From
The Institute of Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-University of Munich, Germany
Chair of Epidemiology: Prof. Dr. Dr. H.-E. Wichmann (emeritus)
and
The Institute of Epidemiology I, Helmholtz Zentrum München – German Research Center for Environmental Health (GmbH)
Director: Dr. J. Heinrich

Longitudinal modeling of growth in children from birth to adolescence and the potential influence of diet

Dissertation
Submitted for a Doctoral degree in Human Biology at the Faculty of Medicine, Ludwig-Maximilians-University of Munich, Germany

By
Zhengcun Pei
from
Liaoning, China
2014

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter:	Prof. Dr. Dr. H.-Erich Wichmann
Mitberichterstatter:	PD. Dr. Maximilian Bielohuby
	Prof. Dr. Rüdiger von Kries
Mitbetreuung durch den promovierten Mitarbeiter:	
Dekan:	Prof. Dr. med. Dr. h.c. M. Reiser, FACR, FRCR
Tag der mündlichen Prüfung:	28.08.2014

CONTENTS

1 Summary

Obesity is a major public health challenge. Modeling growth and identifying children at risk of being overweight in early life is essential for effective prevention and intervention. To date, longitudinal studies from birth to adolescent are rare, and crucial period in childhood for overweight in future life is unclear. In addition, apart from known risk factors of overweight or obesity, further research on other potential risk factors is necessary. Even though it is well accepted that obesity is mainly a consequence of an unbalanced energy status, the impact of specific food item or food group on growth has long been controversial, which calls for more efforts.

In order to contribute to the aforementioned questions and research problems, we conducted a series of studies using data from two ongoing German birth cohorts. 1) Using longitudinal anthropometric data from birth to 5 years, we established a 10-year-overweight prediction model. Our results suggest that from 5 years onwards being overweight become predictive for 10-year overweight. 2) We investigated the association between mode of delivery and childhood obesity using cross-sectional data at age 2, 6 and 10 years. Children delivered by cesarean section were more likely to be obese at 2 years compared to those delivered vaginally, but not at age 6 and 10 years. These results do not support the hypothesis that increasing rates of cesarean section contribute to the childhood obesity epidemic. 3) We analyzed data from food frequency questionnaires which were completed during the 10-year follow-up, where we grouped 82 food items into 11 food groups. Our results suggest that intakes of meat, fish and beverages are important correlates of body weight status. In contrast, confectionery intake conversely associated with being overweight. Further study on the influence of possible reverse causation is needed. 4) We investigated the association between maternal BMI and child food intake at the age of 10 years. Our results suggest that maternal BMI and maternal overweight are important correlates of a child's intake of energy, meat and eggs. Potential impact of mother's weight status should be considered in diet counseling. Moreover, mother's participation in dietary counseling might be helpful to improve offspring diet pattern and weight status.

These studies contributed to the current knowledge on early identification of children at risk of overweight and the potential influence of diet. In addition, our results suggest more efforts on longitudinal studies and more attention on reverse causation and misreport in dietary assessments in future studies.

2 Zusammenfassung

Adipositas stellt eine große Herausforderung für das Gesundheitswesen dar. Die Modellierung von Wachstum sowie die frühzeitige Identifizierung von Kindern, die ein erhöhtes Risiko haben übergewichtig zu werden, sind unerlässlich für eine effektive Prävention und Intervention. Bisher gibt es nur sehr wenige longitudinale Studien von der Geburt bis ins Jugendalter hinein und kritische Lebensphasen während der Kindheit für die Entstehung von Übergewicht im späteren Leben sind noch unklar. Darüber hinaus ist abgesehen von bereits bekannten Risikofaktoren für Übergewicht bzw. Adipositas auch die Erforschung weiterer potentieller Risikofaktoren notwendig. Obwohl es allgemein anerkannt wird, dass Adipositas überwiegend die Konsequenz eines unausgewogenen Energiestatus ist, war der Einfluss des Verzehrs bestimmter Lebensmittel lange Zeit umstritten, was mehr Bemühungen erfordert.

Um zu den zuvor erwähnten Fragestellungen und Forschungsfragen beizutragen, haben wir eine Reihe von Studien basierend auf Daten von zwei laufenden deutschen Geburtskohorten durchgeführt. 1) Mit Hilfe longitudinaler anthropometrischer Daten von der Geburt bis zum Alter von 5 Jahren wurde ein Prädiktionsmodell für die Entstehung von Übergewicht im Alter von 10 Jahren erstellt. Unsere Ergebnisse deuten darauf hin, dass erst ab einem Alter von 5 Jahren Übergewicht deutlich prädiktiv dafür ist, auch mit 10 Jahren übergewichtig zu sein. 2) Wir haben den Zusammenhang zwischen dem Geburtsmodus und kindlicher Adipositas im Alter von 2, 6 und 10 Jahren, erforscht. Im Vergleich zu vaginal entbundenen Kindern haben per Kaiserschnitt entbundene Kinder ein höheres Risiko im Alter von 2 Jahren, nicht aber im Alter von 6 oder 10 Jahren, adipös zu sein. Diese Ergebnisse stützen nicht die Hypothese, dass die steigende Kaiserschnittrate eine höhere Rate an adipösen Kindern zur Folge hat. 3) Wir haben Daten, welche mittels eines Ernährungsfragebogens während des 10 Jahres-Follow-up erhoben wurden, ausgewertet, wobei 82 Nahrungsmittel in 11 verschiedene Nahrungsmittelgruppen zusammengefasst wurden. Unsere Ergebnisse deuten darauf hin, dass die Aufnahmen von Fleisch, Fisch und zuckerhaltigen Getränken wichtige Korrelate des Körpergewichtes sind. Im Gegensatz dazu ist der Konsum von Konditorwaren negativ mit Übergewicht assoziiert. Somit bedarf es weiterer Studien zur Erforschung einer möglichen inversen Kausalität. 4) Wir haben den Zusammenhang zwischen mütterlichem BMI und der Nahrungsaufnahme des Kindes im Alter von 10 Jahren untersucht. Unsere Ergebnisse weisen darauf hin, dass der mütterliche BMI und mütterliches Übergewicht wichtige Korrelate der kindlichen Energieaufnahme sowie der Aufnahme von Fleisch und Eiern sind. Bei der Ernährungsberatung sollten demnach mögliche Auswirkungen des Gewichtsstatus der Mutter

berücksichtigt werden. Zudem könnte die Teilnahme der Mutter an der Ernährungsberatung hilfreich sein, um das Ernährungsverhalten und den Gewichtsstatus des Kindes zu verbessern.

Diese Studien haben zu dem gegenwärtigen Wissen über die frühe Identifizierung von Kindern mit einem erhöhten Risiko übergewichtig zu werden sowie zu dem Wissen über den möglichen Einfluss der Ernährung beigetragen. Außerdem weisen unsere Ergebnisse auf größere Bemühungen bezüglich longitudinaler Studien hin und auch darauf in zukünftigen Studien der inversen Kausalität bei der Ernährungsbewertung mehr Aufmerksamkeit zu schenken.

3 Introduction

3.1 Background

Obesity is a major public health challenge [1]. According to the 2010 International Obesity Task Force analysis, approximately 200 million school-aged children are overweight or obese around the world [2]. Obesity increases the likelihood of numerous diseases, particularly cardiovascular disease [3], type 2 diabetes [4], sleep disorders [5], etc. Being overweight during childhood and adolescence adversely affects mortality and morbidity in adulthood [6, 7]. Obesity accounts for a heavy financial burden on the public health system [8].

1) Early life risk factors of being overweight at 10 years of age

Identifying children at risk of being overweight early in life is essential for effective prevention and intervention [9]. Early life growth parameters are predictive for obesity in later life [10]. High birth weight is associated with increased subsequent risk of obesity [11]. Furthermore, Shankaran et al. reported that children who are overweight at younger ages have a higher risk of being overweight at 11 years of age. Moreover, it was noted that measurements taken closer to 11 years of age had greater predictive power [12]. These results are in line with other studies [13, 14].

There are many other factors which may increase the likelihood of being overweight later in life, such as low parental education level, low socioeconomic status [15], maternal smoking during pregnancy [16], rapid growth during the first two years of life, short duration of breastfeeding, obesity in infancy, <30 min of daily physical activity, and consumption of sugar-sweetened beverages, etc [17, 18].

To date, prediction models for being overweight and obese have been developed based on some of the afore-mentioned determinants. However, prediction models utilizing information on body mass indices (BMIs) collected during very early life (< 5 years) are scarce.

2) Cesarean section and risk of childhood obesity

Mode of delivery shapes the acquisition and structure of infants' microbiota. Infants born by cesarean section (CS) acquire different bacterial communities compared to vaginally delivered infants [19, 20]. The gut microbiota is considered to be a modifying factor for obesity [21-24]. Gut microbiota may contribute to obesity by increasing dietary energy utilization, promoting fat deposition, and triggering systemic inflammation [23, 24].

Previous studies report conflicting results on the association between cesarean section and obesity [25-29]. A recent meta-analysis concluded that CS was moderately associated with offspring overweight and obesity [30]. The 'hygiene hypothesis' is the background of possible relationships [31]. In addition, altered postnatal feeding and metabolic control in CS versus vaginal delivered infants may have long term effects on appetite regulation or energy metabolism and may contribute to the significant increase in body mass [32]. To date, the long-term effect of CS on children's growth remains controversial.

3) Food intake and overweight in school-aged children

Obesity is mainly a consequence of an unbalanced energy status [33]. However, the impact of specific food item or food group on growth has long been controversial [34-36]. Possible reasons for the conflicting results include that different applied models, food habits, portion size estimation, as well as ethnicity and cultural differences [37].

Four types of models (standard multivariate model, residual nutrient model, energy partition model, multivariate nutrient density model) were commonly used in previous studies that adjusted for total energy intake [38, 39]. The results of these models can and have been interpreted using different perspectives. One important difference between energy partition models and other types of models aforementioned is that the coefficient calculated from this former type of model represents both energy and non-energy associations with the nutrient. The coefficient obtained from other model types leads to iso-caloric substitution interpretations [38]. Iso-caloric interpretations are problematic when total energy intake is associated with the outcome under study [38].

However, few studies on food intake and obesity have applied an energy partition model. In addition, food items with similar dietary content possibly have similar effect on growth. Therefore food groups may be of interest in dietary studies. To date, the associations between food groups with BMI z-scores and being overweight during childhood remain controversial.

4) Maternal body mass index and food intake in school-aged children

Parental BMI probably impose genetic and environmental influences on the development of obesity in offspring [40]. Parental BMIs, especially maternal BMI [41, 42], are associated with offspring BMIs and weight statuses [41-44]. Given that eating behavior differs among obese and normal weight individuals [45], and that parental eating behavior traits are

correlated with offspring BMI [46], overweight and normal weight mothers possibly impose different influences on their children's food intake.

Previous studies have focused on the associations between maternal feeding practices (i.e. restriction to eat less or pressure to eat more food) and child food intake or child weight [47, 48]. It is currently unclear whether maternal BMI correlates with child food intake.

In order to contribute to the current knowledge on growth modeling and potential risk factors for overweight or obesity, four studies were conducted with following specific aims. 1) To develop a prediction model that quantifies the risk of being overweight at 10 years of age. Moreover, to investigate which periods during the first 5 years of life are crucial for being overweight at 10 years. 2) To investigate whether delivery by a cesarean section, compared to vaginal delivery, is a risk for childhood obesity. Moreover, to investigate whether the associations between cesarean delivery and childhood obesity are consistent at the age of 2, 6 and 10 years. 3) To investigate associations between intakes of 11 food groups and being overweight in children at the age of 10 years. Moreover, to investigate associations between being overweight with specific food items. 4) To investigate associations between maternal BMI/overweight and intakes of 11 food groups in children. Moreover, to investigate associations between maternal BMI/overweight with specific food items.

3.2 Methods

Data used were from two ongoing German birth cohorts GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) and LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics).

GINIplus is an ongoing birth cohort study initiated to prospectively investigate the influence of a nutritional intervention during infancy, as well as air pollution and genetics, on allergy development. GINIplus participants (N=5991 newborns) were recruited from obstetric clinics in Munich and Wesel between September 1995 and July 1998. Details of the study design are described elsewhere [49].

LISAplus is an ongoing birth cohort examining the impact of lifestyle-related factors, air pollution, and genetics on immune system and childhood allergy development. In total, 3097 neonates were recruited from 14 obstetrical clinics in Munich, Leipzig, Wesel, and Bad

Honnef between November 1997 and January 1999. A detailed description of the study's screening and recruitment has been described previously [50].

Approval by the respective local ethics committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North-Rhine-Westphalia) and written consent from all participating families were obtained for both studies.

1) Early life risk factors of being overweight at 10 years of age

Anthropometric measurements of weight and height were collected by pediatricians during physical examinations at birth, at weeks 4–6, at months 3–4, 6–7, 10–12, 21–24, 46-48, 60-64, and at 10 years of age. In total, 3121 participants from the GINIplus and LISAplus German birth cohorts were recruited.

BMI values were calculated from these weight and height measurements and transformed to standardized deviation scores (z-scores) according to the sex- and age-specific 'WHO-Child-Growth-Standards' for children [51, 52].

We predicted standardized body mass index (BMI) at 10 years of age using standardized BMIs from birth to 5 years. Parental education, family income and maternal smoking during pregnancy were considered as covariates. As the distribution of family income was skewed, this information was grouped into three categories based on the quartiles of monthly average income per person in the household (low for < 25%, medium for 25-75% and high for > 75%). Parental education levels were defined based on the highest number of years either parent attended school (low<10 years, medium=10 years and high> 10 years).Linear and logistic regression models were used to evaluate the impact of risk factors on BMI and on being overweight at 10 years of age, respectively.

2) Cesarean section and risk of childhood obesity

Data were analyzed from the LISAplus study. The number of children for which had information on mode of delivery and anthropometric measurements at 2, 6, and 10 years of age was 1734, 1244, 1170, respectively. Mode of delivery was defined as a binary variable: CS and vaginal delivery.

Potential influencing factors included city of recruitment, parental education, duration of gestation, birth weight, head circumference at 3 days of age, maternal age, maternal pre-pregnancy BMI, and maternal smoking during pregnancy. Sociodemographic data and

maternal characteristics were collected by questionnaires at enrollment and during follow up visits. In addition, the feeding variables (i.e. breastfeeding initiation, exclusive breastfeeding duration, and timing of solid food introduction) were considered as potential mediators.

Multivariable linear and logistic regression models were used to evaluate the association between CS and BMI z-scores, being overweight and obesity. Models were adjusted for socioeconomic status, child characteristics, and maternal pre-pregnancy characteristics.

3) Food intake and overweight in school-aged children

During the 10-year follow-up, information on food intake was collected from 3437 participants (2194 from GINIplus, 1243 from LISAplus) by means of a justified semi quantitative Food Frequency Questionnaire (FFQ). Height and weight were measured for 3116 participants (1918 from GINIplus, 1198 from LISAplus) during the 10-year physical examinations. In the current study, 2565 children (1308 males and 1257 females) from GINIplus (n = 1596) and LISAplus (n = 969) with complete data on FFQ and BMI are included.

Information on food intake frequencies and portion sizes of 82 food items were collected using parent-completed questionnaires, and 11 food groups were defined according to the Codex General Standard for Food Additives' food category system [53]. Intakes were categorized (low, medium and high) using group- and sex-specific tertile cut-offs.

According to the definition of the partition model [38], we calculated energy intake from the food group itself and energy intake from all other food groups. Each model for the association between the energy intake of a specific group and being overweight was adjusted for the energy intake from all other food groups. The set of covariates examined were city of residence, parental education level, family income and screen viewing time. Low screen time included children who spent < 1 hour per day in summer and <2 hours per day in winter; high screen time included children who spent ≥ 1 hour per day in summer and ≥ 2 hours per day in winter. In addition, there were 15 children who spent < 1 hour per day in summer and ≥ 2 hours per day in winter viewing screens. They were finally included into the high screen time category.

Multivariate energy partition models assessed associations between food intake with BMI and being overweight. Models were adjusted for energy intake from other food groups, city, family income, parental education, and screen time.

4) Maternal body mass index and food intake in school-aged children

We analyzed data from 3230 GINIplus and LISAplus participants. The definition of eleven food groups and the energy partition term are the same as described in the previous study.

Based on maternal weight and height information collected at the 10-year questionnaire survey, maternal BMI was calculated. Two categories for maternal weight status were defined (normal weight: BMI < 25 kg/m^2; overweight: BMI ≥ 25 kg/m^2).

Multinomial regression models assessed associations between child food intake and maternal BMI/overweight. Linear regression models assessed associations between total energy intake and maternal BMI. Models were adjusted for study region, maternal education, age, sex, pubertal status, energy intake, and BMIs of the child and father.

For all the four studies, differences of characteristics between groups were tested using the Pearson's χ^2 test for categorical variables, the Student's t-test for normally distributed continuous variables, and the Mann-Whitney test for non-normally distributed continuous variables (i.e. intake of 11 food groups). Study characteristics are described using means and standard deviations (s.d.) or percentages (n/N, %). The food intake characteristics are described using median and percentiles. Model results are presented as linear regression coefficients (ß) and as odds ratios (OR) or risk ratios (RR) with corresponding 95% confidence intervals (CI). Results of multinomial regression models are presented as relative risk ratio (RRR) with 95% CI. Statistical significance was set at the conventional p-value < 0.05. All analyses were performed using the statistical software package R, version 2.14.1 [54].

3.3 Results

1) Early life risk factors of being overweight at 10 years of age

Standardized BMI at 10 years was significantly associated with birth weight (ß = 0.11, 95%CI = [0.03 ; 0.19]), standardized BMI at 60-64 months of age (ß = 0.77, [0.73; 0.81]), high parental education (ß = -0.15 [-0.29; -0.01]) and maternal smoking during pregnancy (ß = 0.13, [0.03; 0.22]), but not with high nor medium family income (ß = -0.01, [-0.11; 0.09] and ß = -0.04, [-0.12; 0.04], respectively).

Being overweight at the age of 60-64 months was a strong risk factor for being overweight at 10 years of age. Children who were overweight at the age of 60-64 months were

approximately 15 times more likely to be overweight at the 10 year examination compared to children who were not overweight at the age of 60-64 months. This effect was strongest among females (Odds Ratio (OR) = 17.75 [11.62; 27.10] vs. OR = 12.40 [8.41; 18.26] for females and males, respectively). The association between high parental education and being overweight at 10 years of age was also statistically significant among females (OR = 0.44 [0.22; 0.89] vs. OR = 0.70 [0.36; 1.35] for females and males, respectively).

2) Cesarean section and risk of childhood obesity

Mothers who underwent a CS delivery (~17%) had higher pre-pregnancy BMI (23.7 kg/m^2 vs. 22.5 kg/m^2) and higher gestational weight gain (15.3 kg vs. 14.5 kg), and shorter duration of exclusive breastfeeding (3.4 vs. 3.8 months) compared to those who delivered vaginally. The proportion of obese children at two years was greater among those delivered by CS compared to vaginally (13.6% vs. 8.3%), but not at older ages.

In the unadjusted linear models, cesarean delivery was positively associated with the BMI z-scores at age 2, 6, and 10 years (ß = 0.12 [0.00 to 0.25], ß = 0.14, [0.00 to 0.29], and ß = 0.24[0.08 to 0.40], respectively), but the estimate was attenuated after adjustment (ß = 0.10 [-0.03 to 0.23], ß = 0.05 [-0.10 to 0.19], ß = 0.11 [-0.05 to 0.28], respectively). Significant associations between CS and being overweight were not observed at all the three time points. Crude and adjusted odds ratios were significant between CS and obesity at age two years (OR_{crude} = 1.78 [1.21 to 2.62] vs. OR_{adj} = 1.68 [1.10 to 2.58]) but not at age six years (OR_{crude} = 2.15 [0.92 to 5.01] vs. OR_{adj} = 1.49 [0.55 to 4.05]) or ten years (OR_{crude} = 1.58 [0.88 to 2.84] vs. OR_{adj} = 1.16 [0.59 to 2.29]).

3) Food intake and overweight in school-aged children

Compared to children with a low intake of meat and meat products, children with medium and high intakes had greater BMI z-scores (ß = 0.10 [0.00; 0.20] and ß = 0.32 [0.21; 0.42], respectively). Children with high fish and beverage intakes had greater BMI z-scores than those with low fish and beverage intakes (ß = 0.13 [0.03 ~ 0.24] and ß = 0.23 [0.11; 0.35], respectively). Compared to children with a low intake of confectionery, children with medium and high confectionery intakes had smaller BMI z-scores (ß = -0.18 [-0.28; -0.07] and ß = -0.22 [-0.33; -0.12], respectively). No significant associations were found for the other food groups.

Compared to low intake groups, those with high intakes of meat, bakery, fish and beverage had a higher risk of being overweight (OR = 2.08 [1.58; 2.73], OR = 1.62 [1.24; 2.11], OR = 1.39 [1.08; 1.80] and OR = 1.36 [1.01; 1.84], respectively). Furthermore, those with medium and high intakes of confectionery were at a decreased risk of being overweight (OR = 0.64 [0.50; 0.83] and OR = 0.53 [0.40; 0.68], respectively). No significant associations were found for the other food groups.

4) Maternal body mass index and food intake in school-aged children

Maternal BMI was associated with high meat intake in children (adjusted relative risk ratio (RRR [95%CI]) = 1.06 [1.03; 1.09]). Maternal overweight was associated with child meat intake (medium vs. low RRR = 1.30 [1.07; 1.59]; high vs. low RRR = 1.50 [1.19; 1.89]) and egg intake (medium vs. low RRR = 1.24 [1.02; 1.50]; high vs. low RRR = 1.30 [1.07; 1.60]). There were no consistent associations for rest food groups.

In crude models, every one-unit increase in maternal BMI was associated with a total energy intake increase of 9.2 kcal [3.67 ~ 14.72] in the entire population. However, this effect was not significant after fully-adjusted (4.2 kcal [-1.9; 10.3]).

3.4 Discussion

1) Based on a large sample, we developed a model that uses measured anthropometric parameters during the first 5 years of life to predict being overweight at 10 years of age, with consideration of potential confounders, such as parental education, family income and maternal smoking during pregnancy, etc. In particular, information before 2 years of age was available at more time points in our study (at birth, at weeks 4-6, at months 3-4, 6-7, and 10-12). One limitation of the current study is a loss-of-follow-up over the time. In this study, 5965 (65.7%) subjects originally recruited at birth did not participate in the 10 year physical examination. Non-participants were more likely to be overweight, come from a family with a low household income and low parental education, and their mothers were more likely to have smoked during pregnancy.

2) Using data at age 2, 6 and 10 years, we investigated the association between cesarean delivery and childhood obesity. The strength of the current study is the use of measured anthropometric data at 2, 6, and 10 years of age in a large birth cohort. We provided long-term data on the association between CS and obesity, after considering various set of potential influencing factors. Our results were adjusted for maternal pre-pregnancy BMI and early feeding variables, which were ignored by several previous studies. We also used unselected

healthy full term infants in our analyses, whereas most previous studies did not exclude premature or small for gestational age babies. One limitation of the current study is a lack of information on an early rupture of membrane in cases of CS. We also lack information on early life antibiotic exposure. In addition, the numbers of obese children in CS group at age 6 and 10 years were small (8 and 16, respectively), which may have led to the null findings.

3) We investigated cross-sectional associations between food group intake with BMI z-scores and with being overweight at 10 years of age, as well as associations between maternal BMI with child energy and food intake, using a qualified FFQ. These two studies has several strengths. Our analyses are based on two large population-based cohorts with measured anthropometric data. The food groups are defined according to the Codex General Standard for Food Additives' food category system, which allows our results to be compared to future studies. Instead of providing isocaloric interpretations, the multivariate energy partition models allowed us to interpret our results while taking both energy and non-energy effects of foods into account. One limitations of these studies is that causal relationship cannot be drawn using the cross-sectional data. A further limitation is that reporting bias may exist in our study as we used data collected from questionnaires. Differential, selective under-reporting may thus be influencing our results, especially for overweight participants. In addition, data on body composition and fat mass, mother's concerns for child's weight, mother's perception of child's weight, and child's own perception and concerns were not available. Future studies should consider these factors.

3.5 Conclusion

Our results revealed that BMI and being overweight at 5 years of age (60-64 months) are strong predictors of being overweight at 10 years of age; cesarean delivery may increase the risk for obesity during early, but not late childhood; intake of meat, fish and beverages may affect body weight status in children; maternal BMI and maternal overweight are important correlates of a child's intake of energy, meat and eggs. Overall, these studies contributed to the current knowledge on crucial periods during early life for overweight in later life, potential risk factors of childhood obesity, diet influences on childhood overweight, as well as potential maternal effect on child food intake. Moreover, our results provided new insights for early identification of children at risk of overweight, as well as overweight prevention and intervention. In addition, our results suggest more efforts on longitudinal studies and more attention on reverse causation and misreport in dietary assessments in future studies.

3.6 References

1. Chiolero A, Lasserre AM, Paccaud F, Bovet P (2007) Childhood obesity: definition, consequences, and prevalence. Rev Med Suisse 3:1262-1269.
2. International Obesity Task Force (2011) Obesity the global epidemic. Available at: http://www.iaso.org/iotf/obesity/obesitytheglobalepidemic/.
3. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH (2006) Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 113:898-918. doi 10.1161/CIRCULATIONAHA.106.171016.
4. Wild SH, Byrne CD (2006) ABC of obesity. Risk factors for diabetes and coronary heart disease. BMJ 333:1009-1011. doi 10.1136/bmj.39024.568738.43.
5. Gami AS, Caples SM, Somers VK (2003) Obesity and obstructive sleep apnea. Endocrinol Metab Clin North Am 32:869-894.
6. Reilly JJ, Kelly J (2011) Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. Int J Obes (Lond) 35:891-898. doi 10.1038/ijo.2010.222.
7. Biro FM, Wien M (2010) Childhood obesity and adult morbidities. Am J Clin Nutr 91:1499S-1505S. doi 10.3945/ajcn.2010.28701B.
8. Breitfelder A, Wenig CM, Wolfenstetter SB, Rzehak P, Menn P, John J, Leidl R, Bauer CP, Koletzko S, Roder S, Herbarth O, von Berg A, Berdel D, Kramer U, Schaaf B, Wichmann HE, Heinrich J (2011) Relative weight-related costs of healthcare use by children--results from the two German birth cohorts, GINI-plus and LISA-plus. Econ Hum Biol 9:302-315. doi 10.1016/j.ehb.2011.02.001.
9. Nader PR, O'Brien M, Houts R (2006) Identifying risk for obesity in early childhood. Pediatrics 118:e594-601. doi 10.1542/peds.2005-2801.
10. Li C, Goran MI, Kaur H, Nollen N, Ahluwalia JS (2007) Developmental trajectories of overweight during childhood: role of early life factors. Obesity (Silver Spring) 15:760-771. doi 10.1038/oby.2007.585.
11. Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, Guo XR (2011) Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. Obes Rev 12:525-542. doi 10.1111/j.1467-789X.2011.00867.x.
12. Shankaran S, Bann C, Das A, Lester B, Bada H, Bauer CR, La Gasse L, Higgins RD (2011) Risk for obesity in adolescence starts in early childhood. J Perinatol 31:711-716. doi 10.1038/jp.2011.14.
13. Angbratt M, Ekberg J, Walter L, Timpka T (2011) Prediction of obesity from infancy to adolescence. Acta Paediatr 100:1249-1252. doi 10.1111/j.1651-2227.2011.02326.x.
14. Janssen I, Katzmarzyk PT, Srinivasan SR, Chen W, Malina RM, Bouchard C, Berenson GS (2005) Utility of childhood BMI in the prediction of adulthood disease: comparison of national and international references. Obes Res 13:1106-1115. doi 10.1038/oby.2005.129.
15. Moens E, Braet C, Bosmans G, Rosseel Y (2009) Unfavourable family characteristics and their associations with childhood obesity: a cross-sectional study. Eur Eat Disord Rev 17:315-323. doi 10.1002/erv.940.
16. Toschke AM, Koletzko B, Slikker W, Jr., Hermann M, von Kries R (2002) Childhood obesity is associated with maternal smoking in pregnancy. Eur J Pediatr 161:445-448. doi 10.1007/s00431-002-0983-z.
17. Han JC, Lawlor DA, Kimm SY (2010) Childhood obesity. Lancet 375:1737-1748. doi 10.1016/S0140-6736(10)60171-7.

