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ARTICLE

Pediatrics

Maternal body mass index, gestational weight gain, and childhood abdominal, pericardial, and liver fat assessed by magnetic resonance imaging

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Abstract

Background/Objectives Maternal obesity and excessive gestational weight gain are associated with an increased risk of obesity in offspring. It remains unclear whether maternal adiposity also affects organ fat, which has important adverse cardiometabolic health consequences and whether the associations reflect intrauterine causal mechanisms. We examined the associations of parental pre-pregnancy body mass index (BMI) and gestational weight gain with general, abdominal, pericardial, and liver fat in 10-year-old children.

Subjects/Methods In a population-based prospective cohort study among 2354 parents and their children, we obtained pre-pregnancy maternal and paternal BMI and gestational weight gain and offspring BMI, fat mass index (total fat/height^4) by dual-energy X-ray absorptiometry, and subcutaneous fat index (subcutaneous fat/height^4), visceral fat index (visceral fat/height^3), pericardial fat index (pericardial fat/height^3), and liver fat fraction by magnetic resonance imaging (MRI) at 10 years.

Results A 1-standard deviation score (SDS) higher maternal pre-pregnancy BMI was associated with higher childhood BMI (difference 0.32 (95% confidence interval (CI) 0.28, 0.36) SDS), fat mass index (difference 0.28 (95% CI 0.24, 0.31) SDS), subcutaneous fat index (difference 0.26 (95% CI 0.22, 0.30) SDS), visceral fat index (difference 0.24 (95% CI 0.20, 0.28) SDS), pericardial fat index (difference 0.12 (95% CI 0.08, 0.16) SDS), and liver fat fraction (difference 0.15 (95% CI 0.11, 0.19) SDS). After conditioning each MRI adiposity measure on BMI at 10 years, higher maternal pre-pregnancy BMI remained associated with higher childhood subcutaneous and visceral fat indices. Smaller but not statistically different effect estimates were observed for paternal BMI. Gestational weight gain was not consistently associated with organ fat.

Conclusions Higher maternal pre-pregnancy BMI, but not gestational weight gain, was associated with higher general and organ fat. Similar associations of pre-pregnancy maternal and paternal BMI with offspring adiposity suggest a role of family shared lifestyle factors and genetics.

Introduction

Maternal obesity is associated with several short-term and long-term adverse health effects, including an increased risk of obesity in the offspring [1, 2]. It has been hypothesized that maternal obesity is related to an increased placental transfer of nutrients to the fetus, which might affect the development of adipocytes, the appetite control system, and the energy metabolism [3]. However, the associations of maternal obesity with offspring outcomes might also be explained by shared family-based lifestyle or genetic factors. To help disentangling the underlying mechanisms, previous studies have compared the strength of associations of maternal and paternal body mass index (BMI) with

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offspring BMI and total fat mass and have shown conflicting results [4–6]. Stronger associations for maternal BMI with offspring outcomes suggest that intrauterine programming effects might be part of the underlying mechanisms, whereas similar or stronger associations for paternal BMI suggest a role for lifestyle or genetic factors.

Although many studies reported the associations between maternal and offspring obesity, it remains unclear whether maternal obesity also affects body fat distribution in the offspring. Information about body fat distribution is important since, as compared to BMI, body fat distribution, and, more specifically, excess visceral, heart, and liver fat, may be better indicators of adverse cardiometabolic health [7–10]. Previous studies have reported that higher maternal BMI is associated with higher abdominal and liver fat in newborns [11, 12]. Maternal pre-pregnancy obesity was also associated with higher visceral fat mass in Greek schoolchildren [13]. Whether these findings reflect an effect on specific fat accumulation or are just explained by general adiposity remains unknown. Next to maternal pre-pregnancy BMI, gestational weight gain may also affect childhood body fat distribution, but evidence remains scarce and not consistent [14–17]. Thus, a better understanding of the influence of maternal adiposity on body fat distribution in offspring, and the underlying mechanisms, is important for development of preventive strategies.

We examined, in a population-based prospective cohort study among 2354 mothers, fathers, and their children, the associations of parental pre-pregnancy BMI and gestational weight gain with offspring BMI, fat mass index measured by dual-energy X-ray absorptiometry (DXA), and subcutaneous fat index, visceral fat index, pericardial fat index, and liver fat fraction measured by magnetic resonance imaging (MRI) at 10 years. We explored whether any association with organ-specific fat measures reflects specific accumulation, or just reflects general adiposity.

Subjects and methods

Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early pregnancy onwards in Rotterdam, the Netherlands [18]. The study was approved by the Medical Ethical Committee of the Erasmus MC, Rotterdam (MEC 198.782/2001/31). Written informed consent was obtained from parents [18]. Pregnant women were enrolled between 2001 and 2005. Of all the eligible children in the study area, 61% participated at birth in the study. In total, 5706 mothers and their singleton children attended the study visit at 10 years, of whom information about pre-pregnancy BMI was available in 4298 subjects. Further, we excluded children without any organ-specific fat measures assessed by MRI ($n = 1944$). Thus, the population for analysis was 2354 mothers and their children (Supplementary Fig. 1).

Parental anthropometrics

Maternal pre-pregnancy BMI was calculated from pre-pregnancy weight obtained by a questionnaire and height measured at enrollment. Paternal height and weight were measured at enrollment and BMI was calculated. Maternal pre-pregnancy BMI was categorized into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥30.0 kg/m^2). For the parental BMI comparison analyses, pre-pregnancy maternal and paternal BMI were categorized into normal weight (18.5–24.9 kg/m^2) and overweight/obesity (≥25.0 kg/m^2) and combined into four groups: maternal and paternal normal weight; only maternal overweight/obesity; only paternal overweight/obesity; and maternal and paternal overweight/obesity. As previously described, we measured maternal weight at early, mid, and late pregnancy (median 13.2 weeks of gestation (95% range 9.8–18.9), median 30.1 weeks of gestation (95% range 20.5–31.4), and median 39.0 weeks of gestation (95% range 32.8–42.0), respectively) [16]. Information about maximum weight during pregnancy was assessed by a questionnaire 2 months after delivery. We calculated maximum weight gain during pregnancy as the difference between maximum weight and pre-pregnancy weight. Further, we divided maximum weight gain by gestational age at birth to obtain the maximum weight gain per week. Maximum gestational weight gain was also classified as insufficient, sufficient, and excessive weight gain in relation to maternal pre-pregnancy BMI according to the Institute of Medicine guidelines [19].

Measures of adiposity at 10 years

We measured child's height and weight without shoes and heavy clothing and calculated BMI (kg/m^2). We calculated sex-adjusted and age-adjusted standard deviation scores (SDS) of childhood BMI based on Dutch reference growth charts (Growth Analyzer 4.0, Dutch Growth Research Foundation) [20]. We measured total body fat mass using a DXA scanner (iDXA, GE-Lunar, 2008, Madison, WI, USA, enCORE software v.12.6), according to standard procedures [21]. Previous studies have validated DXA against computed tomography for body fat assessment [22].

