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Intake of energy and protein is associated with overweight risk at age 5.5 years: Results from the prospective TEDDY study

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Abstract

Objective—We assessed the associations of energy, protein, carbohydrate and fat intake with weight status up to the age of 5.5 years in the prospective TEDDY study.

Methods—Food record data (3 days) and body mass index (BMI) measurements between 0.25 and 5.5 years were available from 5,563 children with increased genetic risk for type 1 diabetes followed from shortly after birth. We calculated odds ratios (ORs) for overweight and obesity by previous intake of energy, protein, carbohydrates and fat with adjustment for potential confounders.

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Results—Overweight and obesity at the age of 5.5 years were positively associated with mean energy intake in previous age intervals (e.g. adjusted OR [95% confidence interval] for overweight: 1.06 [1.04, 1.09] per 100 kcal intake at the age of 4.5–5.0 years), and with protein intake after the age of 3.5 and 4.5 years, respectively (e. g. adjusted OR for overweight: 1.06 [1.03, 1.09] per 1 % of energy intake at the age of 4.5–5.0 years). The respective associations with carbohydrate and fat intake were less consistent.

Conclusions—These findings indicate that energy and protein intake are positively associated with increased risk for overweight in childhood, but yield no evidence for potential programming effects of protein intake in infancy.

Keywords

TEDDY study; protein; carbohydrates; fat; energy intake; overweight; obesity

Introduction

The prevalence of childhood overweight has been increasing worldwide in recent decades (1). This temporal trend is alarming, because overweight in childhood is associated with other long-term health consequences such as overweight, obesity, metabolic syndrome and cardiovascular disease in adulthood (2). Besides physical activity, nutrition in the first years of life is likely to be a key modifiable factor to prevent both short- and long-term obesity (3). Children's environment at this age is largely under their parents' control and is likely to have a long-term effect on their overweight risk (4).

However, there is relatively little evidence on the potential impact of energy and macronutrient intake during childhood on body mass index (BMI). While it appears likely that a greater energy intake is a potential risk factor of overweight (5, 6), much less is known about early fat, carbohydrate and protein intake. Low fat intake has been found to be associated with weight reduction in randomized trials, but not consistently in cohort studies (7). Intake of sugar-sweetened beverages seemed to increase the risk of overweight in childhood (8), but studies which investigated the proportion of carbohydrate intake in relation to total energy intake did not report an increased risk of overweight by a greater carbohydrate intake (9, 10). There is also limited evidence for a long-term programming effect of a greater protein intake during or after weaning age on overweight later in childhood. A large clinical trial indicated that the consumption of an infant formula with a low content of protein may reduce obesity risk at the age of 6 years (11), but the results from other trials on infant formulas with different protein concentrations were less conclusive (12). A recent twin study suggested that a greater protein intake at the age of 21 months may be associated with increased BMI at the age of 3–5 years, but found no significant associations with overweight or obesity at these ages (13). Recent observational studies reported positive associations between childhood overweight and protein intake at different ages (9, 14, 15).

We investigated the hypotheses that early energy and macronutrient intake are associated with subsequent weight status from shortly after birth up to the age of 5.5 years. For this purpose, we analysed data from a large, well-characterized and contemporary prospective

cohort study which had not previously been investigated in this context. The use of time-varying covariates and quantile regression allowed us to gain deeper insight into these associations. Further, we investigated potential gene-environment associations using a number of single nucleotide polymorphisms (SNPs) which had previously been associated with childhood overweight.

Methods

The Environmental Determinants of Diabetes in the Young (TEDDY) is an ongoing prospective cohort study funded by the National Institutes of Health with the primary goal to identify environmental causes of type 1 diabetes. The TEDDY study screened 424,788 newborns for type 1 diabetes-associated human leukocyte antigen (HLA) genotypes between 2004 and 2010 (16), of which 8,676 children were enrolled and followed up in six clinical research centers located in the USA, Finland, Germany, and Sweden. Detailed information on study design, eligibility and methods has been previously published (16, 17, 18). Written informed consents were obtained for all participants from a parent or primary caretaker, separately, for genetic screening and for participation in prospective follow-up. The study was approved by local Institutional Review Boards and is monitored by External Evaluation Committee formed by the National Institutes of Health.