18. Koletzko B, Beyer J, Brands B, Demmelmair H, Grote V, Haile G, Gruszfeld D, Rzehak P, Socha P, Weber M (2013) Early influences of nutrition on postnatal growth. Nestle Nutr Inst Workshop Ser 71:11-27. doi 10.1159/000342533.
19. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R (2010) Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 107:11971-11975. doi 10.1073/pnas.1002601107.
20. Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, Sears MR, Becker AB, Scott JA, Kozyrskyj AL (2013) Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. CMAJ 185:385-394. doi 10.1503/cmaj.121189.
21. Ley RE (2010) Obesity and the human microbiome. Curr Opin Gastroenterol 26:5-11. doi 10.1097/MOG.0b013e328333d751.
22. Thompson AL (2012) Developmental origins of obesity: early feeding environments, infant growth, and the intestinal microbiome. Am J Hum Biol 24:350-360. doi 10.1002/ajhb.22254.
23. Tsai F, Coyle WJ (2009) The microbiome and obesity: is obesity linked to our gut flora? Curr Gastroenterol Rep 11:307-313.
24. Sanz Y, Rastmanesh R, Agostonic C (2013) Understanding the role of gut microbes and probiotics in obesity: how far are we? Pharmacol Res 69:144-155. doi 10.1016/j.phrs.2012.10.021.
25. Huh SY, Rifas-Shiman SL, Zera CA, Edwards JW, Oken E, Weiss ST, Gillman MW (2012) Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study. Arch Dis Child 97:610-616. doi 10.1136/archdischild-2011-301141.
26. Barros FC, Matijasevich A, Hallal PC, Horta BL, Barros AJ, Menezes AB, Santos IS, Gigante DP, Victora CG (2012) Cesarean section and risk of obesity in childhood, adolescence, and early adulthood: evidence from 3 Brazilian birth cohorts. Am J Clin Nutr 95:465-470. doi 10.3945/ajcn.111.026401.
27. Zhou L, He G, Zhang J, Xie R, Walker M, Wen SW (2011) Risk factors of obesity in preschool children in an urban area in China. Eur J Pediatr 170:1401-1406. doi 10.1007/s00431-011-1416-7.
28. Goldani HA BH, Barbieri MA et al (2011) Cesarean section is associated with an increased risk of obesity in adulthood in a Brazilian birth cohort study. Am J Clin Nutr 93:1344-1347.
29. Goldani MZ, Barbieri MA, da Silva AA, Gutierrez MR, Bettiol H, Goldani HA (2013) Cesarean section and increased body mass index in school children: two cohort studies from distinct socioeconomic background areas in Brazil. Nutrition J 12:104. doi 10.1186/1475-2891-12-104.
30. Li HT, Zhou YB, Liu JM (2012) The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis. Int J Obes (Lond). doi 10.1038/ijo.2012.195.
31. Musso G, Gambino R, Cassader M (2010) Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? Diabetes Care 33:2277-2284. doi 10.2337/dc10-0556.
32. Hyde MJ, Mostyn A, Modi N, Kemp PR (2012) The health implications of birth by Caesarean section. Biol Rev Camb Philos Soc 87:229-243. doi 10.1111/j.1469-185X.2011.00195.x.
33. Hill JO, Wyatt HR, Peters JC (2012) Energy balance and obesity. Circulation 126:126-132. doi 10.1161/CIRCULATIONAHA.111.087213.
34. Lanfer A, Hebestreit A, Ahrens W (2010) Diet and eating habits in relation to the development of obesity in children and adolescents. Bundesgesundheitsblatt,

Gesundheitsforschung, Gesundheitsschutz 53:690-698. doi 10.1007/s00103-010-1086-z.
35. Summerbell CD, Douthwaite W, Whittaker V, Ells LJ, Hillier F, Smith S, Kelly S, Edmunds LD, Macdonald I (2009) The association between diet and physical activity and subsequent excess weight gain and obesity assessed at 5 years of age or older: a systematic review of the epidemiological evidence. Int J Obes (Lond) 33 Suppl 3:S1-92. doi 10.1038/ijo.2009.80.
36. Hauner H, Bechthold A, Boeing H, Bronstrup A, Buyken A, Leschik-Bonnet E, Linseisen J, Schulze M, Strohm D, Wolfram G (2012) Evidence-based guideline of the German Nutrition Society: carbohydrate intake and prevention of nutrition-related diseases. Ann Nutr Metab 60 Suppl 1:1-58. doi 10.1159/000335326.
37. Collins CE, Watson J, Burrows T (2010) Measuring dietary intake in children and adolescents in the context of overweight and obesity. Int J Obes (Lond) 34:1103-1115. doi 10.1038/ijo.2009.241.
38. Willett WC, Howe GR, Kushi LH (1997) Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 65:1220S-1228S; discussion 1229S-1231S.
39. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC (1999) Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 149:531-540.
40. Maffeis C (2000) Aetiology of overweight and obesity in children and adolescents. Eur J Pediatr 159 Suppl 1:S35-44.
41. Danielzik S, Langnase K, Mast M, Spethmann C, Muller MJ (2002) Impact of parental BMI on the manifestation of overweight 5-7 year old children. Eur J Nutr 41:132-138. doi 10.1007/s00394-002-0367-1.
42. Linabery AM, Nahhas RW, Johnson W, Choh AC, Towne B, Odegaard AO, Czerwinski SA, Demerath EW (2013) Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels Longitudinal Study. Pediatr Obes 8:159-169. doi 10.1111/j.2047-6310.2012.00100.x.
43. Birbilis M, Moschonis G, Mougios V, Manios Y (2013) Obesity in adolescence is associated with perinatal risk factors, parental BMI and sociodemographic characteristics. Eur J Clin Nutr 67:115-121. doi 10.1038/ejcn.2012.176.
44. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH (1997) Predicting obesity in young adulthood from childhood and parental obesity. NEJM 337:869-873. doi 10.1056/NEJM199709253371301.
45. Laessle RG, Lehrke S, Duckers S (2007) Laboratory eating behavior in obesity. Appetite 49:399-404. doi 10.1016/j.appet.2006.11.010.
46. Gallant AR, Tremblay A, Perusse L, Despres JP, Bouchard C, Drapeau V (2013) Parental eating behavior traits are related to offspring BMI in the Quebec Family Study. Int J Obes (Lond) 37:1422-1426. doi 10.1038/ijo.2013.14.
47. Kroller K, Warschburger P (2008) Associations between maternal feeding style and food intake of children with a higher risk for overweight. Appetite 51:166-172. doi 10.1016/j.appet.2008.01.012.
48. Topham GL, Page MC, Hubbs-Tait L, Rutledge JM, Kennedy TS, Shriver L, Harrist AW (2010) Maternal depression and socio-economic status moderate the parenting style/child obesity association. Public Health Nutr 13:1237-1244. doi 10.1017/S1368980009992163.
49. von Berg A, Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, Hoffmann U, Reinhardt D, Grubl A, Heinrich J, Wichmann HE, Bauer CP, Koletzko S, Berdel D (2013) Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional

Intervention (GINI) study. J Allergy Clin Immunol 131:1565-1573. doi 10.1016/j.jaci.2013.01.006.
50. Heinrich J, Bolte G, Holscher B, Douwes J, Lehmann I, Fahlbusch B, Bischof W, Weiss M, Borte M, Wichmann HE (2002) Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. Eur Respir J 20:617-623.
51. WHO Anthro and macros. version 3.2.2, January 2011. Available at: http://www.who.int/childgrowth/software/en/.
52. WHO AnthroPlus software. Available at: http://wwwwhoint/growthref/tools/en/.
53. Food and Agriculture Organization of the United Nations/World Health Organization. (2011) Codex General Standard for Food Additives food category system. Available at: http://www.codexalimentarius.net/gsfaonline/docs/CXS_192e.pdf.
54. R Development Core Team R: a language and environment for statistical computing. Vienna, Austria, 2010 ISBN 3-900051-07-0 Available at: http://www.R-project.org.

4 Early life risk factors of being overweight at 10 years of age: results of the German birth cohorts GINIplus and LISAplus

Authors: Zhengcun Pei, Claudia Flexeder, Elaine Fuertes, Elisabeth Thiering, Berthold Koletzko, Claudia Cramer, Dietrich Berdel, Irina Lehmann, Carl-Peter Bauer, Joachim Heinrich for the GINIplus and LISAplus Study Group

Journal: European Journal of Clinical Nutrition

Year: 2013

Volume (doi): 67 (10.1038/ejcn.2013.80)

Electronic version:
http://www.nature.com/ejcn/journal/v67/n8/full/ejcn201380a.html

Impact factor: 2.756

OPEN

European Journal of Clinical Nutrition (2013), 1–8

www.nature.com/ejcn

ORIGINAL ARTICLE

Early life risk factors of being overweight at 10 years of age: results of the German birth cohorts GINIplus and LISAplus

Z Pei[1], C Flexeder[1], E Fuertes[1,2], E Thiering[1], B Koletzko[3], C Cramer[4], D Berdel[5], I Lehmann[6], C-P Bauer[7] and J Heinrich[1] for the GINIplus and LISAplus Study Group

OBJECTIVE: To develop a prediction model that quantifies the risk of being overweight at 10 years of age.
SUBJECTS/METHODS: In total, 3121 participants from the GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) and LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics) German birth cohorts were recruited. We predicted standardized body mass index (BMI) at 10 years of age using standardized BMIs from birth to 5 years. Parental education, family income and maternal smoking during pregnancy were considered as covariates. Linear and logistic regression models were used to evaluate the impact of risk factors on BMI and on being overweight at 10 years of age, respectively.
RESULTS: Birth weight, standardized BMI at 5 years (60–64 months) ($\beta = 0.77$; 95% confidence interval (CI): 0.73–0.81) and maternal smoking during pregnancy were positively associated with standardized BMI at 10 years of age. Standardized BMI and overweight at 5 years were strongest predictors of being overweight at 10 years. Conversely, high parental education conferred a protective effect ($\beta = -0.15$; 95% CI: -0.29 to -0.01). Being overweight at 5 years (60–64 months) increased the risk of being overweight at 10 years of age with odds ratios above 10. Among children who were predicted to be overweight at 10 years, cross-validation results showed that 76.8% of female subjects and 68.1% of male subjects would be overweight at 10 years of age.
CONCLUSION: BMI and being overweight at 5 years of age are strong predictors of being overweight at 10 years of age. The effectiveness of targeted interventions in children who are overweight at 5 years of age should be explored.

European Journal of Clinical Nutrition advance online publication, 24 April 2013; doi:10.1038/ejcn.2013.80

Keywords: overweight; obesity; children; risk factors; prediction

INTRODUCTION

Obesity is a major public health challenge. It is associated with numerous illnesses and often persists into adulthood.[1] Being overweight during childhood and adolescence adversely affects the onset of many diseases later in life.[2] Identifying children at risk of being overweight early on in life is essential for effective prevention and intervention.[3]

Shankaran *et al.*[4] reported that children who are overweight at younger ages have a higher risk of being overweight at 11 years of age. Moreover, it was noted that measurements taken closer to 11 years of age had greater predictive power. Similar results are found in other studies.[5,6] Several studies have also shown that birth weight and maternal smoking during pregnancy are associated with childhood obesity.[7–10] Familial factors can explain up to 27% of the variance in a child's weight status.[11] There are also many other factors that increase the likelihood of being overweight later in life, such as rapid growth during the first two years of life, short duration of breastfeeding, obesity in infancy, short sleep duration, <30 min of daily physical activity and consumption of sugar-sweetened beverages, and so on.[12,13] Prediction models for being overweight and obese have previously been developed based on some of these determinants, but those utilizing information on body mass indices (BMIs) collected during very early life (<5 years) are scarce.

In this study, we established an overweight prediction model using standardized deviation scores of anthropometric parameters collected during the first 5 years of life. Considering the availability of covariates and the aim of developing a concise and easily applicable prediction model, we only included parental education, socioeconomic status and maternal smoking during pregnancy as covariates. Cross-validation was used to test the validity of our prediction model.

METHODS

Study population

Data from two ongoing German birth cohorts of healthy full-term neonates were used in this study. GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) is an ongoing birth cohort study initiated to investigate prospectively the influence of a nutritional intervention during infancy, air pollution and genetics on allergy development. GINIplus participants ($N = 5991$ newborns) were recruited from obstetric clinics in Munich, Leipzig, Wesel and Bad Honnef between September 1995 and July 1998. Details of the study design are described elsewhere.[14,15] A total of 2252 newborns with atopic

[1]Institute of Epidemiology I, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany; [2]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada; [3]Dr von Hauner Children's Hospital, University of Munich Medical Centre, Munich, Germany; [4]Leibniz Institute of Environmental Medicine at Heinrich-Heine University, Duesseldorf, Germany; [5]Department of Pediatrics, Marien Hospital Wesel, Wesel, Germany; [6]Department of Environmental Immunology, UFZ-Centre for Environmental Research, Leipzig, Germany and [7]Department of Pediatrics, Technical University Munich and LVA Oberbayern, Munich, Germany. Correspondence: Dr J Heinrich, Institute of Epidemiology I, Helmholtz Zentrum München, Ingolstaedter Landstrasse 1, 85764 Neuherberg, Germany.
E-mail: heinrich@helmholtz-muenchen.de
Received 8 October 2012; revised 13 March 2013; accepted 14 March 2013

heredity participated in a hydrolyzed protein infant formula intervention study for the first 4 months of life.[14] This randomized controlled trial showed marginally different BMIs across formula groups during the first year of life, but this effect did not persist to 6 and 10 years of age.[15] A sensitivity analysis in which formula type was entered into the models as a confounder did not substantially change the results in this study (results not shown). LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics) is an ongoing birth cohort examining the impact of lifestyle-related factors, air pollution and genetics on immune system and childhood allergy development. In total, 3097 neonates were recruited from 14 obstetrical clinics in Munich, Leipzig, Wesel and Bad Honnef between November 1997 and January 1999. Two participants removed their consent to participate at the 6-year follow-up, and are not included in the analysis. A detailed description of the study's screening and recruitment has been described previously.[16,17] Detailed information on allergy and traffic emissions was collected at the 6-year follow-up, and since this time, the term 'plus' was added to the previous names of the cohorts. This analysis is limited to the 3121 children who participated in the physical examination at the 10-year follow-up (1921 from GINIplus and 1200 from LISAplus).

Approval by the respective local ethics committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North-Rhine-Westphalia) and written consent from all participating families were obtained for both studies.

Outcome and covariates

Anthropometric measurements of weight and height were collected by pediatricians during physical examinations at birth, at weeks 4–6, at months 3–4, 6–7, 10–12, 21–24, 46–48 and 60–64 and at 10 years of age. Data from birth to age 60–64 months were obtained from administrative records and that at 10 years from a physical examination conducted as part of the 10-year follow-up of the GINIplus and LISAplus studies.

BMI values were calculated from these weight and height measurements and transformed to standardized deviation scores (*z*-scores) according to the sex- and age-specific 'WHO-Child-Growth-Standards' for children.[18,19] This standardization allows for comparisons across studies.

At every time point, the standard deviation (s.d.) of our population's standardized BMI measurements was calculated. If a child's respective standardized BMI was greater than this s.d., the child was identified as being overweight at this time point, the methodology is consistent with WHO standards.[20]

The set of covariates examined were maternal smoking during pregnancy, family income and parental education level. As the distribution of family income was skewed, this information was grouped into three categories based on the quartiles of monthly average income per person in the household (low for $<25\%$, medium for 25–75% and high for $>75\%$). Parental education levels were defined based on the highest number of years either parent attended school (low <10 years, medium $=10$ years and high >10 years).

Statistical analysis

As male and female subjects have different developmental tracks for obesity,[21] analyses were conducted pooled and stratified by sex.

Linear regression was used to analyze the effects of birth weight, standardized BMI measurements during the first 5 years of life and covariates on standardized BMI measurements at the age of 10 years. Logistic regression was used to assess the risk of being overweight at 10 years and to verify the results obtained from the linear regression model. All models were adjusted for parental education, family income and maternal smoking during pregnancy. Multivariate analyses indicated that only birth weight and standardized BMI at the age of 60–64 months were significantly associated with the outcome of interest. Sensitivity analyses excluding variables at 60–64 months (for example, only including standardized BMIs up to the age of 46–48 months) and including variables at a later age (for example, also including standardized BMI at the age of 6 years) were conducted. On the basis of the results from these models, birth weight and standardized BMI recorded at the age of 60–64 months appeared to be strong predictors of 10-year standardized BMI or being overweight at 10 years of age, and these two variables were selected in the main models (Figure 1, Model B).

Among the available study population ($N=3121$), 2272 children had complete information on all variables included in the linear model. To test the validity of the linear model, two-thirds ($N=1515$) of the complete cases were randomly divided into a training data set, and the remaining third ($N=757$) into a validation data set. The training data set was used to fit the linear regression model. The validation data set was used to compare predicted overweight status at 10 years of age with the true overweight status obtained from the physical examinations. The mean-square prediction error, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were obtained. In this study, sensitivity provides a measure for the percentage of correctly predicted overweight children out of those who were overweight and specificity provides a measure for the percentage of correctly predicted non-overweight children out of those who were not overweight. PPV reflects the probability of being overweight at 10 years if a child was predicted to be overweight using our model, whereas NPV reflects the probability of not being overweight at 10 years if a child was predicted as non-overweight. This procedure was repeated 1000 times and the mean and percentiles of these indices were calculated.

Differences between male and female subjects, as well as between participants ($N=3121$) and non-participants ($N=5965$), of the 10-year physical examination were tested using Pearson's χ^2 test for categorical variables or one-way analysis of variance for continuous variables. Study characteristics are described using means, s.d.'s or percentages. Model results are presented as linear regression coefficients (β) for standardized BMIs and as odds ratios (OR) for being overweight (yes/no), with corresponding 95% confidence intervals (CI). The cross-validation results are presented using means and percentiles for each measure; 2.5th and 97.5 percentiles refer to a 95% CI. *P*-values below 0.05 are considered statistically significant. All analyses were performed using the statistical software package R, version 2.14.1.[22]

RESULTS

Pooled and sex-specific characteristics of the participants of the 10-year physical examination are summarized in Table 1. The mean birth weight was 3.40 kg (s.d. $=0.44$) for female subjects and 3.55 kg (s.d. $=0.46$) for male subjects. The means of the standardized BMIs for examinations conducted during the first 6 months of life were consistently negative for both genders. Those for the standardized BMIs obtained from physical examinations conducted after 1 year of age tended to be positive, with the exception of that calculated for months 60–64 (-0.03 and -0.01 for female subjects and male subjects, respectively). The s.d.'s were all approximately 1.0, as expected.[23] A mean standardized BMI <0 indicates that the entire distribution is shifted downward, which suggests that the majority of the study population have lower BMIs than the reference population. The mean standardized BMI for male subjects (0.24) at 10 years of age was statistically higher than for female subjects (0.13). Overweight rates in male subjects were slightly higher than in female subjects, but were not statistically significant.

The baseline characteristics of participants and non-participants of the 10-year follow-up examination are compared in Table 2. Non-participants were more likely to have parents with low-to-medium levels of education, live in families with low income, have mothers who smoked during pregnancy and to be overweight at the age of 3–4, 46–48 and 60–64 months.

The associations between the investigated covariates and standardized BMI at 10 years are presented in Table 3. When considering the entire study population, standardized BMI at 10 years was significantly associated with birth weight ($\beta=0.11$; 95% CI: 0.03–0.19), standardized BMI at 60–64 months of age ($\beta=0.77$; 95% CI: 0.73–0.81), high parental education ($\beta=-0.15$; 95% CI: -0.29 to -0.01) and maternal smoking during pregnancy ($\beta=0.13$; 95% CI: 0.03–0.22), but neither with high nor medium family income ($\beta=-0.01$; 95% CI: -0.11 to 0.09 and $\beta=-0.04$; 95% CI: -0.12 to 0.04, respectively). As shown in Table 3, a 1-unit increase in standardized BMI at 60–64 months of age increased the standardized BMI at 10 years of age by 0.78 in female subjects and 0.77 in male subjects. Maternal smoking during pregnancy had a positive effect on standardized BMI at 10 years of age among female subjects and male subjects ($\beta=0.15$ and 0.11,

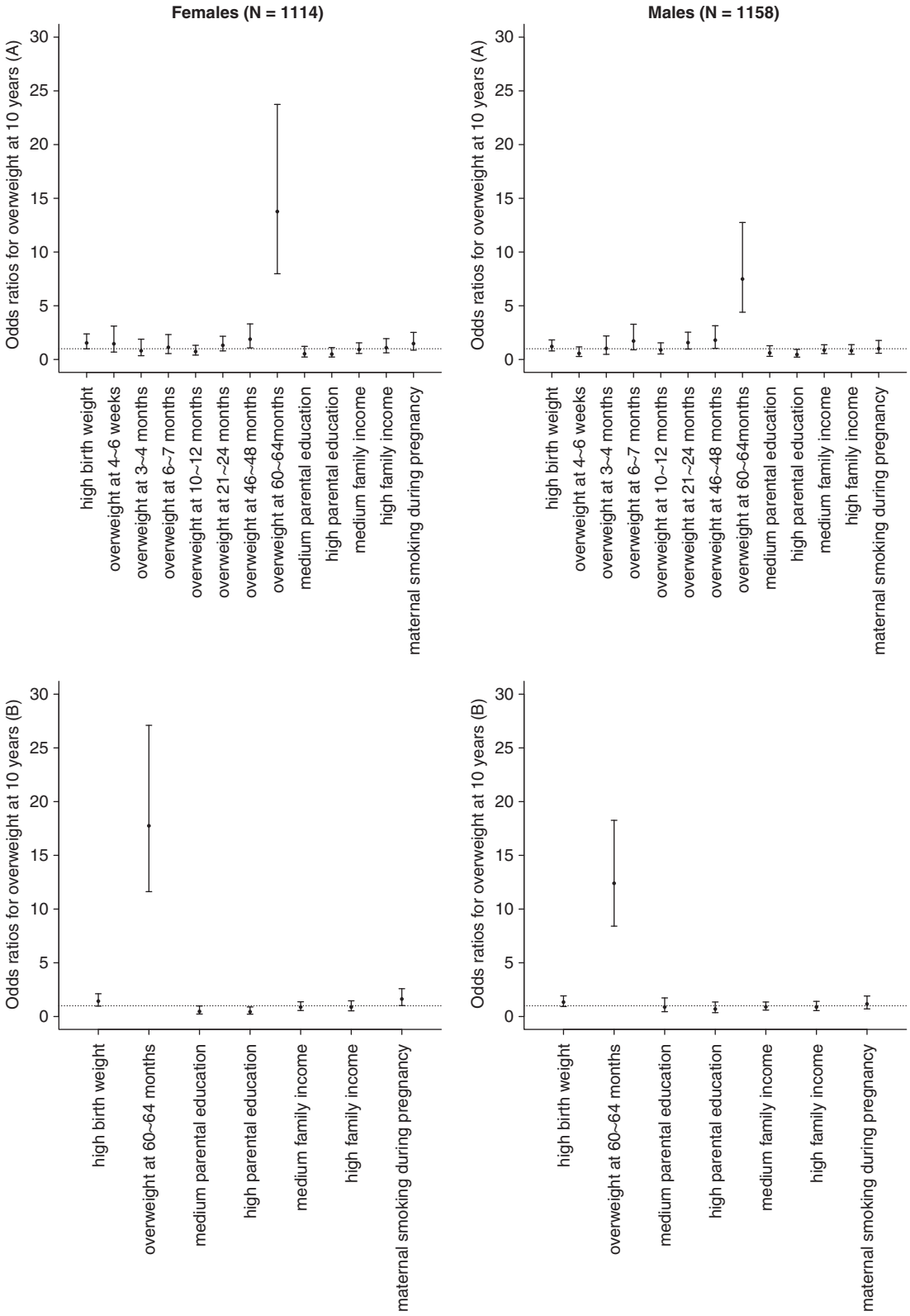


Figure 1. ORs for the association between risk factors and being overweight at 10 years. Models included (A) all categorized standardized BMIs during the first 5 years of life and all covariates and (B) only select variables. Variables were selected based on multivariate models, in which only birth weight and standardized BMI at 60–64 months were constantly associated with the outcome of interest. Parental education, family income and maternal smoking during pregnancy were included as covariates. The reference populations used in the models for being overweight at different ages were the corresponding non-overweight participants. The lowest scales of parental education and family income were used as the reference categories for these variables. Maternal non-smokers were used as the reference population for maternal smoking during pregnancy.

Table 1. Characteristics of participants of the physical examination at 10 years of age

	Mean (s.d.) or % (n/N)	
	Girls (n = 1533)	*Boys (n = 1588)*
Study cohort		
GINIplus	62.9 (964/1533)	60.3 (957/1588)
LISAplus	37.1 (569/1533)	39.7 (631/1588)
Study center		
Munich	53.6 (822/1533)	54.4 (863/1588)
Wesel	30.4 (466/1533)	29.8 (473/1588)
Leipzig	10.7 (164/1533)	11.0 (174/1588)
Bad Honnef	5.3 (81/1533)	4.9 (78/1588)
Parental education[a]		
Low	4.8 (73/1527)	5.9 (93/1582)
Medium	26.6 (406/1527)	26.9 (425/1582)
High	68.6 (1048/1527)	67.3 (1064/1582)
Family income[b]		
Low	20.5 (288/1403)	23.3 (337/1446)
Medium	48.8 (685/1403)	46.7 (675/1446)
High	30.7 (430/1403)	30.0 (434/1446)
Maternal smoking during pregnancy	13.9 (194/1398)	11.8 (173/1469)
Birth weight[c] (kg)	3.40 (0.44)	3.55 (0.46)
Standardized BMI[d]		
4–6 weeks	−0.41 (0.93)	−0.36 (1.04)
3-4 months	−0.52 (0.98)	−0.45 (1.06)
6-7 months	−0.33 (0.99)	−0.33 (1.08)
10–12 months	0.03 (0.95)	0.05 (1.05)
21–24 months	0.26 (0.97)	0.29 (1.06)
46–48 months	0.05 (0.87)	0.12 (0.95)
60–64 months	−0.03 (0.87)	−0.01 (0.97)
10 years[c]	0.13 (1.01)	0.24 (1.10)
Overweight[e]		
4–6 weeks	6.8 (100/1467)	8.1 (123/1515)
3-4 months	6.3 (92/1456)	7.3 (110/1503)
6–7 months	9.1 (132/1445)	9.2 (138/1500)
10–12 months	16.5 (227/1373)	16.3 (232/1424)
21–24 months	21.8 (318/1458)	23.8 (358/1506)
46–48 months	15.1 (219/1452)	15.7 (236/1499)
60–64 months	13.1 (180/1377)	12.8 (180/1411)
10 years	20.3 (311/1529)	21.1 (335/1587)

Abbreviations: BMI, body mass index; GINIplus, German Infant Nutritional Intervention plus environmental and genetic influences on allergy development; LISAplus, Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics; WHO, World Health Organization. [a]Categorized according to the highest number of years either parent attended school: low <10 years, medium = 10 years and high >10 years. [b]Defined according to quartiles of monthly average income: low <25%, medium = 25–75% and high >75%. [c]Significant difference between female and male subjects. [d]Calculated using WHO macros.[18,19] [e]According to WHO definition.[20]

respectively), but was only significant among female subjects ($P = 0.02$).

Being overweight at the age of 60–64 months was a strong risk factor for being overweight at 10 years of age (Figure 1). Children who were overweight at the age of 60–64 months were approximately 15 times more likely to be overweight at the 10-year examination compared with children who were not overweight at the age of 60–64 months. This effect was strongest among female subjects (OR = 17.75; 95% CI: 11.62–27.10 vs OR = 12.40; 95% CI: 8.41–18.26 for female subjects and male subjects, respectively). The association between high parental education and being overweight at 10 years of age was also statistically significant among female subjects (OR = 0.44; 95% CI: 0.22–0.89 vs OR = 0.70; 95% CI: 0.36–1.35 for female subjects and male subjects, respectively). Birth weight and maternal smoking during pregnancy were significant in the prediction model for the entire population. In the stratified analysis, maternal smoking during pregnancy (OR = 1.63; 95% CI: 1.02–2.59 vs OR = 1.17; 95% CI: 0.71–1.91 for female subjects and male subjects, respectively) and high parental education (OR = 0.44; 95% CI: 0.22–0.89 vs OR = 0.70; 95% CI: 0.36–1.35 for female subjects and male subjects, respectively) were more strongly associated with being overweight at 10 years of age among female subjects compared with male subjects.