Measures of organ fat at 10 years were obtained from MRI scans [18]. MRI has been described as an accurate and reproducible technique and has been considered the gold standard for the measurement of intra-abdominal and organ fat deposition [23]. All children were scanned using a 3.0

Tesla MRI (Discovery MR 750w, GE Healthcare, Milwaukee, WI, USA) for body fat imaging using standard imaging and positioning protocols, while performing expiration breath-hold maneuvers of maximum 11 s duration. They wore light clothing without metal objects while undergoing the body scan [24]. Pericardial fat imaging in short axis orientation was performed using an electrocardiogram-triggered black-blood-prepared thin slice single shot fast spin echo acquisition with multi-breath-hold approach. An axial 3-point Dixon acquisition for fat and water separation (IDEAL IQ) was used for liver fat imaging. This technique also enables the generation of liver fat fraction images [25]. An axial abdominal scan from lower liver to pelvis and a coronal scan centered at the head of the femurs were performed with a 2-point DIXON acquisition (LavaFlex).

The obtained fat scans were subsequently analyzed by the Precision Image Analysis company (PIA, Kirkland, WA, USA), using the sliceOmatic (TomoVision, Magog, Canada) software package. All extraneous structures and any image artifacts were removed manually [23]. Pericardial fat included both epicardial and paracardial fat directly attached to the pericardium, ranging from the apex to the left ventricular outflow tract. Total subcutaneous and visceral fat volumes were generated by summing the volumes of the liver, abdominal, and, if necessary, the femoral fat-only scans, encompassing the fat volume ranging from the dome of the liver to the superior part of the femoral head. Fat masses were obtained by multiplying the total volumes by the specific gravity of adipose tissue, 0.9 g/ml. Liver fat fraction was determined by taking four samples of at least 4 cm^2 from the central portion of the hepatic volume. Subsequently, the mean signal intensities were averaged to generate an overall mean liver fat fraction estimation.

To create measures of general and organ fat independent of height at 10 years, we estimated the optimal adjustment by log–log regression analyses and subsequently we divided total and subcutaneous fat mass by $height^4$ (fat mass index and subcutaneous fat index), and visceral and pericardial fat mass by $height^3$ (visceral and pericardial fat indices) (more details are given in Supplementary Methods) [26, 27].

Covariates

Information on maternal and paternal age, educational level, and ethnicity, as well as maternal parity and smoking habits was obtained by questionnaires during pregnancy. Information on child's sex was obtained from medical records. Information on breastfeeding duration and timing of introduction of solid foods was obtained by questionnaires in infancy, and information on the average television watching time was obtained by questionnaires at the age of 10 years.

Statistical analysis

First, we used linear regression models to examine the associations of maternal and paternal pre-pregnancy BMI and maximum gestational weight gain, continuously and using clinical categories, with measures of adiposity (BMI, fat mass index, subcutaneous, visceral and pericardial fat indices, and liver fat fraction) at 10 years. Second, we examined the independent associations of maternal pre, early, mid, and late pregnancy weight with the childhood outcomes using conditional linear regression analyses to account for the correlations between the weight measurements [28]. For these models, we obtained standardized residuals for each weight from the regression of a maternal weight at a specific time point on prior maternal weights. These variables correspond to the difference between the actual weight and the expected weight based on prior weights and thus are statistically independent from each other and can be included simultaneously in the regression models [28]. Third, we used conditional regression analyses to assess whether the associations of maternal and paternal pre-pregnancy BMI and gestational weight gain with measures of organ fat at 10 years were independent of BMI at 10 years. We used as outcomes the standardized residuals for each measure of organ fat at 10 years obtained from the regression of those outcomes on BMI [28]. For all analyses, we used a basic model including child's sex and age at outcome measurements, and a confounder model, which additionally included covariates. We included covariates in the models if they were strongly associated with parental anthropometrics and childhood adiposity in our study, or if they changed the effect estimates substantially (>10%). We log-transformed the non-normally distributed childhood DXA and MRI adiposity measures. We constructed SDS ((observed value −mean)/SD) of the sample distribution for all continuous exposures and DXA and MRI outcomes to enable comparisons of effect sizes. No statistical interactions between maternal pre-pregnancy BMI and gestational weight gain, and between maternal pre-pregnancy BMI and paternal BMI were observed in these associations. We also tested for statistical interaction between maternal pre-pregnancy BMI and gestational weight gain with child's sex since body fat development and body fat distribution pattern during childhood is known to differ between boys and girls, but no significant interaction was observed. Since the maximum gestational weight gain was self-reported, sensitivity analyses using weight gain measured until late pregnancy were performed. Missing values in covariates (ranging from 0 to 28%) were multiple imputed by using Markov chain Monte Carlo approach. Five imputed datasets were created and analyzed together. All statistical analyses were performed using the Statistical Package of Social

Table 1 Characteristics of mothers, fathers, and their children[a]