Genotyping

Blood samples of newborn children were obtained in the maternity clinics either as cord blood or dry blood spots. HLA screening was performed by using either a dried blood spot punch or a small volume of whole blood. SNP analysis was performed using the Illumina ImmunoChip (19).

Assessment of child’s height and weight

Child’s height and weight were obtained at TEDDY clinics by trained TEDDY personnel at each visit, which took place every 3 months between age 3 and 48 months of age and biannually, thereafter. Child’s height was measured as length before age 2 years, and as standing height to the nearest 0.1 cm from age 2 years using a wall-mounted stadiometer. Body weight was measured in kilograms using regularly calibrated electronic scales. For subjects who could not attend a clinical visit, anthropometric data were copied from their pediatricians’ records collected near the TEDDY clinic visit date.

Assessment of diet

The first dietary assessment from children’s primary caretakers was carried out by 24-hr recall at the age of 3 months, and by 3-day food record every 3 months until the child was 12 months old, and then every 6 months. Every participating family was instructed to keep a consecutive 3-day record of the child’s food consumption ideally including 2 weekdays and 1 weekend day. To facilitate the completion of food records, TEDDY staff provided written instructions and examples on how to indicate meal time, meal location, adequate description of foods and beverages, quantity of intake, and use of dietary supplements. Separate food record forms were provided for daycare and for schools which included specific instructions for the personnel how to record the food consumption of the child during the day. Parents

reviewed these records and completed any missing information (e.g. type and amount) by interviewing the caregiver or teacher. To facilitate recalling and recording of infant formula types, the families were provided a booklet containing pictures of infant formulas available on the market in each country. Additionally, TEDDY developed a food portion size booklet that contained colourful pictorial illustrations of multi-ingredient composite dishes and black-and-white shapes and scales to facilitate portion size estimation. In Germany, parents weighed food when keeping the records; the food portion booklet was only used in addition. To calculate the amount of breastmilk, the method proposed by the Institute of Medicine based on the age and weight of the child was applied (20).

The records were entered into country-specific food record databases by trained personnel to assess intake of various nutrients. Each country analysed their food records separately to assess the energy and nutrient intakes of the children at various ages. The four country-specific food composition databases have been harmonized for the TEDDY study (21). After the nutrient values were calculated, the nutrition coordinator in each country estimated the plausible intake value of nutrients based on the overall distribution of nutrients.

Once the intake amount was verified, the final data were electronically submitted to the data coordinating center in Tampa, FL, where an in-built data error notification system flagged any nutrient value that exceeded the set limits. This data error system automatically notified the clinical center about the suspected error and the center had to either correct the information in the food record or verify it in order to get the data accepted. The electronically submitted final data including the energy and nutrient intakes per child and per age from each country were merged together into one dataset in the data coordinating center in Tampa, FL. The TEDDY study did not provide any recommendations or advice on infant feeding or childhood diet to the families.

Assessment of clinical and sociodemographic covariates

Maternal factors such as maternal age, pre-pregnancy BMI, gestational weight gain, education, smoking or alcohol intake during pregnancy and maternal diabetes, as well as child's birth weight were obtained by either questionnaires or structured interviews during one of the follow-up visits in the first year of the study. To assess the duration of breastfeeding, families were asked to record the age at weaning and the age at introduction of all new foods in a specific booklet given to the parents at the study entry.

Data transformations

Child's BMI was calculated as weight (kg) divided by height (m) squared and transformed to standard deviation scores (SDS) using World Health Organization (WHO) reference values (22, 23), which were also used to define overweight (including obesity; BMI SDS > 1) and obesity (BMI SDS > 2). BMI SDS values below −5 or greater than 5 were deemed implausible and excluded. BMI at the age of 5.5 years was defined as BMI assessed at the 66 months' visit, if available, or at the next closest visit between age 54 and 78 months. The intake of protein, carbohydrate and fat was calculated as percentages of the total energy (E %). We then calculated mean intake of energy, protein, carbohydrates and fat at all consecutive visits within one year, e.g. intake at the age of 0.25–1.0 years was defined as

mean intake at the age of 3 to 12 months, and intake at 4.5–5.0 years as mean intake at the age of 54 and 60 months, respectively. Gestational weight gain was classified as inadequate, adequate or excessive according to Institute of Medicine guidelines for total weight gain during pregnancy (24). As in a previous analysis on the TEDDY data (25), child's birth weight was transformed to a z-score adjusting for country, sex, gestational age, birth type (singleton / multiplet) and maternal height.