The cross-validation results of the linear prediction model are presented in Table 4. In all, 37.0% of female subjects and 38.0% of male subjects who were overweight at 10 years of age were predicted as being overweight; 97.2% of female subjects and 95.5% male subjects who were not overweight at 10 years of age were predicted as being not overweight. Among children who were predicted to be overweight at 10 years, 76.8% of female subjects and 68.1% of male subjects were actually overweight at 10 years of age. Finally, among children who were predicted to be not overweight at 10 years, 86.2% of female subjects and 85.8% of male subjects were actually not overweight at 10 years of age.

DISCUSSION

We developed a model that uses anthropometric parameters during the first 5 years of life to predict whether a child will be overweight at 10 years of age. Birth weight, standardized BMI at the age of 60–64 months, parental education, family income and maternal smoking during pregnancy were included in the final prediction model. High birth weight, high standardized BMI at approximately 5 years of age (60–64 months) and maternal smoking during pregnancy increased the risk of being overweight at 10 years. Conversely, children of parents with high parental education were less likely to be overweight at 10 years of age. The sensitivity of our model was low, but the specificity was high. The PPV was higher in the model for female subjects; the NPV was similar across genders.

Previous studies have consistently shown that birth weight is positively associated with being overweight or obese later in life.[4,24] This association is linear in some studies[25] and U-shaped in others.[26] In our study, birth weight was positively and linearly associated with standardized BMI at 10 years, but this effect was only significant among male subjects. High birth weight was associated with being overweight at 10 years of age, although the association was not statistically significant. One possible reason for the linear relationship between birth weight and BMI later in life is that only full-term neonates with a birth weight >2.5 kg were included in our study. Children with low birth weight tend to show catch-up growth, which might be associated with being overweight later in life.

In our study, we considered the effect of standardized BMIs calculated at different time periods throughout early life and childhood on standardized BMI and being overweight at 10 years of age. Only the standardized BMI at 60–64 months of age was significantly associated with being overweight at the age of 10 years in all models. BMIs up to the age of 4 years do not appear to be closely related to BMI at age of 10 years. These results support the concept that the time and slope of the adiposity rebound, that is, the age at and degree of increase in BMI from the age of approximately 5 years onwards, is a key predictor of later obesity risk.[27–30] This hypothesis is in line with the recent observation that preschool and primary school age are the most critical periods for determining obesity later in life.[31] The important impact of the adiposity rebound on later body size may explain why BMI at the approximate age of the adiposity rebound was closely related to

Table 2. Differences between participants and non-participants of the 10-year physical examination

	Mean (s.d.) or % (n/N)		
	Participants (n = 3121)	*Non-participants (n = 5965)*	*Total (n = 9086)*
Gender male	50.9 (1588/3121)	51.5 (2988/5804)	51.3 (4576/8925)
Study cohort[a]			
GINIplus	61.6 (1921/3121)	68.2 (4070/5965)	65.9 (5991/9086)
LISAplus	38.4 (1200/3121)	31.8 (1895/5965)	34.1 (3095/9086)
Study center[a]			
Munich	54.0 (1685/3121)	45.7 (2729/5965)	48.6 (4414/9086)
Wesel	30.1 (939/3121)	41.1 (2451/5965)	37.3 (3390/9086)
Leipzig	10.8 (338/3121)	10.7 (638/5965)	10.7 (976/9086)
Bad Honnef	5.1 (159/3121)	2.5 (147/5965)	3.4 (306/9086)
Parental education[a,b]			
Low	5.3 (166/3109)	13.4 (788/5881)	10.6 (954/8990)
Medium	26.7 (831/3109)	31.0 (1825/5881)	29.5 (2656/8990)
High	67.9 (2112/3109)	55.6 (3268/5881)	59.8 (5380/8990)
Family income[a,c]			
Low	21.9 (625/2849)	25.3 (421/1666)	23.2 (1046/4515)
Medium	47.7 (1360/2849)	47.8 (797/1666)	47.8 (2157/4515)
High	30.3 (864/2849)	26.9 (448/1666)	29.1 (1312/4515)
Maternal smoking during pregnancy[a]	12.8 (367/2867)	20.8 (1112/5358)	18.0 (1479/8225)
Birth weight (kg)	3.47 (0.46)	3.47 (0.46)	3.47 (0.46)
Standardized BMI[d]			
4–6 weeks	−0.38 (0.99)	−0.36 (0.99)	−0.37 (0.99)
3–4 months[a]	−0.48 (1.02)	−0.40 (1.04)	−0.44 (1.03)
6–7 months[a]	−0.33 (1.04)	−0.28 (1.05)	−0.30 (1.05)
10–12 months	0.04 (1.00)	0.07 (1.02)	0.06 (1.01)
21–4 months	0.27 (1.00)	0.25 (1.03)	0.26 (1.02)
46–48 months	0.09 (0.91)	0.09 (1.00)	0.09 (0.96)
60–64 months	−0.02 (0.92)	0.00 (0.99)	−0.01 (0.95)
10 years	0.19 (1.06)	—	0.19 (1.06)
Overweight[e]			
4–6 weeks	7.5 (223/2982)	7.9 (342/4333)	7.7 (565/7315)
3–4 months[a]	6.8 (202/2959)	8.0 (343/4288)	7.5 (545/7247)
6–7 months	9.2 (270/2945)	10.2 (427/4200)	9.8 (697/7145)
10–12 months	16.4 (459/2797)	17.6 (709/4032)	17.1 (1168/6829)
21–24 months	22.8 (676/2964)	22.3 (853/3822)	22.5 (1529/6786)
46–48 months[a]	15.4 (455/2951)	17.1 (551/3214)	16.3 (1006/6165)
60–64 months[a]	12.9 (360/2788)	14.8 (397/2692)	13.8 (757/5480)
10 years	20.7 (646/3116)	—	20.7 (646/3116)

Abbreviations: BMI, body mass index; GINIplus, German Infant Nutritional Intervention plus environmental and genetic influences on allergy development; LISAplus, Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics; WHO, World Health Organization. [a]Significant difference between participants and non-participants. [b]Categorized according to the highest number of years either parent attended school: low <10 years, medium = 10 years and high >10 years. [c]Defined according to quartiles of monthly average income: low <25%, medium = 25–75% and high >75%. [d]Calculated using WHO macros[18,19]. [e]According to WHO definition.[20]

BMI at 10 years of age, and BMIs at earlier ages were not. Children who already have a high BMI at the age of 60–64 months are expected to have an earlier age at and a steeper slope of the adiposity rebound. In line with our observation, Angbratt *et al.*[5] also reported that BMI at 5 years was closely associated with BMI at 15 years.

We did several additional sensitivity analyses to confirm the observed high ORs at 60–64 months of age. First, we included being overweight restricted up to the age of 46–48 months in the models, but excluded being overweight at 60–64 months of age. In these models, being overweight at 4 years (46–48 months) was significantly associated with being overweight at 10 years. The magnitude of the 4-year effect decreased substantially when variables at 60–64 months were reintroduced into the models. Second, when we added being overweight at 6 years to the models, being overweight at 5 years remained significantly associated with being overweight at 10 years, whereas the estimate associated with 46–48 months was no longer significant. In summary, BMI/overweight at 5 years (60–64 months) is a stronger predictor of body weight status at 10 years than any other earlier ages we examined. However, these models also imply that being overweight closer to age 10 years may better predict being overweight at 10 years of age. This hypothesis is in line with another longitudinal study based on 907 children, followed from birth to age 11 years, which concluded measurements closer to 11 years of age better predicted being overweight at 11 years of age.[4] As the numbers of subjects with measured BMI at 6 years in this study were only half of the total population available, and as our results already revealed that from age 5 years onwards, being overweight was predictive of being overweight at 10 years of age, we did not include information collected at 6 years in the main models.

Table 3. Linear regression coefficients for the association between potential risk factors and standardized BMIs at 10 years

Risk factors[a]	*Females (N = 1114)*			*Males (N = 1158)*			*Total (N = 2272)*		
	β[b]	*95% CI*	P-*value*	β	*95% CI*	P-*value*	β	*95% CI*	P-*value*
Birth weight	0.09	−0.01, 0.19	0.08	0.11	0.01, 0.21	0.03	0.11	0.03, 0.19	0.002
Standardized BMI[c] at 60–64 months	0.78	0.72, 0.84	<0.001	0.77	0.73, 0.81	<0.001	0.77	0.73, 0.81	<0.001
Family income[d]									
Low	Ref.			Ref.			Ref.		
Medium	0.00	−0.12, 0.12	0.93	−0.07	−0.19, 0.05	0.23	−0.04	−0.12, 0.04	0.37
High	0.04	−0.10, 0.18	0.50	−0.06	−0.20, 0.08	0.35	−0.01	−0.11, 0.09	0.76
Parental education[e]									
Low	Ref.			Ref.			Ref.		
Medium	−0.12	−0.34, 0.10	0.27	−0.06	−0.26, 0.14	0.53	−0.10	−0.26, 0.06	0.19
High	−0.15	−0.37, 0.07	0.15	−0.15	−0.35, 0.05	0.14	−0.15	−0.29, −0.01	0.03
Maternal smoking during pregnancy	0.15	0.01, 0.29	0.02	0.11	−0.05, 0.27	0.16	0.13	0.03, 0.22	0.01

Abbreviations: CI, confidence interval; Ref., reference; WHO, World Health Organization. [a]Only risk factors that were associated with standardized BMI at 10 years were included in our prediction model. [b]Estimated change in 10-year standardized BMI. [c]Calculated using WHO macros.(18, 19). [d]Defined according to quartiles of monthly average income: low <25%, medium = 25–75% and high >75%. [e]Categorized according to the highest number of years either parent attended school: low <10 years, medium = 10 years and high >10 years.

Table 4. Cross-validation results ($n = 1000$ iterations) for the prediction model[a]

	Girls (N = 1114)			*Boys (N = 1158)*			*Total (N = 2272)*		
	Mean	*2.5% Quantile*	*97.5% Quantile*	*Mean*	*2.5% Quantile*	*97.5% Quantile*	*Mean*	*2.5% Quantile*	*97.5% Quantile*
MSE	<0.001	<0.001	0.003	0.002	<0.001	0.005	<0.001	<0.001	0.002
Sensitivity (%)	37.0	27.2	47.1	38.0	28.8	48.3	37.1	30.8	44.1
Specificity (%)	97.2	95.3	98.9	95.5	93.1	97.6	96.5	95.1	97.8
PPV (%)	76.8	63.3	88.9	68.1	56.0	80.5	72.5	64.0	81.1
NPV (%)	86.2	82.8	89.5	85.8	82.7	89.0	86.1	83.9	88.3

Abbreviations: BMI, body mass index; MSE, mean-square prediction error; PPV, positive predictive value; NPV, negative predictive value. [a]Based on the linear prediction model. Being overweight was defined using standard deviations of standardized BMIs at 10 years of age (girls: >1.01; boys: >1.10; total: >1.06).

Several studies have shown that maternal smoking during pregnancy increases the risk of being overweight or obese among children.[9,32,33] In our study, we found a significant association only among female subjects. Further studies are needed to replicate this result and investigate whether and why gender-specific effects exist. One hypothesis may be that tobacco smoke exposure impacts the metabolism in female subjects differently than that in male subjects. Because second-hand smoking is also a risk factor for being overweight or obese,[34] we also studied the effect of this covariate on standardized BMI at 10 years, but found no significant associations.

In previous works, parental education, family household income and occupational status were combined into one socioeconomic status variable (SES).[35,36] Parental education is an independent risk factor for being overweight,[37] and there are complex patterns that govern the associations between family income and being overweight, which can also differ by race and gender.[38] To try to disentangle these effects, we studied the effect of parental education and family income on the risk of being overweight at 10 years using two separate variables.

A recent Dutch study reported that changes in BMI s.d. scores in each 1-year-interval from birth up to the age of 8 years were all significantly associated with being overweight at 8 years of age. The results of this study suggest that there is no specific critical time period during development that is notably associated with being overweight later in childhood.[39] In contrast, our results show that BMI at approximately 5 years of age, which might be the time of the adiposity rebound, is a strong predictor of being overweight later in life. There are important differences between this study and the recent Dutch study, which may explain the differing results. First, self-reported and measured anthropometric data were combined in the Dutch study, whereas only anthropometric data collected during physical examinations was used in our study. Thus, reporting bias and consequently misclassification of being overweight is likely lower in this study. Second, the previous Dutch paper had a larger sample size than this study (3963 vs 2272), but had fewer children with complete information on all variables (489 vs 2272). Missing data were imputed in the Dutch study, whereas we limited our analysis to only those children who provided complete information. Imputing values may introduce more information bias and a greater uncertainty in the results, which could offset the benefits of a greater sample size. Third, confounding variables were taken into account in our study, whereas models were not adjusted for potential confounders in the Dutch study. Finally, information before 2 years of age was available at more time points in our study (at birth, at weeks 4–6, at months 3–4, 6–7, 10–12 in our study compared to at birth, at 3 months, at 1 year of age for the Dutch study).

Nonetheless, our study is not without limitations. Loss to follow-up is inevitable in cohort studies. In our study, 5965 (65.7%) subjects originally recruited at birth did not participate in the 10-year physical examination. Non-participants were more likely to be overweight, come from a family with a low household income and low parental education, and their mothers were more likely to have smoked during pregnancy. A second limitation of this study

is that we did not consider all known causes of childhood obesity, such as genetic variation, epigenetics, endocrine disease, diet, physical activity and sleep.[12] These risk factors are not available in both the GINIplus and LISAplus study. Furthermore, including a large number of covariates into the prediction model would have hindered our goal of developing a concise and simple model for application.

On the basis of our prediction model, we found that high birth weight, high standardized BMI at approximately 5 years of age and maternal smoking during pregnancy increased the risk of being overweight at 10 years of age. Conversely, having parents with a high level of education decreases this risk. The effects of targeted interventions focused on 5-year-old overweight children should be explored. The prediction model we have developed can be used to identify children at high risk of becoming overweight at the age of 10 years.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

GINIplus study group: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Munich (JH, HEW, SS, AZ, CMC, MS, PR); Department of Pediatrics, Marien-Hospital, Wesel (DB, AvB, CB, IG); Department of Pediatrics, Ludwig Maximilians University, Munich (SK, DR, SK-E); Department of Pediatrics, Technical University, Munich (CPB, IB, AG, UH); IUF—Institut für Umweltmedizinische Forschung at the Heinrich-Heine-University, Düsseldorf (UK, EL, CC).

LISAplus study group: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Munich (JH, HEW, SS, CMC, MS); Department of Pediatrics, Municipal Hospital 'St Georg', Leipzig (MB, UD), Marien-Hospital Wesel, Department of Pediatrics, Wesel (AvB, CB, IG); Pediatric Practice, Bad Honnef (BS); Helmholtz Centre for Environmental Research—UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (IL, MB, CG, SR, MS); University of Leipzig, Institute of Hygiene and Environmental Medicine, Leipzig (OH, CD, JM); IUF—Institut für Umweltmedizinische Forschung, Düsseldorf (UK, EL, CC); Technical University Munich, Department of Pediatrics, Munich (CPB, UH); ZAUM—Center for Allergy and Environment, Technical University, Munich (HB, JG, FM).

The GINI study was funded by Helmholtz Zentrum München and grants of the Federal Ministry for Education, Science, Research and Technology 292 (Grant No. 01 EE 9401-4), and the 6- and 10-year follow-up of the GINIplus study was partly funded by the Federal Ministry of Environment (IUF, FKZ 20462296). The LISAplus study was funded by Helmholtz Zentrum München, Munich Center of Health (MC-Health) and partly by grants of the Federal Ministry of Environment (BMU) (for IUF, 298 FKZ 20462296), and Federal Ministry for Education, Science, Research and Technology (Nos. 01 EG 9705/2 and 01 EG 9732).

This work was supported by the Kompetenznetz Adipositas (Competence Network Obesity) funded by the Federal Ministry of Education and Research (FKZ: 01GI1121A).

REFERENCES

1 Chiolero A, Lasserre AM, Paccaud F, Bovet P. Childhood obesity: definition, consequences, and prevalence. *Rev Med Suisse* 2007; **3**: 1262–1269.
2 Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *Int J Obes (Lond)* 2011; **35**: 891–898.
3 Nader PR, O'Brien M, Houts R. Identifying risk for obesity in early childhood. *Pediatrics* 2006; **118**: e594–e601.
4 Shankaran S, Bann C, Das A, Lester B, Bada H, Bauer CR *et al.* Risk for obesity in adolescence starts in early childhood. *J Perinatol* 2011; **31**: 711–716.
5 Angbratt M, Ekberg J, Walter L, Timpka T. Prediction of obesity from infancy to adolescence. *Acta Paediatr* 2011; **100**: 1249–1252.
6 Janssen I, Katzmarzyk PT, Srinivasan SR, Chen W, Malina RM, Bouchard C *et al.* Utility of childhood BMI in the prediction of adulthood disease: comparison of national and international references. *Obes Res* 2005; **13**: 1106–1115.
7 Kelly LA, Lane CJ, Ball GD. Birth weight and body composition in overweight Latino youth: a longitudinal analysis. *Obesity (Silver Spring, MD)* 2008; **16**: 2524–2528.
8 Li C, Goran MI, Kaur H, Nollen N, Ahluwalia JS. Developmental trajectories of overweight during childhood: role of early life factors. *Obesity (Silver Spring, MD)* 2007; **15**: 760–771.
9 Gorog K, Pattenden S, Antova T, Niciu E, Rudnai P, Scholtens S *et al.* Maternal smoking during pregnancy and childhood obesity: results from the CESAR Study. *Matern Child Health J* 2011; **15**: 985–992.
10 Toschke AM, Koletzko B, Slikker Jr W, Hermann M, von Kries R. Childhood obesity is associated with maternal smoking in pregnancy. *Eur J Pediatr* 2002; **161**: 445–448.
11 Moens E, Braet C, Bosmans G, Rosseel Y. Unfavourable family characteristics and their associations with childhood obesity: a cross-sectional study. *Eur Eat Disord Rev* 2009; **17**: 315–323.
12 Han JC, Lawlor DA, Kimm SY. Childhood obesity. *Lancet* 2010; **375**: 1737–1748.
13 Koletzko B, Beyer J, Brands B, Demmelmair H, Grote V, Haile G *et al.* Early influences of nutrition on postnatal growth. *Nutr Mol Endocr Perspect* 2013; **71**: 11–27.
14 von Berg A, Koletzko S, Filipiak-Pittroff B, Laubereau B, Grubl A, Wichmann HE *et al.* Certain hydrolyzed formulas reduce the incidence of atopic dermatitis but not that of asthma: three-year results of the German Infant Nutritional Intervention Study. *J Allergy Clin Immunol* 2007; **119**: 718–725.
15 Rzehak P, Sausenthaler S, Koletzko S, Reinhardt D, von Berg A, Kramer U *et al.* Long-term effects of hydrolyzed protein infant formulas on growth—extended follow-up to 10 y of age: results from the German Infant Nutritional Intervention (GINI) study. *Am J Clin Nutr* 2011; **94**(Suppl): 1803S–1807SS.
16 Chen CM, Rzehak P, Zutavern A, Fahlbusch B, Bischof W, Herbarth O *et al.* Longitudinal study on cat allergen exposure and the development of allergy in young children. *J Allergy Clin Immunol* 2007; **119**: 1148–1155.
17 Flexeder C, Thiering E, Brüske I, Koletzko S, Bauer C.-P, Wichmann H.-E *et al.* Growth velocity during infancy and onset of asthma in school-aged children. *Allergy* 2012; **67**: 257–264.
18 WHO Anthro and macros. version 3.2.2. Available at http://www.who.int/child-growth/software/en/ (January 2011).
19 WHO AnthroPlus software. Available at http://www.who.int/growthref/tools/en/.
20 WHO BMI-for-age cut-offs. Available at http://www.who.int/growthref/who2007_bmi_for_age/en/index.html.
21 Munakata H, Sei M, Ewis AA, Umeno M, Sato Y, Nakano T *et al.* Prediction of Japanese children at risk for complications of childhood obesity: gender differences for intervention approaches. *J Med Invest* 2010; **57**: 62–68.
22 R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria, 2010 ISBN 3-900051-07-0. Available at http://www.R-project.org.
23 Global Database on Child Growth and Malnutrition. Available at http://www.who.int/nutgrowthdb/about/introduction/en/index5.html.
24 Gaskins RB, LaGasse LL, Liu J, Shankaran S, Lester BM, Bada HS *et al.* Small for gestational age and higher birth weight predict childhood obesity in preterm infants. *Am J Perinatol* 2010; **27**: 721–730.
25 Rasmussen F, Johansson M. The relation of weight, length and ponderal index at birth to body mass index and overweight among 18-year-old males in Sweden. *Eur J Epidemiol* 1998; **14**: 373–380.
26 Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation* 1996; **94**: 3246–3250.
27 Williams SM, Goulding A. Patterns of growth associated with the timing of adiposity rebound. *Obesity (Silver Spring, MD)* 2009; **17**: 335–341.
28 Williams SM, Goulding A. Early adiposity rebound is an important predictor of later obesity. *Obesity (Silver Spring, MD)* 2009; **17**: 1310.
29 Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound: causes and consequences for obesity in children and adults. *Int J Obes (Lond)* 2006; **30**(Suppl 4): S11–S17.
30 Williams SM. Weight and height growth rate and the timing of adiposity rebound. *Obes Res* 2005; **13**: 1123–1130.
31 von Kries R, Beyerlein A, Müller MJ, Heinrich J, Landsberg B, Bolte G *et al.* Different age-specific incidence and remission rates in pre-school and primary school suggest need for targeted obesity prevention in childhood. *Int J Obes (Lond)* 2012; **36**: 505–510.
32 Koshy G, Delpisheh A, Brabin BJ. Dose response association of pregnancy cigarette smoke exposure, childhood stature, overweight and obesity. *Eur J Public Health* 2011; **21**: 286–291.
33 von Kries R, Toschke AM, Koletzko B, Slikker W. Maternal smoking during pregnancy and childhood obesity. *Am J Epidemiol* 2002; **156**: 954–961.
34 Raum E, Kupper-Nybelen J, Lamerz A, Hebebrand J, Herpertz-Dahlmann B, Brenner H. Tobacco smoke exposure before, during, and after pregnancy and risk of overweight at age 6. *Obesity (Silver Spring, MD)* 2011; **19**: 2411–2417.
35 Lin SL, Leung GM, Hui LL, Lam TH, Schooling CM. Is informal child care associated with childhood obesity? Evidence from Hong Kong's 'Children of 1997' birth cohort. *Int J Epidemiol* 2011; **40**: 1238–1246.

36 Jones-Smith JC, Gordon-Larsen P, Siddiqi A, Popkin BM. Cross-national comparisons of time trends in overweight inequality by socioeconomic status among women using repeated cross-sectional surveys from 37 developing countries, 1989–2007. *Am J Epidemiol* 2011; **173**: 667–675.
37 Huerta M, Bibi H, Haviv J, Scharf S, Gdalevich M. Parental smoking and education as determinants of overweight in Israeli children. *Prev Chronic Dis* 2006; **3**: A48.
38 Wang Y, Zhang Q. Are American children and adolescents of low socioeconomic status at increased risk of obesity? Changes in the association between overweight and family income between 1971 and 2002. *Am J Clin Nutr* 2006; **84**: 707–716.
39 Willers SM, Brunekreef B, Smit HA, van der Beek EM, Gehring U, de Jongste C *et al.* BMI development of normal weight and overweight children in the PIAMA study. *PloS One* 2012; **7**: e39517.

5 Cesarean section and risk of childhood obesity: Results from the longitudinal LISAplus study

Authors: Zhengcun Pei, Joachim Heinrich, Elaine Fuertes, Claudia Flexeder, Barbara Hoffmann, Irina Lehmann, Beate Schaaf, Andrea von Berg, Sibylle Koletzko on behalf of the LISAplus Study Group

Accepted on 19.12.2013, in press

Journal: The Journal of Pediatrics

Year: 2014

Electronic version (e-pub):

http://dx.doi.org/10.1016/j.jpeds.2013.12.044

Impact factor: 4.035

5.1 Confirmation letter

Date: Dec 19, 2013

To: "Zhengcun Pei" zhengcun.pei@helmholtz-muenchen.de

From: "Journal Office" journal.pediatrics@cchmc.org

Subject: Your Manuscript # 20131506R1 submitted to JPediatr

Ref.: Ms. No. 20131506R1
Cesarean delivery and risk of childhood obesity
The Journal of Pediatrics

Dear Mr. Pei,

Thank you for revising and resubmitting your manuscript. The Editors appreciate your efforts. We are pleased to accept your revised manuscript for publication in The Journal of Pediatrics. Please note the title change, as written above. The Appendix of study group members and the Table will be published in the online version of The Journal; a reference to the electronic material will appear in the print version. Additionally, portions of the manuscript have been deleted. We have made other editorial changes, which you will see in the proofs.

We will forward your manuscript to Elsevier, Inc. Before the final publication date, the publisher will send you galley proofs and other relevant material. Please read the proofs carefully and contact the publisher if anything is unclear or incorrect; the authors have final responsibility for the accuracy of the publication.

Congratulations.

Stephen R. Daniels, M.D., Ph.D.
Associate Editor

William F. Balistreri, M.D.
Editor

5.2 Accepted manuscript

Cesarean section and risk of childhood obesity:
Results from the longitudinal LISAplus study

Zhengcun Pei MSc[1,2], Joachim Heinrich PhD[1], Elaine Fuertes MSc[1,3], Claudia Flexeder, MSc[1]; Barbara Hoffmann PhD[4, 5], Irina Lehmann PhD[6,7], Beate Schaaf MD[8], Andrea von Berg MD[9], Sibylle Koletzko MD. PhD[10] on behalf of the LISAplus Study Group

Affiliations:

[1] Institute of Epidemiology I, Helmholtz Zentrum München, Neuherberg, Germany;

[2] Faculty of Medicine, Ludwig-Maximilians-University of Munich, Munich, Germany;

[3] School of Population and Public Health, University of British Columbia, Canada;

[4] IUF Leibniz Research Institute for Environmental Medicine at the University of Düsseldorf, Düsseldorf, Germany;

[5] Medical Faculty, University of Düsseldorf, Düsseldorf;

[6] Department of Environmental Immunology, UFZ-Centre for Environmental Research, Leipzig, Germany;

[7] Department of Pediatrics, Technical University Munich and LVA Oberbayern, Munich, Germany;

[8] Medical Practice for Pediatrics, Bad Honnef, Germany;

[9] Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany;

[10] Dr. von Hauner Children's Hospital, University of Munich, Munich, Germany.

Address correspondence to: Sibylle Koletzko, Division of Pediatric, Gastroenterology and Hepatology, Dr. v. Haunersches Kinderspital, Ludwig-Maximilians-University of Munich, Lindwurmstraße 4, München, Germany, 80337, [sibylle.koletzko@med.uni-muenchen.de], +49-89-51607854.

Short title: Cesarean section and childhood obesity

Key Words: Cesarean section, mode of delivery, childhood obesity, BMI

Abstract

Objective Longitudinal data from a population based German birth cohort were used to investigate whether delivery by a cesarean section (CS), compared to vaginal delivery, is a risk for childhood obesity.

Study design Healthy, full-term infants were recruited. Being overweight and obesity were defined using measured weight and height according to WHO reference data. Associations between CS and being overweight or obese were investigated at age 2, 6 and 10 years (n=1734, 1244, 1170, respectively) by multivariable logistic regression models adjusted for socioeconomic status, child characteristics, and maternal pre-pregnancy characteristics.

