles have been associated with higher BMI[10], body fat percentage, and unfavorable lipid profile[11] at 5-9 years of age. Whether growth profiles of offspring from pregnancies with hyperglycemia and/or obesity follow similar patterns and offer a comparable predictive value, is unknown. Moreover, previous studies have not been able to consider lifestyle factors of the offspring[12].

The aim of this study was first to identify the potential early growth trajectories based on ponderal index from birth to 2 years of the offspring from high-risk pregnancies complicated with either GDM and/or maternal obesity using LCMM. Secondly, we wanted to examine the possible associations between growth trajectories and adiposity of the offspring at the age of 5 years, taking into account also current diet and physical activity of the child. Finally, we evaluated the associations between the identified growth trajectories and several antenatal and postnatal exposures such as maternal adiposity, glycemic status, and early feeding of offspring.

2. Materials and Methods:

Study design

This is a secondary analysis and follow-up of children born during the Finnish Gestational Diabetes Prevention Study (RADIEL) aiming at prevention of GDM through a lifestyle intervention. It was a randomized controlled study, performed during years 2008 – 2013 in Helsinki (Helsinki University Hospital) and Lappeenranta (South Karelia Central Hospital), Finland. Altogether 724 women at high risk for GDM (BMI >30 and/or prior GDM) voluntarily entered the study before or in early pregnancy (<20 gestational weeks). Medications altering glucose metabolism, overt diabetes, severe psychiatric problems, multiple pregnancy, physical disabilities, and communication problems based on inadequate language skills led to exclusion. Participants were randomly allocated to a control group or to a combined lifestyle intervention group, emphasizing dietary goals following Nordic nutrition recommendations, physical activity (150 min/week), and limiting gestational weight gain. Study visits took place every 3 months before pregnancy, once in each trimester of pregnancy, and 6 weeks, 6 and 12 months after delivery [13].

Five years after delivery, during years 2014 - 2017, all 607 participants with a live birth received an invitation to participate with their children in a follow-up study[14]. Altogether 332 mother-child dyads visited the study nurse either together or separately, according to their own preference. Our previous study reports the flow chart and characteristics of drop-outs compared to those participating in the follow-up[15] In addition to the measurements at the study visit, we collected anthropometric data and records on infant feeding from communal child care clinics from birth to 5 years of age, which was available for 582 of the participants. All mothers gave a written informed consent and entered the study voluntarily. The study complied with the declaration of Helsinki and received approval from the ethics committees of the HUH (Dnro 300/E9/06) and SKCH (Dnro M06/08).

Measurements

Pregnancy

Each study visit included anthropometric measurements, except for height, which was measured only at the initial visit. Blood pressure was measured from the right arm, in a sitting position with a sphygmomanometer. Blood tests performed in conjunction with the visits after 10-12 hours of fasting included a 75-g 2-hour oral glucose tolerance test (OGTT) (only at the first visit before pregnancy, in the 1st and 2nd trimesters of pregnancy, and 6 weeks and 12 months after delivery), GHbA1c, lipids (cholesterol, low-density lipoprotein LDL, high-density lipoprotein HDL, and triglycerides), and insulin. We also extracted DNA from whole blood samples using Qiagen Maxipreps (Qiagen, Valencia, CA, USA) and genotyped the most common single-nucleotide-polymorphisms (SNPs) associated with obesity and diabetes including MTNR1B risk allele Rs10830963 by using a Sequenom iPLEX platform (Sequenom, San Diego, CA, USA)[16]. Medical records provided the information on pregnancy complications and a jury consisting of two independent physicians confirmed all diagnoses. Diagnosis of GDM was based on having 1 or more pathological values, following the current national thresholds: 5.3 – 10.0 – 8.6 in the OGTT. Previous studies present the detailed information on the measurements [14,17].

Pre-pregnancy weight and BMI (weight/height^2) were based either on the self-reported weight before pregnancy (for those recruited in early pregnancy) or the weight at the last study visit before pregnancy (for those recruited before pregnancy). The difference between pre-pregnancy weight and the weight at the 3rd trimester study visit was the definition for gestational weight gain (GWG).

Background questionnaires provided the data on maternal socioeconomic status (i.e. years of education), smoking, and physical activity (PA) (self-reported duration of moderate-intensity PA min/week). Food frequency questionnaires (FFQ) offered the data for calculating the Healthy Food Intake Index (HFII), demonstrating the diet as an entity during pregnancy[18]. Participants received points reflecting their consumption of high-energy/low-nutrient snacks (0–2 points), sugar-sweetened beverages(0–1 points), fast food (0–1 points), high-fiber grains (0–2 points), bread fat spread (0–2 points), low-fat cheese (0–1 points), low-fat milk (0–2 points), fish (0–2 points), red and processed meat (0–2 points), vegetables (0–2 points), and fruits and berries (0–1 points). The maximum score available was 18, with a higher score indicating a healthier diet.

