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Subcutaneous fat mass in infancy and cardiovascular risk factors at school-age. The Generation R Study

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Abstract

Objective—To examine the associations of infant subcutaneous fat with cardiovascular risk factors at school-age.

Methods—In a population-based prospective cohort study among 808 children, we estimated total subcutaneous fat (sum of biceps, triceps, suprailiacal and subscapular skinfold thicknesses) and central-to-total subcutaneous fat ratio (sum of suprailiacal and subscapular skinfold thicknesses/total subcutaneous fat) at 1.5 and 24 months. At 6 years, we measured body mass index, blood pressure, cholesterol, triglycerides, and insulin levels.

Results—Infant subcutaneous fat measures were not associated with childhood blood pressure, triglycerides or insulin levels. A 1-standard-deviation scores (SDS) higher total subcutaneous fat at 1.5 months was, independently of body mass index, associated with lower low-density lipoprotein (LDL)-cholesterol levels at 6 years. In contrast, a 1-SDS higher total subcutaneous fat at 24 months was associated with higher total-cholesterol (difference 0.13 (95% Confidence Interval

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Authors' contributions

The authors' contributions to this study were as follows: SS, RG and VWVJ designed the research project; AH and VWVJ were involved in the design and planning of the study and data collection; SS and RG conducted the analyses; SS, RG and VWVJ wrote the paper; AO, HB, AH and OHF critically reviewed the manuscript; SS, RG and VWVJ had primary responsibility for the final content. All authors read and approved the final manuscript.

Conflict of interest

None of the authors had a financial or personal conflict of interest.

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(CI) 0.03, 0.23) SDS) and LDL-cholesterol levels (difference 0.12 (95% CI 0.02, 0.21) SDS) at 6 years. We did not observe associations of central-to-total subcutaneous fat ratio with childhood cholesterol levels.

Conclusions—Our results suggest that infant total subcutaneous fat is weakly associated with cholesterol levels at school-age. Further studies are needed to assess the long-term cardiometabolic consequences of infant body fat.

Keywords

infancy; subcutaneous fat; cardiovascular risk; childhood

Introduction

Early infant and childhood growth rates are associated with cardiovascular disease risk in later life (1). Results from longitudinal studies suggest that rapid weight gain in infancy or gain in body mass index in childhood are associated with an adverse cardiovascular risk profile in adulthood (2–4). Weight or body mass index are suboptimal measures of fat mass development and provide no information about body fat distribution (5). Several studies have shown that as compared to body mass index, body fat distribution plays a greater role in the development of risk factors for cardiovascular disease (6). We have previously reported in a cross-sectional study among 6-year-old children that both general and abdominal fat mass measures are associated with cardiovascular risk factors, independently of body mass index (7). Also, previous studies have shown that high total subcutaneous fat mass measured by the sum of skinfold thicknesses is associated with high blood pressure, an unfavorable blood lipids profile and high glucose and insulin levels in childhood (8–12). Currently, it is not known whether, next to rapid weight gain, total and regional subcutaneous fat mass development in infancy are associated with cardiovascular risk factors in later life. Assessing the contribution of fatness in infancy to later cardiovascular risk status is particularly relevant to identify early critical periods of fat development that influence the risk for cardiovascular disease.

Therefore, we examined, in a population-based prospective cohort study among 808 children, the associations of infant subcutaneous fat mass measures with cardiovascular risk factors at school-age. We used skinfold thickness measurements at 1.5 and 24 months to estimate total subcutaneous fat mass and central-to-total subcutaneous fat mass ratio. Cardiovascular risk factors of interest include blood pressure, total-, high-density lipoprotein (HDL)-, and low-density lipoprotein (LDL)-cholesterol levels, triglycerides levels and insulin levels at 6 years.