Results Mothers who underwent a CS delivery (~17%) had higher pre-pregnancy BMI (23.7 kg/m^2 vs. 22.5 kg/m^2) and higher gestational weight gain (15.3 kg vs. 14.5 kg), and shorter duration of exclusive breastfeeding (3.4 vs. 3.8 months) compared to those who delivered vaginally. The proportion of obese children at two years was greater among those delivered by CS compared to vaginally (13.6% vs. 8.3%), but not at older ages. Regression analyses revealed that children delivered by CS were more likely to be obese at 2 years compared to those delivered vaginally (OR_{adj} = 1.68 [1.10 to 2.58]), but not at age 6 (OR_{adj} = 1.49 [0.55 to 4.05] or 10 years (OR_{adj} = 1.16 [0.59 to 2.29]).

Conclusion Cesarean delivery may increase the risk for obesity during early childhood. Our results do not support the hypothesis that increasing rates of cesarean section contribute to the childhood obesity epidemic. Further studies are necessary to confirm our findings.

Abbreviations: BMI – body mass index; CS – cesarean section; LISAplus – Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics; OR – odds ratio; SD – standard deviation; WHO – world health organization; VD – vaginal delivery.

Introduction

Obesity is recognized as a major public health challenge[1]. Childhood obesity often persists into adulthood and increases the risk of metabolic syndrome and adult morbidities[2, 3]. The gut microbiota is considered to be a modifying factor for obesity[4, 5]. Gut microbiota may contribute to obesity by increasing dietary energy utilization, promoting fat deposition, and triggering systemic inflammation[6, 7].

Within the last 20 years, cesarean section (CS) rates have doubled in Germany (1991: 15.3% vs. 2010: 31.9%)[8]. Delivery by CS has been recognized as a risk factor of short-term impaired lung function, hypoglycemia, reduced breast feeding initiation[9, 10], altered immune responses[11], and long-term effects on immune related conditions such as asthma[12], respiratory morbidity[13] and type 1 diabetes[14]. Mode of delivery shapes the acquisition and structure of infants' microbiota. Infants born by CS acquire different bacterial communities compared to vaginally delivered infants[15, 16].

Several cohort and case control studies report conflicting results on the association between CS and obesity[17-25]. A recent meta-analysis concluded that CS was moderately associated with offspring overweight and obesity[26]. The 'hygiene hypothesis' is the background of possible relationships[27]. In additional, altered postnatal feeding and metabolic control in CS versus vaginal delivered infants may have long term effects on appetite regulation or energy metabolism and may contribute to the significant increase in body mass[9]. Generalizations of the findings of these studies is challenging given that these studies were performed in different countries, with participants born in different time periods and followed for different lengths of time, and various confounding control strategies were used. In particular, several important potential confounders were not consistently included in the analyses. For instance, maternal pre-pregnancy BMI may influence both the decision of having a CS[28] and the risk of obesity in offspring[29]; premature or small for gestational age versus full term infants may have altered growth trajectories[30, 31] and therefore a higher risk for obesity later in life[32, 33]; and early feeding pattern and a lower rate of breast feeding initiation and duration are known to be consequences of CS[9] and may play a role on the biological pathway between CS and later-life obesity[5].

To date, the effect of CS on long-term children's growth remains controversial. In the current study, we used longitudinal data from a German birth cohort, which recruited healthy full term infants, to examine whether CS is associated with growth and whether the effect of CS on growth persists into school age after adjusting for socioeconomic status, maternal and children characteristics.

Methods

Study population

Data were analyzed from the ongoing German birth cohort LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics). The study design of this birth cohort study has been described previously[34]. From November 1997 to January 1999, 3097 healthy full term neonates (gestational age > 37 weeks and birth weight > 2500 grams) were recruited from Munich, Leipzig, Wesel, and Bad Honnef. Infants with congenital disorders or perinatal problems were excluded. Physical examinations including anthropometric measurements were performed when the children were 2, 6, and 10 years old. The number of children for which had information on mode of delivery and anthropometric measurements at 2, 6, and 10 years of age was 1734, 1244, 1170, respectively.

The study was approved by the respective local ethics committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North-Rhine-Westphalia) and all participating families provided written consent.

Outcome

Body Mass Index (BMI; weight in kg/(height in m)^2) were calculated using height and weight measurements collected during the physical examines. BMI z-scores were calculated using WHO macros[35]. We defined overweight and obesity using WHO reference data (overweight: BMI ≥ 85th and < 95th percentile for age and sex; obesity: BMI ≥ 95th percentile for age and sex)[36].

Exposure and potential influencing factors

Information about mode of delivery was collected by questionnaires at enrollment. Mode of delivery was defined as a binary variable: CS and vaginal delivery. Data on whether the CS was elective or emergency cesarean section and perinatal maternal exposure to antibiotics were not available.

Potential influencing factors included city of recruitment, parental education, duration of gestation, birth weight, head circumference at 3 days of age, maternal age, maternal pre-pregnancy BMI, and maternal smoking during pregnancy. Sociodemographic data and

maternal characteristics were collected by questionnaires at enrollment and during follow up visits. We categorized parental education according to the highest number of years either parent attended school (low < 10 years, medium = 10 years, and high > 10 years). In addition, the feeding variables (i.e. breastfeeding initiation, exclusive breastfeeding duration, and timing of solid food introduction) were considered as potential mediators.

Statistical analysis

Study characteristics are presented stratified by mode of delivery; all available data were used in the analyses. Multivariable linear and logistic regression models were used to evaluate the association between CS and BMI z-scores, being overweight and obesity.

Results from three models are provided. Model 1 includes only the association between mode of delivery and the three outcome variables (crude model); model 2 includes an adjustment for parental education, city of recruitment, birth weight, duration of gestation, and head circumference; model 3 is additionally adjusted for maternal age, maternal pre-pregnancy BMI, and maternal smoking during pregnancy. In addition, stratified analyses by feeding variables and further adjustment for these variables were conducted.

Differences in study characteristics between children delivered by CS and vaginal delivery were tested by t-test for continuous variables, Chi-square for binary variables, and Fisher's exact test for multi-level variables (first-levels used as the reference level). Study characteristics are described using means (standard deviation (SD)) or number (%). Model results are presented as linear regression coefficients (ß) and as odds ratios (OR) with corresponding 95% confidence intervals [95% CI]. P-values below 0.05 are considered statistically significant. All analyses were performed using the statistical software package R, version 2.14.1[37].

Results

Participant characteristics at each time point are shown in table 1. Seventeen percent of children were delivered by CS (range at different time points: 17.01 – 17.44 %). For participants at two years of age, mothers who delivered by CS had higher pre-pregnancy BMI (23.7 kg/m^2 vs. 22.5 kg/m^2, $p<0.05$), gestational weight gain during pregnancy (15.3 kg vs. 14.5kg, $p<0.05$), and proportion of smoking during pregnancy (19.4% vs. 14.3%, $p<0.05$), and shorter exclusive breastfeeding duration (3.4 vs. 3.8 months, $p<0.05$) compared to those delivered vaginally. Similar distribution of above variables was observed for participants at six and ten years of age.

Similar distribution of birth weight was observed between CS and vaginal delivery. Children delivered by CS had higher BMI at 10 years than those delivered vaginally (17.5 kg/m^2 vs

17.2 kg/m^2, p<0.05). BMI z-scores at two and ten years of age were higher in children delivered by CS (0.37 vs. 0.25, p<0.05; 0.33 vs. 0.09, p<0.05 for two and ten years, respectively). The prevalence of obesity at 2 years of age was higher among children delivered by CS compared to those delivered vaginally (13.6% vs. 8.3%, p<0.05). This difference did not persist to 6 and ten years of age.

Comparing basic characteristics of participants and non-participants revealed that there were no major differences in the BMI characteristics and the CS rate between participants and non-participants for all time points (Supplement table 1). Children recruited in Leipzig, and those born to a young mother or to parents with low levels of education (<ten years) were more likely to drop out.

Results from the multivariable models are shown in Figure 1~3. In the unadjusted linear models, cesarean delivery was positively associated with the BMI z-scores at age 2, 6, and 10 years (ß = 0.12 [95% CI: 0.00 to 0.25], ß = 0.14, [95% CI: 0.00 to 0.29], and ß = 0.24, [95% CI: 0.08 to 0.40], respectively), but the estimate was attenuated after adjustment (ß = 0.10, [95% CI: -0.03 to 0.23], ß = 0.05, [95% CI: -0.10 to 0.19], ß = 0.11, [-0.05 to 0.28], respectively). Significant associations between CS and being overweight were not observed at all the three time points. Crude and adjusted odds ratios were significant between CS and obesity at age two years (OR_{crude} = 1.78, [1.21 to 2.62] vs. OR_{adj} = 1.68, [1.10 to 2.58]) but not at age six years (OR_{crude} = 2.15, [0.92 to 5.01] vs. OR_{adj} = 1.49, [0.55 to 4.05]) or ten years (OR_{crude} = 1.58, [0.88 to 2.84] vs. OR_{adj} = 1.16, [0.59 to 2.29]). Further adjustments for feeding variables did not substantially change the results at the three time points (detailed numbers for all models are provided in Supplement table 2). In addition, stratified analyses by feeding variables showed similar results among groups (results not shown).

Discussion

In this study, we found that children delivered by CS were more likely to be obese at age two years. Although there was still a trend at six and ten years of age, significance was lost, particularly after adjustment for maternal characteristics.

Data from a birth cohort of 1255 US children suggest that delivery by CS compared to vaginal delivery increases the risk of obesity at 3 years of age (OR 2.10, [1.36 to 3.23])[17]. This birth cohort is similar to ours with respect to the time period of recruitment, the inclusion criteria and confounders considered. The OR for being obese at 3 years in the US study is comparable to our result at 2 years (OR = 1.74, [1.12 to 2.70]). However, no follow up data beyond 3 years of age was presented in this US study.

Results from a Chinese birth cohort (n=181380) recruited from 1993 to 1996 indicate a higher risk of being overweight at the age of 5 years for children born by CS (OR = 1.13, [1.08 to 1.18])[23]. However, premature infants were included in these analyses (inclusion criteria: gestational age ≥ 28 weeks). One Brazilian study examined the impact of CS on obesity at the age of 4, 11, 15, and 23 years. In the crude models, subjects delivered by CS had an approximately 50% higher ratio of obesity at each age group. However, after adjusting for potential confounders (family income, maternal schooling, maternal pre-pregnancy BMI, maternal skin color, birth weight), all associations were null except among 4-year-old boys[18]. Another Brazilian study reported an increased risk of obesity at the age of 23 to 25 years among individuals delivered by CS, after adjusting for birth weight, maternal smoking, and maternal schooling (prevalence ratio: 1.58, [1.23 to 2.02]). Information on maternal BMI and breastfeeding was not available[22]. One recent Brazilian study demonstrated a positive association between CS and increased BMI z-score in two distinct socioeconomic status cities. However, positive associations between CS and obesity were only observed in city Ribeirao Preto, where information on pre-pregnancy maternal weight was not available[25].

A recent Danish study based on mandatory conscription data (n = 21051) observed a higher prevalence of obesity at the age of 18 years among males delivered by CS[19]. However, the shortage of socioeconomic and maternal information is an important limitation of this study. The outcome variable was defined using data from two sources which yielded quite different obesity rates; one used measured BMI (6% obesity rate) and the other used a diagnosis of obesity in the conscription record (0.6% based rate). Moreover, this study recruited men born between 1977 and 1983, a period during which CS was almost exclusively conducted in case of medical indications. This may also explain the low CS rate (10%) in this study. Factors such as socioeconomic region[38], socioeconomic status[39], education level[40], and a higher prevalence of obesity in pregnant women[28] are known to be influential in the decision to have a CS nowadays.

A recent meta-analysis concluded that those delivered by CS have a moderately increased risk of being overweight between 3 to 23 years of age (overall pooled OR: 1.33 [1.19,1.48])[25]. However, many studies included in this meta-analysis did not have information on early feeding pattern and maternal pre-pregnancy BMI, and none excluded premature and small for gestational age infants. These important differences may explain the conflicting results observed between studies. From the published data and our own results, we hypothesize that the effect of CS on obesity may be stronger during early childhood (e.g. ≤ 3 years of age), but that the magnitude of this effect may decline in later life. One possible explanation may be

that as children grow older, several other risk factors for obesity may become more important than the mode of delivery. These may include dietary habits in the family[41], television viewing[42], physical activity and an obesogenic environment[43].

Previous studies have hypothesized that delivered by CS affects the onset of obesity through an altered gut microbiota[17-19]. An altered microbiota composition may lead to excess body weight gain through several possible mechanisms: (i) microbiota can transform non-digestible food into biochemically absorbable nutrients, contributing to increased energy harvest; (ii) the microbiota may regulate gut gene expression leading to an increase in free fatty acids and adipose levels; (iii) gut bacteria may initiate an inflammatory state of obesity through activated lipopolysaccharides[7, 27].

Children delivered by CS have different pattern of intestinal colonization at birth, due to a different first oral microbial ingestion[15, 44]. Compared with vaginally delivered infants, CS born infants were reported to have a lower proportion of Bacteriodes[16, 45] and a higher proportion of Firmicutes[16] at 6 weeks and 4 months of age. Similar results were found in animal models[46, 47]. Moreover, an elevated Firmicutes-to-Bacteroidetes ratio was found in obese children between 6 and 16 years of age, compared to lean children[48]. Other specific patterns of gut microbiota (increased Lactobacillus reuteri with lack of Bifidobacteria) may also be associated with human obesity[49, 50], but potential mechanisms are unclear. Given that Firmicutes and Bacteroidetes are two prominent divisions in mammalian gut microbiota[51], and Bacteroidetes was reported to be protective against later obesity[50], an altered gut flora pattern seems to play a role for metabolism and later-life obesity. Results from previous cross-sectional studies indicate that gut microbiota influences or is influenced by host body weight status[52]. Long-term studies on the gut colonization in humans are scarce. We hypothesize that gut microbiota plays a more important role for the risk of obesity during early life, but that this effect or the microbiome itself may be mantled by other life style factors later on. Our findings should stimulate future studies to assess gut microbiota patterns throughout childhood in order to investigate potential mechanisms.

Several short term physiological changes in response to delivery by CS has been described, both in humans and animal models including altered fat and glucose metabolism and feeding pattern (failure of breast feeding initiation and decreased milk intake, different maternal hormones, etc)[9]. This may have long term consequences for the appetite regulation or metabolic control[9]. These differences could contribute to the increased body mass either independently or in conjunction with altered gut microbiota.

There are other possible explanations for our findings. First, CS is strongly recommended for certain medical indications (e.g. placenta previa, the infant or head circumference is too large for VD, unusual position, labor is not progressing which is common in obese mothers etc). However, CS are also increasingly now conducted without any clear medical indication: some mothers have extreme fear of pain during vaginal delivery, hospitals and physicians benefit from the higher costs of reimbursement for operative delivery, CS is more culturally acceptable and sometimes considered a "better or modern" option than VD. This could lead to selection bias, and it may vary among studies. Second, multiple factors may play more important roles than CS on obesity later in life. For instance, maternal pre-pregnancy BMI is known to influence a child's birth weight[53] and is an independent determinant of a child's BMI in later life[54-56]. CS may be only an intermediate factor for the association between maternal pre-pregnancy BMI and offspring obesity. Moreover, there are possibly other similar influencing factors (e.g. birth weight, feeding habits, food intake, physical activity, etc).

The strength of the current study is the use of measured anthropometric data at 2, 6, and 10 years of age in a large birth cohort. We provided long-term data on the association between CS and obesity, after considering various set of potential influencing factors. Our results were adjusted for maternal pre-pregnancy BMI and early feeding variables, which were ignored by several previous studies. We also used unselected healthy full term infants in our analyses, whereas most previous studies did not exclude premature or small for gestational age babies. We could confirm our data by performing a sensitivity analysis using children who participated in all the three measurements. The risk of CS for obesity at 2 years of age was even stronger (OR_{adj} = 2.91, [1.48 to 5.72]), whilst no association between CS and BMI z-score (ß = 0.16, [-0.05 to 0.37]) or being overweight could be seen (OR_{adj} = 1.02, [0.53 to 1.95]).

One limitation of the current study is a lack of information on an early rupture of membrane in cases of CS. In this situation, the infant may acquire some of the maternal vaginal flora. However, the maternal fecal flora is still lacking in these situations. A rupture of membrane is more likely in an unplanned CS, but one study which compared planned and unplanned CS did not find differences in terms of obesity and standardized BMI[17]. We also lack information on early life antibiotic exposure. Antibiotics are commonly used during CS, particularly in the case of ruptured membranes. Antibiotics have an effect on the mother and offspring's microbiota and early antibiotic exposure has been associated with an increased risk of being

overweight[57]. Mice models also indicate that antibiotics in early life may alter microbiota colonization[29].

A further limitation of our study is a loss-of-follow-up over times, which may lead to selection bias. We compared participants and non-participants at each time of measurement and found that children who left the study were more likely to have been recruited from Leipzig and be born to young mothers and to parents with less education. Neither BMI characteristics nor cesarean delivery rates significantly differed between participants and non-participants at all three time points making a bias due to selected drop outs unlikely. More than 50% of participants at 2 years continued with the 6- and 10-year follow-ups, where they showed similar BMI characteristics as the drop-outs. Participants at age 10 years were comprised from both participants and non-participants at age 2 and 6 years, and these two groups of children also had very similar BMI characteristics. Participants at age 10 years were comprised from both participants and non-participants at age 2 and 6 years, and these two groups of children also had very similar BMI characteristics. In addition, the numbers of obese children in CS group at age 6 and 10 years were small (8 and 16, respectively), which may have led to the null findings. Therefore the results must be interpreted with caution. Furthermore, we cannot exclude the possibility that our models may be over adjusted, as some of the covariates in our analysis may be correlated. For instance, maternal pre-pregnancy BMI is associated with birth weight[58], childhood BMI[56], and cesarean delivery[59, 60]. We cautiously conducted our analyses using a forward-stepwise strategy and performed stratified analyses for factors that had strong effects on the outcomes, such as birth weight and maternal pre-pregnancy BMI. Delivery by CS was associated with a higher risk of obesity for normal weight mothers (results not shown). Finally, the potential that residual confounding may be affecting the results is always a possibility.

Conclusion

Delivery by CS may increase the risk of obesity during early childhood. Our results do not support the hypothesis that the increasing rates of CS are contributing to the childhood obesity epidemic. Further studies are necessary to confirm our findings.

References

1. Chiolero A, Lasserre AM, Paccaud F, Bovet P. Childhood obesity: definition, consequences, and prevalence. Rev Med Suisse. 2007;3:1262-1269.
2. Lloyd LJ, Langley-Evans SC, McMullen S. Childhood obesity and risk of the adult metabolic syndrome: a systematic review. Int J Obes (Lond). 2012;36:1-11.
3. Biro FM, Wien M. Childhood obesity and adult morbidities. Am J Clin Nutr. 2010;91:1499S-1505S.
4. Ley RE. Obesity and the human microbiome. Curr Opin Gastroenterol. 2010;26:5-11.
5. Thompson AL. Developmental origins of obesity: early feeding environments, infant growth, and the intestinal microbiome. Am J Hum Biol. 2012;24:350-360.
6. Tsai F, Coyle WJ. The microbiome and obesity: is obesity linked to our gut flora? Curr Gastroenterol Rep. 2009;11:307-313.
7. Sanz Y, Rastmanesh R, Agostonic C. Understanding the role of gut microbes and probiotics in obesity: How far are we? Pharmacol Res. 2012;69:87-113.
8. Statistisches Bundesamt. Almost a third of all deliveries at hospital done by Caesarean. Available at: https://www.destatis.de/EN/PressServices/Press/pr/2012/03/PE12_098_231.html.
9. Hyde MJ, Mostyn A, Modi N, Kemp PR. The health implications of birth by Caesarean section. Biol Rev Cam Philos Soc. 2012;87:229-243.
10. Karlstrom A, Lindgren H, Hildingsson I. Maternal and infant outcome after caesarean section without recorded medical indication: findings from a Swedish case-control study. BJOG. 2013;120:479-486; discussion 486.
11. Cho CE, Norman M. Cesarean section and development of the immune system in the offspring. Am J Obstet Gynecol. 2012;208:249-254.
12. Boutsikou T, Malamitsi-Puchner A. Caesarean section: impact on mother and child. Acta Paediatr. 2011;100:1518-1522.
13. Bailit JL, Gregory KD, Reddy UM, Gonzalez-Quintero VH, Hibbard JU, Ramirez MM, et al. Maternal and neonatal outcomes by labor onset type and gestational age. Am J Obstet Gynecol. 2010;202:245.e1-245.e12.
14. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia. 2008;51:726-735.
15. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across

multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107:11971-11975.

16. Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. CMAJ. 2013;185:385-394.
17. Huh SY, Rifas-Shiman SL, Zera CA, Edwards JW, Oken E, Weiss ST, et al. Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study. Arch Dis Child. 2012;97:610-616.
18. Barros FC, Matijasevich A, Hallal PC, Horta BL, Barros AJ, Menezes AB, et al. Cesarean section and risk of obesity in childhood, adolescence, and early adulthood: evidence from 3 Brazilian birth cohorts. Am J Clin Nutr. 2012;95:465-470.
19. Svensson E, Hyde MJ, Modi N, Ehrenstein V. Caesarean section and body mass index among danish adult men. Obesity (Silver Spring). 2013;21:429-433.
20. Zhou L, He G, Zhang J, Xie R, Walker M, Wen SW. Risk factors of obesity in preschool children in an urban area in China. Eur J Pediatr. 2011;170:1401-1406.
21. Ajslev TA, Andersen CS, Gamborg M, Sorensen TI, Jess T. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. Int J Obes (Lond). 2011;35:522-529.
22. Goldani HA, Bettiol H, Barbieri MA, Silva AA, Agranonik M, Morais MB, et al. Cesarean section is associated with an increased risk of obesity in adulthood in a Brazilian birth cohort study. Am J Clin Nutr. 2011;93:1344-1347.
23. Li H, Ye R, Pei L, Ren A, Zheng X, Liu J. Caesarean delivery, caesarean delivery on maternal request and childhood overweight: a Chinese birth cohort study of 181 380 children. Pediatr Obes. 2013. Epub.
24. Li H. A national epidemiological survey on obesity of children under 7 years of age in nine cities of China, 2006. Zhonghua er ke za zhi. 2008;46:174-178.
25. Goldani MZ, Barbieri MA, da Silva AA, Gutierrez MR, Bettiol H, Goldani HA. Cesarean section and increased body mass index in school children: two cohort studies from distinct socioeconomic background areas in Brazil. Nutr J. 2013;12:104.
26. Li HT, Zhou YB, Liu JM. The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis. Int J Obes (Lond). 2012. Epub.
27. Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? Diabetes care. 2010;33:2277-2284.

28. Barau G, Robillard PY, Hulsey TC, Dedecker F, Laffite A, Gerardin P, et al. Linear association between maternal pre-pregnancy body mass index and risk of caesarean section in term deliveries. BJOG. 2006;113:1173-1177.
29. Li C, Kaur H, Choi WS, Huang TT, Lee RE, Ahluwalia JS. Additive interactions of maternal prepregnancy BMI and breast-feeding on childhood overweight. Obes Res. 2005;13: 362-371.
30. Bocca-Tjeertes IF, van Buuren S, Bos AF, Kerstjens JM, Ten Vergert EM, Reijneveld SA. Growth of preterm and full-term children aged 0-4 years: integrating median growth and variability in growth charts. J Pediatr. 2012;161:460-465. e1.
31. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. Pediatr Res. 1995;38:733-739.
32. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life--a systematic review. Obes Rev. 2005;6:143-154.
33. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ. 2000;320:967-971.
34. Negele K, Heinrich J, Borte M, von Berg A, Schaaf B, Lehmann I, et al. Mode of delivery and development of atopic disease during the first 2 years of life. Pediatr Allergy Immunol. 2004;15:48-54.
35. WHO Anthro and macros. version 3.2.2. Available at: http://www.who.int/childgrowth/software/en/(January 2011).
36. WHO BMI-for-age cut-offs. Available at: http://www.who.int/growthref/who2007_bmi_for_age/en/index.html; http://www.who.int/childgrowth/standards/bmi_for_age/en/index.html.
37. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria, 2010 ISBN 3-900051-07-0 Available at: http://www.R-project.org.
38. Feng XL, Xu L, Guo Y, Ronsmans C. Factors influencing rising caesarean section rates in China between 1988 and 2008. Bull World Health Organ. 2012;90:30-39, 39A.
39. Fairley L, Dundas R, Leyland AH. The influence of both individual and area based socioeconomic status on temporal trends in Caesarean sections in Scotland 1980-2000. BMC Public Health. 2011;11:330.

40. Gilbert A, Benjamin A, Abenhaim HA. Does education level influence the decision to undergo elective repeat caesarean section among women with a previous caesarean section? J Obstet Gynaecol Can. 2010;32:942-947.
41. Moreno LA, Rodriguez G. Dietary risk factors for development of childhood obesity. Curr Opin Clin Nutr Metab Care. 2007;10:336-341.
42. Hebebrand J, Hinney A. Environmental and genetic risk factors in obesity. Child Adolesc Psychiatr Clin N Am. 2009;18:83-94.
43. Durand CP, Andalib M, Dunton GF, Wolch J, Pentz MA. A systematic review of built environment factors related to physical activity and obesity risk: implications for smart growth urban planning. Obes Rev. 2011;12:e173-182.
44. Huurre A, Kalliomaki M, Rautava S, Rinne M, Salminen S, Isolauri E. Mode of delivery - effects on gut microbiota and humoral immunity. Neonatology. 2008;93:236-240.
45. Fallani M, Young D, Scott J, Norin E, Amarri S, Adam R, et al. Intestinal microbiota of 6-week-old infants across Europe: geographic influence beyond delivery mode, breast-feeding, and antibiotics. J Pediatr Gastroenterol Nutr. 2010;51:77-84.
46. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A. 2005;102:11070-11075.
47. Pedersen R, Ingerslev HC, Sturek M, Alloosh M, Cirera S, Christoffersen BO, et al. Characterisation of gut microbiota in Ossabaw and Gottingen minipigs as models of obesity and metabolic syndrome. PloS one. 2013;8:e56612.
48. Bervoets L, Van Hoorenbeeck K, Kortleven I, Van Noten C, Hens N, Vael C, et al. Differences in gut microbiota composition between obese and lean children: a cross-sectional study. Gut Pathog. 2013;5:10. Epub.
49. Million M, Maraninchi M, Henry M, Armougom F, Richet H, Carrieri P, et al. Obesity-associated gut microbiota is enriched in Lactobacillus reuteri and depleted in Bifidobacterium animalis and Methanobrevibacter smithii. Int J Obes (Lond). 2012;36:817-825.
50. Kalliomaki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. Am J Clin Nutr. 2008;87:534-538.
51. Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science. 2005;307:1915-1920.

52. Holmes E, Li JV, Athanasiou T, Ashrafian H, Nicholson JK. Understanding the role of gut microbiome-host metabolic signal disruption in health and disease. Trends Microbiol. 2011;19:349-359.
53. Brynhildsen J, Sydsjo A, Ekholm-Selling K, Josefsson A. The importance of maternal BMI on infant's birth weight in four BMI groups for the period 1978-2001. Acta Obstet Gynecol Scand. 2009;88:391-396.
54. Mesman I, Roseboom TJ, Bonsel GJ, Gemke RJ, van der Wal MF, Vrijkotte TG. Maternal pre-pregnancy body mass index explains infant's weight and BMI at 14 months: results from a multi-ethnic birth cohort study. Arch Dis Child. 2009;94:587-595.
55. Hernandez-Valero MA, Wilkinson AV, Forman MR, Etzel CJ, Cao Y, Barcenas CH, et al. Maternal BMI and country of birth as indicators of childhood obesity in children of Mexican origin. Obesity (Silver Spring). 2007;15:2512-2519.
56. Li C, Kaur H, Choi WS, Huang TT, Lee RE, Ahluwalia JS. Additive interactions of maternal prepregnancy BMI and breast-feeding on childhood overweight. Obes Res. 2005;13(2):362-371.
57. Ray K. Gut microbiota: Adding weight to the microbiota's role in obesity-exposure to antibiotics early in life can lead to increased adiposity. Nat Rev Gastroenterol Hepatol. 2012;9(11):615.
58. Olson CM, Strawderman MS, Dennison BA. Maternal weight gain during pregnancy and child weight at age 3 years. Matern Child Health J. 2009;13(6):839-846.
59. Sheiner E, Levy A, Menes TS, Silverberg D, Katz M, Mazor M. Maternal obesity as an independent risk factor for caesarean delivery. Paediatr Perinat Epidemiol. 2004;18(3):196-201.
60. Poobalan AS, Aucott LS, Gurung T, Smith WC, Bhattacharya S. Obesity as an independent risk factor for elective and emergency caesarean delivery in nulliparous women--systematic review and meta-analysis of cohort studies. Obes Rev. 2009;10(1):28-35.