We also calculated a success score based on achieving the goals of the RADIEL lifestyle intervention in the 3rd trimester, with a maximum score of 5: 1) GWG adequate or less than adequate according to IOM guidelines[19] (0-1points), 2) self-reported duration of moderate intensity PA per week $\geq$150 minutes (0-1 points), 3) consumption of 5 or more portions of fruits, berries and vegetables per day (0-1 points), 4) fiber intake $\geq$ 30 grams (0-1 points), and 5) intake of saturated fats < 10% of daily energy intake (0-1 points). The definition for a successful intervention was receiving 3 out of 5 points.

Birth

Hospital birth records provided the data on the date of delivery, gestational weeks at delivery, and delivery mode, as well as newborn characteristics at birth (weight, length, head circumference, and Apgar points) and placental weight. For our analyses we used birth weight SD.

Offspring follow-up

The follow-up study visit at 5 years of age [20] included measurements of height and weight, as well as measuring the waist circumference twice in the horizontal plane midway between the lowest rib and iliac crest to the nearest 0.1 cm. As an indicator of adiposity at 5 years of age we used ISO-BMI levels, which are sex specific BMI levels equivalent for overweight and obesity in adulthood (≥ 25 kg/m^2 and ≥30 kg/m^2, respectively)[21]. Blood pressure was measured in a sitting position three times from the right arm. Approximately 4 hours of fasting preceded the blood tests which covered glucose (glucose, GHbA1c, insulin) and lipid (total cholesterol, HDL, LDL, triglycerides) metabolism.

Body composition was measured with the bioimpedance method (InBody 720/InBody 3.0, Biospace Co., Ltd, Seoul, Korea). Physical activity (PA) at 5 years was monitored by hip-worn accelerometer (ActiGraph) for 7 consecutive days, excluding water-activities (such as shower and swimming). Sleeping time was excluded based on diaries. Data was collected at 30 Hz sample rate and averaged into 10 s epochs for further analysis. Moderate-to-vigorous intensity PA (MVPA) was calculated based Evenson et al. [22] cut-points and used as a marker of PA. Periods longer than 30 minutes of consecutive zero counts were defined as non-wear time[23]. To be included in the analyses, we required

at least 8 hours of wearing time from 3 days, including one weekend day[23]. 3-day food diaries assessed the diet of the children, and also day care personnel were instructed to fill in the questionnaires. As an indicator of a healthy diet we used consumption of fruit, vegetables, and berries during a day. All analyses concerning offspring diet were adjusted for energy intake.

Communal child care clinic records provided the growth data (weight and height). For assessing offspring adiposity and investigating the longitudinal growth profiles, we calculated a ponderal index (PI)(weight/height^3). As indicators of diet during infancy, we used the data from communal child care clinic records including total duration of breastfeeding, duration of exclusive breastfeeding, and the age at introduction of solid foods.

Statistical methods

We examined normal distribution of the variables with the Shapiro–Wilk test. Descriptive characteristics are presented as means with standard deviations (SD), medians with interquartile range (IQR), or as frequencies with percentages. Chi square test, the Mann–Whitney U test, ANOVA, or the independent sample T test were used for between-groups comparisons, when appropriate.

In order to investigate the growth differences between children, latent class mixed models (LCMM) were applied for ponderal index (PI) from the first two years of life. Flexible LCMM is a method for modelling longitudinal outcomes and can be used to assign observations to classes based on their measurements at different times. LCMM allows the number and timing of the measurements vary between individuals and it does not assume linearity of the outcome [24]. The figures representing

growth profiles often use LOESS smoothening to capture the main features of non-linear development in e.g. growth.

All available growth data from the first two years (N=582) was used and a model for PI was fitted. Because of the nature of the Ponderal Index, the model allowed for curvilinear curves (using link function I-spline with 4 knots at quartiles), including quadratic polynomial function of child's age. Models with 1, 2 and 3 classes were explored and the best model was chosen based on Bayesian Information criteria (BIC), relative entropy, average posterior probability (APP), latent class size, and clinical interpretability by visually inspecting loess curves (with 95% CI) for the classes.

R statistical software 3.6.2 and its LCMM package[24] was used for the LCMM analysis.

To study the associations between the distinct growth profiles and body fat percentage and ISO-BMI at 5 years of age, we used the linear regression model, which we additionally adjusted with child's age, sex, diet, PA, maternal years of education, gestational age at delivery, pre-pregnancy BMI, and birth weight SD. We used multinomial logistic regression to examine the associations of different antenatal and postnatal exposures with three early growth profiles, and chose the descending profile as the reference. All analysis other than LCMM were performed with the SPSS 24.0 software program (SPSS Inc., Chicago, IL, USA) and we considered a p-value < 0.05 as statistically significant.

3. Results:

a. Characteristics of the cohort

Altogether 570 children were included in the analysis, having adequate data on both birth and growth from health care center records. The mean maternal age in the 1st trimester was 32 years (SD 4.7), pre-pregnancy BMI was 31.5 kg/m^2 (5.9), and 33.5% were primiparous. In total 381 of the participant mothers were obese (67%) and 48% (270/558) had GDM in the index pregnancy, and 77% (441) of the mothers entered the study in early pregnancy. Among the 332 children attending the follow-up, we

have data on growth profiles from 311 children, PA data on 247 children, and dietary data on 315 children.

b. Growth profiles

The best-fitting latent class mixed model identified 3 distinct growth profile classes based on ponderal index during the period from birth to 2 years of life (Figure 1). The classes included 14.1%, 25.6% and 60.3% of the children. Each class had an average posterior probability > 0.8, which indicates satisfactory class assignment (0 indicating the worst possible and 1 the best possible class assignment). Relative entropy was 0.72, indicating good level of class discrimination (0 indicating poor, and 1 perfect discrimination).