Methods

Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early pregnancy onwards among 9,778 mothers and their children living in Rotterdam, the Netherlands (13, 14). The study protocol was approved by the local Medical Ethical Committee. Written informed consent was obtained from all mothers. Additional

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detailed assessments of fetal and postnatal growth and development were conducted in a subgroup of Dutch mothers and their children from late pregnancy onwards. Of all approached women, 80% agreed to participate. Of the total of 1,205 singleton children participating in the subgroup study, 965 children had body mass index or skinfold thicknesses measured at the age of 1.5 or 24 months. Of these children, 808 children had cardiovascular risk factors measurements at the age of 6 years (Flow chart is given in Supplemental Figure S1). Missing measurements were mainly due to crying behavior or non-consent for venous puncture at 6 years old.

Body fat measurements during infancy

We measured weight to the nearest gram in naked infants at the age of 1.5 months by using an electronic infant scale and at 24 months by using a mechanical personal scale (SECA, Almere, The Netherlands). Body length at the age of 1.5 months was measured in supine position to the nearest millimeter by using a neonatometer and body height at 24 months was measured in standing position by using a Harpenden stadiometer (Holtain Limited, Dyfed, UK). Body mass index (kg/m^2) was calculated.

We measured skinfold thicknesses at the ages of 1.5 and 24 months on the left side of the body at the biceps, triceps, suprailiacal and subscapular area by using a skinfold caliper (Slim Guide, Creative Health Products) according to standard procedures described in detail previously (15). We calculated total subcutaneous fat mass from the sum of all four skinfold thicknesses, and central subcutaneous fat mass from the sum of suprailiacal and subscapular skinfold thicknesses (16). Measurements of body fat quantity and distribution require appropriate adjustment for body size or total fat mass, respectively, in order to undertake informative comparisons between children and within children over time. To create total subcutaneous fat mass independent of length or height and central subcutaneous fat mass independent of total subcutaneous fat mass, we estimated the optimal adjustment by log-log regression analyses (17). Details of these regressions are given in the Supplemental Methods. Based on these analyses, total subcutaneous fat mass was only weakly correlated with length at 1.5 months or height at 24 months, and was not adjusted for height whereas a central-to-total subcutaneous fat mass ratio was calculated as central divided by total subcutaneous fat mass.

Cardiovascular risk factors at school-age

Blood pressure was measured at the right brachial artery four times with one-minute intervals, using the validated automatic sphygmanometer Datascope Accutor Plus (Paramus, NJ) (18). We calculated the mean value for systolic and diastolic blood pressure using the last three blood pressure measurements of each participant. Thirty-minutes fasting blood samples were collected to measure total-, HDL-, and LDL-cholesterol, triglycerides, and insulin concentrations, using Cobas 8000 analyser (Roche, Almere, The Netherlands). Quality control samples demonstrated intra- and interassay coefficients of variation ranging from 0.77 to 1.39%, and 0.87 to 2.40%, respectively.

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Covariates

Information on maternal age, educational level, parity, pre-pregnancy weight and smoking habits during pregnancy was assessed using self-reported questionnaires during pregnancy. We measured maternal height at enrolment and calculated pre-pregnancy body mass index (kg/m^2). First trimester maternal nutritional information was obtained by food frequency questionnaire (19). Gestational weight gain was calculated as the difference between maternal weight measured at 30 weeks of gestation and pre-pregnancy weight. Information about gestational diabetes and gestational hypertensive disorders, child's sex, gestational age and weight at birth was obtained from medical records. Information about breastfeeding duration, timing of introduction of solid foods and average television watching time at 6 years old was obtained by questionnaires. At the age of 6 years, we measured child's height and weight in standing position without shoes and heavy clothing, and calculated body mass index (kg/m^2).