Statistical analyses

From the 8,676 children enrolled in TEDDY, data of 5,563 children were available for this analysis (figure 1). Exclusions applied to children who were followed up for less than 5 years, or who had missing or implausible BMI-SDS values at the age of 5.5 years. To assess potential attrition bias, subjects included and excluded were compared with respect to covariates using Chi-Square tests. We calculated odds ratios (ORs) with respective 95% confidence intervals (CIs) for overweight and obesity at the age of 5.5 years, respectively, by intake of energy, protein, carbohydrates and fat at previous ages using separate logistic regression models for each predictor variable and age. Additionally, we determined the age of incident overweight / obesity as the age when overweight / obesity persisting until the age of 5.5 years first occurred. For example, if a child became overweight at 4 years of age and remained overweight until 5.5 years, the incidence age was set to 4 years, irrespectively of whether the child had already been intermittently overweight at an earlier age. We assessed short-term associations of energy, protein, carbohydrates and fat intake at each visit with incident overweight and obesity at each following visit using logistic regression with time-varying predictors. For this analysis, we excluded all visits when children were found to have only intermittently overweight / obesity. All models were calculated both unadjusted and adjusted for the potential confounders sex, country, birth weight z-score, maternal age, maternal pre-pregnancy BMI, gestational weight gain rate, maternal diabetes (yes/no), maternal smoking in pregnancy (yes/no), maternal alcohol intake in pregnancy (any/none), maternal education (high-school or lower/more than high-school), and duration of any breastfeeding (less/more than 6 months). We further assessed percentile-specific associations between energy, protein, carbohydrate and fat intake at the age of 4.5–5.0 years and BMI-SDS at the age of 5.5 years using quantile regression (26), and used interaction terms to explore potential effect modifications of intakes at this age with the following genotypes / SNPs which had previously been found to be associated with childhood overweight risk (25, 27, 28): HLA-DQ 2/2, rs9939609 (in/near to FTO); rs17782313 (MC4R), rs6548238 (TMEM18), rs10938397 (GNPDA2), rs368794 (KCTD15), rs2568958 (NEGR1), rs925946 (BDNF), rs7647305 (ETV5), rs1421085 (FTO), and rs987237 (TFAP2B). In a sensitivity analysis, we excluded all children who did not have a weight and height measurement between age 63 and 69 months or who had already developed type 1 diabetes at the time of the weight and height measurement which was used to define BMI-SDS at the age of 5.5 years, in order to investigate potential bias by reverse causation or potential weight loss due to type 1 diabetes. For all analyses, the significance level was set to 0.05, with the exception of the genetic interaction analyses, where we set the significance level to 0.05/11=0.0045 to account for multiple testing by the number of investigated genotypes / SNPs. All calculations were carried out with SAS 9.4 (SAS Institute Inc, Cary, North Carolina) and R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Children included in the analyses had a median BMI-SDS of 0.28 (interquartile range −0.31, 0.92) at the age of 5.5 years. In our dataset, 1,253 children (22.5 %) were classified as having overweight (including obesity), and 337 (6.1 %) as having obesity at the age of 5.5 years (table 1). The respective weight and height measurements had been recorded at a median age of 66 (interquartile range: 65–67) months. Not having a BMI-SDS measurement at the age of 5.5 years due to loss to follow-up or missing / implausible BMI values was significantly associated with being female (p=0.03), country (only 21 % of the Finnish children were excluded compared to 40 % of the US children; p<0.01), maternal smoking (p<0.01) and low maternal education (p<0.01), but not with maternal alcohol intake (p=0.11) or pre-pregnancy overweight (BMI > 25 kg/m^2; p=0.23). Of all children who had overweight / obesity at the age of 5.5 years, 44 % and 63 % had already persistent overweight from the age of 2 and 4 years, as well as 16 % and 38 % persistent obesity, respectively (figure S1).

Mean energy intake increased steadily by age, while, relative to energy intake (E%), protein and carbohydrate intake increased and mean fat intake decreased until age 18 months and remained relatively stable, thereafter (table S1). Compared to normal-weight children, subjects who were overweight at the age of 5.5 years had slightly higher mean values of protein intake from the age of 3.5 years onwards, and of energy intake over the whole observation period, while there seemed to be no obvious differences for carbohydrate and fat intake.