During the first 6 months of life, each of the profiles show an individual direction, either ascending, intermediate, or descending, and after that they proceed rather parallel until reaching similar levels at 2 years of age. Thereafter the growth profiles continued in a rather linear manner until 5 years of age (Figure 2).

Table 1 presents the characteristics of these children and their mothers. At 5 years of age, ascending group children were heavier, had a higher body fat percentage, ISO-BMI, systolic blood pressure, and waist circumference ($p<0.05$).

c. Growth profiles and metabolic health at 5 years of age

In linear regression, a higher body fat percentage at 5 years of age was detected among the ascending group [B 4.09 (CI 1.60-6.58), p=0.001] and intermediate group children [B 2.27 (CI 0.50-4.03), p=0.012] compared to the descending group (adjusted R2 of this model was 0.034). This was evident even when adjusted with child's age, sex, diet, MVPA, maternal years of education, gestational age at delivery, and pre-pregnancy BMI: ascending group B 3.78 (CI 1.21 – 6.36, p=0.004) and intermediate

group B 2.17 (CI 0.36 – 3.99, p=0.019) (adjusted R2 0.163). There was a similar association with growth profiles and offspring ISO-BMI at 5 years of age: children in the ascending [B 3.12 (CI 1.61 – 4.63, p<0.001] and intermediate groups [B 2.06, CI 0.999 – 3.112, p<0.001] showed higher ISO-BMI at 5 years of age compared to the descending group (adjusted R2 0.057). The results remained similar after adjustment for child's age, sex, diet, PA, maternal years of education, gestational age at delivery, and pre-pregnancy BMI: ascending group: B 3.65 (1.98 – 5.32, p<0.001) and intermediate group: B 2.20 (CI 1.06 – 3.33, p<0.001) (adjusted R2 0.152). These associations remained significant even when adjusted with birth weight SD (data not shown).

d. Association between antenatal and postnatal exposures and growth trajectories

In multinomial logistic regression, using the descending growth group as the reference, belonging to the ascending growth group was associated with higher maternal pre-pregnancy BMI (crude OR 1.07, CI 1.02 – 1.12), younger age in 1st trimester (0.94, CI 0.89 – 0.99), primiparity (3.21, CI 1.80 – 5.72), gestational age at delivery (0.82, CI 0.70 – 0.96), smoking (6.44, CI 1.18 – 35.31), lower 1st trimester GHbA1c (0.17, CI 0.04 – 0.71), lower 3rd trimester fasting glucose (0.356, CI 0.13 – 0.99) and GHbA1c (0.23, CI 0.06 – 0.91), and belonging to the RADIEL intervention group (2.31, CI 1.32 - 4.07). The growth profiles were not associated with GWG, GDM, or years of education (Table 2).

When adjusting with only age and education (model 1), there was an association with the ascending group and higher pre-pregnancy BMI, primiparity, cesarean section, lower gestational age at delivery, and belonging to the intervention group. When adjusted with age, years of education, pre-pregnancy BMI, smoking, and primiparity (model 2), only RADIEL intervention, primiparity, gestational age, and delivery by a cesarean section remained significant. In this fully adjusted model there was no

association with any antenatal exposure such as maternal PA, HFII, fasting glucose, GHbA1c, or triglycerides in any trimester. Higher 3rd trimester HDL, insulin, and HOMA-IR were associated with lower odds of belonging to the ascending growth profile.

We also assessed postnatal factors such as months of exclusive breastfeeding, total duration of breastfeeding, and age at introduction of solid foods. When adjusted with maternal age and education (model 1), exclusive breastfeeding for 3 months or more decreased the odds for belonging to the ascending growth group. Furthermore, natural conception (no IVF) was associated with higher odds of belonging to the intermediate growth group (3.26, 1.01 – 10.58). Neither one of them was no longer statistically significant in the fully adjusted model (model 2).

e. RADIEL lifestyle intervention and growth profiles

To further explore the association between RADIEL intervention and growth profiles, we performed multinomial logistic regression analysis in several sub-groups separately. As a result, lifestyle intervention during pregnancy was associated with higher odds of belonging to the ascending group among multiparous women, obese women (BMI>30), and in pregnancies with female offspring, when adjusted with age, education, and smoking. There was no difference according to GDM diagnosis or among women with early GDM. Furthermore, the association was not different among heterozygous or homozygous carriers of MTNR1b risk allele.

We also calculated a success score based on achieving the pre-defined goals of the RADIEL intervention. There was no association between successful (score ≥3/5) intervention and any of the profiles, but a higher success score was associated with lower odds of belonging to the ascending growth profile (B -.316, OR 0.73, CI 0.532 – 0.999) (model 1).