Statistical analysis

We assessed the associations of body mass index, total subcutaneous fat mass and central-to-total subcutaneous fat mass ratio at 1.5 and 24 months and the change between these ages, with cardiovascular risk factors (blood pressure, total-, HDL-, and LDL-cholesterol, triglycerides and insulin levels) at school-age using linear regression models. The regression models were adjusted for maternal age, educational level, parity, pre-pregnancy body mass index, maternal total energy intake, smoking habits and total weight gain during pregnancy, gestational diabetes, gestational hypertensive disorders, and child's sex, gestational age-adjusted birth weight standard-deviation scores (SDS), breastfeeding duration, timing of introduction of solid foods, and TV watching time. We included covariates in the models when they were strongly associated with body fat mass and cardiovascular risk factors in our or previous studies, or when they changed the effect estimates substantially (>10%). Additionally, we adjusted these models for childhood body mass index to assess whether any association of infant fat mass measures with childhood cardiovascular risk factors was independent of body mass index at 6 years. For the models with body mass index as main exposure, we constructed a conditional body mass index variable at 6 years that was statistically independent of body mass index at 1.5 and 24 months, allowing simultaneous inclusion in multiple regression models (20). Details of these models are given in the Supplemental Methods. For the models with subcutaneous fat mass measures as exposures, body mass index at 6 years was simultaneously included in the regression models since no collinearity was observed. We did not observe significant interactions between infant fat mass measures and sex, breastfeeding groups (never, ever) and body mass index categories at 1.5 or 24 months in the associations with childhood cardiovascular risk factors. For all analyses, we log-transformed not normally distributed cardiovascular risk factors (triglycerides and insulin levels). We constructed SDS [(observed value - mean)/SD] of the sample distribution for all variables to enable comparisons in effect size. Missing values in covariates were multiple-imputed, by using Markov chain Monte Carlo approach. Five imputed datasets were created and analyzed together. We performed statistical analyses using the Statistical Package of Social Sciences version 21.0 for Windows (SPSS Inc, Chicago, IL, USA).

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Results

Subject characteristics

Tables 1 and 2 show the subject characteristics. Of all participating children, 50.1% were boys, the mean (SD) birth weight was 3535 (517) g and the median (95% range) gestational age at birth was 40.3 (36.4-42.4) weeks.

Non-response analyses showed that as compared to mothers who did not participate in the follow-up studies, those who did participate were slightly older, had a higher educational level and pre-pregnancy body mass index and were more likely to be nulliparous and non-smokers ($p<0.05$). Their children were born with a higher weight and gestational age at birth and were breastfed for a longer period ($p<0.05$) (Supplemental Table S1).

Infant body fat and cardiovascular risk factors at school-age

Table 3 shows that, after adjustment for potential confounders, body mass index at 1.5 and 24 months or its change over infancy was not associated with cardiovascular risk factors at school-age. Similarly, total subcutaneous fat mass and central-to-total subcutaneous fat mass ratio at 1.5 and 24 months or its change over infancy were not associated with childhood blood pressure and triglycerides or insulin levels. A 1-SDS higher total subcutaneous fat mass at 1.5 months was associated with lower LDL-cholesterol levels at the age of 6 years (difference -0.10 (95% Confidence Interval (CI) -0.20, -0.01) SDS), whereas 1-SDS higher total subcutaneous fat mass at 24 months was associated with higher childhood total- and LDL-cholesterol levels (differences 0.15 (95% CI 0.05, 0.24) SDS and 0.14 (95% CI 0.04, 0.23) SDS, respectively). Also, 1-SDS increase in total subcutaneous fat mass from 1.5 to 24 months was associated with higher childhood total- and LDL-cholesterol levels (differences 0.10 (95% CI 0.03, 0.18) SDS and 0.11 (95% CI 0.04, 0.19) SDS, respectively). These results were not materially affected by additional adjustment for childhood body mass index (Table 3). Results from the unadjusted analyses are given in Supplemental Table S2.

Discussion

We observed in this population-based prospective cohort study that infant subcutaneous fat mass measures at 1.5 and 24 months were not associated with childhood blood pressure and triglycerides or insulin levels, but were weakly associated with childhood cholesterol levels at 6 years, independently of body mass index.

Methodological considerations

Major strengths of this study are the population-based prospective design with detailed infant body fat and childhood cardiovascular risk factors measurements available. Some methodological issues need to be considered. Of the 965 singleton children with information on body fat mass measures at the age of 1.5 or 24 months, 84% (808) participated in the adiposity and cardiovascular follow-up study at 6 years old. The non-response could lead to biased effect estimates if the associations of infant subcutaneous fat mass with cardiovascular risk factors at school-age differ between children included and not included in the present analyses. However, this seems unlikely since children that did not participate