Characteristics	Total group ($n = 2354$)	Maternal underweight ($n = 97$)	Maternal normal weight ($n = 1639$)	Maternal overweight ($n = 451$)	Maternal obesity ($n = 167$)	p value[b]
Maternal characteristics						
Age, mean (SD) (years)	31.0 (4.8)	29.0 (5.3)	31.1 (4.7)	31.0 (4.7)	30.3 (4.8)	<0.001
Education, *n* (%)						
Low	160 (6.9)	7 (7.3)	87 (5.4)	53 (12.1)	13 (8.2)	<0.001
Medium	935 (40.5)	41 (42.7)	594 (36.8)	200 (45.8)	100 (63.3)	
High	1211 (52.5)	48 (50.0)	934 (57.8)	184 (42.1)	45 (28.5)	
Ethnicity, *n* (%)						
European	1532 (65.3)	60 (61.9)	1135 (69.4)	253 (56.6)	84 (50.3)	<0.001
Non-European	815 (34.7)	37 (38.1)	501 (30.6)	194 (43.4)	83 (49.7)	
Parity, *n* (%)						
Nulliparous	1419 (60.3)	55 (56.7)	1036 (63.2)	237 (52.5)	91 (54.5)	<0.001
Multiparous	934 (39.7)	42 (43.3)	602 (36.8)	214 (47.5)	76 (45.5)	
Pre-pregnancy body mass index, median (95% range) (kg/m^2)	22.5 (18.0–34.9)	17.9 (15.8–18.5)	21.7 (18.8–24.8)	26.7 (25.1–29.8)	33.0 (30.1–44.7)	<0.001
Maximum gestational weight gain, mean (SD) (kg)	14.8 (5.8)	15.2 (5.5)	15.3 (5.2)	14.3 (6.3)	11.0 (9.0)	<0.001
Gestational weight gain clinical categories (IOM criteria), *n* (%)						
Insufficient gestational weight gain	299 (20.5)	16 (31.4)	236 (22.2)	25 (9.6)	22 (25.3)	<0.001
Sufficient gestational weight gain	505 (34.5)	25 (49.0)	407 (38.3)	56 (21.5)	17 (19.5)	
Excessive gestational weight gain	658 (45.0)	10 (19.6)	421 (39.6)	179 (68.8)	48 (55.2)	
Weight in early pregnancy, mean (SD) (kg)	69.0 (12.9)	53.6 (9.2)	64.3 (7.2)	78.4 (8.7)	97.0 (14.2)	<0.001
Weight in mid pregnancy, mean (SD) (kg)	76.0 (12.6)	61.7 (8.8)	72.0 (8.4)	84.8 (9.5)	100.4 (13.2)	<0.001
Weight in late pregnancy, mean (SD) (kg)	81.6 (12.5)	66.5 (6.2)	78.0 (9.0)	91.4 (10.5)	105.6 (13.2)	<0.001
Smoking during pregnancy, *n* (%)						
Yes	504 (22.3)	27 (28.4)	336 (21.3)	104 (24.5)	37 (23.0)	0.238
No	1757 (77.7)	68 (71.6)	1244 (78.7)	321 (75.5)	124 (77.0)	
Paternal characteristics						
Age, mean (SD) (years)	33.6 (5.3)	31.9 (4.9)	33.7 (5.3)	33.6 (5.3)	33.7 (6.5)	0.052
Education, *n* (%)						
Low	83 (4.9)	4 (6.3)	50 (4.1)	20 (6.6)	9 (9.6)	<0.001
Medium	652 (38.6)	20 (31.7)	428 (34.9)	150 (49.3)	54 (57.4)	
High	953 (56.5)	39 (61.9)	749 (61.0)	134 (44.1)	31 (33.0)	
Ethnicity, *n* (%)						
European	1383 (74.4)	52 (70.3)	1020 (76.5)	233 (69.1)	78 (67.8)	0.011
Non-European	477 (25.6)	22 (29.7)	314 (23.5)	104 (30.9)	37 (32.2)	
Body mass index, mean (SD) (kg/m^2)	25.3 (3.3)	23.4 (2.8)	25.0 (3.1)	26.2 (3.3)	27.5 (4.5)	<0.001
Body mass index clinical categories, *n* (%)						
Underweight	9 (0.5)	1 (1.4)	6 (0.4)	1 (0.3)	1 (0.8)	<0.001
Normal weight	945 (50.3)	53 (71.6)	726 (54.0)	128 (37.8)	38 (31.7)	
Overweight	771 (41.1)	19 (25.7)	521 (38.8)	180 (53.1)	51 (42.5)	
Obesity	152 (8.1)	1 (1.4)	91 (6.8)	30 (8.8)	30 (25.0)	

Table 1 (continued)

Characteristics	Total group ($n = 2354$)	Maternal underweight ($n = 97$)	Maternal normal weight ($n = 1639$)	Maternal overweight ($n = 451$)	Maternal obesity ($n = 167$)	p value[b]
Birth and infant characteristics						
Child's sex, *n* (%)						
Boys	1151 (48.9)	52 (53.6)	812 (49.5)	206 (45.7)	81 (48.5)	0.389
Girls	1203 (51.1)	45 (46.4)	827 (50.5)	245 (54.3)	86 (51.5)	
Breastfeeding duration, median (95% range) (months)	3.5 (0.0–12.0)	2.5 (0.0–12.0)	3.5 (0.0–12.0)	3.5 (0.0–12.0)	1.5 (0.0–12.0)	<0.001
Introduction of solid foods, *n* (%)						
<3 months	123 (7.0)	6 (10.0)	68 (5.4)	33 (10.4)	16 (13.6)	0.002
3–6 months	1435 (81.7)	47 (78.3)	1044 (82.7)	251 (79.2)	93 (78.8)	
>6 months	199 (11.3)	7 (11.7)	150 (11.9)	33 (10.4)	9 (7.6)	
Childhood characteristics						
Age, mean (SD) (years)	9.8 (0.3)	9.9 (0.4)	9.8 (0.3)	9.8 (0.4)	9.9 (0.4)	0.012
Television watching time, *n* (%)						
<2 h per day	1342 (70.0)	60 (82.2)	996 (72.5)	221 (64.4)	65 (50.8)	<0.001
≥2 h per day	575 (30.0)	13 (17.8)	377 (27.5)	122 (35.6)	63 (49.2)	
Body mass index, mean (SD) (kg/m^2)	17.5 (2.6)	16.2 (2.1)	17.1 (2.3)	18.5 (2.9)	20.0 (3.5)	<0.001
Total fat mass, median (95% range) (g)	8451 (4549–21,235)	7268 (3782–17,498)	8003 (4549–19,478)	9749 (4829–23,547)	13,014 (4791–31,236)	<0.001
Subcutaneous fat mass, median (95% range) (g)	1297 (603–5226)	1063 (539–4516)	1210 (601–4632)	1638 (656–5994)	2335 (738–6032)	<0.001
Visceral fat mass, median (95% range) (g)	365 (163–1004)	285 (128–800)	350 (159–905)	416 (176–1119)	494 (233–1305)	<0.001
Pericardial fat mass, median (95% range) (g)	10.6 (4.6–22.6)	9.4 (3.5–18.2)	10.4 (4.4–21.9)	11.1 (5.2–23.5)	13.3 (5.5–25.1)	<0.001
Liver fat fraction, median (95% range) (%)	2.0 (1.2–5.2)	1.9 (1.1–5.1)	2.0 (1.2–4.7)	2.1 (1.3–6.0)	2.3 (1.4–9.3)	<0.001

IOM Institute of Medicine, *SD* standard deviation

[a]Values are observed data and represent means (SD), medians (95% range), or number of subjects (valid %)

[b]Differences in subject characteristics between groups were evaluated using one-way ANOVA tests for continuous variables and χ^2 tests for proportions

Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Subject characteristics

Table 1 shows the subject characteristics. In our sample, 26.3% of mothers and 49.2% of fathers had overweight/obesity and 45.0% of mothers gained excessive weight during pregnancy. Non-response analyses showed that parents of children with MRI follow-up data available were slightly older and had a higher educational level, and mothers were more likely to be non-smokers (p values <0.05). No differences were observed for maternal pre-pregnancy BMI and gestational weight gain and paternal BMI (Supplementary Table 1). Supplementary Table 2 shows that the correlation coefficients of BMI and fat mass index with subcutaneous and visceral fat indices are moderate to strong and higher than the correlation coefficients with pericardial fat index and liver fat fraction.