Accordingly, overweight and obesity at the age of 5.5 years were positively associated with mean energy intake in previous age intervals, particularly during the first year of life. For example, the adjusted ORs [95% CI] for overweight were 1.47 [1.37, 1.58] and 1.06 [1.04, 1.09] per 100 kcal intake at the age of 0.25–1.0 and 4.5–5.0 years, indicating that an increase in energy intake by 100 kcal elevated the risk for overweight by 47% and 6%, respectively. Increased risks of overweight and obesity were also observed with respect to a greater protein intake after the age of 3.5 and 4.5 years, respectively, but not at earlier ages (e. g. adjusted OR for overweight: 1.06 [1.03, 1.09] per 1 % of energy intake at the age of 4.5–5.0 years, figure 2). The respective associations with carbohydrate and fat intake across age of intake were less consistent, with significantly increased ORs for obesity (but not overweight) at the age of 5.5 years by a greater fat intake at 2.5–3.0 and 3.5–4.0 years only, and significantly decreased ORs by a greater carbohydrate intake at the same ages. The observed associations did not change considerably when the data were restricted to those subjects who had a weight and height measurement between age 63 and 69 months and had not already developed type 1 diabetes at the age of 5.5 years (data not shown). Energy and protein intake were also positively associated with both incident overweight and obesity risk in analyses using time-varying predictors (e.g. adjusted ORs for overweight: 1.06 [1.04, 1.08] per 100 kcal energy intake and 1.03 [1.02, 1.05] per E% protein intake), while carbohydrate and fat intake were not (table 2).

There was no clear pattern of increasing or decreasing quantile regression estimates across the investigated BMI-SDS percentiles at the age of 5.5 years with respect to energy, protein,

carbohydrate or fat intake at the age of 4.5–5.0 years with almost all 95% CIs covering the linear regression estimates (figure 3), thus not indicating considerable percentile-specific associations. There were also no significant interactions between energy, protein, carbohydrate or fat intake at age 4.5–5.0 years and any of the available overweight risk genotypes / SNPs with respect to overweight at 5.5 years (data not shown).

Discussion

These analyses showed that protein intake is positively associated with increased risk for overweight within up to one or two years, but did not yield evidence for early programming effects of a greater protein intake in early infancy with respect to overweight / obesity at the age of 5.5 years. In contrast, we observed that a greater energy intake at any previous age was associated with increased risk for overweight at 5.5 years. We found no consistent associations with respect to carbohydrate and fat intake.

Our findings confirm previous studies that energy intake is positively associated with higher BMI and overweight risk (29, 30). Interestingly, we observed that BMI at the age of 5.5 years was associated with protein intake around the age of 4–5 years, but not at earlier ages. Further, we observed that the incidence of overweight / obesity persisting until the age of 5.5 years was positively associated with intake of protein about 3–6 months prior. Our findings therefore seem to indicate that a greater protein intake may be relevant for both initiating and maintaining overweight in children. However, we found no evidence for potential programming effects by protein intake in very early life as suggested by other studies (11, 31, 32). Instead, a greater energy intake during the first year of life was found to be a strong predictor of overweight at the age of 5.5 years in our data. The odds ratio for overweight by energy intake at this age was even by far larger than the respective odds ratios by energy intake at later ages. This may, however, simply be due to the fact that 100 kcal of energy intake, which was used as the reference unit in all models, is a much larger proportion in relation to the body weight of an infant compared to a toddler or older child. In our models, a relative increase of 50% in the prevalence of overweight at 5.5 years was associated with a difference in daily energy intake of about 100 kcal at the age of 0.25–1.0 years and of 700 kcal at the age of 4.5–5.0 years.

We observed neither major percentile-specific associations nor evidence for effect modification by increased genetic susceptibility. While we had found corresponding association patterns for a number of risk factors of childhood overweight such as maternal overweight, low parental education or exclusive formula-feeding (33), we had already observed less evidence for such patterns or for effect modification by genetic factors with respect to nutritional variables in a previous study (34). Based on these findings, we consider it rather unlikely that the associations of energy and protein intake with childhood overweight are largely driven by genetically susceptible subgroups, although we cannot rule out that other genetic variants which we were not able to investigate here may play a role.