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in the follow-up studies did not differ from those who did participate regarding body mass index and subcutaneous fat mass measures at 1.5 and 24 months. Our study group was ethnically homogeneous (Dutch only), which may limit the generalizability of our results to other ethnic groups (21). We used skinfold thickness as a measure of subcutaneous fat mass and therefore we were not able to measure intra-abdominal depots. However, during the first months of life approximately 90% of body fat is located subcutaneously (22) and preperitoneal fat mass seems to increase only from the second year of life onwards (23). Previous studies have shown that skinfold thickness is a valid measurement of fat mass in children, but in extremely overweight children the measurement error is larger (24). The inter- and intra-observer measurement error is also larger as compared to other anthropometric measurements (25, 26). The use of thirty-minutes fasting blood samples may have resulted in misclassification and thus may have led to underestimation of the observed associations. However, it has been shown in adults that non-fasting blood lipid levels can accurately predict increased risks of cardiovascular events in later life (27). Finally, we adjusted for a large number of potential confounders but residual confounding in the observed associations might still occur, as in any observational study. For example, in our study, we were unable to adjust our results for detailed nutritional information during infancy and at school-age.

Interpretation of main findings

A high body mass index is an important risk factor for an adverse cardiovascular risk profile in late childhood (7, 12, 28). Also, a high body mass index gain during childhood has been associated with cardiovascular risk in adolescence and adulthood (3, 29). Few studies have assessed the relation of body mass index and cardiovascular risk in preschool children and have found weak or no associations with blood lipid and insulin levels (30–32). Rapid weight gain in the first 3 months of life has been associated with increased adiposity and an unfavorable cardiovascular profile in later life (2). However, it remains unknown whether gain in body mass index or ponderal index in infancy predisposes individuals to cardiovascular risk. A study among 4,601 UK subjects has shown that changes in ponderal index from 0 to 2 years were not associated with cardiovascular risk factors in adolescence (29). In the present study, we observed no associations of body mass index at the ages of 1.5 and 24 months or its change in this period with cardiovascular risk factors at school-age. Also, we did not observe differences in results when we used ponderal index calculated as weight/height^3 at 1.5 months (data not shown) (33).

Body mass index may not be an accurate measure of total fat mass and provides no information on body fat distribution (5). An accumulating body of evidence has suggested that body fat distribution is more strongly associated with cardiovascular disease and type 2 diabetes than body mass index (6). We have previously reported in a cross-sectional study among 6-year-old children that high fat mass percentage and android-to-gynoid fat mass ratio measured by dual-energy X-ray absorptiometry were associated with adverse levels of cardiovascular risk factors, independently of body mass index. The associations of these more detailed body fat mass measures with blood lipid levels tended to be stronger than the associations for body mass index (7).

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Previous studies have also shown that high total and central subcutaneous fat mass measures, estimated from skinfold thicknesses, are associated with an adverse cardiovascular risk profile, namely high blood pressure, an unfavorable blood lipids profile and high insulin levels, in late childhood (8–10, 12, 34). Another study has shown that an increase in total subcutaneous fat mass from 8 to 18 years old was associated with an increase in total-cholesterol, LDL-cholesterol and triglycerides levels and a decrease in HDL-cholesterol levels (11). Few studies have assessed the associations of subcutaneous fat mass measures with cardiovascular risk in preschool children (31, 35). Those studies have found that total subcutaneous fat mass was positively but weakly related to fasting insulin in children aged 2 to 3 years (31) while no association was found with blood lipid levels in children aged 4 years (35). It is not known whether total and regional subcutaneous fat mass in infancy is associated with cardiovascular risk factors in later life. We observed no associations of infant subcutaneous fat mass measures with childhood blood pressure and triglycerides or insulin levels. At 1.5 months, total subcutaneous fat mass was inversely associated with LDL-cholesterol at the age of 6 years old. We cannot explain this finding. Child's dietary intake and physical activity may have confounded this association, since we had only available information about breastfeeding, age at introduction of solid foods and TV watching time at 6 years. At 24 months, total subcutaneous fat mass, but not central-to-total subcutaneous fat mass ratio, was positively but also weakly associated with childhood total- and LDL-cholesterol, independently of body mass index at 6 years old. LDL-cholesterol is an important determinant of cardiovascular risk and a causal agent in the atherothrombotic process (36).