Maternal and paternal BMI and childhood organ fat measures

Table 2 shows that a 1-SDS higher maternal pre-pregnancy BMI was associated with higher childhood BMI (difference 0.32 (95% confidence interval (CI) 0.28, 0.36) SDS), fat mass index (difference 0.28 (95% CI 0.24, 0.31) SDS), subcutaneous fat index (difference 0.26 (95% CI 0.22, 0.30)

Table 2 Maternal BMI and childhood general and organ fat measures[a]

	Measures of adiposity at 10 years in SDS[b]					
	BMI ($n = 2354$)	Fat mass index ($n = 2339$)	Subcutaneous fat index ($n = 2049$)	Visceral fat index ($n = 2052$)	Pericardial fat index ($n = 2123$)	Liver fat fraction ($n = 2319$)
BMI (kg/m^2 in SDS)	0.32 (0.28, 0.36)*	0.28 (0.24, 0.31)*	0.26 (0.22, 0.30)*	0.24 (0.20, 0.28)*	0.12 (0.08, 0.16)**	0.15 (0.11, 0.19)*
Underweight (<18.5 kg/m^2)	−0.49 (−0.69, −0.29)*	−0.32 (−0.50, −0.14)*	−0.31 (−0.50, −0.12)*	−0.37 (−0.58, −0.17)*	−0.26 (−0.47, −0.05)**	−0.17 (−0.37, 0.04)
Normal weight (18.5 – 24.9 kg/m^2)	Reference	Reference	Reference	Reference	Reference	Reference
Overweight (25.0–29.9 kg/m^2)	0.46 (0.36, 0.56)*	0.39 (0.30, 0.48)*	0.40 (0.30, 0.50)*	0.35 (0.24, 0.45)*	0.15 (0.04, 0.26)*	0.19 (0.09, 0.30)*
Obesity (≥30.0 kg/m^2)	0.88 (0.73, 1.04)*	0.81 (0.66, 0.95)*	0.76 (0.61, 0.92)*	0.69 (0.52, 0.86)*	0.42 (0.24, 0.59)*	0.45 (0.28, 0.61)*

	MRI measures of adiposity at 10 years in SDS conditional on BMI[c]			
	Subcutaneous fat index ($n = 2049$)	Visceral fat index ($n = 2052$)	Pericardial fat index ($n = 2123$)	Liver fat fraction ($n = 2319$)
BMI (kg/m^2 in SDS)	0.05 (0.01, 0.09)**	0.07 (0.03, 0.11)*	0.02 (−0.02, 0.07)	0.03 (−0.01, 0.07)
Underweight (<18.5 kg/m^2)	0.09 (−0.09, 0.28)	−0.12 (−0.33, 0.10)	−0.10 (−0.31, 0.11)	0.02 (−0.19, 0.23)
Normal weight (18.5–24.9 kg/m^2)	Reference	Reference	Reference	Reference
Overweight (25.0–29.9 kg/m^2)	0.12 (0.03, 0.22)**	0.13 (0.02, 0.24)**	0.02 (−0.09, 0.13)	0.02 (−0.09, 0.13)
Obesity (≥30.0 kg/m^2)	0.26 (0.10, 0.41)*	0.24 (0.07, 0.42)*	0.16 (−0.01, 0.34)	0.12 (−0.04, 0.29)

SDS standard deviation scores

*p value <0.01, **p value <0.05

[a]Estimates are based on multiple imputed data. Model includes child's sex and age at outcome measurements (except for sex-adjusted and age-adjusted BMI SDS), maternal age, educational level, ethnicity, parity, and smoking habits during pregnancy, and child's breastfeeding duration, timing of introduction of solid foods, and television watching time. Results from the basic model are given in Supplementary Table 3

[b]Values are regression coefficients (95% confidence intervals) from linear regression models that reflect differences in childhood outcomes in SDS per SDS change in maternal pre-pregnancy BMI or for BMI clinical groups as compared to the reference group (normal weight)

[c]Values are regression coefficients (95% confidence intervals) from linear regression models that reflect differences in the standardized residuals of the childhood outcomes (obtained by conditional regression analyses on BMI at 10 years) per SDS change in maternal pre-pregnancy BMI or for BMI clinical groups as compared to the reference group (normal weight)