4. Discussion

This study demonstrated, that ascending early growth is a marker of later adiposity among offspring from high-risk pregnancies, despite their normal gestational age and weight at birth. We identified three distinct early growth profiles; compared to the intermediate or descending profiles, the ascending profile was associated with the highest body fat percentage and ISO-BMI at 5 years of age. This was evident even when adjusted with age, sex, gestational age at delivery, birthweight, offspring diet and objectively measured PA at 5 years of age. Among the antenatal exposures, maternal pre-pregnancy BMI, primiparity, and delivery by cesarean section were associated with the ascending profile after adjusting with maternal age and education. Exclusive breastfeeding for more than 3 months decreased the odds for ascending growth profile. Additionally, achieving the predefined goals of the lifestyle intervention seemed beneficial for the offspring – it was associated with lower odds of ascending growth.

Ending childhood obesity is a high priority of the WHO[25], and currently we are in urgent need of methods for identification of individuals at highest risk, as well as possible periods for efficient intervention. A few studies focusing on rapid early growth have used LCMM to assess non-linear growth trajectories. Among Ethiopian children, ascending growth profile associated with adverse body composition and metabolic markers at 5 years of age[11]. Studies identifying 4 distinct profiles have also demonstrated the high-stable and ascending profiles showing an association with higher BMI at 5 years of age[26] and 9 years of age[10]. These have also been connected to insulin resistance in adolescence[27]. Similar to previous studies, also in our study the ascending growth profile was associated with the highest adiposity and ISO-BMI at 5 years of age.

There have been, however, also conflicting results. In the study by Liu et al [28] high stable BMI trajectory, and not ascending trajectory, was associated with obesity at 6 years. In their study only two BMI measurement points were needed to be included in the analyses and anthropometrics at 6 years were measured by mothers at home. Also, Pryor et al. suggested the high-rising profile to be the most adverse. In their study, however, the measurements started at 6 months of age, therefore

missing the early growth period[29]. One study connected rapid early growth to more lean and not fat mass at 9 years of age[30]. In contrast to our study, these studies have been performed in general populations and it might therefore explain some of the differences, as in our high-risk population the offspring are exposed to increased disease burden, high-risk genetic background, and an obesogenic environment already form fetal period onwards.

Limitations of most of the previous studies include the low number of reliable measurement points during the first year of life and using only BMI as the end-point. Another suggested reason for the conflicting results could be the lack of data on the lifestyle of the offspring. Earlier studies on childhood obesity and cardiometabolic health have shown that also offspring's own PA[31] and diet[32] play a role. Therefore, studies on early growth should assess also confounding factors such as maternal smoking, breastfeeding, offspring PA, and sedentary lifestyle [12]. The important finding in our study is, that early growth profile in high-risk pregnancies is associated with adverse body composition independent of offspring's lifestyle.

One of the most important antenatal factors connected to early growth in previous studies is maternal pre-pregnancy adiposity[10,26,27,29], and our study was no exception. Higher maternal pre-pregnancy BMI was associated with higher odds of accelerating early growth. Obesity is an inflammatory state and has a strong potential to influence offspring health in numerous ways including e.g. genetic, epigenetic, nutritional, and environmental[3,33]. Placentas in pregnancies complicated by obesity display inflammatory changes and increased lipid accumulation[34]. In our study, pre-pregnancy BMI correlated with hs-CRP in all trimesters, suggesting low-grade inflammation, and this in turn correlated with lower birth weight (unpublished results). This might also have an influence in programming the later growth of the offspring. Also, GWG has been connected to childhood adiposity[35], but in our study there was no association with the adverse growth profile.

Delivery by a cesarean section has been connected to numerous adverse maternal and offspring outcomes, including offspring obesity[36]. In our study, cesarean section was associated with

accelerating growth profile, even in the fully adjusted model. Recently the focus of the research has been on the associations between delivery mode and the future microbiome of the offspring. Microbiome then again might have an impact on childhood obesity and future health [37]. There are, however, many confounding factors. Obesity, pregnancy complications, and primiparity all increase the odds for cesarean sections and have a potential of confusing the results [38].

One strong antenatal factor for adverse growth profile in our study was primiparity, which has been demonstrated also earlier[39]. Primiparous women are also at higher risk of pregnancy complications related to immune response, such as pre-eclampsia [40]. There are also studies showing that offspring of primiparous women are smaller at birth[41]. Hypothetically, the immune response of first-time mothers is stronger, consequently interfering with the placental formation. Interestingly, in contrast to our results, Giles at al [10] demonstrated an association with multiparity and the accelerating trajectory.

Another antenatal factor suggesting an immunological background was in our results the association between in vitro fertilization (IVF) and lower odds of intermediate growth. Pregnancies following IVF are at higher risk of complications, e.g. IUGR, cesarean sections, GDM, and hypertensive disorders of pregnancy [42]. Several underlying mechanisms have been suggested behind these associations: in addition to immunology, also the pathophysiology of infertility might confer some reasons, as well as the milieu in IVF, and the hormones used.