In line with the previous cross-sectional studies performed among preschool children (31, 35), our study suggests that subcutaneous fat mass measures in infancy seem to be poor indicators of cardiovascular risk profile in later childhood. These findings may be partially explained by the fact that fat mass measures in infancy represent the accumulation of fat mass over a short period of time, which may not be long enough to influence cardiovascular risk profile. Further studies are needed to assess the long-term cardiovascular consequences of infant total and regional fat mass measures.

Conclusion

Our results suggest that infant subcutaneous fat mass measures do not affect childhood blood pressure and triglycerides or insulin levels, and are weakly associated with childhood total- and LDL-cholesterol levels at 6 years, independently of body mass index.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this subject?

- Early infant and childhood weight gain is associated with an adverse cardiovascular risk profile in later life.
- High levels of subcutaneous fat mass in childhood are associated with high blood pressure, an unfavorable blood lipids profile and high insulin levels.

What does your study add?

- Infant subcutaneous fat measures were not associated with childhood blood pressure and triglycerides or insulin levels.
- Infant total subcutaneous fat was weakly associated with childhood cholesterol levels, independently of body mass index, at 6 years.
- Subcutaneous fat measures in infancy seem to be poor indicators of cardiovascular risk profile in later childhood.

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Table 1

Characteristics of study participants[1]

	Total group (n = 808)
Maternal characteristics	
Age (years), mean (SD)	32.0 (3.8)
Highest completed education, n (%)	
Primary school	10 (1.2)
Secondary school	261 (32.5)
Higher education	533 (66.3)
Parity, n (%) nulliparous	512 (63.4)
Pre-pregnancy body mass index (kg/m^2), mean (SD)	23.6 (4.2)
Total energy intake (kcal), mean (SD)	2131 (499)
Total weight gain during pregnancy (kg), mean (SD)	10.2 (4.6)
Smoking habits during pregnancy, n (%)	
No	575 (78.7)
Yes	156 (21.3)
Gestational diabetes, n (%)	9 (1.1)
Gestational hypertensive disorders, n (%)	64 (8.1)
Child's characteristics	
Boys, n (%)	405 (50.1)
Birth weight (g), mean (SD)	3535 (517)
Gestational age at birth (weeks), median (95% range)	40.3 (36.4-42.4)
Breastfeeding duration (months), mean (SD)	4.7 (3.9)
Introduction of solid foods, n (%)	
<3 months	41 (5.5)
3 to 6 months	569 (76.6)
>6 months	133 (17.9)
TV watching time, n (%)	
< 2 hours/day	668 (91.3)
≥ 2 hours/day	64 (8.7)
Body mass index at 6 years (kg/m^2), mean (SD)	15.9 (1.4)
Overweight and obesity at 6 years (IOTF criteria), n (%)	87 (10.8)

[1]Values are observed data and represent means (SD), medians (95% range) or numbers of subjects (valid %). IOTF, International Obesity Task Force; SD, standard deviation.

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Table 2

Body fat at 1.5 and 24 months by skinfold thicknesses and cardiovascular risk factors at 6 years old[1]

	Total group (n = 808)
Fat mass measures at 1.5 months	**n = 731**
Age (months), mean (SD)	1.6 (0.4)
Body mass index (kg/m^2), mean (SD)	15.2 (1.4)
Total subcutaneous fat mass (mm), mean (SD)	23.9 (7.0)
Central-to-total subcutaneous fat mass ratio, mean (SD)	0.50 (0.05)
Fat mass measures at 24 months	**n = 735**
Age (months), mean (SD)	25.2 (1.1)
Body mass index (kg/m^2), mean (SD)	16.0 (1.3)
Total subcutaneous fat mass (mm), mean (SD)	27.4 (7.5)
Central-to-total subcutaneous fat mass ratio, mean (SD)	0.43 (0.06)
Cardiovascular risk factors at 6 years	**n = 808**
Age (years), mean (SD)	6.0 (0.3)
Systolic blood pressure (mm/Hg), mean (SD)	102.4 (7.9)
Diastolic blood pressure (mm/Hg), mean (SD)	60.2 (6.4)
Total-cholesterol (mmol/l), mean (SD)	4.2 (0.6)
HDL-cholesterol (mmol/l), mean (SD)	1.3 (0.3)
LDL-cholesterol (mmol/l), mean (SD)	2.3 (0.6)
Triglycerides (mmol/l), median (95% range)	1.0 (0.4-2.2)
Insulin (U/I), median (95% range)	116 (18-384)