Table 1 Characteristics of participants at each time point. Values are mean (SD) or number (%). Stratified by delivery mode

Age	2 years		6 years		10 years	
	Vaginal (n=1439)	Caesarean (n=295)	Vaginal (n=1027)	Caesarean (n=217)	Vaginal (n=966)	Caesarean (n=204)
Maternal characteristics						
Age, years	30.8 (4.4)	31.8 (4.4)*	31.5 (4.1)	31.9 (4.2)	31.6 (4.2)	32.2 (4.4)
City, n(%)						
Munich	498 (34.6)	118 (40.0)	486 (47.3)	106 (48.8)	461 (47.7)	104 (51.0)
Leipzig	577 (40.1)	111 (37.6)	291 (28.3)	66 (30.4)	269 (27.8)	58 (28.4)
Bad Honnef	219 (15.2)	32 (10.8)*	150 (14.6)	25 (11.5)	135 (14.0)	21 (10.3)
Wesel	145 (10.1)	34 (11.5)	100 (9.7)	20 (9.2)	101 (10.5)	21 (10.3)
Parental education[a], n (%)						
low	56 (3.9)	11 (3.7)	38 (3.7)	6 (2.8)	32 (3.3)	6 (3.0)
medium	458 (32.1)	78 (26.5)	259 (25.4)	49 (22.7)	252 (26.3)	43 (21.2)
high	913 (64.0)	205 (69.7)	721 (70.8)	161 (74.5)	675 (70.4)	154 (75.9)
Smoking during pregnancy, n (%)	198 (14.3)	55 (19.4)*	119 (12.0)	42 (20.1)*	119 (12.7)	36 (18.5)*
Pre-pregnancy BMI, kg/m^2	22.5 (3.8)	23.7 (4.5)*	22.5 (3.9)	24.0 (4.9)*	22.5 (3.8)	23.8 (4.9)*
Gestational weight gain, kg	14.5 (5.0)	15.3 (5.6)*	13.9 (4.7)	15.5 (5.9)*	14.1 (4.7)	15.8 (5.9)*
Child characteristics						
Female sex, n (%)	706 (49.1)	127 (43.1)	487 (47.4)	91 (41.9)	471 (48.8)	86 (42.2)
Head circumference ≥ 37 cm, n (%)	154 (10.9)	61 (21.0)*	109 (10.8)	46 (21.4)*	113 (11.9)	41 (20.3)*
Age, months	24.1 (0.6)	24.2 (0.6)*	73.2 (2.0)	73.0 (1.5)	122.3 (2.5)	122.3 (2.4)
Gestational age at birth, weeks	39.9 (1.2)	39.7 (1.4)	39.9 (1.2)	39.7 (1.4)	39.9 (1.2)	39.6 (1.4)*
Birth weight, kg	3.5 (0.4)	3.5 (0.5)	3.5 (0.4)	3.5 (0.6)	3.5 (0.4)	3.5 (0.6)
Breastfeeding initiation, n (%)	1356 (94.4)	273 (92.9)	983 (96.4)	200 (93.0)*	922 (95.9)	188 (93.1)
Exclusive breastfeeding duration, months	3.8 (2.3)	3.4 (2.4)*	4.0 (2.2)	3.4 (2.5)*	4.0 (2.2)	3.4 (2.5)*
Total breastfeeding duration, months	4.7 (2.0)	4.6 (2.1)	5.0 (1.8)	4.6 (2.1)*	4.9 (1.8)	4.6 (2.1)*
Timing of solid food introduction, n (%)						
<4 months	134 (12.9)	24 (11.0)	77 (10.0)	17 (10.1)	70 (9.9)	14 (8.9)
4-6 months	686 (65.9)	156 (71.6)	516 (67.2)	120 (71.4)	474 (66.9)	114 (72.2)
≥7 months	221 (21.2)	38 (17.4)	175 (22.8)	31 (18.5)	164 (23.2)	30 (19.0)
BMI, kg/m^2	16.1 (1.3)	16.3 (1.5)	15.6 (1.6)	15.8 (1.7)	17.2 (2.6)	17.7 (2.5)*
BMI z-score	0.25 (0.98)	0.37(1.06)*	0.08 (0.99)	0.22 (1.00)	0.09 (1.07)	0.33 (1.06)*
BMI category, n (%)						
<85th percentile	1111 (77.2)	208 (70.5)	971 (94.5)	201 (92.6)	785 (81.3)	153 (75.0)
85th to <95th percentile	208 (14.5)	47 (15.9)	38 (3.7)	8 (3.7)	129 (13.4)	35 (17.2)
≥95th percentile	120 (8.3)	40 (13.6)*	18 (1.8)	8 (3.7)	52 (5.4)	16 (7.8)
Height, cm	88.2 (3.2)	88.2 (3.4)	119.0 (5.1)	119.4 (4.9)	143.6 (6.5)	143.9 (6.6)

[a] categorized according to the highest number of years either parent attended school: low<10 years, medium=10 years and high> 10 years

* significant difference between caesarean delivery and vaginal delivery, tested by t-test for continuous variables, chi-square for binary variables, Fisher's exact test for multi-level variables (first-levels were set as reference level)

Figure legend

Figure 1 Estimate coefficients for the association between CS and BMI z-score at 2, 6, and 10 years of age. Model 1 unadjusted model. Model 2 added socioeconomic status and child characteristics. Model 3 added maternal characteristics.

Figure 2 Odds ratios for the association between CS and overweight at 2, 6, and 10 years of age. Model 1 unadjusted model. Model 2 added socioeconomic status and child characteristics. Model 3 added maternal characteristics.

Figure 3 Odds ratios for the association between CS and obesity at 2, 6, and 10 years of age. Model 1 unadjusted model. Model 2 added socioeconomic status and child characteristics. Model 3 added maternal characteristics.

Figure 1

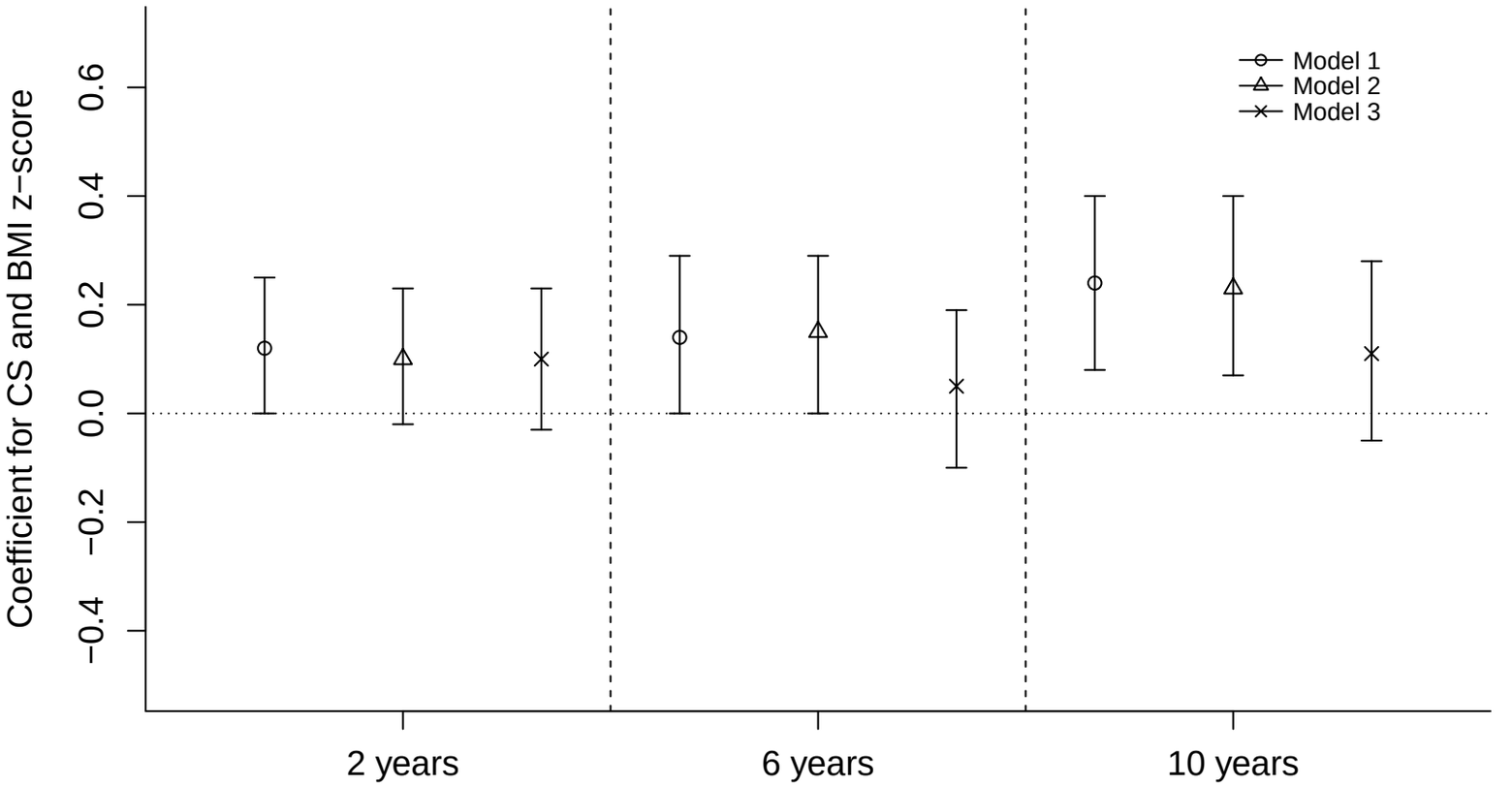


Figure 2

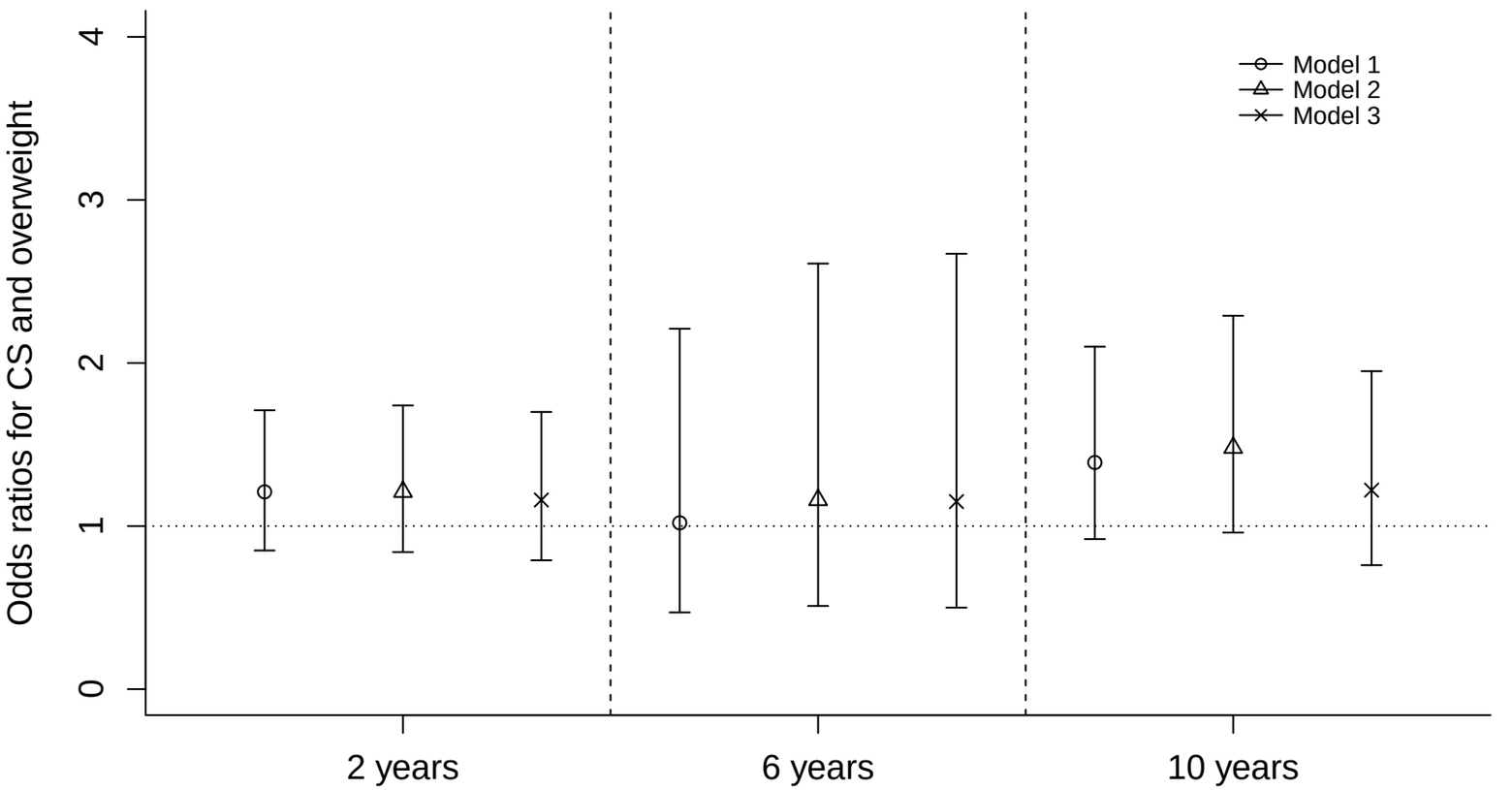
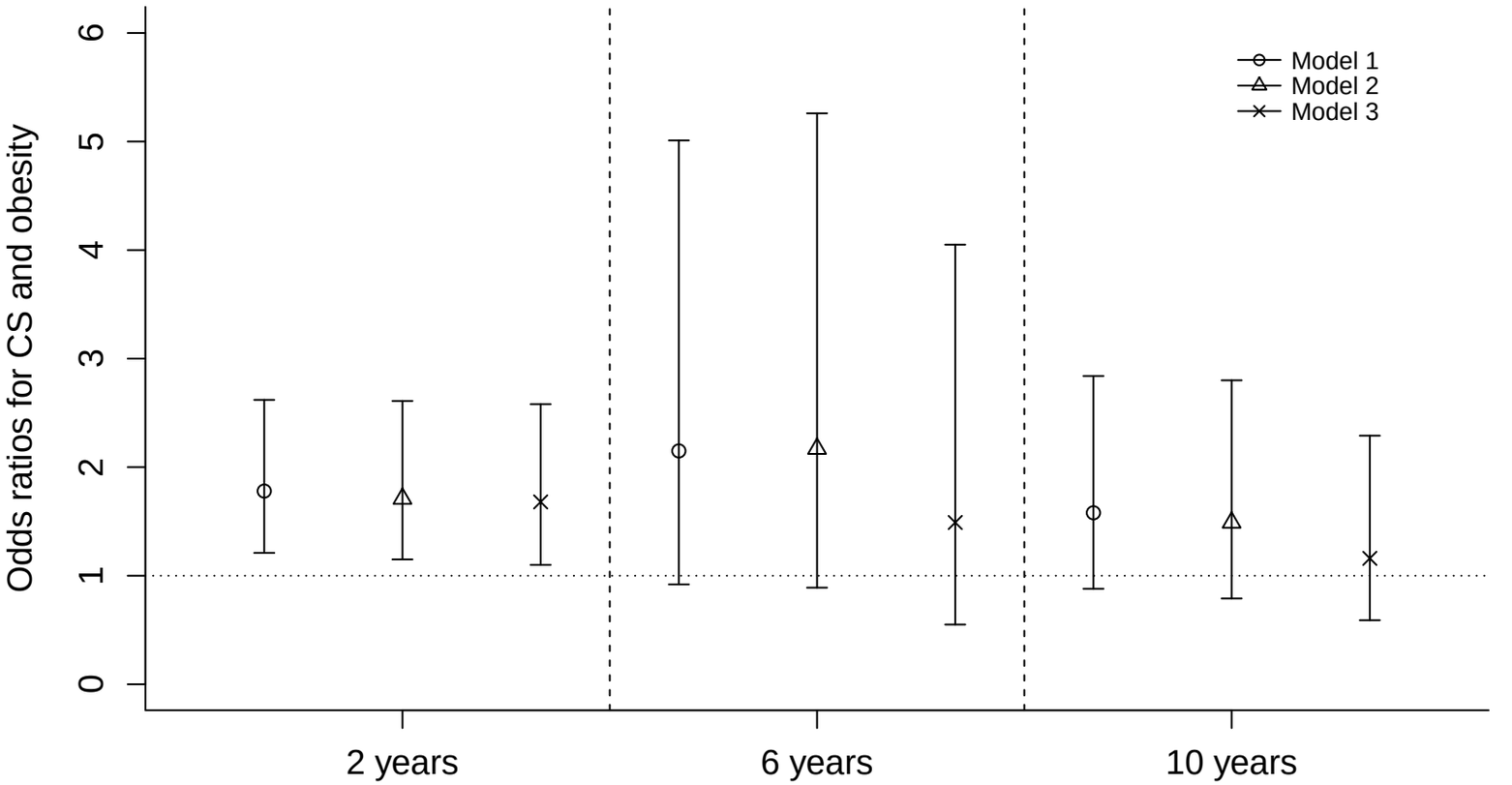


Figure 3


Odds ratios for CS and obesity
0
1
2
3
4
5
6
Model 1
Model 2
Model 3
2 years
6 years
10 years

6 Food intake and overweight in school-aged children in Germany. Results of the GINIplus and LISAplus studies

Authors: Zhengcun Pei, Claudia Flexeder, Elaine Fuertes, Marie Standl, Anette Buyken, Dietrich Berdel, Andrea von Berg, Irina Lehmann, Beate Schaaf, Joachim Heinrich for the GINIplus and LISAplus Study Group

Accepted on 07.04.2014, in press

Journal: Annals of Nutrition and Metabolism

Year: 2014

Impact factor: 1.661

6.1 Confirmation letter

From: ANM@med.uni-muenchen.de

To: zhengcun.pei@helmholtz-muenchen.de

Subject: Your manuscript 201401014.R1 has been officially accepted for publication

Body: 07-Apr-2014

Dear Mr. Pei:

It is a pleasure to inform you that your manuscript entitled "Food intake and overweight in school-aged children in Germany. Results of the GINIplus and LISAplus studies" has been accepted by Annals of Nutrition and Metabolism.

Thank you for your fine contribution. On behalf of the Editors of Annals of Nutrition and Metabolism, we look forward to your continued contributions to the Journal.

Sincerely,

Prof. Berthold Koletzko
Ludwig Maximilian Universität
Annals of Nutrition and Metabolism

ANM@med.uni-muenchen.de

Date Sent: 07-Apr-2014

6.2 Accepted manuscript

Food intake and overweight in school-aged children in Germany. Results of the GINIplus and LISAplus studies

MSc. Zhengcun Pei[1,2], MSc. Claudia Flexeder[1], MSc. Elaine Fuertes[1, 3], PhD. Marie Standl[1], PhD. Anette Buyken[4], MD. Dietrich Berdel[5], MD. Andrea von Berg[6], PhD. Irina Lehmann[6], MD. Beate Schaaf[7], PhD. Joachim Heinrich[1] for the GINIplus and LISAplus Study Group

[1] Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany;

[2] Faculty of Medicine, Ludwig-Maximilians-University of Munich, Munich, Germany;

[3] School of Population and Public Health, University of British Columbia, Canada;

[4] University of Bonn, IEL-Nutritional Epidemiology, DONALD Study at the Research Institute of Child Nutrition, Bonn, Germany;

[5] Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany;

[6] Department of Environmental Immunology, UFZ-Centre for Environmental Research, Leipzig, Germany;

[7] Medical Practice for Pediatrics, Bad Honnef, Germany.

Correspondence

Dr. Joachim Heinrich

Institute of Epidemiology I

Helmholtz Zentrum München - German Research Center for Environmental Health

Ingolstaedter Landstr. 1

85764 Neuherberg, Germany

Telephone: +49-(0)89-3187-4150

Fax: +49-(0)89-3187-3380

E-Mail: heinrich@helmholtz-muenchen.de

Abstract

Objective Investigate the cross-sectional association between food intake and overweight in children.

Methods Height and weight were measured in 2565 school-aged children. Intakes of 11 food groups were categorized (low, medium and high) using specific tertile cut-offs. Multivariate energy partition models were applied. Adjustment included energy intake from other food groups, city, family income, parental education, and screen time. Possible under-reporters was identified and used in sensitivity analyses.

Results Compared to low intake, high intakes of meat, fish, beverages and bakery products were associated with greater BMI z-scores (ß [95% CI] = 0.32 [0.21; 0.42], ß = 0.13 [0.03; 0.24], ß = 0.23 [0.11; 0.35] and ß = 0.10 [-0.01; 0.20]) and increased risk of being overweight (OR = 2.08 [1.58; 2.73], OR = 1.39 [1.08; 1.80], OR = 1.36 [1.01; 1.84] and OR = 1.62 [1.24; 2.11]). Conversely, medium and high intakes of confectionery were associated with smaller BMI z-scores (ß = -0.18 [-0.28; -0.07] and ß = -0.22 [-0.33; -0.12]) and decreased risk of being overweight (OR = 0.64 [0.50; 0.83] and OR = 0.53 [0.40; 0.68]). These associations were robust to sensitivity analyses.

Conclusions Intakes of meat, fish, beverages and bakery products correlate with body weight status.

Key Words: Food intake, overweight, child, BMI z-score, energy partition model, epidemiology

Introduction

Obesity is a major public health concern [1, 2]. Childhood obesity often persists into adulthood and can substantially decrease quality of life [3], increase the risk of metabolic syndrome and adult morbidities [4, 5], and be a heavy financial burden on the public health system [6].

Obesity is mainly a consequence of an unbalanced energy status [7]. Hence, the influence of diet (intake of individual nutrients and certain food items, dietary patterns and habits) and energy intake have been considered in many studies on the etiology of obesity [8-11]. However, the findings are difficult to reconcile [12, 13]. Several different types of models (i.e. standard multivariate model, residual nutrient model, energy partition model, multivariate nutrient density model) are commonly used in epidemiological studies, which are adjusted for total energy intake [14]. The results of these models can and have been interpreted using different perspectives. One important difference between energy partition models and other types of models aforementioned is that the coefficient calculated from this former type of model represents both energy and non-energy associations with the nutrient. The coefficient obtained from other model types leads to isocaloric substitution interpretations [14, 15]. Isocaloric interpretations are problematic when total energy intake is associated with the outcome under study [14], which may be one potential explanation for the conflicting results of previous studies. Another possibility could be the misreporting of energy intake in dietary assessment [16]. Moreover, selective reporting possibly exists. Results from the ALSPAC study revealed that under-reporters had lower records of fat/sugar-containing foods such as biscuits, cakes, chocolates and sweets [17]. Additionally, factors including food habits, portion size estimation, as well as ethnicity and cultural differences may also influence the accuracy of food intake data [16].

The association between food intake with BMI z-scores and being overweight during childhood remains controversial [18]. In the current study, we used data from two German birth cohorts to examine cross-sectionally whether the intake levels of specific food groups are associated with being overweight or obese at the age of 10 years, after adjusting for energy from all other food groups and other potential confounding factors.

Materials and methods

Study population

Data from two ongoing German birth cohort studies were used in the current analysis. GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) is an ongoing birth cohort study initiated to prospectively investigate

the influence of a nutritional intervention during infancy, as well as air pollution and genetics on allergy development. GINIplus participants (N=5991 newborns) were recruited from obstetric clinics in Munich and Wesel between September 1995 and July 1998. Details of the study design are described elsewhere [19]. During the first 4 months, a total of 2252 newborns with atopic heredity participated in a hydrolyzed protein infant formula intervention study [20]. This randomized controlled study showed that the BMIs of children at 1 year were marginally different among the formula groups, but not at 6 and 10 years of age [21].

LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics) is an ongoing birth cohort examining the impact of lifestyle-related factors, air pollution and genetics on immune system and allergy development in childhood. In total, 3097 neonates were recruited from 14 obstetrical clinics in Munich, Leipzig, Wesel and Bad Honnef between November 1997 and January 1999. A detailed description of the study's screening and recruitment has been described previously [22].

During the 10-year follow-up, information on food intake was collected from 3437 participants (2194 from GINIplus, 1243 from LISAplus) by means of a validated semi quantitative Food Frequency Questionnaire (FFQ). Height and weight were measured for 3116 participants (1918 from GINIplus, 1198 from LISAplus) during the 10-year physical examinations. In the current study, 2565 children (1308 males and 1257 females) from GINIplus (n = 1596) and LISAplus (n = 969) with complete data on FFQ and BMI are included (Figure 1).

Approval by the respective local ethics committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North-Rhine-Westphalia) and written consent from all participating families were obtained for both studies.

Definition of outcomes: BMI z-scores and overweight

Weight and height were measured by physicians during the 10-year physical examinations. BMI values were calculated and transformed to age- and sex-specific BMI z-scores using WHO macros [23]. Children were defined as being overweight or obese using the BMI z-score standard deviation (SD), according to WHO guidelines [24]. Children with BMI z-scores greater than one SD (BMI z-score > +1 SD) were defined as overweight. Children of normal weight (BMI z-score ≤ +1SD) were used as the reference group in all models. As the number of obese (BMI z-score > +2 SD) children was small (n=116), we included these children with the overweight group.

Definition of predictors: eleven food groups

The details and effectiveness of the FFQ have been published elsewhere [25]. Briefly, information on food intake frequencies and portion sizes of 82 food items were collected using parent-completed questionnaires. Seventy-nine food items were grouped into 11 food groups according to the Codex General Standard for Food Additives' food category system [26]. We excluded three food items: nut-nougat-cream, water and syrup. Nut-nougat-cream has a complex composition and could not be adequately classified into one food group. Syrup intake was very low in the current study. Water intake was excluded as its consumption does not yield energy. However, we used water intake as an additional adjustment variable when assessing the association between beverage intake and the outcomes, as beverage intake is reported to be associated with water intake [27]. Information on the intake of sweeteners, salts, spices, soups, sauces, and foodstuffs intended for particular nutritional uses were not available in the current study.

For each of the 11 food groups, the intake for each child in grams per day was calculated. Because the distributions of the food intakes were positively skewed, we categorized these values into three levels (low, medium, high) using group- and sex-specific tertile cut-offs.

Potential confounding factors

We included several potential confounding factors that confound the association between food intake and the outcomes of interest. The set of covariates examined were city of residence (Munich, Wesel, Bad Honnef, Leipzig), parental education level, family income and screen viewing time. Parental education levels were defined according to the highest number of years either parent attended school (low < 10 years, medium = 10 years and high > 10 years). Family income was defined into three categories according to the city-specific quartiles of monthly average income (low < 25%, medium 25 - 75% and high > 75%). We used time spent in front of a screen (including TV, video and computer viewing), hereon referred to as "screen time", as a sedentary behavior covariate, as sedentary behavior has been associated with greater increases in BMI between ages 9 and 15 years [28]. This variable was collapsed into 2 categories: low screen time included children who spent < 1 hour per day in summer and <2 hours per day in winter in front of a screen; high screen time included children who spent ≥ 1 hour per day in summer and ≥ 2 hours per day in winter in front of a screen. In addition, there were 15 children who spent < 1 hour per day in summer and ≥ 2 hours per day in winter in front of a screen. These children were included into the high screen time category.

We additionally defined a variable "under-reporter versus plausible energy intake reporter" based on a ratio of total energy intake (TEI) to basal metabolic rate (BMR). BMR is estimated using height, weight, and age according to Milffin et al [29]. Because approximately 70% of total energy expenditure is used for basal life processes [30], we defined an under-reporter as a child with 0.7*TEI < BMR. A plausible energy intake reporter was defined as a child with 0.7*TEI ≥ BMR. As the estimation of BMR and the cut-off used to differentiate under-reporters and plausible energy intake reporters may not be entirely accurate [31], this variable was not included in the final models, but rather was used for descriptive and sensitivity analyses only.