In comparison to previous studies, we also had detailed knowledge on the maternal lipid and glucose metabolism throughout pregnancy. Of all time points assessed, only third trimester HDL and insulin resistance showed any association with growth profiles. Higher 3rd trimester HDL associated with lower odds of an accelerating profile, possibly indicating the negative impact of the atherogenic adverse lipid profile seen also previously[43]. This association with lipid levels might be mediated through changes in fuel supply or oxidative stress[44]. Surprisingly we saw no connection between growth profiles and glucose measurements in any trimester. However, a random glucose measurement is not a good marker of glucose levels, and continuous glucose monitoring (CGM) would have given a

better overview of the glucose load of the fetus. Additionally, fetal genetic background seems to have both glucose-dependent and glucose-independent effects on fetal growth[45], including pathways leading to e.g. increased placental transfer of certain fatty acids and amino acids[46]. In our study, similarly to that of Giles et al.[10], GDM was not associated with growth profiles, but the reason behind this might be the high level of treatment of these participants and also this concentrated study population with high incidence of GDM. A recent cohort study actually demonstrated that offspring from current GDM pregnancies have similar birth weight compared to offspring from normoglycemic pregnancies and even lower adiposity, possibly related to efficient treatment [47]. Another reason might lie in the heterogeneous risk groups as there have been suggestions that gestational hyperglycemia influences growth of offspring of non-obese mothers only[48].

Among the postnatal exposures, our results highlight the importance of early feeding as exclusive breastfeeding 3 months or more was associated with a more beneficial growth profile. This has been demonstrated also in previous studies[39,49,50]. Longer duration of breastfeeding has been associated especially with body composition and not BMI at 6 years of age[50]. Also, the content of human milk seems to vary according to the intensity of breastfeeding, with exclusively breastfeeding mothers having milk qualities favoring less weight gain during 3 to 12 months and less adiposity at 12 months of age[51,52]. There have been, however, several studies without similar association [10,26,29,53]. One reason might be the heterogeneous methods of reporting breastfeeding as only duration of any breastfeeding, or differentiating exclusive breastfeeding. Some studies have not taken into account maternal adiposity, which also influences breastfeeding. Additionally, the age at initiation of solid foods has been a focus of interest[10,53], but similarly to previous studies, we did not find any association.

The original RADIEL study was an intervention study aiming at prevention of GDM by lifestyle changes during pregnancy. In this study, the more the participant achieved the predefined goals of the intervention, the lower were the odds of adverse growth. Hence, exercising, improving diet quality, and limiting GWG seems beneficial for the growth of the offspring. The importance of lifestyle interventions in high-risk pregnancies for offspring's future metabolic health has been

emphasized by several earlier studies, and a meta-analysis demonstrated this effect mainly among obese women[54]. The UPBEAT lifestyle intervention decreased offspring adiposity at 6 months of age [55] and the LIMIT lifestyle intervention had minor effects in decreasing fetal adipose tissue [56]. Interestingly, in our study belonging to the intervention group showed an association with the adverse growth profile. There was no association, however, between the profiles and maternal GWG, PA, or diet in any trimester, and no differences between the participants in the intervention and control groups. Hypothetically, recommending these women to change their lifestyle might influence their mental health. Our previously published results, however, show that there was no difference between the groups in self-rated health and quality of life[57,58]. The association could also be varying in heterogenous groups. Different genotypes can influence the individual response to lifestyle changes[59], which was evident also in the RADIEL study: carriers of the MTNR1B risk allele did not respond to the lifestyle intervention[16]. Performing the analyses in subgroups based on MTNR1b risk allele did not modify the results. Pure coincidence or paternal factors, such as lifestyle and genetics, are of course other potential explanations.

The strength of our study lies in the large well-documented cohort with detailed information on lifestyle and metabolic parameters during all trimesters of pregnancy. We also have exceptionally large number of growth measurements during the first 5 years of life, allowing us to use LCMM and investigate the non-linear growth profiles. One special feature of our study is the device-measured PA and dietary information of the offspring at 4-6 years of age. All our participants were of Caucasian origin, therefore limiting the generalizability of our findings. These also were all high-risk pregnancies, and not having a low-risk control group should be considered a limitation of our study. The measurements collected from communal clinics were not standardized, but we assume that the large number of measurement points counteracts this limitation. Also, in the final models, the number of children in the ascending group was rather small, and it may limit the strength of our findings and provide a possible bias. Body composition measurements at birth would have given a better view of the start of the offspring, and CGM would have provided a more detailed profile of pregnancy glucose metabolism. An additional limitation is the lack of paternal anthropometric data.

Despite the limitations acknowledged, our study provides relevant data on the importance of accelerated early growth also in high-risk pregnancies of normal gestational age. Fighting childhood obesity is a high priority of WHO, and identifying those at highest risk allows us to organize enhanced follow-ups and explore feasible interventions. Maternal pre-pregnancy BMI is a crucial target in the fight against childhood obesity and more effort should be steered to lifestyle interventions focusing on women in fertile age and in the postpartum and interpregnancy period. Furthermore, avoiding unnecessary cesareans and supporting exclusive breastfeeding are also relevant. Future studies should investigate the safety of intervening with the early growth trajectories, and whether attenuating the growth curve by e.g. a lifestyle intervention could lead to lower levels of obesity and metabolic morbidity of the offspring. There is already some preliminary data from animal studies suggesting that attenuating the early growth curve by restricted early feeding can alleviate obesity and insulin resistance of the offspring[60]. We need to use all possible means during the first 1000 days to interfere in the intergenerational cycle of obesity and to fight the childhood obesity epidemic. All children deserve a healthy start for their life.