[1]Values are expressed as means (SD) or medians (95% range). Body mass index = weight/height^2. Total subcutaneous fat mass = biceps + triceps + suprailiacal + subscapular skinfold thicknesses. Central-to-total subcutaneous fat mass ratio = (suprailiacal + subscapular skinfold thicknesses)/total subcutaneous fat mass. HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; SD, standard deviation.

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Table 3

Associations of infant subcutaneous fat mass measures with cardiovascular risk factors at 6 years old[1-2]

	Cardiovascular risk factors at 6 years in standard-deviation scores Difference (95% Confidence Interval)						
Fat mass measures	**Systolic blood pressure**	**Diastolic blood pressure**	**Total-cholesterol**	**HDL-cholesterol**	**LDL-cholesterol**	**Triglycerides**	**Insulin**
1.5 months							
Body mass index							
Model 1	0.08 (-0.01,0.16)	0.04 (-0.04,0.12)	0.05 (-0.05,0.16)	0.04 (-0.06,0.14)	0.02 (-0.09,0.12)	0.03 (-0.07,0.13)	0.03 (-0.07,0.14)
Model 2	0.08 (0.01,0.16)*	0.04 (-0.04,0.12)	0.06 (-0.05,0.16)	0.04 (-0.06,0.14)	0.02 (-0.08,0.12)	0.03 (-0.07,0.13)	0.04 (-0.06,0.14)
Total subcutaneous fat mass							
Model 1	0.06 (-0.02,0.14)	-0.01 (-0.08,0.07)	-0.03 (-0.13,0.07)	0.05 (-0.05,0.15)	-0.10 (-0.20,-0.01)*	-0.03 (-0.13,0.06)	0.06 (-0.04,0.16)
Model 2	0.05 (-0.03,0.13)	-0.01 (-0.09,0.07)	-0.04 (-0.14,0.06)	0.05 (-0.05,0.15)	-0.11 (-0.21,-0.01)*	-0.04 (-0.14,0.06)	0.04 (-0.06,0.14)
Central-to-total subcutaneous fat mass ratio							
Model 1	-0.02 (-0.09,0.06)	-0.04 (-0.12,0.04)	0.06 (-0.04,0.15)	0.03 (-0.06,0.13)	0.02 (-0.07,0.12)	0.08 (-0.01,0.17)	0.03 (-0.07,0.12)
Model 2	-0.02 (-0.10,0.05)	-0.04 (-0.12,0.04)	0.05 (-0.04,0.14)	0.04 (-0.06,0.13)	0.02 (-0.07,0.11)	0.08 (-0.01,0.17)	0.02 (-0.07,0.11)
24 months							
Body mass index							
Model 1	-0.01 (-0.09,0.06)	-0.03 (-0.11,0.05)	-0.03 (-0.13,0.06)	-0.09 (-0.19,0.01)	0.01 (-0.09,0.10)	0.01 (-0.08,0.11)	-0.05 (-0.14,0.05)
Model 2	0.00 (-0.08,0.07)	-0.03 (-0.11,0.05)	-0.03 (-0.12,0.07)	-0.09 (-0.19,0.01)	0.01 (-0.08,0.10)	0.02 (-0.08,0.11)	-0.04 (-0.13,0.06)
Total subcutaneous fat mass							
Model 1	-0.01 (-0.09,0.06)	0.01 (-0.07,0.09)	0.15 (0.05,0.24)**	0.02 (-0.07,0.11)	0.14 (0.04,0.23)**	0.03 (-0.07,0.12)	0.02 (-0.08,0.12)
Model 2	-0.07 (-0.14,0.01)	-0.01 (-0.09,0.07)	0.13 (0.03,0.23)**	0.03 (-0.07,0.12)	0.12 (0.02,0.21)*	0.01 (-0.09,0.11)	-0.04 (-0.14,0.05)
Central-to-total subcutaneous fat mass ratio							
Model 1	0.02 (-0.06,0.10)	0.02 (-0.06,0.10)	0.05 (-0.05,0.15)	-0.08 (-0.18,0.01)	0.09 (-0.01,0.19)	0.03 (-0.07,0.13)	-0.02 (-0.12,0.08)
Model 2	0.01 (-0.07,0.08)	0.02 (-0.06,0.09)	0.04 (-0.07,0.14)	-0.08 (-0.18,0.02)	0.08 (-0.02,0.18)	0.02 (-0.08,0.12)	-0.05 (-0.16,0.05)
Change from 1.5 to 24 months							
Body mass index							
Model 1	-0.06 (-0.13,0.01)	-0.05 (-0.12,0.01)	-0.05 (-0.14,0.03)	-0.06 (-0.15,0.02)	-0.02 (-0.10,0.07)	-0.03 (-0.11,0.06)	-0.03 (-0.12,0.06)
Model 2	-0.07 (-0.14,-0.01)*	-0.06 (-0.12,0.01)	-0.06 (-0.14,0.03)	-0.06 (-0.15,0.02)	-0.02 (-0.10,0.07)	-0.03 (-0.11,0.06)	-0.04 (-0.12,0.05)
Total subcutaneous fat mass							