Statistical analysis

As preliminary analyses suggested no differences in the associations between food intakes and BMI z-scores by sex, data for males and females were pooled for all analyses. For each of the 11 food groups, unadjusted and multivariate energy partition models [15] were used to examine the associations between each food group intake (in grams per day) with BMI z-scores and being overweight. Low intake levels were used as the reference group in all models. According to the definition of the partition model [14], we calculated energy intake from the food group itself and energy intake from all other food groups. Instead of total energy intake, energy intake from all other food groups was included as a covariate in the models. For each food group, there was a specific energy intake from all other food groups.

Differences between respondents and non-respondents as well as overweight and normal weight subjects were tested using Pearson's χ^2 test for categorical variables and Student's t-test for continuous variables. Study characteristics are described using means and standard deviations (s.d.) or percentages (n/N, %). Model results are presented as linear regression coefficients (ß) for BMI z-scores and odds ratios (OR) for being overweight, with corresponding 95% confidence intervals (ß [95% CI] or OR [95% CI], respectively). All analyses were performed using the statistical software package R, version 2.14.1 [32].

Additional sensitivity analyses were performed. 1) To examine whether the formula intervention in GINIplus study attenuated our results, sensitivity analyses in which the models were additionally adjusted for formula type was conducted. 2) To study the potentially existing under-reporting issue in the present study, analyses were stratified by "under-reporter versus plausible energy intake reporter". In addition, sensitivity analyses adjusting for this variable in the pooled models were performed. 3) To compare the effect size of the associations between food items that had similar dietary content with BMI z-scores and being overweight, we performed analyses in several pairs: red meat (i.e. pork, beef

and sausages) vs. white meat (i.e. chicken), fresh water fish vs. sea water fish, fish sticks vs. other fish-subgroups, vegetables vs. fruits, chocolate/chocolate bars vs. soft sweets. 4) We additionally investigated associations between BMI z-scores and the individual food items which had been combined into the bakery products and beverages food groups.

Results

Characteristics of the study population at 10 years of age are shown in table 1. Female participants comprised 49.0% of the sample. The mean BMI z-score was 0.16, which suggests that the majority of the study population had a larger BMI than the reference population. The standard deviation was approximately 1.00, as expected [33]. The prevalence of overweight was 19.7%. The average total energy intake was 2082 ± 606 kcal. The characteristics of children included in the current analyses and those from the original birth cohorts who are not included are significantly different in the following three aspects: weight of children at age 10 years, family income at age 10 years and parental education level. The children who were excluded from the present study were more likely to be overweight at age 10 years (25.4%), from low-income families (25.2%) and to have parents with low education level (13.0%) compared to those included in this analysis (19.7%, 21.3% and 4.7%, respectively) (data not shown).

The proportion of under-reporters among overweight and normal weight participants is shown in table 2. Compared to participants of normal weight, there was a significantly higher proportion of under-reporters among overweight participants for both males and females (32.6% vs. 19.2% and 27.6% vs. 17.1%, respectively, $p<0.001$).

Details of which food items were grouped into which food groups are shown in table 3.

The food intake of each food group in grams per day as well as percent energy consumed per day is shown in table 4.

The adjusted coefficients for the association between food group intakes and BMI z-scores at age 10 years are shown in figure 2. Compared to children with a low intake of meat and meat products, children with medium and high intakes had greater BMI z-scores (ß = 0.10 [0.00; 0.20] and ß = 0.32 [0.21; 0.42], respectively). Children with high fish and beverage intakes had greater BMI z-scores than those with low fish and beverage intakes (ß = 0.13 [0.03 ~ 0.24] and ß = 0.23 [0.11; 0.35], respectively). Compared to children with a low intake of confectionery, children with medium and high confectionery intakes had smaller BMI z-scores (ß = -0.18 [-0.28; -0.07] and ß = -0.22 [-0.33; -0.12], respectively). No significant associations were found for the other food groups.

Adjusted ORs for the association between food intake groups and being overweight at age 10 years are shown in figure 3. Compared to low intake groups, those with high intakes of meat, bakery, fish and beverage had a higher risk of being overweight (OR = 2.08 [1.58; 2.73], OR = 1.62 [1.24; 2.11], OR = 1.39 [1.08; 1.80] and OR = 1.36 [1.01; 1.84], respectively). Furthermore, those with medium and high intakes of confectionery were at a decreased risk of being overweight (OR = 0.64 [0.50; 0.83] and OR = 0.53 [0.40; 0.68], respectively). No significant associations were found for the other food groups.

Additional adjustment for formula type did not substantially change our results (data not shown).

Adjusting additionally for "under-reporter versus plausible energy intake reporter" attenuated the effect size, but the association between BMI z-scores and confectionery intake was still significant (ß [95% CI]: -0.18 [-0.28; -0.07] vs. -0.12 [-0.23;-0.02] and -0.22 [-0.33; -0.12] vs. -0.13 [-0.24; -0.03] for medium and high intake of confectionery before and after adjustment, respectively). The association between being overweight and confectionery intake also remained significant with attenuated effect size (OR [95% CI]: 0.64 [0.50; 0.83] vs. 0.71 [0.55; 0.93] and 0.53 [0.40; 0.68] vs. 0.63 [0.48; 0.82] for medium and high intake of confectionery before and after adjustment, respectively). Moreover, effect estimates for under-reporters were not notably different than those for plausible energy intake reporters. Detailed numbers are provided in Supplement table 1.

Analyses stratified by red meat and white meat yielded significantly positive associations with BMI z-scores (ß for medium intake: 0.07 [-0.03; 0.18] vs. 0.27 [0.11; 0.42] and ß for high intake: 0.20 [0.09; 0.31] vs. 0.22 [0.13; 0.31] for red meat and white meat, respectively) and being overweight (OR for medium intake: 1.16 [0.89; 1.52] vs. 1.77 [1.22; 2.58] and OR for high intake: 1.57 [1.20; 2.06] vs. 1.64 [1.31; 2.05] for intake of red meat and white meat, respectively) for both subgroups. Also, the analyses stratified by fresh water fish and sea water fish showed similar results (OR for medium intake: 1.22 [1.01; 1.65] vs. 1.27 [1.00; 1.66] and OR for high intake: 1.28 [1.02; 1.68] vs 1.32 [1.02; 1.72] for fresh water fish and sea water fish, respectively). High intake of fish sub-groups that exclude fish stick was significantly associated with being overweight (OR: 1.47 [1.15; 1.87]), but not the case for high fish stick intake (0.94 [0.75; 1.19]). Analyses stratified by fruit and vegetables yielded marginally significant association between high intake of vegetable and increased BMI z-score (ß: 0.11 [0.01; 0.22]). However, high vegetable intake was not associated with being overweight (OR: 1.26 [0.97; 1.64]). Analyses stratified by chocolate/chocolate bars and soft sweets revealed that chocolate/chocolate bars had smaller estimate coefficients than soft

sweets (medium intake: 0.67 [0.52; 0.87] vs. 0.94 [0.73; 1.22] and high intake: 0.68 [0.53; 0.89] vs. 0.71 [0.55; 0.92], respectively). The estimate coefficients only slightly differed among the different bakery food items, and were all significant (data not shown). The effect estimates and significance in sugar sweetened beverages (e.g. cola, nectars, lemonade, energy drinks and etc.) were greater compared to that in juices (e.g. fruit juices, diluted juices, vegetable juices, etc.), the associations between BMI z-scores and beverages were all significant (data not shown).

Discussion

In the present study, we observed significant positive cross-sectional associations between high intakes of meat, fish, bakery products and beverages with BMI z-scores and with being overweight at 10 years of age. Moreover, confectionery intake was negatively associated with BMI z-scores and being overweight. Additional model adjustments for energy reporting status and other sensitivity analyses did not substantially change our results.

Meat and fish intake and BMI

Although data from a cross-sectional KiGGS study (n=13450) revealed a similar association between high intake of meat with overweight and obesity in 3- to 17-year old children [34], our findings should be interpreted with caution as our study is cross-sectional. Animal protein may play a role in the associations, as meat and fish are rich in it. Results from the DONALD study showed significantly positive associations between animal protein intake during puberty and fat-free mass in young adulthood [35], which is in line with evidence from randomized controlled trials in children [36, 37] and adults [38]. Thus, the association between BMI with intake of meat and fish may be a reflection of accumulating fat-free mass. The association between BMI z-scores with fat mass and fat-free mass is reported to vary according to the degree of body fatness (overall multiple R^2 ranged from 0.90 to 0.96) [39]. Among children with BMI z-scores > 1, BMI z-scores were more strongly associated with fat-free mass than fat mass. In contrast, among children with BMI z-scores ≤ 1, BMI z-scores were more strongly associated with fat mass than fat-free mass [39].

Several studies have reported positive associations between protein intake during early life (<1 year) and obesity in childhood [40-42]. The hypothesis behind this observation is that higher protein intake during early life is associated with faster weight gain [40]. However, the protein intake of rapid growers at age 2 years did not influence the change in BMI z-scores between age 2 and 5 years in the DONALD study [43]. Our study population (of 10-year old children) is nearing puberty, a developmental stage during which fast weight gain is possible.

Whether protein intake in puberty contributes to weight gain remains unclear, could not be addressed in this analysis, and needs to be explored in future studies.

Meat consumption has been identified as a lifestyle indicator in several adult studies [44, 45]. Compared to vegetarians, meat consumers had lower education levels, lower social economic statuses and lower household incomes. These factors may have an impact on the onset of obesity [46, 47]. Overall, the associations between meat intake with BMI z-scores and being overweight were robust, regardless of which models were used or which confounders were considered. These consistent associations highlight the need for future prevention and intervention against overweight and obesity among children.

Confectionery intake and BMI

We observed negative associations between confectionery intake and BMI z-scores. Associations between confectionery intake and BMI z-scores are conflicting [48, 49]. We believe there are two possible explanations for our results. First, the seemingly protective effect of confectionery might be attributable to reverse causation. Energy-dense, high-fat, low-fiber dietary pattern has been identified as a correlate of increased adiposity during childhood and adolescent [50]. Parents of overweight or obese children, or the children themselves, may have consciously reduced or limited their confectionery intake to lose weight. This artifact would have caused the results to indicate that children of normal weight consume more chocolate and candies than overweight children. Moreover, potential reporting bias may be possible as under-reporters usually have higher weight statuses [16, 50, 51]. It is also possible that children and parents under-reported the intake of “unhealthy food” [17]. However, adjusting for under-reporters did attenuate the effect size, but the association was still significant. Second, as sugars can be satiety-stimulating in the short-term (2 hours) [52], intake of confectionery could have reduced subsequent food intake, which could lead to lower BMI. In the current study, the overall energy contribution of confectionery was low (median %En: 3.0%), which does not support a major causal role of confectionery for high BMI.

O'Neil et al [53] examined the effect of candy consumption on obesity using data from the NHANES study in 11181 participants (age ranged from 2 to 18 years). Candy consumers (approximately 25% of the total population) had lower ORs for being overweight (0.78, 95% CI: 0.68 to 0.90) and obese (0.74, 95% CI: 0.66 to 0.82) after adjusting for sex, ethnicity, age and energy intake. However, a study in 1139 Saudi Arabian males aged 10 to 14 years reported that children who consumed sweets and candy one or more times per day were at a

higher risk of being overweight (OR: 1.7, 95% CI: 1.3 to 2.3). However, this OR was not adjusted for potential covariates [54].

Intakes of bakery products and beverages and BMI

In the current study, eleven kinds of bread or cakes were combined into a bakery products group (e.g. whole-grain bread, refined bread, cream cake, etc.). The materials used in the production of these items likely differ (e.g. polyols, sugar alcohols, natural sweeteners, sucrose, etc.). Therefore, the associations between BMI z-scores and these food items were examined individually. However, the estimate coefficients of different bakery food items only slightly differed. In general, bakery products belong to medium-to-high glycemic index categories [55], which may help explain the associations between BMI and consumption of bakery products [56]. In addition, reverse causation and misreporting may exist in the association between bakery products intake and overweight, as bakery products are also energy-dense, high-fat, low-fiber food [17, 50]. Therefore, the true ORs may be even larger than the observed. However, to which extent these possibilities may affect the results must be interpreted cautiously. Take confectionery and bakery products for example, intake of confectionery is usually between meals, which is likely to be restricted, especially for overweight children; whilst bakery products are always consumed during meals, a child is unlikely to skip main meals even if he is overweight. Thus, the potential effect of reverse causation may be stronger for confectionery intake compared to bakery products. Future studies are needed to explore these possibilities in different food groups.

Previous studies suggest a possible link between intake of soft drinks with increased BMI and obesity [18, 57]. Beverage intake may contribute to a higher BMI by increasing total energy intake. This hypothesis is supported by several studies in children and adolescents [58, 59]. Greater effect estimates and significance in sugar sweetened beverages compared to that in juices were observed. Both the higher levels of sugar in sugar sweetened beverages and lower consumptions of juices could have contributed to this difference.

Strengths and limitations

The current study has several strengths. Our analyses are based on two large population-based cohorts with measured anthropometric data. The food groups are defined according to the WHO food category system, which allows our results to be compared to future studies. Instead of providing isocaloric interpretations, the multivariate energy partition models allowed us to interpret our results while taking both energy and non-energy effects of foods into account. Sensitivity analyses were nevertheless conducted using different models (i.e.

multivariate standard model and multivariate density model, results not shown), and similar results were obtained.

Our study has some limitations. First, only cross-sectional data was available for this exploratory analysis. Thus, cause and effect associations cannot be drawn. Second, data on body composition and fat mass were not available. These data would have provided more information on weight status rather than only using BMI. However, it has been shown that the percentage of body fat and BMI have similar patterns over time [60]. Third, reporting bias may exist in our study as we used data collected from questionnaires. Differential, selective under-reporting may thus be influencing our results, especially for overweight participants, as has been previously observed [16, 50, 51]. We did observe a higher proportion of under-reporters in overweight participants for both males and females, although the definition of under-reporters used in our study is not ideal. However, additional adjustment for the "under-reporter vs. plausible energy intake reporter" did not notably change our results. Still, the high proportion of potential under-reporters (approximately 30%) calls for the use of caution in future studies.

Conclusion

Our results suggest that a high intake of meat, fish, beverages and bakery products is associated with increased body weight status. Particularly, meat intake may be an important correlate of being overweight. The influence of possible reverse causation on the association between food intake and being overweight needs to be explored in future studies.

Acknowledgement

GINIplus study group: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Munich (JH, HEW, SS, AZ, CMC, MS, PR); Department of Pediatrics, Marien-Hospital, Wesel (DB, AvB, CB, IG); Department of Pediatrics, Ludwig Maximilians University, Munich (SK, DR, SK-E); Department of Pediatrics, Technical University, Munich (CPB, IB, AG, UH); IUF—Institut für Umweltmedizinische Forschung at the Heinrich-Heine-University, Düsseldorf (UK, EL, CC).

LISAplus study group: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Munich (JH, HEW, SS, CMC, MS); Department of Pediatrics, Municipal Hospital 'St Georg', Leipzig (MB, UD), Marien-Hospital Wesel, Department of Pediatrics, Wesel (AvB, CB, IG); Pediatric Practice, Bad Honnef (BS); Helmholtz Centre for Environmental Research—UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (IL, MB, CG, SR, MS); University of Leipzig, Institute of Hygiene and Environmental Medicine, Leipzig (OH, CD,

JM); IUF—Institut für Umweltmedizinische Forschung, Düsseldorf (UK, EL, CC); Technical University Munich, Department of Pediatrics, Munich (CPB, UH); ZAUM—Center for Allergy and Environment, Technical University, Munich (HB, JG, FM).

Funding

The GINIplus study was mainly supported for the first 3 years of the Federal Ministry for Education, Science, Research and Technology (interventional arm) and Helmholtz Zentrum Munich (former GSF) (observational arm). The 4 year, 6 year, and 10 year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5 study centres (Helmholtz Zentrum Munich (former GSF), Research Institute at Marien-Hospital Wesel, LMU Munich, TU Munich and from 6 years onwards also from IUF - Leibniz Research-Institute for Environmental Medicine at the University of Düsseldorf) and a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). The LISAplus study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research - UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2 years. The 4 year, 6 year, and 10 year follow-up examinations of the LISAplus study were covered from the respective budgets of the involved partners (Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research - UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF – Leibniz-Research Institute for Environmental Medicine at the University of Düsseldorf) and in addition by a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296).

This work was supported by the Kompetenznetz Adipositas (Competence Network Obesity) funded by the Federal Ministry of Education and Research (FKZ: 01GI1121A).

Conflicts of interest

None to declare.

References:

1. Chiolero A, Lasserre AM, Paccaud F, Bovet P. Childhood obesity: definition, consequences, and prevalence. Rev Med Suisse 2007;3:1262-1269.
2. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obes Res 9 Suppl 2001;4:228S-233S. doi 10.1038/oby.2001.123.
3. Mitchell NS, Catenacci VA, Wyatt HR, Hill JO. Obesity: overview of an epidemic. Psychiatr Clin North Am 2011;34:717-732. doi 10.1016/j.psc.2011.08.005.
4. Lloyd LJ, Langley-Evans SC, McMullen S. Childhood obesity and risk of the adult metabolic syndrome: a systematic review. Int J Obes (Lond) 2012;36:1-11. doi 10.1038/ijo.2011.186.
5. Biro FM, Wien M. (2010) Childhood obesity and adult morbidities. Am J Clin Nutr 91:1499S-1505S. doi 10.3945/ajcn.2010.28701B.
6. Breitfelder A, Wenig CM, Wolfenstetter SB, Rzehak P, Menn P, John J, Leidl R, Bauer CP, Koletzko S, Roder S, Herbarth O, von Berg A, Berdel D, Kramer U, Schaaf B, Wichmann HE, Heinrich J. Relative weight-related costs of healthcare use by children--results from the two German birth cohorts, GINI-plus and LISA-plus. Econ Hum Biol 2011;9:302-315. doi 10.1016/j.ehb.2011.02.001.
7. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. Circulation 2012;126:126-132. doi 10.1161/CIRCULATIONAHA.111.087213.
8. Vitariusova E, Babinska K, Kost'alova L, Rosinsky J, Hlavata A, Pribilincova Z, Babinska K, Jr., Kovacs L. Food intake, leisure time activities and the prevalence of obesity in schoolchildren in Slovakia. Cent Eur J Public Health 2010;18:192-197.
9. Bradlee ML, Singer MR, Qureshi MM, Moore LL. Food group intake and central obesity among children and adolescents in the Third National Health and Nutrition Examination Survey (NHANES III). Public Health Nutr 2010;13:797-805. doi 10.1017/S1368980009991546.
10. Rosenheck R. Fast food consumption and increased caloric intake: a systematic review of a trajectory towards weight gain and obesity risk. Obes Rev 2008;9:535-547. doi 10.1111/j.1467-789X.2008.00477.x.
11. Kral TV, Stunkard AJ, Berkowitz RI, Stallings VA, Brown DD, Faith MS. Daily food intake in relation to dietary energy density in the free-living environment: a prospective analysis of children born at different risk of obesity. Am J Clin Nutr 2007;86:41-47.

12. Lanfer A, Hebestreit A, Ahrens W. Diet and eating habits in relation to the development of obesity in children and adolescents. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 2010;53:690-698. doi 10.1007/s00103-010-1086-z.
13. Summerbell CD, Douthwaite W, Whittaker V, Ells LJ, Hillier F, Smith S, Kelly S, Edmunds LD, Macdonald I. The association between diet and physical activity and subsequent excess weight gain and obesity assessed at 5 years of age or older: a systematic review of the epidemiological evidence. Int J Obes (Lond) 2009;33 Suppl 3:S1-92. doi 10.1038/ijo.2009.80.
14. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65:1220S-1228S; discussion 1229S-1231S.
15. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531-540.
16. Collins CE, Watson J, Burrows T. Measuring dietary intake in children and adolescents in the context of overweight and obesity. Int J Obes (Lond) 2010;34:1103-1115. doi 10.1038/ijo.2009.241.
17. Cribb VL, Jones LR, Rogers IS, Ness AR, Emmett PM. Is maternal education level associated with diet in 10-year-old children? Public Health Nutr 2011;14(11):2037-48. doi: 10.1017/S136898001100036X.
18. Hauner H, Bechthold A, Boeing H, Bronstrup A, Buyken A, Leschik-Bonnet E, Linseisen J, Schulze M, Strohm D, Wolfram G. Evidence-based guideline of the German Nutrition Society: carbohydrate intake and prevention of nutrition-related diseases. Ann Nutr Metab 2012;60 Suppl 1:1-58. doi 10.1159/000335326.
19. von Berg A, Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, Hoffmann U, Reinhardt D, Grubl A, Heinrich J, Wichmann HE, Bauer CP, Koletzko S, Berdel D. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. J Allergy Clin Immunol 2013;131:1565-1573. doi 10.1016/j.jaci.2013.01.006.
20. von Berg A, Koletzko S, Filipiak-Pittroff B, Laubereau B, Grubl A, Wichmann HE, Bauer CP, Reinhardt D, Berdel D. Certain hydrolyzed formulas reduce the incidence

of atopic dermatitis but not that of asthma: three-year results of the German Infant Nutritional Intervention Study. J Allergy Clin Immunol 2007;119:718-725. doi 10.1016/j.jaci.2006.11.017.

21. Rzehak P, Sausenthaler S, Koletzko S, Reinhardt D, von Berg A, Kramer U, Berdel D, Bollrath C, Grubl A, Bauer CP, Wichmann HE, Heinrich J. Long-term effects of hydrolyzed protein infant formulas on growth--extended follow-up to 10 y of age: results from the German Infant Nutritional Intervention (GINI) study. Am J Clin Nutr 2011;94:1803S-1807S. doi 10.3945/ajcn.110.000679.
22. Heinrich J, Bolte G, Holscher B, Douwes J, Lehmann I, Fahlbusch B, Bischof W, Weiss M, Borte M, Wichmann HE. Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. Eur Respir J 2002;20:617-623.
23. World Health Organization. BMI-for-age cut-offs. Available at: http://www.who.int/growthref/who2007_bmi_for_age/en/index.html; http://www.who.int/childgrowth/standards/bmi_for_age/en/index.html.
24. World Health Organization. Growth reference 5-19 years. Available at: http://www.who.int/growthref/who2007_bmi_for_age/en/index.html.
25. Stiegler P, Sausenthaler S, Buyken AE, Rzehak P, Czech D, Linseisen J, Kroke A, Gedrich K, Robertson C, Heinrich J. A new FFQ designed to measure the intake of fatty acids and antioxidants in children. Public Health Nutr 2010;13:38-46. doi 10.1017/S1368980009005813.
26. Food and Agriculture Organization of the United Nations/World Health Organization. Codex General Standard for Food Additives food category system. Available at: http://www.codexalimentarius.net/gsfaonline/docs/CXS_192e.pdf (accessed 10 October 2012).
27. Sichieri R, Yokoo EM, Pereira RA, Veiga GV. Water and sugar-sweetened beverage consumption and changes in BMI among Brazilian fourth graders after 1-year follow-up. Public Health Nutr 2013;16:73-77. doi 10.1017/S1368980012001309.
28. Mitchell JA, Pate RR, Beets MW, Nader PR. Time spent in sedentary behavior and changes in childhood BMI: a longitudinal study from ages 9 to 15 years. Int J Obes (Lond) 2012;37(1): 54-60. doi 10.1038/ijo.2012.41.
29. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr 1990;51:241-247.

30. Bandini LG, Schoeller DA, Dietz WH. Energy expenditure in obese and nonobese adolescents. Pediatr Res 1990;27:198-203. doi 10.1203/00006450-199002000-00022.
31. Adriaens MP, Schoffelen PF, Westerterp KR. Intra-individual variation of basal metabolic rate and the influence of daily habitual physical activity before testing. The Br J Nutr 2003;90:419-423.
32. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria, 2010 ISBN 3-900051-07-0. Available at: http://www.R-project.org.
33. Global Database on Child Growth and Malnutrition. Available at: http://www.who.int/nutgrowthdb/about/introduction/en/index5.html.
34. Kleiser C, Schaffrath Rosario A, Mensink GB, Prinz-Langenohl R, Kurth BM. Potential determinants of obesity among children and adolescents in Germany: results from the cross-sectional KiGGS Study. BMC Public Health 2009;9:46. doi 10.1186/1471-2458-9-46.
35. Assmann KE, Joslowski G, Buyken AE, Cheng G, Remer T, Kroke A, Gunther AL. Prospective association of protein intake during puberty with body composition in young adulthood. Obesity (Silver Spring) 2013;21(12): E782-789. doi 10.1002/oby.20516.
36. Neumann CG, Jiang L, Weiss RE, Grillenberger M, Gewa CA, Siekmann JH, Murphy SP, Bwibo NO. Meat supplementation increases arm muscle area in Kenyan schoolchildren. Br J Nutr 2013;109:1230-1240. doi 10.1017/S0007114512003121.
37. Albala C, Ebbeling CB, Cifuentes M, Lera L, Bustos N, Ludwig DS. Effects of replacing the habitual consumption of sugar-sweetened beverages with milk in Chilean children. Am J Clin Nutr 2008;88:605-611.
38. Bray GA, Smith SR, de Jonge L, Xie H, Rood J, Martin CK, Most M, Brock C, Mancuso S, Redman LM. Effect of dietary protein content on weight gain, energy expenditure, and body composition during overeating: a randomized controlled trial. JAMA 2012;307:47-55. doi 10.1001/jama.2011.1918.
39. Freedman DS, Wang J, Maynard LM, Thornton JC, Mei Z, Pierson RN, Dietz WH, Horlick M. Relation of BMI to fat and fat-free mass among children and adolescents. Int J Obes (Lond) 2005;29:1-8. doi 10.1038/sj.ijo.0802735.
40. Escribano J, Luque V, Ferre N, Mendez-Riera G, Koletzko B, Grote V, Demmelmair H, Bluck L, Wright A, Closa-Monasterolo R, Trial ECO. Effect of protein intake and weight gain velocity on body fat mass at 6 months of age: The EU Childhood Obesity Programme. Int J Obes 2012;36:548-553. doi Doi 10.1038/Ijo.2011.276.

41. Gunther AL, Buyken AE, Kroke A. Protein intake during the period of complementary feeding and early childhood and the association with body mass index and percentage body fat at 7 y of age. Am J Clin Nutr 2007;85:1626-1633.
42. Gunther AL, Buyken AE, Kroke A. The influence of habitual protein intake in early childhood on BMI and age at adiposity rebound: results from the DONALD Study. Int J Obes (Lond) 2006;30:1072-1079. doi 10.1038/sj.ijo.0803288.
43. Karaolis-Danckert N, Gunther AL, Kroke A, Hornberg C, Buyken AE. How early dietary factors modify the effect of rapid weight gain in infancy on subsequent body-composition development in term children whose birth weight was appropriate for gestational age. Am J Clin Nutr 2007;86:1700-1708.
44. Hoek AC, Luning PA, Stafleu A, de Graaf C. Food-related lifestyle and health attitudes of Dutch vegetarians, non-vegetarian consumers of meat substitutes, and meat consumers. Appetite 2004;42:265-272. doi 10.1016/j.appet.2003.12.003.
45. Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. Public Health Nutr 2003;6:259-269. doi 10.1079/PHN2002430.
46. Kipping RR, Jago R, Lawlor DA. Obesity in children. Part 1: Epidemiology, measurement, risk factors, and screening. BMJ 2008;337:a1824. doi 10.1136/bmj.a1824.
47. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nat Rev Endocrino 2013;l 9:13-27. doi 10.1038/nrendo.2012.199.
48. Parnell W, Wilson N, Alexander D, Wohlers M, Williden M, Mann J, Gray A. Exploring the relationship between sugars and obesity. Public Health Nutr 2008;11:860-866. doi 10.1017/S1368980007000948.
49. Gibson S, Neate D. Sugar intake, soft drink consumption and body weight among British children: further analysis of National Diet and Nutrition Survey data with adjustment for under-reporting and physical activity. Int J Food Sci Nutr 2007;58:445-460. doi 10.1080/09637480701288363.
50. Ambrosini GL, Emmett P, Northstone K, Howe LD, Tilling K, Jebb SA. Identification of a dietary pattern prospectively associated with increased adiposity during childhood and adolescence. Int J Obesity 2012;36(10):1299-305. doi: 10.1038/ijo.2012.127.