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Data availability

Present informed consents do not allow archiving clinical or register data in open repositories. Data described in the manuscript, code book, and analytic code will be made available upon reasonable request and requests are subject to further review by the national register authority and by the ethical committees.

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Legends for tables and figures

Table 1. Characteristics of participant mothers and children, based on distinct early growth profile groups; ascending, intermediate, and descending.

Table 2. Multinomial logistic regression models on associations between different antenatal and postnatal exposures and the ascending group, using the descending group as the reference.

Figure 1. Growth profiles based on ponderal index (PI) during first 2 years of life

Figure 2. Extended follow-up of ponderal index (PI) development in distinct growth profiles from birth to 5 years of age

Table 1.

	Early growth profile of the offspring			
	Ascending	Intermediate	Descending	p value
Maternal characteristics, n (%)	80 (14%)	344 (60%)	145 (26%)	
Pre-pregnancy BMI	32.9 (6.0)	31.6 (5.8)	30.5 (5.8)	**0.013**
Gestational weight gain (GWG) (kg)	8.7 (6.0)	8.2 (5.8)	8.8 (6.2)	0.677
- Inadequate GWG	21 (33)	93 (37)	36 (33)	0.667
- Adequate GWG	20 (31)	76 (30)	36 (33)	0.885
- Excessive GWG	23 (36)	81 (32)	37 (34)	0.856
Age (years)	31.2 (5.1)	32.0 (4.8)	32.5 (4.3)	0.136
Smoking during pregnancy, n (%)	8 (13)	19 (7)	5 (4)	0.091
Cesarean section, n (%)	27 (34)	78 (23)	27 (19)	**0.032**
Education (years)	15 [12, 15]	15 [12, 17]	15 [12, 17]	0.337
Primiparous, n (%)	41 (51.2)	114 (33.1)	36 (24.7)	**<0.001**
GDM, n (%)	33 (41.3)	164 (49.1)	73 (50.7)	0.367
Preeclampsia, n (%)	7 (8.8)	14 (4.1)	8 (5.5)	0.222
Hepatogestosis, n (%)	4 (5)	2 (0.6)	0	**0.001**
PA in 1st trimester	60 [30, 100]	68 [30, 148]	60 [30, 160]	0.528
PA in 3rd trimester	33 [0, 108]	60 [0, 120]	46 [0, 120]	0.789
HFII 1st trimester	9.7 (0.4)	10.1 (0.19)	10.1 (0.25)	0.633
HFII 3rd trimester	9.8 (0.4)	10.7 (0.18)	10.5 (0.27)	0.110
Offspring characteristics at birth, n (%)	80 (14%)	344 (60%)	145 (26%)	
Birth weight (g)	3419 (636)	3672 (502)	3828 (577)	**<0.001**
Birth height (cm)	50.0 (3.3)	50.6 (2.2)	51.0 (2.3)	**0.010**
Birth weight SD	-0.05 [-0.80, 0.52]	0.26 [-0.44, 0.86]	0.77 [-0.03, 1.18]	**<0.001**
Head circumference (cm)	34.7 (2.3)	35.3 (1.5)	35.5 (1.4)	**0.006**
Sex (boy/girl), n (%)	42 / 38 (52/48)	175 / 169 (51/49)	82 / 64 (56/44)	0.562
Gestational age at delivery (weeks)	39.3 (2.4)	39.9 (1.3)	40.0 (1.9)	**0.005**
Placenta (g)	595 [495, 710]	623 [526, 714]	665 [578, 744]	**0.039**
Child characteristics at 5-year follow-up, n (%)	41 (13%)	195 (63%)	75 (24%)	
Age (years)	5.2 (0.6)	5.0 (0.5)	5.0 (0.5)	0.291
Weight (kg)	21.4 (3.4)	20.4 (3.4)	19.9 (3.0)	**0.008**