We believe that the quality of the data analysed is high. Dietary assessment in the TEDDY study was based on 24h recalls at 3 months of age and 3-day food records from 6 months of age. The 24h recall was conducted at 3 months of age, where infants predominantly received

breastmilk or infant formula and only few infants were introduced to solid food already (35). The low variability in diet during that age may facilitate recalling, therefore we do not think that the use of the different dietary assessment methods affected our results. The calculation of nutrients is based on established, harmonized and up-to-date food databases from each country (21). Although the country-specific recording of foods may affect the comparability of specific nutrients such as soluble fiber (36), the intake of energy and macronutrients have been harmonized to be well comparable across countries. The mean values of these nutrients over time as observed in our data appear plausible and are comparable to those from other studies (37).

We used the WHO references for BMI to define overweight and obesity, because these had been established also for the age of 0–2 years and thus allowed us to use a uniform definition of overweight / obesity across different ages. Further, we aimed to use international references for this multinational cohort.

It should be noted, however, that the TEDDY cohort is not population based as participation was restricted to infants with increased genetic risk to develop type 1 diabetes. Such children usually have a slightly higher background prevalence of overweight, partly due to exposure to hyperglycemia in utero (38), but apart from that are not likely to be considerably different from a comparable population of healthy children. Unfortunately, we were not able to assess associations with BMI during school age, because some of the TEDDY subjects did not have sufficient follow-up yet. Follow-up compliance until age 5.5 years was better in children of high-educated, non-smoking mothers. However, we do not think that this may have biased our findings considerably, as we adjusted our analyses for these factors. We observed that 44 % and 16 % of all children who were deemed having overweight / obesity at the age of 5.5 years had already persistent overweight / obesity from the age of 2 years, respectively. These proportions are relatively similar to persistence rates of overweight and obesity at comparable ages as observed in other studies (39, 40). In summary, our results indicate that energy and protein intake are positively associated with increased risk for overweight in childhood, but yield no evidence for potential programming effects of protein intake in early infancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

BMI	body mass index
CI	confidence interval
E%	percent of energy intake
HLA	human leukocyte antigen
OR	odds ratio
SDS	standard deviation score
SNP	single nucleotide polymorphism
TEDDY	The Environmental Determinants of Diabetes in the Young

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What is already known about this subject?

- There is limited evidence on the potential impact of dietary intake during childhood on body mass index (BMI)
- It appears likely that a greater energy intake is a potential risk factor of overweight, much less is known about early fat, carbohydrate and protein intake.
- In particular, greater protein intake in infancy has been associated with potential long-term programming effects of overweight.

What does this study add?

- In data from a prospective cohort study of children with increased genetic risk of type 1 diabetes, energy intake at any previous age was positively associated with increased risk for overweight at 5.5 years.
- A greater intake of protein was associated with increased risk for overweight within up to one or two years, but there was no evidence for early programming effects of a greater protein intake.
- We found no consistent associations with respect to carbohydrate and fat intake.