51. Fisher JO, Johnson RK, Lindquist C, Birch LL, Goran MI. Influence of body composition on the accuracy of reported energy intake in children. Obes Res 2000;8:597-603. doi 10.1038/oby.2000.77.
52. Anderson GH, Woodend D. Consumption of sugars and the regulation of short-term satiety and food intake. Am J Clin Nutr 2003;78:843S-849S.
53. O'Neil CE, Fulgoni VL, 3rd, Nicklas TA. Association of candy consumption with body weight measures, other health risk factors for cardiovascular disease, and diet quality in US children and adolescents: NHANES 1999-2004. Food Nutr Res 2011;55. doi 10.3402/fnr.v55i0.5794.
54. Amin TT, Al-Sultan AI, Ali A. Overweight and Obesity and their Association with Dietary Habits, and Sociodemographic Characteristics Among Male Primary School Children in Al-Hassa, Kingdom of Saudi Arabia. Indian J Community Med 2008;33:172-181. doi 10.4103/0970-0218.42058.
55. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. Diabetes Care 2008;31:2281-2283. doi 10.2337/dc08-1239.
56. Gogebakan O, Kohl A, Osterhoff MA, van Baak MA, Jebb SA, Papadaki A, Martinez JA, Handjieva-Darlenska T, Hlavaty P, Weickert MO, Holst C, Saris WH, Astrup A, Pfeiffer AF. Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: the diet, obesity, and genes (DiOGenes) study: a randomized, controlled trial. Circulation 2011;124:2829-2838. doi 10.1161/CIRCULATIONAHA.111.033274.
57. Libuda L, Alexy U, Sichert-Hellert W, Stehle P, Karaolis-Danckert N, Buyken AE, Kersting M. Pattern of beverage consumption and long-term association with body-weight status in German adolescents--results from the DONALD study. Br J Nutr 2008;99:1370-1379. doi 10.1017/S0007114507862362.
58. O'Connor TM, Yang SJ, Nicklas TA. Beverage intake among preschool children and its effect on weight status. Pediatrics 2006;118:e1010-1018. doi 10.1542/peds.2005-2348.
59. Rodriguez-Artalejo F, Garcia EL, Gorgojo L, Garces C, Royo MA, Martin Moreno JM, Benavente M, Macias A, De Oya M. Consumption of bakery products, sweetened soft drinks and yogurt among children aged 6-7 years: association with nutrient intake and overall diet quality. Br J Nutr 2003;89:419-429. doi 10.1079/BJN2002787.

60. Plachta-Danielzik S, Gehrke MI, Kehden B, Kromeyer-Hauschild K, Grillenberger M, Willhoft C, Bosy-Westphal A, Muller MJ. Body fat percentiles for German children and adolescents. Obes Facts 2012;5:77-90. doi 10.1159/000336780

Table 1. Characteristics of study population at 10 years of age with available BMI and FFQ data (n=2565)

	Mean (s.d.) or % (n/N)
Female	49.0 (1257/2565)
Study	
GINIplus	62.2 (1596/2565)
LISAplus	37.8 (969/2565)
City of residence	
Munich	56.1 (1438/2565)
Leipzig	9.3 (238/2565)
Bad Honnef	4.9 (125/2565)
Wesel	29.8 (764/2565)
Family income[a]	
Low	21.3 (499/2346)
Medium	48.0 (1126/2346)
High	30.7 (721/2346)
Parental education[b]	
Low	4.7 (120/2555)
Medium	26.0 (665/2555)
High	69.3 (1770/2555)
High screen time[c]	31.4 (796/2532)
Age at 10-year physical examination, months	122.5 (2.7)
BMI, kg/m^2	17.3 (2.4)
BMI z-score[d]	0.16 (1.05)
BMI z-score category[e]	
normal weight	80.3 (2059/2565)
overweight	19.7 (506/2565)
Total energy intake, kcal	2082 (606)

[a] Defined according to quartiles of monthly average income: low < 25%, medium 25–75% and high > 75%

[b] Categorized according to the highest number of years either parent attended school: low < 10 years, medium = 10 years and high > 10 years

[c] Low for < 1 hour per day in summer and <2 hours per day in winter; high for ≥ 1 hour per day in summer and ≥ 2hours per day in winter

[d] Calculated using WHO macros [23]

[e] According to WHO guidelines [24]

Table 2. Under-reporters[a] by weight status in the study population, stratified by sex

Weight status[b]		Male		Female		Total	
		Under-reporter	Plausible energy intake reporter	Under-reporter	Plausible energy intake reporter	Under-reporter	Plausible energy intake reporter
Normal weight	Number	200	841	174	844	374	1685
	Percantage, %	19.2%	80.8%	17.1%	82.9%	18.2%	81.8%
Overweight	Number	87	180	66	173	153	353
	Percantage[*], %	32.6%	67.4%	27.6%	72.4%	30.2%	69.8%

[a] Under-reporter: Basal metabolic rate (BMR) < 70% total energy intake, plausible energy intake reporter: BMR ≥ 70% total energy intake

[b] Normal weight: BMI z-score < +1SD, overweight: BMI z-score ≥ 1

[*] Significant difference between overweight and non-overweight groups, tested by Pearson's χ^2 test, $p < 0.001$

Table 3. Definition of food groups[a]

Food groups	Food items included
Dairy and dairy products	cheeses, milk and yogurts, cream, fresh cream
Fats and oils	butter and margarines, oils
Fruits and vegetables	cooked potatoes, nuts, pumpkin, pine seeds, sunflower seeds, carrots, peppers, spinach, chard, cabbage, lettuce, apples, pears, citrus fruits, berries
Confectionery	chocolate, chocolate bars, soft sweets
Cereal	muesli, cereals, corn flakes, crispy, rice, pasta, noodles
Bakery products	bread, toast, multi-grain bread, whole wheat bread, white rolls, pretzels, croissants, chocolate rolls, cakes, pastries, cookies, biscuits
Meat and meat products	pork, beef, veal, poultry, organ meats, wiener, sausage, salami
Fish and fish products	freshwater fish, saltwater fish, herring, fish sticks, canned fish
Eggs and egg products	egg, scrambled egg, fried egg, semolina, pudding, rice pudding
Beverages	fruit juices, fruit nectars, vegetable juices, diluted juices, sparkling drinks, lemonade, cola, ice tea, sport drinks, energy drinks, tea
Ready-to-eat savories	crisps, chips, croquettes, pizza

[a] Defined according to the Codex General Standard for Food Additives food category system [26]

Table 4. Distribution of food intake in the study population (grams per day)

Food groups[a]	median	33rd percentile		66th percentile		%En[b]
		Male	Female	Male	Female	
Dairy and dairy products	315	259	217	477	378	14.4
Fats and oils	14	11	10	19	18	4.0
Fruits and vegetables	279	214	235	325	348	7.4
Confectionery	16	11	10	25	20	3.0
Cereal	80	66	60	108	95	14.3
Bakery products	141	119	112	173	161	18.4
Meat and meat products	97	84	68	133	109	12.0
Fish and fish products	16	12	10	24	21	1.2
Eggs and egg products	18	13	12	26	22	1.4
Beverages	573	399	339	852	728	8.0
Ready-to-eat savories	41	35	29	53	46	4.9

[a] Defined according to the Codex General Standard for Food Additives food category system [26]

[b] %En, median percent energy consumed per day

Figure legend

Figure 1 Flow chart of study population. FFQ: food frequency questionnaire, BMI: body mass index

Figure 2 Adjusted coefficients for the association between food group intake tertiles and BMI z-scores. Models are adjusted for energy intake from other food groups, city of residence, family income, parental education, and screen time. *The association between beverage intake and BMI z-scores was additionally adjusted for water intake

Figure 3 Adjusted ORs for the association between food group intake tertiles and being overweight. Models are adjusted for energy intake from other food groups, city of residence, family income, parental education, and screen viewing time. *The association between beverage intake and being overweight was additionally adjusted for water intake

Figure 1

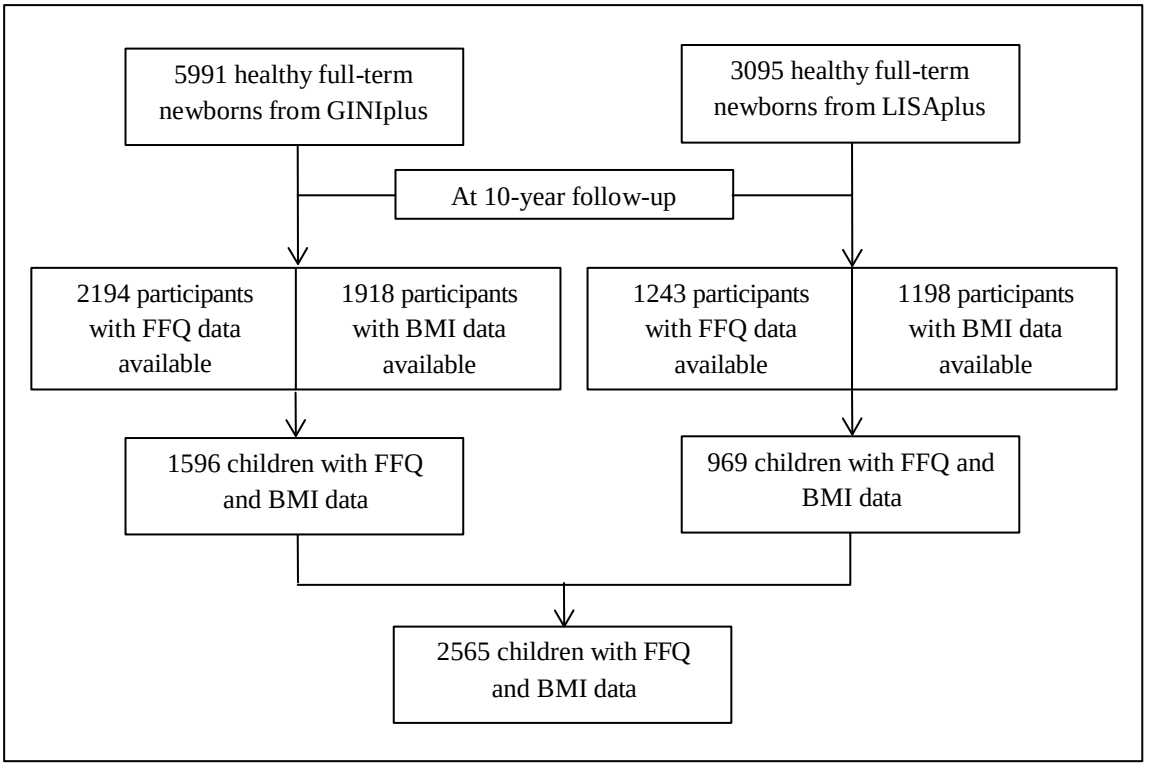
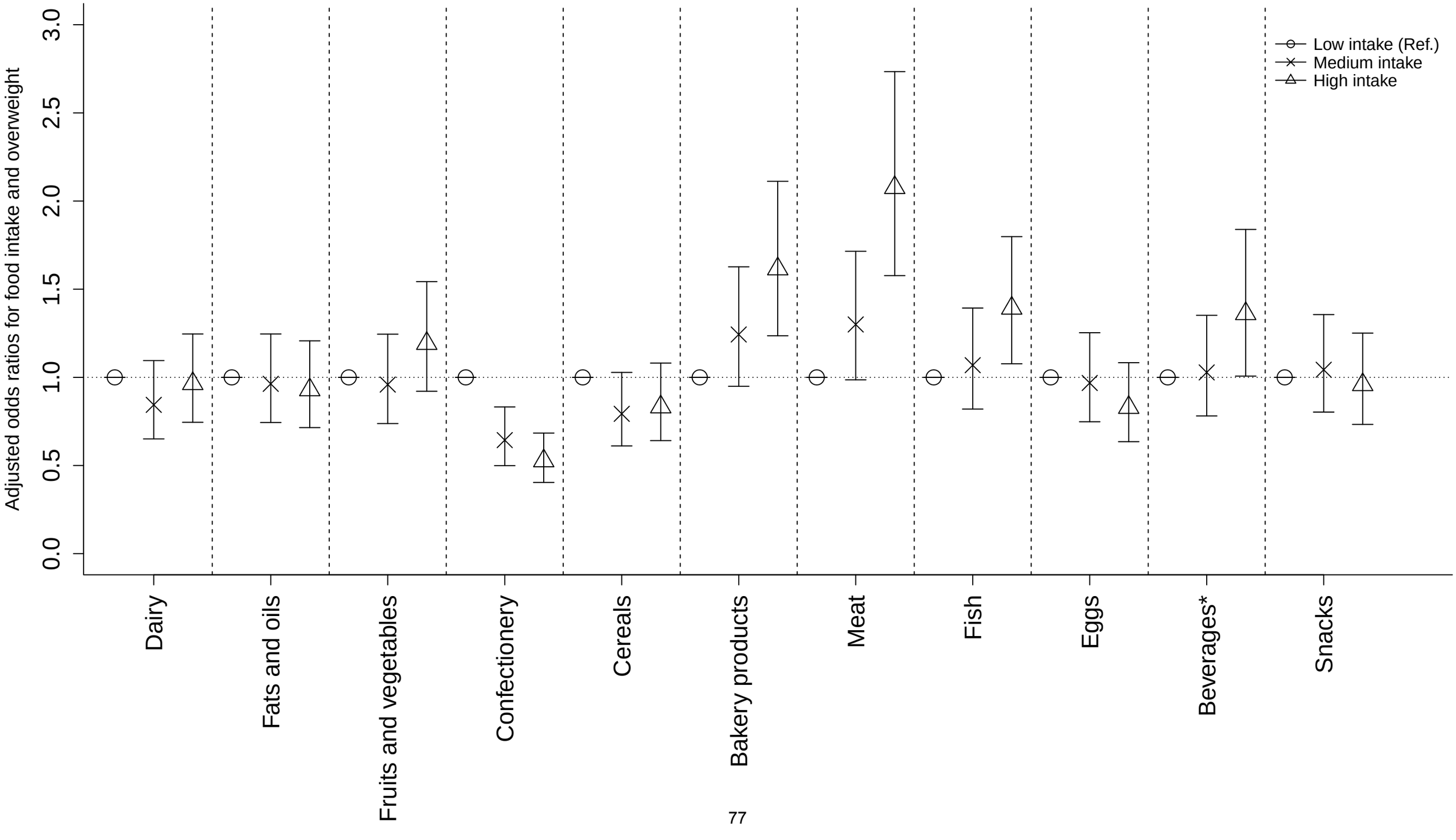

5991 healthy full-term newborns from GINIplus
3095 healthy full-term newborns from LISAplus
At 10-year follow-up
2194 participants with FFQ data available
1918 participants with BMI data available
1243 participants with FFQ data available
1198 participants with BMI data available
1596 children with FFQ and BMI data
969 children with FFQ and BMI data
2565 children with FFQ and BMI data

Figure 2

Adjusted β−coefficients for food intake and BMI z−scores
−0.2
0.0
0.2
0.4
Low intake (Ref.)
Medium intake
High intake
Dairy
Fats and oils
Fruits and vegetables
Confectionery
Cereals
Bakery products
Meat
Fish
Eggs
Beverages*
Snacks

Figure 3


Adjusted odds ratios for food intake and overweight
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Low intake (Ref.)
Medium intake
High intake
Dairy
Fats and oils
Fruits and vegetables
Confectionery
Cereals
Bakery products
Meat
Fish
Eggs
Beverages*
Snacks

7 Maternal body mass index and food intake in school-aged children. Results of the GINIplus and the LISAplus studies

Authors: Zhengcun Pei, Claudia Flexeder, Elaine Fuertes, Marie Standl, Dietrich Berdel, Andrea von Berg, Sibylle Koletzko, Beate Schaaf, Joachim Heinrich for the GINIplus and LISAplus Study Group

Accepted on 27.03.2014, in press

Journal: European Journal of Clinical Nutrition

Year: 2014

Impact factor: 2.756

7.1 Confirmation letter

Von: ejcn@nature.com [mailto:ejcn@nature.com]
Gesendet: Donnerstag, 27. März 2014 14:38
An: Heinrich, Joachim, Dr.
Betreff: Decision for manuscript 2014EJCN0048R

Manuscript Number: 2014EJCN0048R

Title: Mother's body mass index and food intake in school-aged children. Results of the GINIplus and the LISAplus studies

Corresponding Author: Dr Heinrich

Dear Dr Heinrich,

I am very pleased to inform you that your above mentioned manuscript has now been accepted for publication in the *European Journal of Clinical Nutrition*.

You can now use a single sign-on for all your accounts, view the status of all your manuscript submissions and reviews, access usage statistics for your published articles and download a record of your refereeing activity for the Nature journals.

In addition, NPG encourages all authors and reviewers to associate an Open Researcher and Contributor Identifier (ORCID) to their account. ORCID is a community-based initiative that provides an open, non-proprietary and transparent registry of unique identifiers to help disambiguate research contributions.

Thank you for submitting your work to the *European Journal of Clinical Nutrition*.

Yours sincerely,

Manfred Müller
Editor, EJCN
Nature Publishing Group
The Macmillan Building
4 Crinan Street London N1 9XW
UK
Email: ejcn@nature.com

7.2 Accepted manuscript

Mother's body mass index and food intake in school-aged children. Results of the GINIplus and the LISAplus studies

Running head: Mother's BMI and child food intake

MSc. Zhengcun Pei[1, 2], MSc. Claudia Flexeder[1], MSc. Elaine Fuertes[1, 3], PhD. Marie Standl[1], MD. Dietrich Berdel[4], MD. Andrea von Berg[4], MD. PhD. Sibylle Koletzko[5], MD. Beate Schaaf[6], PhD. Joachim Heinrich[1] for the GINIplus and LISAplus Study Group

[1] Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany;

[2] Faculty of Medicine, Ludwig-Maximilians-University of Munich, Munich, Germany

[3] School of Population and Public Health, University of British Columbia, Canada;

[4] Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany;

[5] Dr. von Hauner Children's Hospital, University of Munich, Munich, Germany;

[6] Medical Practice for Pediatrics, Bad Honnef, Germany.

Correspondence

Dr. Joachim Heinrich

Institute of Epidemiology I

Helmholtz Zentrum München - German Research Center for Environmental Health

Ingolstaedter Landstr. 1

85764 Neuherberg, Germany

Telephone: +49-(0)89-3187-4150

Fax: +49-(0)89-3187-3380

E-Mail: heinrich@helmholtz-muenchen.de

Abstract

Objectives Mother's BMI is a strong predictor of child BMI. Whether mother's BMI correlates with child food intake is unclear. We investigated associations between mother's BMI/overweight and child food intake using data from two German birth cohorts.

Methods Food intakes from 3230 participants were derived from parent-completed food frequency questionnaires. Intakes of eleven food groups were categorized into three levels using group- and sex-specific tertile cut-offs. Mother's BMI and overweight were calculated based on questionnaire data. Multinomial regression models assessed associations between child food intake and mother's BMI/overweight. Linear regression models assessed associations between total energy intake and mother's BMI. Models were adjusted for study region, maternal education, age, sex, pubertal status, energy intake, and the BMIs of the child and father.

Results Mother's BMI was associated with high meat intake in children (adjusted relative risk ratio (RRR [95%CI]) = 1.06 [1.03; 1.09]). Mother's overweight was associated with child meat intake (medium vs. low RRR = 1.30 [1.07; 1.59]; high vs. low RRR = 1.50 [1.19; 1.89]) and egg intake (medium vs. low RRR = 1.24 [1.02; 1.50]; high vs. low RRR = 1.30 [1.07; 1.60]). There were no consistent associations for rest food groups. For every one-unit increase in mother's BMI, the total energy intake in children increased by 9.2 kcal [3.7; 14.7]. However, this effect was not significant after adjusting for child BMI.

Conclusion Our results suggest that mother's BMI and mother's overweight are important correlates of a child's intake of energy, meat and eggs.

Key words: Mother's BMI, food intake, energy partition model, overweight, obesity, child

Introduction

Obesity is a major public health concern. (1) According to the 2010 International Obesity Task Force analysis, approximately 200 million school-aged children are overweight or obese around the world. (2) Childhood obesity often persists into adulthood and is associated with increased adult morbidities. (3)

Parental BMIs are associated with offspring BMIs and weight statuses. (4-6) A child's BMI has been shown to be more strongly associated with their mother's BMI than their father's BMI. (5,7) The observed associations between parental BMI and the development of obesity in offspring may be mediated through genetic and environmental influences. (8)

Food intake, as a major environmental factor influencing obesity, has been considered in many studies on the etiology of obesity. (9,10) Obesity is mainly believed to be a consequence of an unbalanced energy status. (11) It is known that parents play a role in shaping their child's eating patterns and eating behavior. (12,13) Given that eating behavior differs among obese and normal weight individuals (14) and that parental eating behavior traits are correlated with offspring BMI (15), overweight and normal weight mothers probably impose different influences on the food intake patterns of their children.

Previous studies have focused on maternal/parental influences on child's eating behavior (16-19), but very few considered mother's BMI at the same time. (19) It is currently unclear whether mother's BMI correlates with child food intake, especially specific food groups. The present study aims to investigate the association between mother's BMI and child food intake at the age of 10 years using data from the population based German birth cohorts GINIplus and LISAplus.

Materials and methods

Study population

Data from two population based German birth cohort studies were analyzed. GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) is an ongoing birth cohort study initiated to prospectively investigate the influence of a nutritional intervention during infancy, as well as air pollution and genetics, on allergy development. GINIplus participants (N=5991 newborns) were recruited from obstetric clinics in Munich and Wesel between September 1995 and July 1998. Details of the study design are described elsewhere. (20)

LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics) is an ongoing birth cohort examining the impact of lifestyle-related factors, air pollution and genetics on immune

system and childhood allergy development. In total, 3097 neonates were recruited from 14 obstetrical clinics in Munich, Leipzig, Wesel and Bad Honnef between November 1997 and January 1999. A detailed description of the study's screening and recruitment has been described previously. (21)

This analysis includes 3230 children who participated in the 10-year Food Frequency Questionnaire (FFQ) survey, and for whom data on mother's body mass index (BMI) and socioeconomic status variables were available.

Approval by the respective local ethics committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North-Rhine-Westphalia) and written consent from all participating families were obtained for both studies.

Definition of outcomes: total energy intake and intake of 11 food groups

The outcomes of interest were derived from the FFQ. The details and effectiveness of the FFQ have been published elsewhere. (22,23) Briefly, information on food intake frequencies and portion sizes for 82 food items were collected using parent-completed questionnaires. Seventy-nine food items were clustered into 11 food groups according to the Codex General Standard for Food Additives' food category system. (24) We excluded three food items: nut-nougat-cream, water and syrup. Nut-nougat-cream has a complex composition and could not be adequately classified into one food group. Syrup intake was very low in the current study. Water intake was excluded as its consumption does not yield energy. However, we used water intake as an additional adjustment variable when assessing the association between beverage intake and the outcomes, as beverage intake may be associated with water intake. (25) Information on the intake of sweeteners, salts, spices, soups, sauces, salads and foodstuffs intended for particular nutritional uses were not available in the current study.

Details of the grouping of food items into food groups are given in Table 1. The 11 food groups were labeled as dairy and dairy products, fats and oils, fruits and vegetables, confectionery, cereal, bakery products, meat and meat products, fish and fish products, eggs and egg products, beverages and ready-to-eat savories.

Total energy intake in kilo-calories per day was calculated based on the intake frequencies and portion sizes of the food items. For each of the 11 food group, the average intake in grams per day was calculated. Because the distributions of the food intakes were positively skewed, and linear associations with BMI z-scores were only observed for some of the 11 food groups, the food intakes were categorized into three levels (low, medium and high) using food group- and sex-specific tertile cut-offs. Low intake levels were used as the reference group in all models.

Definition of predictors: mother's BMI and mother's weight status

Based on mother's weight and height information collected at the 10-year questionnaire survey, mother's BMIs (weight in kg/(height in m)^2) were calculated. Four categories for mother's weight status were initially defined (underweight: BMI < 18.5 kg/m2; normal weight: BMI: 18.5 – 24.9 kg/m^2; overweight: BMI: 25 – 29.9 kg/m^2 and obese: BMI ≥ 30 kg/m^2). However, as the number of underweight mothers was relatively small (n = 83) and analyses excluding these participants did not yield substantially different results, the underweight and normal weight categories were combined as "normal weight". Furthermore, as preliminary results showed similar effect estimates for the overweight and obese categories (results not shown), these two groups were also combined as "overweight". Ultimately, two categories were available for this variable (normal weight versus overweight).

Potential confounding factors

Study region (Munich, Wesel, Bad Honef and Leipzig), maternal education, sex, age, pubertal status, and BMIs of the child and father were considered as potential covariates in the analysis. The parents were asked to indicate whether their child exhibited characteristics indicative of puberty onset (yes/no). The child's age in months was calculated using the birth date and date of the 10-year questionnaire. Maternal education was defined according to the highest number of years the mother attended school and grouped into three categories (low < 10 years, medium = 10 years, and high > 10 years). BMIs of the child and father were calculated based on weight and height information collected at the 10-year questionnaire survey.

Statistical analysis

Differences between male and female subjects were tested using the Pearson's χ^2 test for categorical variables, the Student's t-test for normally distributed continuous variables, and the Mann-Whitney test for non-normally distributed continuous variables (i.e. intake of 11 food groups). Study characteristics are described using means and standard deviations (S.D.) or percentages (n/N, %). The food intake characteristics are described using median and percentiles. Statistical significance was set at the conventional p-value < 0.05. All analyses were performed using the statistical software package R, version 2.14.1 (ref. 26).

For each of the 11 food groups, crude and adjusted multinomial regression models were used to examine associations between food intake with mother's BMI and mother's overweight. As preliminary analyses indicated no major differences by sex or interactions among the covariates, pooled analyses were conducted. Three types of models were initially calculated: A) crude models, B) models adjusted for study region, sex, maternal education, child pubertal

status, age and partition energy intake (27), C) models additionally adjusted for the BMIs of the child and father. The partition energy intake was calculated from the food group itself and the energy intake from all other food groups. Each model for the association between the energy intake of a specific group with mother's BMI and mother's overweight was adjusted for the respective energy intake from all other food groups. As a child's BMI is likely to be affected by his/her food intake, results of model C may be over-adjusted. Therefore we additionally conducted stratified analyses by child weight status (overweight versus. non-overweight). Finally, we presented coefficients from model B in the results section. For comparison purpose, we also present results from model C in the figures. Model results are presented as relative risk ratios (RRR) with corresponding 95% confidence intervals (RRR [95% CI]).

Crude and adjusted linear regression models were used to study the association between total energy intake with mother's BMI and mother's overweight. The same three types of models were calculated as described above. Model results are presented as linear regression coefficients (ß) with corresponding 95% confidence intervals (ß [95% CI]). For models in which mother's BMI is the predictor, the ß-coefficient represents the mean increase in total energy intake for a one-unit increase in mother's BMI. For models in which mother's weight status is the predictor, the ß-coefficient represents the difference in total energy intake between mother's overweight and mother's normal weight.

Results

The characteristics of the participants are summarized in Table 2. Female participants comprised 48.7% of the sample. The mean age was 120.6 months (S.D. = 2.4) and 28.9% of participants exhibited signs of puberty (11.6% and 47.2% for males and females, respectively, $p < 0.001$). The average total energy intake was 2106 kcal (S.D. = 673). Males had higher total energy intake than females (2278 kcal (723) versus 1927 kcal (560), $p < 0.001$). Over half of the participants had mothers with a high level of education (50.4%). The mean mother's BMI was 23.8 (S.D. = 4.1), and 20.2% of mothers were overweight and 8.0% were obese.

The average food intakes in grams per day are shown in Table 3. The median intake of meat products was 97g per day (33^{rd} and 66^{th} percentile [75; 122]), which corresponds to a median percent energy (%En) of 12.0% [9.7; 14.7]. The median egg intake was 18 g per day ([12; 24], %En = 1.4% [1.0; 1.9]). Compared to males, females had significantly lower intakes of all 11 food groups (e.g. median meat intake: 108 versus 86 grams per day; median egg intake: 19 versus 16 grams per day), except for fruit and vegetables (median intake: 270 versus 287

grams per day). Compared to males, females had a significantly lower %En of dairy products as well as meat and meat products (14.4% versus 15.2% and 11.3% versus 12.4%, respectively), but a significantly higher %En of fats and oils, fruit and vegetables as well as bakery products (4.0% versus 3.8%, 8.1% versus 6.6%, and 18.8% versus 17.8%, respectively).