Height (cm)	112 (5.3)	111 (5.8)	113 (5.9)	0.134
ISO-BMI (kg/m^2)	24.4 (4.6)	23.4 (4.1)	21.3 (3.2)	**<0.001**
Waist (cm)	56.5 (4.6)	55.2 (4.8)	53.6 (3.2)	**0.003**
Systolic blood pressure (mmHg)	99 (7.7)	99 (7.5)	102 (7.0)	**0.010**
Diastolic blood pressure (mmHg)	62 (6.6)	63 (6.7)	63 (5.8)	0.542
Body fat (%)	19.5 [14.0, 23.7]	16.7 [13.0, 20.8]	14.3 [12.0, 17.3]	**0.001**
Skeletal muscle mass (kg)	8.6 [7.3, 9.2]	8.0 [7.1, 9.0]	7.7 [7.0, 9.4]	0.533
GHbA1c (%)	5.2 (0.2)	5.2 (0.3)	5.3 (0.2)	0.414
Plasma glucose (mmol/L)	5.0 [4.8, 5.2]	5.0 [4.8, 5.2]	5.1 [4.9, 5.4]	0.066
Serum insulin (mU/L)	4.1 [2.3, 5.8]	3.9 [2.1, 7.5]	4.5 [2.5, 8.8]	0.242
Lipids (mml/L)				
- HDL - LDL - KOL - triglycerides	1.5 (0.3) 2.5 (0.6) 4.1 (0.7) 0.8 (0.3)	1.5 (0.3) 2.4 (0.6) 4.0 (0.6) 0.8 (0.3)	1.6 (0.3) 2.4 (0.7) 4.2 (0.7) 0.9 (0.5)	0.231 0.489 0.252 0.302
Exclusive breastfeeding duration (months)	1 [0, 4]	3 [0, 4]	3 [0, 4]	0.209
Breastfeeding duration (months)	11 [4, 14]	10 [5, 14]	11 [6, 13]	0.818
Age at introduction of solids (months)	4 [3, 5]	4 [3, 4]	4 [3, 5]	0.168
Physical activity				
- Daily steps (count)	9517 [8002, 10555]	9209 [8187, 10457]	9545 [7712, 10792]	0.974
- MVPA (min/day)	66 [50, 77]	71 [55, 87]	80 [59, 91]	0.187
Fruit, vegetables, and berries (g/day)	224 [157, 337]	238 [153, 337]	239 [160, 317]	0.878

Values are presented as mean values (with SD), median [with interquartile range], unless otherwise stated.

BMI = body mass index

GDM = gestational diabetes

PA = physical activity

HFII = Healthy Food Intake Index

MVPA = Moderate-to-vigorous physical activity

Table 2.

	Model 1: adjusted for age and education	**Model 2:** adjusted for age, education, smoking, pre-pregnancy BMI, parity
	OR (95% CI)	OR (95%CI)
Pre-pregnancy BMI	**1.06 (1.01 - 1.12)**	1.02 (0.96 – 1.09)
Primiparity	**3.07 (1.68 - 5.62)**	**2.53 (1.22 – 5.25)**
Cesarean section	**2.23 (1.18 - 4.21)**	**2.27 (1.07 – 4.82)**
Gestational age at delivery	**0.83 (0.71 – 0.97)**	**0.74 (0.59 – 0.93)**
Smoking during pregnancy	3.23 (0.98 – 10.66)	2.80 (0.83 – 9.43)
GWG	0.99 (0.94 – 1.04)	1.01 (0.95 – 1.08)
Inadequate GWG	1.09 (0.51 – 2.33)	0.95 (0.39 – 2.29)
GDM	0.69 (0.39 – 1.22)	0.88 (0.46 – 1.69)
Hepatogestosis[a]	**n/a**	n/a
Essential hypertension	1.21 (0.38 – 3.85)	0.83 (0.19 – 3.60)
Pre-eclampsia	1.68 (0.58 – 4.87)	0.93 (0.24 – 3.69)
Triglycerides in 1st trimester	1.66 (0.99 – 2.78)	1.27 (0.68 – 2.38)
Triglycerides in 3rd trimester	1.30 (0.89 – 1.89)	1.33 (0.90 – 1.96)
HDL in 1st trimester	0.77 (0.33 – 1.81)	0.80 (0.29 – 2.17)
HDL in 3rd trimester	**0.34 (0.14 – 0.85)**	**0.37 (0.14 – 0.96)**
LDL in 1st trimester	0.81 (0.52 – 1.25)	0.87 (0.54 – 1.43)
LDL in 3rd trimester	0.91 (0.68 – 1.22)	1.06 (0.78 – 1.43)
HOMA-IR in 1st trimester	0.95 (0.75 – 1.20)	0.78 (0.56 – 1.09)
HOMA-IR in 3rd	0.83 (0.66 – 1.04)	**0.67 (0.51 – 0.90)**
Insulin 1st trimester	0.997 (0.94 – 1.05)	0.96 (0.90 – 1.04)
Insulin 3rd trimester	0.96 (0.92 – 1.02)	**0.92 (0.86 – 0.98)**
Fasting glucose 1st trimester	0.76 (0.38 – 1.52)	0.70 (0.31 – 1.58)
Fasting glucose 3rd trimester	0.51 (0.24 – 1.08)	0.48 (0.21 – 1.07)
GHbA1c in 1st trimester	0.46 (0.16 – 1.31)	0.38 (0.12 – 1.24)
GHbA1c in 3rd trimester	0.55 (0.21 – 1.45)	0.57 (0.20 – 1.61)
Months of exclusive breastfeeding	0.90 (0.78 - 1.03)	0.99 (0.84 – 1.19)
Exclusive breastfeeding for 3 months or more	**0.46 (0.26 – 0.83)**	0.60 (0.30 -1.24)
Age at introduction of solid foods	1.14 (0.83 – 1.56)	1.39 (0.97 – 2.99)
Intervention group	**2.56 (1.44 – 4.57)**	**2.89 (1.49 – 5.59)**