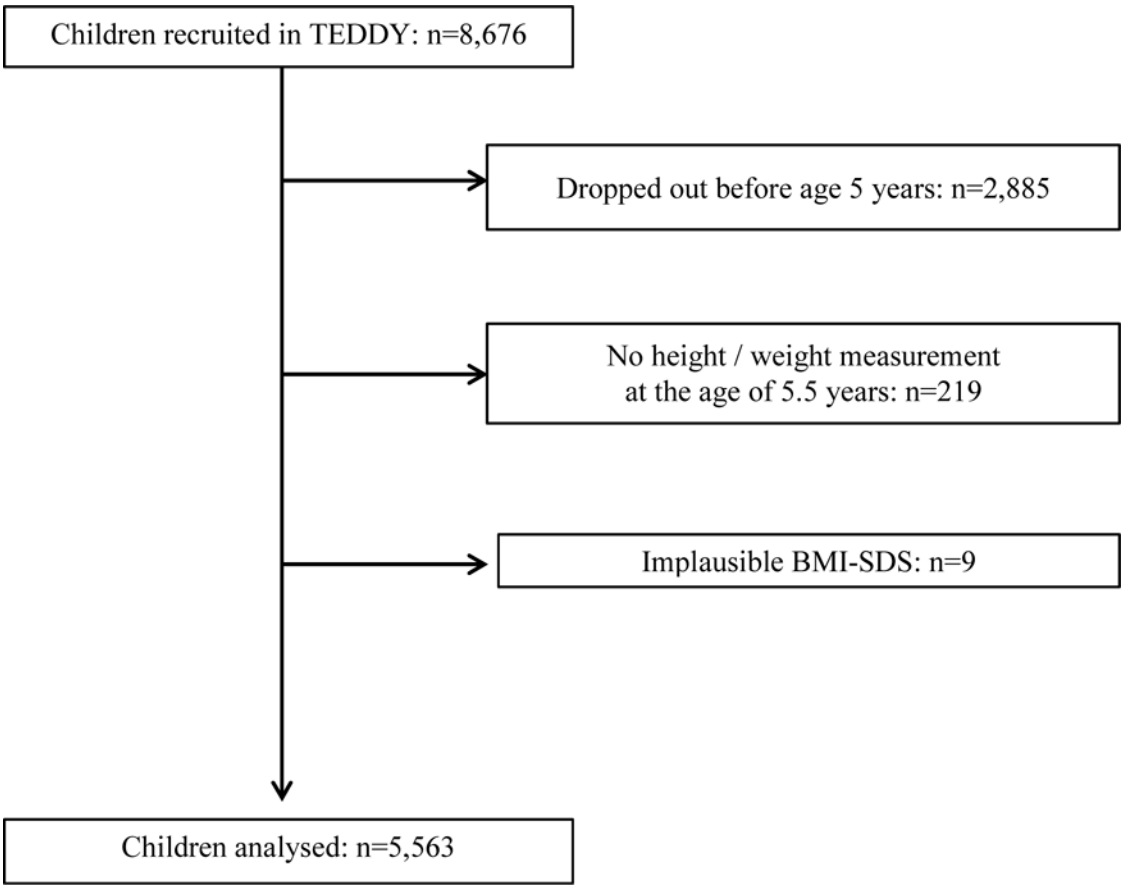

Figure 1.
Flowchart of children analysed.