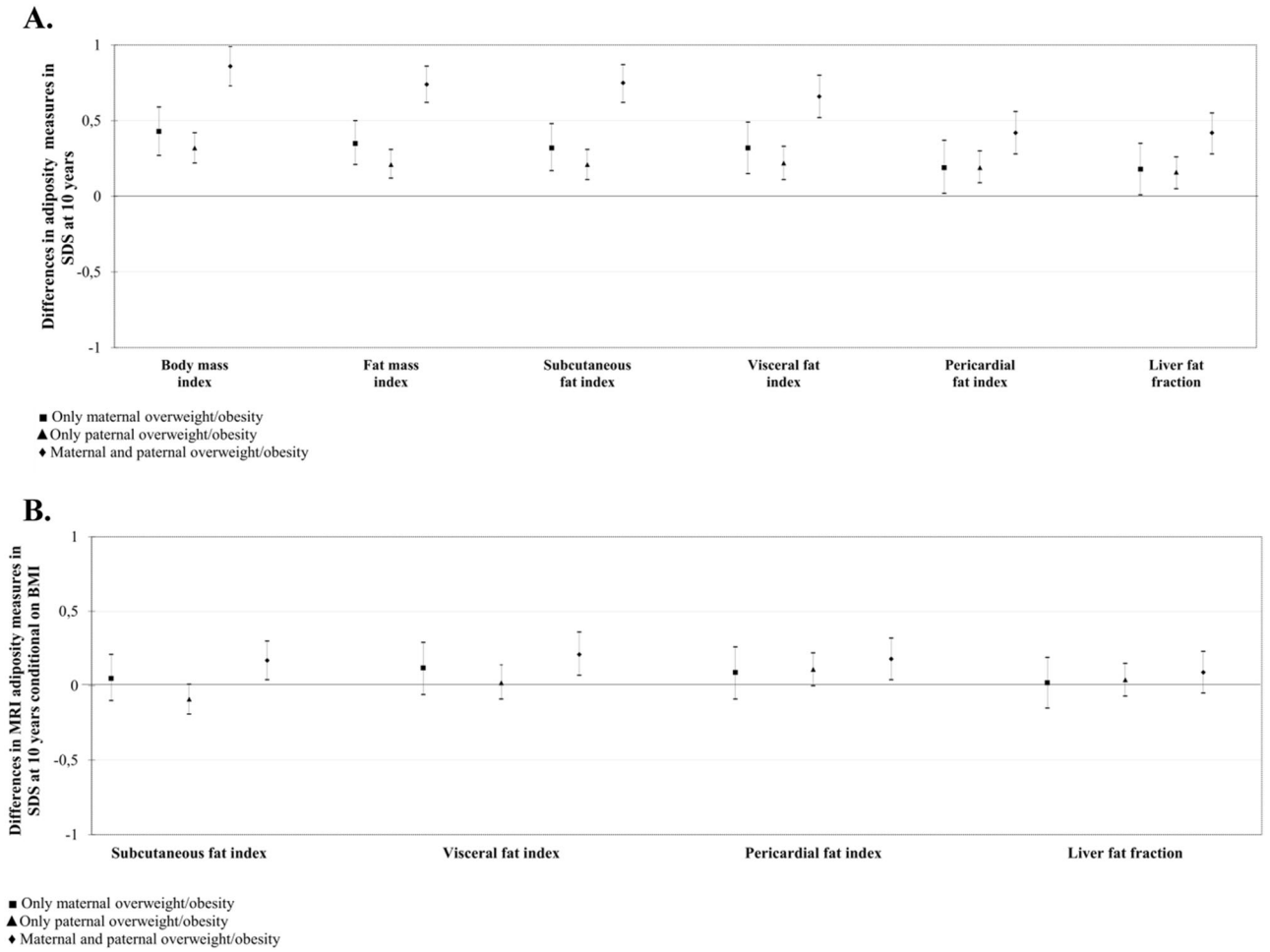


Fig. 1 Parental body mass index and childhood general and organ fat measures ($n = 1795$). Estimates are based on multiple imputed data. Model includes child's sex and age at outcome measurements (except for sex-adjusted and age-adjusted body mass index SDS), parental age, educational level, and ethnicity, parity, maternal smoking habits during pregnancy, and child's breastfeeding duration, timing of introduction of solid foods, and television watching time. Results from the basic model are given in Supplementary Fig. 2. Values in **a** are regression coefficients (95% confidence intervals) from linear regression models that reflect differences in childhood outcomes in SDS for parental body mass index clinical groups as compared to the reference group (maternal and paternal normal weight). Values in **b** are regression coefficients (95% confidence intervals) from linear regression models that reflect differences in the standardized residuals of the childhood outcomes (obtained by conditional regression analyses on body mass index at 10 years) for parental body mass index clinical groups as compared to the reference group (maternal and paternal normal weight). SDS standard deviation scores

SDS), visceral fat index (difference 0.24 (95% CI 0.20, 0.28) SDS), pericardial fat index (difference 0.12 (95% CI 0.08, 0.16) SDS), and liver fat fraction (difference 0.15 (95% CI 0.11, 0.19) SDS). As compared to maternal pre-pregnancy normal weight, maternal pre-pregnancy underweight was associated with lower fat measures, whereas maternal pre-pregnancy overweight and obesity were associated with higher fat measures in childhood (p values <0.05). After conditioning each MRI measure of adiposity on BMI at 10 years, higher maternal pre-pregnancy BMI remained associated with higher childhood subcutaneous and visceral fat indices (p values <0.05).

Figure 1a shows that, as compared to normal weight parents, those in which only mothers or only fathers were overweight/obese had children with higher levels of all adiposity measures at the age of 10 years (p values <0.05). The associations tended to be stronger when only mothers rather than only fathers were overweight/obese but had overlapping CI and thus seem not to be statistically different. The strongest associations were observed for children in which both parents were overweight/obese. After conditioning each MRI measure of child's adiposity on BMI at 10 years (Fig. 1b), no significant associations were observed for couples in which only mothers or only fathers were overweight/obese. Those couples in which both parents were overweight/obese had children with higher subcutaneous, visceral, and pericardial fat indices (p values <0.05).

Maternal gestational weight gain and childhood organ fat measures

Table 3 shows that a 1-SDS higher maximum weight gain per week was only associated with higher childhood BMI (difference 0.08 (95% CI 0.03, 0.13) SDS). Excessive weight gain, as compared to sufficient weight gain, was associated with higher childhood BMI, fat mass index, and subcutaneous and visceral fat indices (p values <0.05). After conditioning each MRI measure of adiposity on BMI at 10 years, a 1-SDS higher maximum weight gain per week was associated with lower childhood subcutaneous fat index (p value <0.05). Similar results were observed when using maternal weight gain measured until late pregnancy (Supplementary Table 5). Figure 2a shows that independent of weights in other periods, higher pre-pregnancy weight was associated with higher levels of all adiposity measures (p values <0.05). Higher early pregnancy weight was associated with higher BMI and fat mass index, but not with organ fat measures at 10 years. No associations were observed for mid and late pregnancy weight. After conditioning each MRI measure of adiposity on BMI at 10 years (Fig. 2b), higher pre-pregnancy weight remained associated with higher subcutaneous and visceral fat indices. No associations were observed for early, mid, and late pregnancy weight.

Discussion

We observed, in this population-based prospective cohort study, that higher maternal pre-pregnancy BMI was associated with higher BMI, fat mass index, subcutaneous, visceral and pericardial fat indices, and liver fat fraction at 10 years. The associations of maternal pre-pregnancy BMI with offspring subcutaneous and visceral fat indices seemed to be independent of offspring BMI. Total and period-specific gestational weight gain were not consistently associated with organ fat measures.

Interpretation of main findings

Maternal obesity is a major public health concern [29]. A meta-analysis of published studies showed an increased risk of overweight in offspring of mothers with overweight and obesity, as compared to offspring of mothers with normal weight [1]. In the same cohort as the current study, we have previously reported that maternal overweight and obesity were strongly associated with increased risks of overweight and obesity in the offspring aged 4 and 6 years [6, 30]. In the present study, maternal pre-pregnancy overweight and obesity were associated with higher BMI and fat mass index at 10 years.

Large cohort studies such as the Framingham Heart Study and the Jackson Heart Study have reported that excess visceral, pericardial, and liver fat depositions are related to various cardiometabolic abnormalities in adults [7–10, 31]. As compared to visceral abdominal fat, excess subcutaneous abdominal fat was less strongly associated with an adverse cardiometabolic risk profile in adults [8, 31]. In 105 healthy mother–newborn pairs, higher maternal BMI was associated with higher infant abdominal fat, independently of weight, and higher intrahepatocellular lipid content [11]. In another study among 25 newborns, infants born to obese mothers with gestational diabetes had higher intrahepatocellular fat compared with infants born to normal weight mothers [12]. Maternal pre-pregnancy obesity was also associated with higher visceral fat mass levels in 1228 Greek children aged 9–13 years [13]. In the present study, higher maternal pre-pregnancy BMI was associated with higher subcutaneous, visceral and pericardial fat indices, and liver fat fraction at 10 years. The associations of maternal pre-pregnancy BMI with offspring subcutaneous and visceral fat indices seemed to be independent of offspring BMI. This means that higher maternal pre-pregnancy BMI is associated with a specific accumulation of fat in abdominal depots that is not a result of general adiposity. We did not observe differences in the results when we conditioned on fat mass index instead of BMI. These results are not in line with those of our previous study in 6-year-old children, suggesting that higher maternal pre-pregnancy BMI was not associated with subcutaneous and preperitoneal abdominal fat measured by ultrasound, independently of child's BMI [6]. The differences in results may be due to different ages or different imaging methods.