Successful intervention (filling 3/5 goals)	0.52 (0.18 – 1.49)	0.73 (0.25 – 2.18)
Success score (0-5 points)	**0.73 (0.53 – 0.999)**	0.79 (0.57 – 1.11)
PA in 1st trimester	0.998 (0.99 – 1.00)	0.998 (0.99 – 1.00)
PA in 3rd trimester	0.998 (0.99 – 1.00)	0.997 (0.99 – 1.00)
HFII 1st trimester	0.96 (0.87 – 1.07)	0.97 (0.86 – 1.09)
HFII 3rd trimester	0.93 (0,84 – 1.04)	0.98 (0.87 – 1.10)

[a] 0 cases in reference group

GDM= gestational diabetes mellitus

GWG= gestational weight gain

HOMA-IR= Homeostatic model assessment for insulin resistance

PA= physical activity

HFII= healthy food intake index

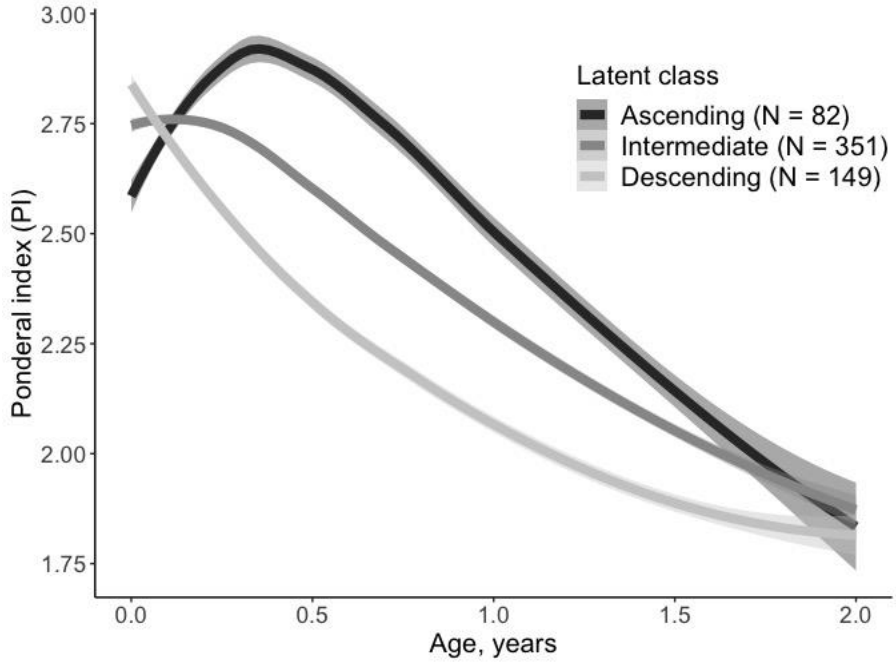

Figure 1.

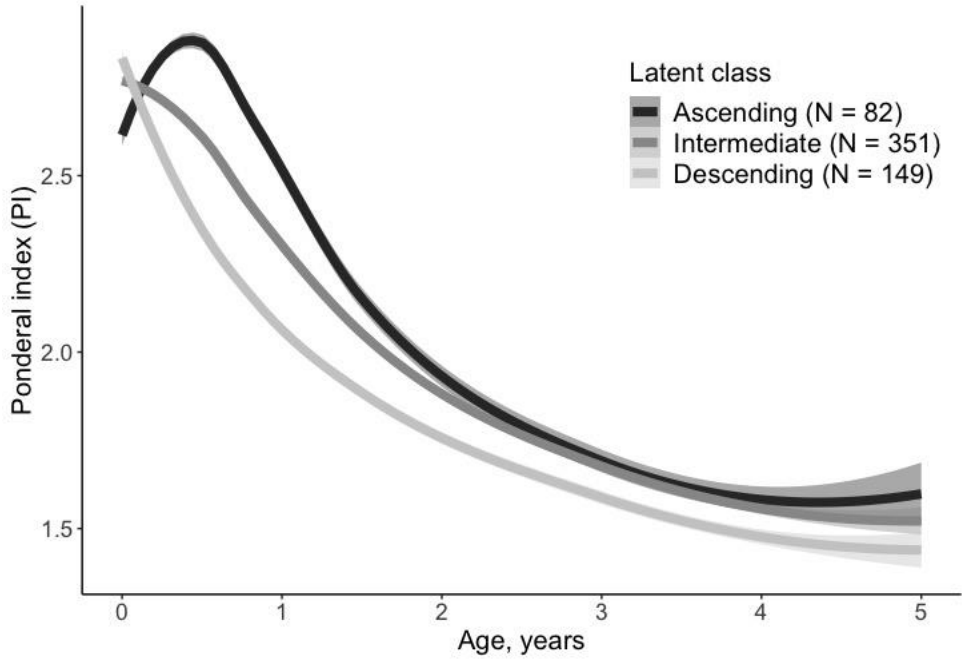

Figure 2.