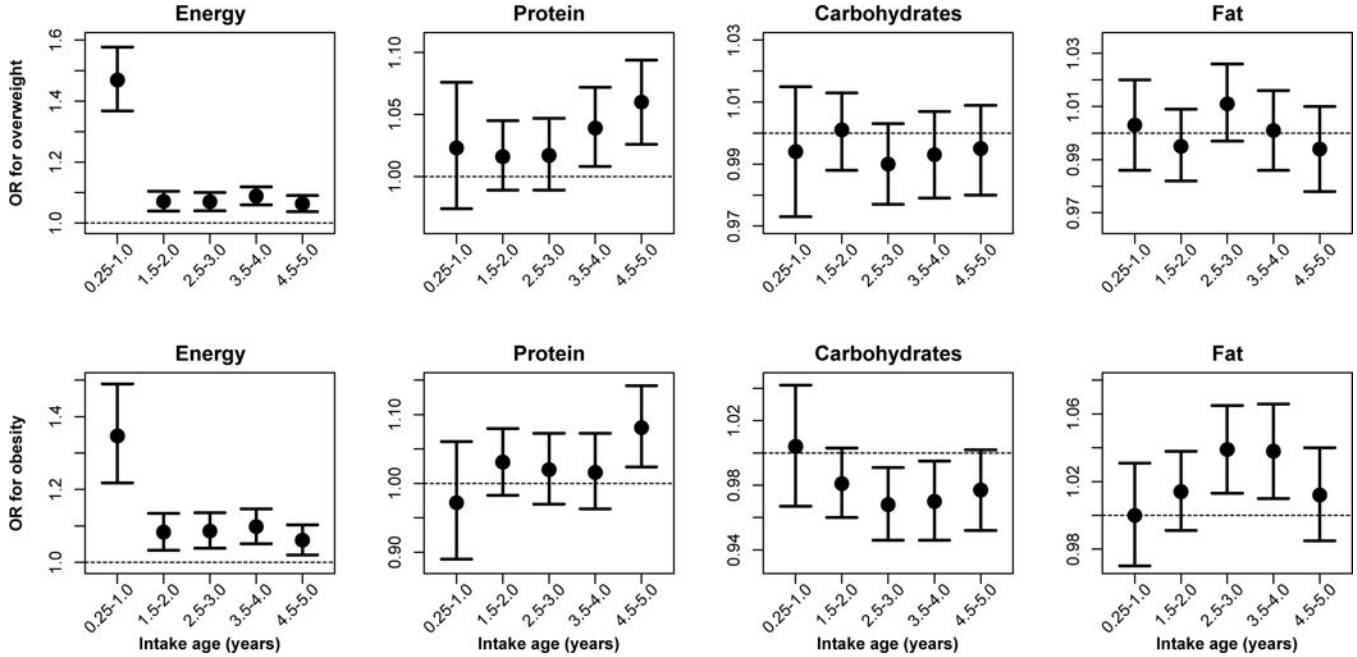

Figure 2.

Odds ratios (ORs) and 95% confidence intervals of overweight and obesity at the age of 5.5 years by age of intake of energy (per kcal/day), protein, carbohydrates and fat (per 1 % of energy intake), adjusted for sex, country, birth weight, maternal age, maternal pre-pregnancy body mass index, gestational weight gain, maternal diabetes, maternal smoking in pregnancy, maternal alcohol intake in pregnancy, maternal education, and duration of breastfeeding. The dashed horizontal lines depict 1.00 as reference.