Previously, we reported that higher paternal BMI was associated with higher BMI but was not associated with subcutaneous and preperitoneal abdominal fat at the age of 6 years, independently of child's BMI [6]. In the present study, paternal overweight was associated with higher BMI, fat mass index, and organ fat measures in children aged 10 years. The associations observed with MRI adiposity measures were not independent of BMI at 10 years. Our results suggest that both maternal and paternal BMI before pregnancy may be risk factors for offspring cardiometabolic health by influencing general and organ fat accumulation in later life. Previous studies comparing the associations of maternal and paternal BMI with childhood BMI and total fat mass have shown conflicting results [4–6]. A recent study using genetic variants in a Mendelian randomization approach found little evidence to support strong causal intrauterine effects of maternal BMI on offspring adiposity [32]. Although we observed a tendency for stronger associations of maternal pre-pregnancy BMI, as compared to paternal BMI, with general and abdominal fat measures, the differences between the maternal and

Table 3 Maternal gestational weight gain and childhood general and organ fat measures[a]

	Measures of adiposity at 10 years in SDS[b]					
	BMI ($n = 1462$)	Fat mass index ($n = 1451$)	Subcutaneous fat index ($n = 1287$)	Visceral fat index ($n = 1288$)	Pericardial fat index ($n = 1336$)	Liver fat fraction ($n = 1444$)
Maximum weight gain per week (kg in SDS)	0.08 (0.03, 0.13)*	0.02 (−0.03, 0.06)	0.01 (−0.04, 0.05)	0.03 (−0.02, 0.08)	0.02 (−0.03, 0.08)	0.00 (−0.05, 0.05)
Insufficient weight gain	−0.09 (−0.23, 0.05)	0.01 (−0.12, 0.14)	−0.01 (−0.14, 0.13)	−0.03 (−0.17, 0.12)	0.04 (−0.11, 0.20)	0.05 (−0.09, 0.19)
Sufficient weight gain	Reference	Reference	Reference	Reference	Reference	Reference
Excessive weight gain	0.19 (0.07, 0.30)*	0.14 (0.04, 0.25)*	0.12 (0.01, 0.23)**	0.16 (0.04, 0.28)**	0.09 (−0.03, 0.22)	0.06 (−0.05, 0.18)

	MRI measures of adiposity at 10 years in SDS conditional on body mass index[c]			
	Subcutaneous fat index ($n = 1287$)	Visceral fat index ($n = 1288$)	Pericardial fat index ($n = 1336$)	Liver fat fraction ($n = 1444$)
Maximum weight gain per week (kg in SDS)	−0.09 (−0.13, −0.04)*	−0.02 (−0.07, 0.04)	0.00 (−0.06, 0.05)	−0.04 (−0.09, 0.02)
Insufficient weight gain	0.11 (−0.02, 0.23)	0.04 (−0.10, 0.19)	0.08 (−0.07, 0.23)	0.10 (−0.04, 0.24)
Sufficient weight gain	Reference	Reference	Reference	Reference
Excessive weight gain	−0.03 (−0.13, 0.08)	0.07 (−0.05, 0.19)	0.04 (−0.09, 0.16)	−0.01 (−0.12, 0.11)

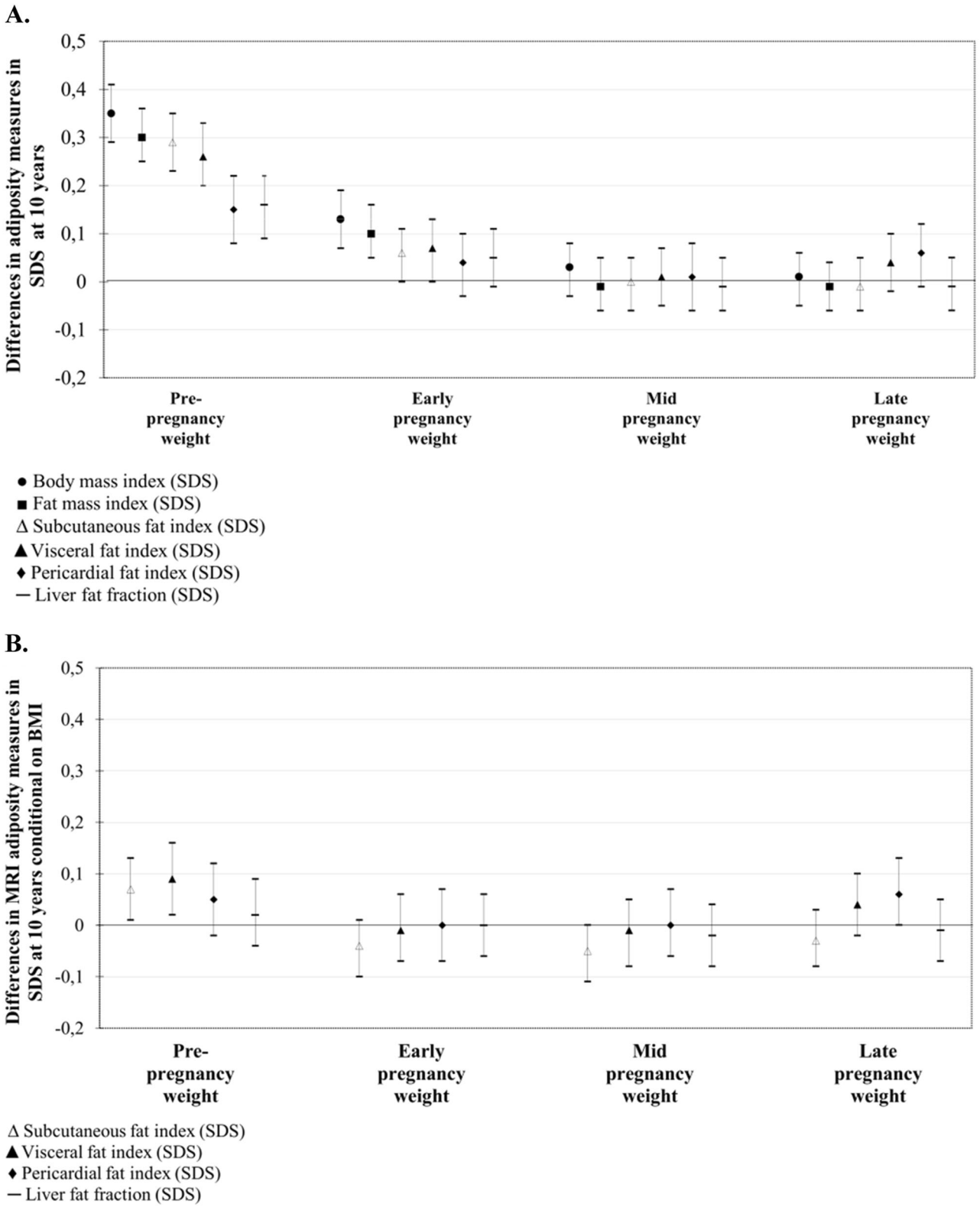
SDS standard deviation scores

*p value <0.01, **p value < 0.05

[a]Estimates are based on multiple imputed data. Model includes child's sex and age at outcome measurements (except for sex-adjusted and age-adjusted body mass index SDS), maternal age, educational level, ethnicity, parity, smoking habits during pregnancy, and child's breastfeeding duration, timing of introduction of solid foods, and television watching time. Models for maximum weight gain per week were additionally adjusted for pre-pregnancy body mass index. Results from the basic model are given in Supplementary Table 4