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	Cardiovascular risk factors at 6 years in standard-deviation scores Difference (95% Confidence Interval)						
Fat mass measures	**Systolic blood pressure**	**Diastolic blood pressure**	**Total-cholesterol**	**HDL-cholesterol**	**LDL-cholesterol**	**Triglycerides**	**Insulin**
Model 1	-0.02 (-0.08,0.03)	0.01 (-0.05,0.07)	0.10 (0.03,0.18) **	-0.01 (-0.08,0.06)	0.11 (0.04,0.19) **	0.03 (-0.04,0.11)	0.00 (-0.08,0.08)
Model 2	-0.05 (-0.11,0.01)	0.01 (-0.05,0.07)	0.10 (0.02,0.17) *	-0.01 (-0.08,0.07)	0.11 (0.03,0.18) **	0.02 (-0.05,0.10)	-0.03 (-0.10,0.05)
Central-to-total subcutaneous fat mass ratio							
Model 1	0.01 (-0.04,0.07)	0.03 (-0.03,0.09)	-0.05 (-0.12,0.03)	-0.06 (-0.14,0.01)	0.02 (-0.06,0.09)	-0.05 (-0.12,0.03)	-0.01 (-0.09,0.07)
Model 2	0.01 (-0.05,0.07)	0.03 (-0.03,0.09)	-0.05 (-0.13,0.02)	-0.06 (-0.14,0.01)	0.01 (-0.07,0.09)	-0.05 (-0.13,0.02)	-0.03 (-0.10,0.05)

[1]Values are standardized regression coefficients (95% confidence interval) and represent the difference in standard-deviation scores for cardiovascular risk factors at 6 years per 1-standard-deviation scores increase in body mass index and subcutaneous fat mass measures. Body mass index = weight/height^2. Total subcutaneous fat mass = biceps + triceps + suprailiacal + subscapular skinfold thicknesses. Central-to-total subcutaneous fat mass ratio = (suprailiacal + subscapular skinfold thicknesses)/total subcutaneous fat mass. HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol.

[2]Model 1 is adjusted for maternal age, educational level, parity, pre-pregnancy body mass index, maternal total energy intake, smoking habits and total weight gain during pregnancy, gestational diabetes, gestational hypertensive disorders and child's sex, gestational age-adjusted birth weight standard-deviation scores, breastfeeding duration, timing of introduction of solid foods, and TV watching time. Model 2 is additionally adjusted for body mass index standard-deviation scores at 6 years. Conditional analysis was used in body mass index models to allow the adjustment for body mass index at 6 years.

*P-value<0.05;

**P-value<0.01.

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