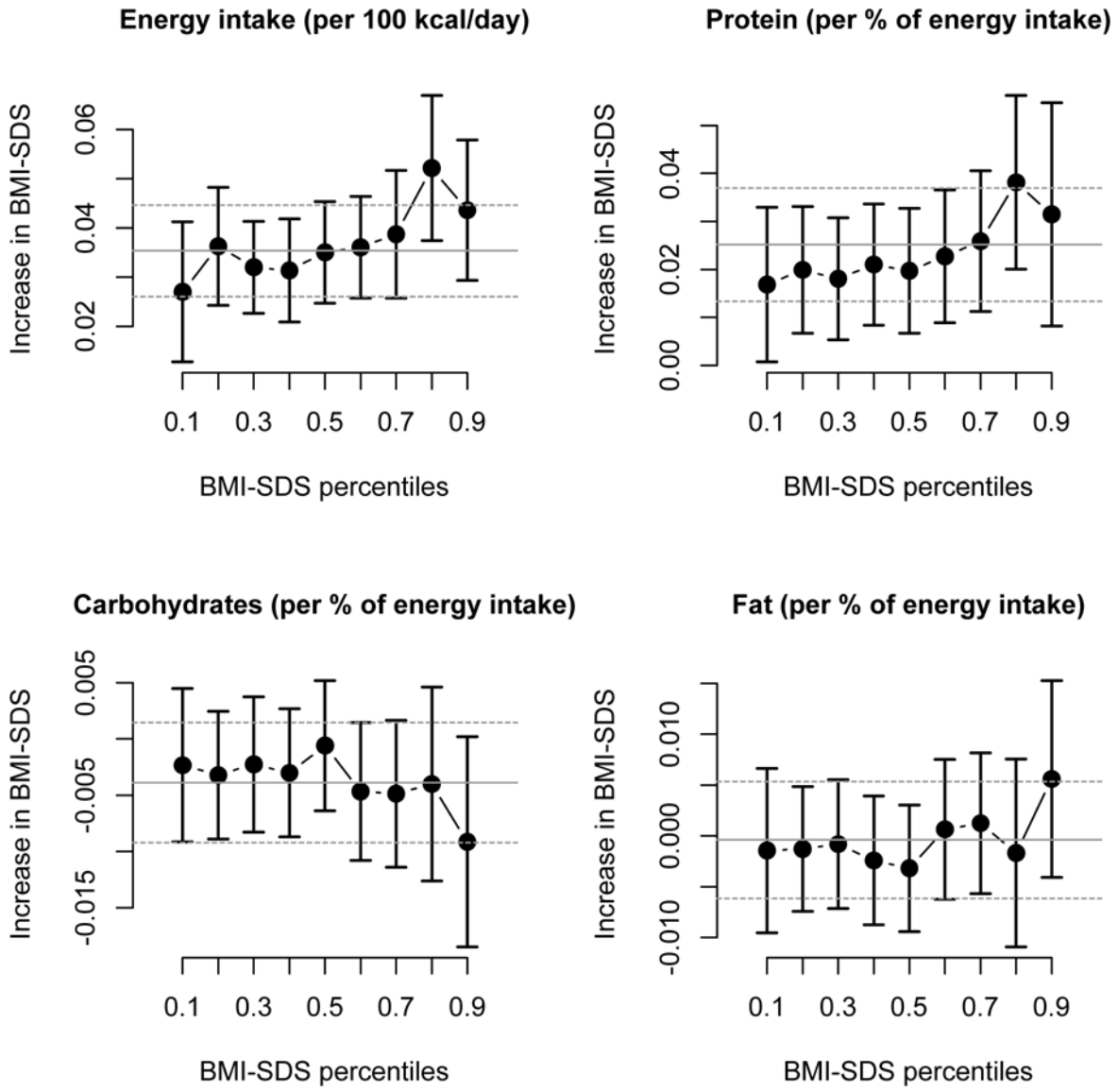

Figure 3.

Quantile regression estimates and 95% confidence intervals for differences in sex- and age-specific BMI-SDS percentiles (0.1 to 0.9 deciles) at the age of 5.5 years by intake of energy, protein, carbohydrates and fat at the age of 4.5–5.0 years. The grey horizontal lines represent the linear regression coefficients and their respective confidence intervals. All models were adjusted for sex, country, birth weight, maternal age, maternal pre-pregnancy body mass index, gestational weight gain, maternal diabetes, maternal smoking in pregnancy, maternal alcohol intake in pregnancy, maternal education, and duration of breastfeeding.

Table 1

Description of the study population (n=5,563). Values are reported as n (% of non-missing observations) for categorical variables and median (interquartile range (IQR)) for continuous variables.

Variable	n missing	n (%)/median (IQR)
BMI SDS at the age of 5.5 years	–	0.28 (−0.31, 0.92)
Overweight at the age of 5.5 years	–	1253 (22.5 %)
Obesity at the age of 5.5 years	–	337 (6.1%)
Males	–	2862 (51.5%)
Country	–	
US	–	2104 (37.8%)
Finland	–	1301 (23.4%)
Germany	–	307 (5.5%)
Sweden	–	1851 (33.3%)
Birth weight (grams)	127	3525 (3175, 3860)
Maternal age at birth of child (years)	–	31.0 (28.0, 34.0)
Maternal pre pregnancy BMI (kg/m^2)	91	23.5 (21.3, 27.0)
High maternal education (high school)	92	4532 (82.8%)
Breastfeeding ≥ 6 months	–	3603 (64.8%)
Excessive total gestational weight gain (according to Institute of Medicine guidelines (21))	126	2519 (46.3%)
Maternal diabetes (yes)	172	571 (10.6%)
Maternal smoking during pregnancy (yes)	47	541 (9.8%)
Maternal alcohol intake during pregnancy (yes)	45	1911 (34.6%)

BMI – body mass index; SDS – standard deviation score

Table 2

Odds ratios [95% confidence intervals] for incident overweight/obesity by intake of energy (per 100 kcal/day), protein, carbohydrates and fat (each per 1 % of energy intake) within 6 months after each diet record, modelled as time-varying predictors. Models were calculated with and without adjustment for sex, country, birth weight, maternal age, maternal pre-pregnancy body mass index, gestational weight gain, maternal diabetes, maternal smoking in pregnancy, maternal alcohol intake in pregnancy, maternal education, and duration of breastfeeding.

Outcome	**Energy intake**		**Protein intake**		**Carbohydrate intake**		**Fat intake**	
	Unadjusted model	***Adjusted model***	***Unadjusted model***	***Adjusted model***	***Unadjusted model***	***Adjusted model***	***Unadjusted model***	***Adjusted model***
Overweight	1.06 [1.04, 1.07]	1.06 [1.04, 1.08]	1.03 [1.01, 1.04]	1.03 [1.02, 1.05]	0.99 [0.98, 1.002]	0.99 [0.98, 1.002]	1.00 [0.99, 1.01]	1.00 [0.99, 1.01]
Obesity	1.14 [1.12, 1.17]	1.15 [1.12, 1.18]	1.12 [1.08, 1.15]	1.12 [1.08, 1.16]	1.00 [0.98, 1.02]	1.00 [0.98, 1.02]	0.97 [0.95, 0.98]	0.97 [0.95, 0.98]