[b]Values are regression coefficients (95% confidence intervals) from linear regression models that reflect differences in childhood outcomes in SDS per SDS change in maternal maximum weight gain per week or for IOM weight gain clinical groups as compared to the reference group (sufficient weight gain)

[c]Values are regression coefficients (95% confidence intervals) from linear regression models that reflect differences in the standardized residuals of the childhood outcomes (obtained by conditional regression analyses on body mass index at 10 years) per SDS change in maternal maximum weight gain per week or for IOM weight gain clinical groups as compared to the reference group (sufficient weight gain)



paternal effect estimates were not statistically significant. These findings may suggest that the associations of maternal pre-pregnancy BMI with offspring adiposity might be explained by shared family-based lifestyle and genetic characteristics rather than by intrauterine programming [33].

Next to maternal pre-pregnancy obesity, excessive gestational weight gain also seems to be associated with an

◀ **Fig. 2** Maternal pre, early, mid, and late pregnancy weight with childhood general and organ fat measures ($n = 1121$). Estimates are based on multiple imputed data. Model includes child's sex and age at outcome measurements (except for sex-adjusted and age-adjusted body mass index SDS), maternal age, educational level, and ethnicity, parity, height at intake, smoking habits during pregnancy, and child's breastfeeding duration, timing of introduction of solid foods, and television watching time. Results from the basic model are given in Supplementary Fig. 3. Values in **a** are regression coefficients (95% confidence intervals) from linear regression models that reflect differences in childhood outcomes in SDS per SDS change in maternal pre-pregnancy weight and per change in standardized residuals of maternal early, mid, and late pregnancy weight obtained from conditional regression analyses. Values in **b** are regression coefficients (95% confidence intervals) from linear regression models that reflect differences in the standardized residuals of the childhood outcomes (obtained by conditional regression analyses on body mass index at 10 years) per SDS change in maternal pre-pregnancy weight and per change in standardized residuals of maternal early, mid, and late pregnancy weight obtained from conditional regression analyses. SDS standard deviation scores

increased risk of childhood overweight [34]. In our study, excessive weight gain was associated with higher BMI and fat mass index. A previous study among 313 mother–child pairs reported that higher maternal BMI was associated with higher childhood subcutaneous and visceral fat, particularly among mothers with excessive gestational weight gain [15]. However, in the same cohort as the current study, maternal weight gain in early, mid, and late pregnancy was not associated with childhood subcutaneous and preperitoneal abdominal fat mass levels at 6 years, independently of BMI [16]. In our study, total and period-specific weight gain was not consistently associated with any MRI adiposity measures. Thus, gestational weight gain, contrary to BMI before pregnancy, seems to have a limited influence on offspring organ fat in later life.

The mechanisms by which maternal adiposity during pregnancy affects offspring organ fat accumulation are not fully known yet. Maternal overnutrition may affect the development of adipocytes and their capacity to expand or contract the appetite control system and the energy metabolism in later life [3], which might lead to increased body fat in the offspring. Maternal overnutrition might also lead to accumulation of fat in the liver and other developing organs of the fetus, especially during early and mid pregnancy due to the absence of adipose tissue [35]. The postnatal persistence of increased fat in these depots might be related to reduced fatty acid oxidation, changes in lipogenesis, and lipoprotein export [35].

Our study shows that higher maternal pre-pregnancy BMI, as opposed to gestational weight gain, is related to higher organ fat measures, which have important adverse cardiometabolic health consequences. Future preventive strategies focused on promoting a healthy weight in women of reproductive age before pregnancy are needed to improve cardiometabolic health of the offspring. Considering the uncertainty about the causality of the associations, strategies directed at both parents might be more effective. Future studies may also analyze body fat distribution patterns based on various measures of general and organ fat by cluster analyses and relate these to early life exposures and later life outcomes.

Methodological considerations

Strengths of this study were the large sample size, prospective design, and data available on multiple maternal weight measurements throughout pregnancy and detailed childhood adiposity measures. Of the 4298 mothers and their singleton children with information on pre-pregnancy BMI available, 2354 had information on MRI adiposity measures at 10 years. The non-response could lead to biased effect estimates if the associations of maternal pre-pregnancy BMI and gestational weigh gain with childhood adiposity measures differ between mothers and children included and not included in the present analyses. However, this seems unlikely since participants and non-participants did not differ regarding maternal pre-pregnancy BMI and weight gain during pregnancy. We relied on self-reported pre-pregnancy weight and maximum weight during pregnancy. Women tend to underestimate their weight on self-report [36], which might have led to an underestimation of observed effects for maternal pre-pregnancy BMI and weight gain. However, bias seems unlikely since strong correlations were observed between self-reported pre-pregnancy weight and weight measured at enrollment ($r = 0.96$, p value <0.01) as well as between self-reported maximum weight and weight measured at late pregnancy ($r = 0.99$, p value <0.01). Also, since pre-pregnancy weight and maximum gestational weight are both self-reported and probably underestimated, the influence on maximum weight gain is likely to be minimal, which is confirmed by the fact that similar results were observed for weight gain measured until late pregnancy. Finally, although we adjusted for a large number of potential confounders, residual confounding due to lifestyle-related characteristics such as parental and child nutritional intake and physical activity might still be present in the observed associations. Thus, from the current observational data, no conclusions can be drawn on the causality and mechanisms underlying the observed associations.

Conclusions

Our study suggests that higher maternal pre-pregnancy BMI, but not gestational weight gain, is associated with organ fat accumulation, especially abdominal fat, in the offspring. Our findings emphasize the importance of

promoting a healthy BMI in women who are planning to become pregnant rather than influencing weigh gain during pregnancy. Similar associations were observed in our study for pre-pregnancy maternal and paternal BMI with offspring adiposity, suggesting a role of family shared lifestyle factors and genetics.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. PLoS ONE. 2013;8:e61627.
2. Marchi J, Berg M, Dencker A, Olander EK, Begley C. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. Obes Rev. 2015;16:621–38.
3. Fall CH. Evidence for the intra-uterine programming of adiposity in later life. Ann Hum Biol. 2011;38:410–28.
4. Lawlor DA, Timpson NJ, Harbord RM, Leary S, Ness A, McCarthy MI, et al. Exploring the developmental overnutrition hypothesis using parental–offspring associations and FTO as an instrumental variable. PLoS Med. 2008;5:e33.
5. Patro B, Liber A, Zalewski B, Poston L, Szajewska H, Koletzko B. Maternal and paternal body mass index and offspring obesity: a systematic review. Ann Nutr Metab. 2013;63:32–41.
6. Gaillard R, Steegers EA, Duijts L, Felix JF, Hofman A, Franco OH, et al. Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study. Hypertension. 2014;63:683–91.
7. Liu J, Fox CS, Hickson D, Sarpong D, Ekunwe L, May WD, et al. Pericardial adipose tissue, atherosclerosis, and cardiovascular disease risk factors: the Jackson Heart Study. Diabetes Care. 2010;33:1635–9.
8. Preis SR, Massaro JM, Robins SJ, Hoffmann U, Vasan RS, Irlbeck T, et al. Abdominal subcutaneous and visceral adipose tissue and insulin resistance in the Framingham Heart Study. Obesity (Silver Spring, MD). 2010;18:2191–8.
9. Tadros TM, Massaro JM, Rosito GA, Hoffmann U, Vasan RS, Larson MG, et al. Pericardial fat volume correlates with inflammatory markers: the Framingham Heart Study. Obesity (Silver Spring, MD). 2010;18:1039–45.
10. Liu J, Fox CS, Hickson D, Bidulescu A, Carr JJ, Taylor HA. Fatty liver, abdominal visceral fat, and cardiometabolic risk factors: the Jackson Heart Study. Arterioscler Thromb Vasc Biol. 2011;31:2715–22.
11. Modi N, Murgasova D, Ruager-Martin R, Thomas EL, Hyde MJ, Gale C, et al. The influence of maternal body mass index on infant adiposity and hepatic lipid content. Pediatr Res. 2011;70:287–91.
12. Brumbaugh DE, Tearse P, Cree-Green M, Fenton LZ, Brown M, Scherzinger A, et al. Intrahepatic fat is increased in the neonatal offspring of obese women with gestational diabetes. J Pediatr. 2013;162:930–6. e931
13. Moschonis G, Kaliora AC, Karatzi K, Michaletos A, Lambrinou CP, Karachaliou AK, et al. Perinatal, sociodemographic and lifestyle correlates of increased total and visceral fat mass levels in schoolchildren in Greece: the Healthy Growth Study. Public Health Nutr. 2016;20:660–70.
14. Ensenauer R, Chmitorz A, Riedel C, Fenske N, Hauner H, Nennstiel-Ratzel U, et al. Effects of suboptimal or excessive gestational weight gain on childhood overweight and abdominal adiposity: results from a retrospective cohort study. Int J Obes (Lond). 2013;37:505–12.
15. Kaar JL, Crume T, Brinton JT, Bischoff KJ, McDuffie R, Dabelea D. Maternal obesity, gestational weight gain, and offspring adiposity: the exploring perinatal outcomes among children study. J Pediatr. 2014;165:509–15.
16. Gaillard R, Steegers EA, Franco OH, Hofman A, Jaddoe VW. Maternal weight gain in different periods of pregnancy and childhood cardio-metabolic outcomes. The Generation R Study. Int J Obes (Lond). 2015;39:677–85.
17. Santos S, Severo M, Gaillard R, Santos AC, Barros H, Oliveira A. The role of prenatal exposures on body fat patterns at 7 years: intrauterine programming or birthweight effects? Nutr Metab Cardiovasc Dis. 2016;26:1004–10.
18. Kooijman MN, Kruithof CJ, van Duijn CM, Duijts L, Franco OH, van IMH, et al. The Generation R Study: design and cohort update 2017. Eur J Epidemiol. 2016;31:1243–64.
19. Institute of Medicine and National Research Council Committee to Reexamine IOM Pregnancy Weight Guidelines. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: National Academy Press; 2009.
20. Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996–7 compared with 1980. Arch Dis Child. 2000;82:107–12.
21. Gishti O, Gaillard R, Manniesing R, Abrahamse-Berkeveld M, van der Beek EM, Heppe DH, et al. Fetal and infant growth

patterns associated with total and abdominal fat distribution in school-age children. J Clin Endocrinol Metab. 2014;99:2557–66.
22. Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD, et al. Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity (Silver Spring, MD). 2012;20:1313–8.
23. Hu HH, Nayak KS, Goran MI. Assessment of abdominal adipose tissue and organ fat content by magnetic resonance imaging. Obes Rev. 2011;12:e504–515.
24. Langeslag SJ, Schmidt M, Ghassabian A, Jaddoe VW, Hofman A, van der Lugt A, et al. Functional connectivity between parietal and frontal brain regions and intelligence in young children: the Generation R Study. Hum Brain Mapp. 2013;34:3299–307.
25. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. J Magn Reson Imaging. 2011;34:spcone.
26. VanItallie TB, Yang MU, Heymsfield SB, Funk RC, Boileau RA. Height-normalized indices of the body's fat-free mass and fat mass: potentially useful indicators of nutritional status. Am J Clin Nutr. 1990;52:953–9.
27. Wells JC, Cole TJ, steam As. Adjustment of fat-free mass and fat mass for height in children aged 8 y. Int J Obes Relat Metab Disord. 2002;26:947–52.
28. Keijzer-Veen MG, Euser AM, van Montfoort N, Dekker FW, Vandenbroucke JP, Van Houwelingen HC. A regression model with unexplained residuals was preferred in the analysis of the fetal origins of adult diseases hypothesis. J Clin Epidemiol. 2005;58:1320–4.
29. Poston L, Caleyachetty R, Cnattingius S, Corvalan C, Uauy R, Herring S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. Lancet Diabetes Endocrinol. 2016;4:1025–36.
30. Gaillard R, Durmus B, Hofman A, Mackenbach JP, Steegers EA, Jaddoe VW. Risk factors and outcomes of maternal obesity and excessive weight gain during pregnancy. Obesity (Silver Spring, MD). 2013;21:1046–55.
31. Liu J, Fox CS, Hickson DA, May WD, Hairston KG, Carr JJ, et al. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: the Jackson Heart Study. J Clin Endocrinol Metab. 2010;95:5419–26.
32. Richmond RC, Timpson NJ, Felix JF, Palmer T, Gaillard R, McMahon G, et al. Using genetic variation to explore the causal effect of maternal pregnancy adiposity on future offspring adiposity: a Mendelian randomisation study. PLoS Med. 2017;14:e1002221.
33. Gaillard R, Santos S, Duijts L, Felix JF. Childhood health consequences of maternal obesity during pregnancy: a narrative review. Ann Nutr Metab. 2016;69:171–80.
34. Mamun AA, Mannan M, Doi SA. Gestational weight gain in relation to offspring obesity over the life course: a systematic review and bias-adjusted meta-analysis. Obes Rev. 2014;15:338–47.
35. Ugalde-Nicalo PA, Schwimmer JB. On the origin of pediatric nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr. 2015;60:147–8.
36. Russell A, Gillespie S, Satya S, Gaudet LM. Assessing the accuracy of pregnant women in recalling pre-pregnancy weight and gestational weight gain. J Obstet Gynaecol Can. 2013;35:802–9.