Crude and adjusted relative risk ratios for the associations between child intake of the 11 food groups and mother's BMI are shown in Table 4 and Figure 1. The crude RRRs for the comparison of low intake to medium and high intake are presented in Figure1A, partially-adjusted RRRs in Figure1B and fully-adjusted RRRs in Figure1C. Mother's BMI was associated with high meat intake in children (adjusted RRR = 1.06 [1.03; 1.09]). In addition, mother's BMI was marginally associated with a high intake of fats and oils as well as intake of eggs (adjusted RRR = 0.98 [0.96; 1.00] and 1.03 [1.00; 1.05], respectively). No consistent associations between mother's BMI and child intake of the other food groups were observed.

Crude and adjusted relative risk ratios for the association between child intake of 11 food groups and mother's overweight are shown in Table 5 and Figure 2. The crude RRRs for the comparison of low intake to medium and high intake are presented in Figure2A, partially-adjusted RRRs in Figure2B and fully-adjusted RRRs in Figure2C. Mother's overweight was associated with child meat intake (medium versus low RRR = 1.30 [1.07; 1.59]; high versus low RRR = 1.50 [1.19; 1.89]) and egg intake (medium versus low RRR = 1.24 [1.02; 1.50]; high versus low RRR = 1.30 [1.07; 1.60]). No consistent associations between mother's overweight and child intake of the other food groups were observed.

In addition, the significant associations for meat and eggs were observed in both overweight and non-overweight subgroups with similar effect sizes (results not shown).

Sex-specific and pooled increases in child total energy intake per one-unit increase in mother's BMI are shown in Figure 3. In the pooled crude models, every one-unit increase in mother's BMI was associated with a total energy intake increase of 9.2 kcal [3.67 ~ 14.72]. However, this effect was not significant after full adjustment (4.2 kcal [-1.9; 10.3]). In addition, this effect was more pronounced among males. Associations among females were of smaller magnitude and not significant. No association between mother's overweight and energy intake was observed (results not shown).

Discussion

In the current study, we analyzed associations between mother's BMI/overweight and child food intake using data from two German birth cohorts. We observed significantly positive associations between mother's BMI/overweight and child intakes of meat, eggs and energy.

Currently, little is known regarding associations between child food intake and mother's BMI. To the best of our knowledge, no other published studies exist with which we can compare our results. Nevertheless, we provide here several possible explanations for the trends observed.

As parents appear to have a strong influence on their child's eating behavior and patterns (12,13), children are likely to have similar dietary patterns as their parents. Results from the NHANES study have shown a positive association between meat intake and obesity in adults. (28) It is possible that a child may imitate his/her overweight mother's eating pattern, and thus may consume more meat. It is also possible that overweight mothers include more meat products in the family meals compared to mothers of normal weight. Hence, their children have an increased availability to meat, which may contribute to a higher meat intake. (29,30) Based on our prior research using the same study population (under review), a high meat intake appears to be associated with being overweight at 10 years of age. These associations suggest a potential pathway of the mother-child weight relationship, although any causal relationship between food intake and being overweight may be bi-directional.

There is also limited evidence for the association between egg intake and BMI. A breakfast which includes eggs is reported to be beneficial for weight loss. (31) However, it is unclear whether the satiating effect of eggs (32) or the fact that a high-protein breakfast is consumed instead of a high carbohydrate breakfast is responsible for this beneficial effect. Information on whether overweight mothers consume or prepare more eggs than mothers of normal weight is not available in the current study.

We observed significant associations between mother's BMI and total energy intake in male children in the crude models. This effect was no longer significant after adjustment for child BMI. This result was not replicated among females of the same age. There are very few studies that have investigated associations between mother's BMI and energy intake in children. Thus, it is challenging to compare our results with previous work. We attempt here, to provide some possible explanations for the observed results.

In a sample of 563 mother-child (2-11 years of age) pairs, mothers with higher BMI levels were reported to have a lower level of control on their child's diet than mothers with normal BMI levels. (33) A lower level of control may lead to a higher food intake. In addition, mother's perception and concern of their child's weight may also play an important role on the investigated association. (34,35) Parental feeding control was reported to have a greater impact on girls than boys in an American mid-high socio-economic population. (36,37) This may have led to the observed sex differences. Also, mother's perception of child weight

status may differ by sex (e.g. mothers may be more sensitive to their daughters weight status), although these associations are also likely to vary by culture. (38, 39)

Previous studies have focused on associations between mother's feeding practices (i.e. restriction to eat less or pressure to eat more food) and child food intake or child weight (33,34,40-43), which are believed to be mediated by mother's concerns for their child's weight and the perception of their child's weight. (34,35) Mother's feeding practices were reported to explain 22.2-26.9% of the variance in food intake of children aged 3 to 6 years who were at risk for becoming overweight. (40) It was reported that a higher child weight at 7 to 9 years of age was associated with a lower 'pressure to eat' and a higher 'restriction' score from mothers. (34) Another study reported that perceived child weight and concern for child weight explains around 40% of the variance of BMI z-score changes at 12 years of age. (41) Moreover, the results from a study on 296 low-income African-American children suggested that feeding strategies may differ according to mother's weight status. (44) Factors such as mother's food intake (42), child weight (40), ethnicity (33), family income and parental education level (40,43) may also influence mother's feeding practices.

The current study investigated associations between mother's BMI with child energy and food intake, using data from two large population-based cohorts from Germany, which included the use of the qualified FFQ. Energy and food intake were classified into 11 food groups according to the Codex General Standard for Food Additives' food category system, which will allow our results to be compared to future studies. Instead of providing isocaloric interpretations, the multivariate energy partition models allowed us to interpret our results while taking both energy and non-energy effects of foods into account.

Our study has some limitations. First, as the data were collected using questionnaires completed by the parents, reporting bias is possible. A parent's perception of their child's food intake might be a biased measure of true consumption. Second, the cross-sectional design of this study prevents us from establishing causal relationships. Third, some of our analyses may have been over-adjusted. As child food intake is likely to be in the pathway between mother's BMI and child's BMI, adjusting for child's BMI may represent an over-adjustment. However, the associations between mother's overweight and high child intakes of meat and eggs remained significant, even after adjustment for child's BMI. Last, we lack information on important mediators such as mother's concerns for child's weight, mother's perception of child's weight, and child's own perception and concerns. Future studies should consider these factors.

Conclusion

Mother’s BMI and mother’s overweight appear to be important correlates of a child’s intake of meat and egg products. The potential impact of a mother’s weight status should be considered in diet counseling. Moreover, a mother’s participation in dietary counseling might be a helpful method by which to improve their child’s diet pattern and weight status.

Acknowledgement

GINIplus study group: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Munich (JH, HEW, SS, AZ, CMC, MS, PR); Department of Pediatrics, Marien-Hospital, Wesel (DB, AvB, CB, IG); Department of Pediatrics, Ludwig Maximilians University, Munich (SK, DR, SK-E); Department of Pediatrics, Technical University, Munich (CPB, IB, AG, UH); IUF—Institut für Umweltmedizinische Forschung at the Heinrich-Heine-University, Düsseldorf (UK, EL, CC).
LISAplus study group: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Munich (JH, HEW, SS, CMC, MS); Department of Pediatrics, Municipal Hospital 'St Georg', Leipzig (MB, UD), Marien-Hospital Wesel, Department of Pediatrics, Wesel (AvB, CB, IG); Pediatric Practice, Bad Honnef (BS); Helmholtz Centre for Environmental Research—UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (IL, MB, CG, SR, MS); University of Leipzig, Institute of Hygiene and Environmental Medicine, Leipzig (OH, CD, JM); IUF—Institut für Umweltmedizinische Forschung, Düsseldorf (UK, EL, CC); Technical University Munich, Department of Pediatrics, Munich (CPB, UH); ZAUM—Center for Allergy and Environment, Technical University, Munich (HB, JG, FM).

Funding

The GINIplus study was mainly supported for the first 3 years of the Federal Ministry for Education, Science, Research and Technology (interventional arm) and Helmholtz Zentrum Munich (former GSF) (observational arm). The 4 year, 6 year, and 10 year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5 study centres (Helmholtz Zentrum Munich (former GSF), Research Institute at Marien-Hospital Wesel, LMU Munich, TU Munich and from 6 years onwards also from IUF - Leibniz Research-Institute for Environmental Medicine at the University of Düsseldorf) and a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). The LISAplus study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research - UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2 years. The 4 year, 6 year, and 10 year follow-up examinations of the LISAplus study were covered from the respective budgets of the involved partners (Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research - UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF – Leibniz-Research Institute for Environmental

Medicine at the University of Düsseldorf) and in addition by a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296).

This work was supported by the Kompetenznetz Adipositas (Competence Network Obesity) funded by the Federal Ministry of Education and Research (FKZ: 01GI1121A).

Conflicts of interest

None to declare.

References

1. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. *Obes Res*. 2001;9 Suppl 4:228S-233S.
2. International Obesity Taskforce. Obesity the global epidemic. 2011. Available at: http://www.iaso.org/iotf/obesity/obesitytheglobalepidemic/
3. Biro FM, Wien M. Childhood obesity and adult morbidities. *Am J Clin Nutr*. 2010;91(5):1499S-1505S.
4. Birbilis M, Moschonis G, Mougios V, Manios Y. Obesity in adolescence is associated with perinatal risk factors, parental BMI and sociodemographic characteristics. *Eur J Clin Nutr*. 2013;67(1):115-121.
5. Danielzik S, Langnase K, Mast M, Spethmann C, Muller MJ. Impact of parental BMI on the manifestation of overweight 5-7 year old children. *Eur J Clin Nutr*. 2002;41(3):132-138.
6. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med*. 1997;337(13):869-873.
7. Linabery AM, Nahhas RW, Johnson W, Choh AC, Towne B, Odegaard AO, *et al*. Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels Longitudinal Study. *Pediatr Obes*. 2013;8(3):159-169.
8. Maffeis C. Aetiology of overweight and obesity in children and adolescents. *Eur J Pediatr*. 2000;159 Suppl 1:S35-44.
9. Bradlee ML, Singer MR, Qureshi MM, Moore LL. Food group intake and central obesity among children and adolescents in the Third National Health and Nutrition Examination Survey (NHANES III). *Public Health Nutr*. 2010;13(6):797-805.
10. Kral TV, Stunkard AJ, Berkowitz RI, Stallings VA, Brown DD, Faith MS. Daily food intake in relation to dietary energy density in the free-living environment: a prospective analysis of children born at different risk of obesity. *Am J Clin Nutr*. 2007;86(1):41-47.
11. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. *Circulation*. 2012;126(1):126-132.
12. Savage JS, Fisher JO, Birch LL. Parental influence on eating behavior: conception to adolescence. *J Law Med Ethics*. 2007;35(1):22-34.

13. Mitchell GL, Farrow C, Haycraft E, Meyer C. Parental influences on children's eating behaviour and characteristics of successful parent-focussed interventions. *Appetite*. 2013;60:85-94.
14. Laessle RG, Lehrke S, Duckers S. Laboratory eating behavior in obesity. *Appetite*. 2007;49(2):399-404.
15. Gallant AR, Tremblay A, Perusse L, Despres JP, Bouchard C, Drapeau V. Parental eating behavior traits are related to offspring BMI in the Quebec Family Study. *Int J Obes (Lond)*. 2013;37(11):1422-1426.
16. Webber L, Hill C, Cooke L, Carnell S, Wardle J. Associations between child weight and maternal feeding styles are mediated by maternal perceptions and concerns. *Eur J Clin Nutr*. 2010;64(3):259-65.
17. Francis LA, Birch LL. Maternal influences on daughters' restrained eating behavior. *Health Psychol*. 2005;24(6):548-54.
18. Francis LA, Birch LL. Maternal weight status modulates the effects of restriction on daughters' eating and weight. *Int J Obes (Lond).* 2005;29(8):942-9.
19. Birch LL, Fisher JO. Mothers' child-feeding practices influence daughters' eating and weight. *Am J Clin Nutr*. 2000;71(5):1054-61.
20. von Berg A, Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, *et al*. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunol*. 2013;131(6):1565-1573.
21. Heinrich J, Bolte G, Holscher B, Douwes J, Lehmann I, Fahlbusch B, *et al*. Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. *Eur Respir J*. 2002;20(3):617-623.
22. Kohlboeck G, Sausenthaler S, Standl M, Koletzko S, Bauer CP, von Berg A, *et al*. Food intake, diet quality and behavioral problems in children: results from the GINI-plus/LISA-plus studies. *Ann Nutr Metab*. 2012;60(4):247-256.
23. Stiegler P, Sausenthaler S, Buyken AE, Rzehak P, Czech D, Linseisen J, *et al*. A new FFQ designed to measure the intake of fatty acids and antioxidants in children. *Public Health Nutr*. 2010;13(1):38-46.
24. Food and Agriculture Organization of the United Nations/World Health Organization. Codex General Standard for Food Additives food category system. 2011. Available at: http://www.codexalimentarius.net/gsfaonline/docs/CXS_192e.pdf.

25. Sichieri R, Yokoo EM, Pereira RA, Veiga GV. Water and sugar-sweetened beverage consumption and changes in BMI among Brazilian fourth graders after 1-year follow-up. *Public Health Nutr*. 2013;16(1):73-77.
26. R Development Core Team R: a language and environment for statistical computing. Vienna, Austria, 2010 ISBN 3-900051-07-0 Available at: http://www.R-project.org.
27. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr*. 1997;65(4 Suppl):1220S-1228S; discussion 1229S-1231S.
28. Wang Y, Beydoun MA. Meat consumption is associated with obesity and central obesity among US adults. *Int J Obes (Lond)*. 2009;33(6):621-628.
29. Arcan C, Hannan PJ, Fulkerson JA, Himes JH, Rock BH, Smyth M, *et al*. Associations of home food availability, dietary intake, screen time and physical activity with BMI in young American-Indian children. *Public Health Nutr*. 2013;16(1):146-155.
30. Raynor HA, Polley BA, Wing RR, Jeffery RW. Is dietary fat intake related to liking or household availability of high- and low-fat foods? *Obes Res*. 2004;12(5):816-823.
31. Vander Wal JS, Gupta A, Khosla P, Dhurandhar NV. Egg breakfast enhances weight loss. *Int J Obes (Lond)*. 2008;32(10):1545-1551.
32. Vander Wal JS, Marth JM, Khosla P, Jen KL, Dhurandhar NV. Short-term effect of eggs on satiety in overweight and obese subjects. *J Am Coll Nutr*. 2005;24(6):510-515.
33. Cachelin FM, Thompson D. Predictors of maternal child-feeding practices in an ethnically diverse sample and the relationship to child obesity. *Obesity (Silver Spring)*. 2013;21(8):1676-1683.
34. Webber L, Hill C, Cooke L, Carnell S, Wardle J. Associations between child weight and maternal feeding styles are mediated by maternal perceptions and concerns. *Eur J Clin Nutr*. 2010;64(3):259-265.
35. Francis LA, Hofer SM, Birch LL. Predictors of maternal child-feeding style: maternal and child characteristics. *Appetite*. 2001;37(3):231-243.
36. Birch LL, Fisher JO. Development of eating behaviors among children and adolescents. *Pediatrics*. 1998;101(3 Pt 2):539-549.
37. Johnson SL, Birch LL. Parents' and children's adiposity and eating style. *Pediatrics*. 1994;94(5):653-661.
38. Hughes SO, Power TG, Orlet Fisher J, Mueller S, Nicklas TA. Revisiting a neglected construct: parenting styles in a child-feeding context. *Appetite*. 2005;44(1):83-92.

39. Spruijt-Metz D, Li C, Cohen E, Birch L, Goran M. Longitudinal influence of mother's child-feeding practices on adiposity in children. *J Pediatr*. 2006;148(3):314-320.
40. Kroller K, Warschburger P. Associations between maternal feeding style and food intake of children with a higher risk for overweight. *Appetite*. 2008;51(1):166-172.
41. Mulder C, Kain J, Uauy R, Seidell JC. Maternal attitudes and child-feeding practices: relationship with the BMI of Chilean children. *Nutr J*. 2009;8:37.
42. Hart CN, Raynor HA, Jelalian E, Drotar D. The association of maternal food intake and infants' and toddlers' food intake. *Child Care Health Dev*. 2010;36(3):396-403.
43. Topham GL, Page MC, Hubbs-Tait L, Rutledge JM, Kennedy TS, Shriver L, *et al*. Maternal depression and socio-economic status moderate the parenting style/child obesity association. *Public Health Nutr*. 2010;13(8):1237-1244.
44. Powers SW, Chamberlin LA, van Schaick KB, Sherman SN, Whitaker RC. Maternal feeding strategies, child eating behaviors, and child BMI in low-income African-American preschoolers. *Obesity (Silver Spring)*. 2006;14(11):2026-2033.

Table 1. Definition of food groups[a]

Food groups	Food items
Dairy and dairy products	cheeses, milk and yogurts, cream, fresh cream
Fats and oils	butter and margarines, oils
Fruit and vegetables	cooked potatoes, nuts, pumpkin, pine seeds, sunflower seeds, carrots, peppers, spinach, chard, cabbage, lettuce, apples, pears, citrus fruits, berries
Confectionery	chocolate, chocolate bars, soft sweets
Cereal	muesli, cereals, corn flakes, crispy, rice, pasta, noodles
Bakery products	bread, toast, multi-grain bread, whole wheat bread, white rolls, pretzels, croissants, chocolate rolls, cakes, pastries, cookies, biscuits
Meat and meat products	pork, beef, veal, poultry, organ meats, wiener, sausage, salami
Fish and fish products	freshwater fish, saltwater fish, herring, fish sticks, canned fish
Eggs and egg products	egg, scrambled egg, fried egg, semolina, pudding, rice pudding
Beverages	fruit juices, fruit nectars, vegetable juices, diluted juices, sparkling drinks, lemonade, cola, ice tea, sport drinks, energy drinks, tea
Ready-to-eat savories	crisps, chips, croquettes, pizza

[a] Defined according to the Codex General Standard for Food Additives food category system. (24)

Table 2. Characteristics of the study population at 10 years of age, Mean (S.D.) or % (n/N)

	Males (n=1684)	Females (n=1596)	Overall (n=3280)
Study			
GINIplus	63.1 (1062/1684)	65.6 (1047/1596)	64.3 (2109/3280)
LISAplus	36.9 (622/1684)	34.4 (549/1596)	35.7 (1171/3280)
Study region			
Munich	50.7 (853/1684)	50.5 (806/1596)	50.6 (1659/3280)
Leipzig	7.7 (129/1684)	7.4 (118/1596)	7.5 (247/3280)
Bad Honnef	4.2 (71/1684)	4.8 (76/1596)	4.5 (147/3280)
Wesel	37.5 (631/1684)	37.3 (596/1596)	37.4 (1227/3280)
Maternal education[a]			
Low	9.8 (164/1674)	8.6 (137/1592)	9.2 (301/3266)
Medium	41.5 (695/1674)	39.1 (623/1592)	40.4 (1318/3266)
High	48.7 (815/1674)	52.3 (832/1592)	50.4 (1647/3266)
Maternal BMI, kg/m^2	23.8 (4.2)	23.7 (4.1)	23.8 (4.2)
Maternal weight status[b]			
Normal weight	71.4 (1203/1684)	71.9 (1147/1596)	71.6 (2350/3280)
Overweight	28.6 (481/1684)	28.2 (449/1596)	28.3 (930/3280)
Child BMI, kg/m^2	16.9 (2.3)	16.7 (2.3)	16.8 (2.3)
Age, months	120.6 (2.4)	120.7 (2.4)	120.6 (2.4)
Puberty onset[c], %	11.6 (193/1665)	47.2 (743/1574)[*]	28.9 (936/3239)
Total energy intake, kcal/day	2278 (723)	1927 (560)[*]	2107 (672)
Paternal BMI, kg/m^2	25.9 (3.3)	26.0 (3.4)	25.9 (3.3)

[a] Categorized according to the highest number of years the mother attended school: low < 10 years, medium = 10 years and high > 10 years;
[b] Normal weight: BMI < 25 kg/m^2; overweight: BMI ≥ 25 kg/m^2;
[c] Indicated by the parents whether their child exhibited characteristics indicative of puberty onset (yes/no);
[*] Significant difference between males and females.

Table 3. Intake of the 11 food groups, stratified by sex

Food intake, g/day	Males (N=1684)				Females (N=1596)				Overall (N=3280)			
	Median	Percentiles		%En	Median	Percentiles		%En	Median	Percentiles		%En
		33rd	66th			33rd	66th			33rd	66th	
Dairy products	369	271	511	15.2	293*	216	380	14.4*	324	245	441	14.8
Fats and oils	15	11	20	3.8	13*	10	18	4.0*	14	10	19	3.9
Fruits and vegetables	270	215	327	6.6	287*	234	343	8.1*	278	224	335	7.3
Confectionery	16	11	25	3.0	14*	10	20	2.9	15	10	22	3.0
Cereals	83	65	106	13.5	75*	58	93	14.4	78	62	99	14.0
Bakery products	147	121	176	17.8	134*	110	159	18.8*	141	116	168	18.3
Meat and meat products	108	86	137	12.4	86*	67	108	11.3*	97	75	122	12.0
Fish and fish products	17	12	24	1.1	14*	10	21	1.1	16	11	22	1.1
Eggs and egg products	19	13	26	1.4	16*	12	22	1.4	18	12	24	1.4
Beverages	603	387	839	8.1	522*	335	721	7.7	560	357	781	7.9
Ready-to-eat savouries	44	35	54	4.9	38*	30	47	5.0	42	33	51	4.9

Food groups were defined according to the Codex General Standard for Food Additives food category system (24);
%En: Percent energy provided from the food group;
* Significant differences between males and females were tested by the Mann-Whitney test.

Table 4. Relative risk ratios (RRR) for the associations between intake of food groups and mother's BMI

		Model A			Model B			Model C		
Food groups[a]	Intake level[b]	RRR	95%CI		RRR	95%CI		RRR	95%CI	
Dairy products	Low	ref.			ref.			ref.		
	Medium	0.99	[0.97;	1.01]	0.99	[0.97;	1.02]	1.00	[0.98;	1.02]
	High	1.02	[1.00;	1.05]	1.01	[0.99;	1.03]	1.01	[0.99;	1.04]
Fats and oils	Low	ref.			ref.			ref.		
	Medium	1.00	[0.98;	1.02]	1.00	[0.98;	1.02]	1.00	[0.97;	1.02]
	High	0.98	[0.96;	1.01]	0.98	[0.96;	1.00]	0.98	[0.95;	1.00]
Fruits and vegetables	Low	ref.			ref.			ref.		
	Medium	1.00	[0.98;	1.02]	1.00	[0.98;	1.02]	1.01	[0.98;	1.03]
	High	0.99	[0.97;	1.01]	0.99	[0.97;	1.01]	0.99	[0.96;	1.01]
Confectionery	Low	ref.			ref.			ref.		
	Medium	0.99	[0.97;	1.01]	0.99	[0.97;	1.01]	1.00	[0.98;	1.02]
	High	0.99	[0.97;	1.01]	0.97	[0.95;	1.00]	0.99	[0.96;	1.01]
Cereals	Low	ref.			ref.			ref.		
	Medium	0.98	[0.96;	1.00]	0.98	[0.96;	1.00]	0.99	[0.97;	1.02]
	High	0.98	[0.96;	1.00]	0.99	[0.96;	1.01]	1.01	[0.98;	1.03]
Bakery products	Low	ref.			ref.			ref.		
	Medium	1.00	[0.98;	1.03]	1.00	[0.98;	1.02]	1.01	[0.98;	1.03]
	High	1.01	[0.99;	1.03]	1.00	[0.97;	1.02]	0.99	[0.97;	1.02]
Meat and meat products	Low	ref.			ref.			ref.		
	Medium	1.04	[1.01;	1.06]	1.03	[1.01;	1.05]	1.02	[0.99;	1.04]
	High	1.07	[1.05;	1.09]	1.06	[1.03;	1.09]	1.04	[1.01;	1.06]
Fish and fish products	Low	ref.			ref.			ref.		
	Medium	1.00	[0.98;	1.02]	1.00	[0.98;	1.02]	1.00	[0.97;	1.02]
	High	1.01	[0.99;	1.03]	1.00	[0.98;	1.03]	1.00	[0.98;	1.03]
Eggs and egg products	Low	ref.			ref.			ref.		
	Medium	1.03	[1.01;	1.05]	1.03	[1.00;	1.05]	1.03	[1.00;	1.05]
	High	1.03	[1.01;	1.06]	1.03	[1.00;	1.05]	1.02	[0.99;	1.04]
Beverages	Low	ref.			ref.			ref.		
	Medium	1.00	[0.98;	1.02]	1.00	[0.97;	1.02]	1.00	[0.98;	1.03]
	High	1.02	[1.00;	1.04]	1.01	[0.99;	1.04]	1.02	[1.00;	1.05]
Ready-to-eat savouries	Low	ref.			ref.			ref.		
	Medium	1.01	[0.99;	1.03]	1.01	[0.99;	1.03]	1.00	[0.98;	1.03]
	High	1.02	[1.00;	1.04]	1.01	[0.99;	1.03]	1.01	[0.98;	1.03]

Model A - crude model

Model B - adjusted for study region, maternal education, sex, age, pubertal status and energy intake from other food groups

Model C - additionally adjusted for the BMIs of the child and father

[a] Food groups were defined according to the Codex General Standard for Food Additives food category system (24);

[b] Defined using sex- and group-specific tertile cut-offs

Table 5. Relative risk ratios (RRR) for the associations between intake of food groups and mother's overweight

		Model A			Model B			Model C		
Food groups[a]	Intake level[b]	RRR	95%CI		RRR	95%CI		RRR	95%CI	
Dairy products	Low	ref.			ref.			ref.		
	Medium	0.97	[0.80;	1.17]	0.97	[0.80;	1.17]	0.96	[0.77;	1.19]
	High	1.13	[0.94;	1.36]	1.03	[0.85;	1.26]	1.01	[0.81;	1.25]
Fats and oils	Low	ref.			ref.			ref.		
	Medium	1.06	[0.88;	1.27]	1.08	[0.90;	1.31]	1.06	[0.94;	1.19]
	High	0.85	[0.70;	1.03]	0.84	[0.69;	1.04]	0.84	[0.75;	0.94]
Fruits and vegetables	Low	ref.			ref.			ref.		
	Medium	1.11	[0.93;	1.34]	1.13	[0.94;	1.37]	1.25	[1.11;	1.40]
	High	0.91	[0.75;	1.09]	0.96	[0.79;	1.17]	0.98	[0.88;	1.09]
Confectionery	Low	ref.			ref.			ref.		
	Medium	0.95	[0.79;	1.15]	0.94	[0.78;	1.14]	1.07	[0.95;	1.19]
	High	0.92	[0.76;	1.10]	0.88	[0.72;	1.07]	0.96	[0.86;	1.06]
Cereals	Low	ref.			ref.			ref.		
	Medium	0.87	[0.72;	1.05]	0.91	[0.75;	1.11]	1.01	[0.81;	1.25]
	High	0.86	[0.71;	1.03]	0.98	[0.79;	1.21]	1.16	[0.93;	1.45]
Bakery products	Low	ref.			ref.			ref.		
	Medium	1.01	[0.84;	1.22]	0.99	[0.81;	1.21]	1.04	[0.84;	1.29]
	High	0.95	[0.79;	1.15]	0.91	[0.73;	1.13]	0.93	[0.74;	1.16]
Meat and meat products	Low	ref.			ref.			ref.		
	Medium	1.37	[1.13;	1.66]	1.30	[1.07;	1.59]	1.21	[1.07;	1.36]
	High	1.53	[1.26;	1.84]	1.50	[1.19;	1.89]	1.22	[1.10;	1.36]
Fish and fish products	Low	ref.			ref.			ref.		
	Medium	0.99	[0.82;	1.20]	0.99	[0.82;	1.20]	1.01	[0.90;	1.13]
	High	1.06	[0.88;	1.27]	1.02	[0.84;	1.23]	0.96	[0.85;	1.07]
Eggs and egg products	Low	ref.			ref.			ref.		
	Medium	1.28	[1.06;	1.54]	1.24	[1.02;	1.50]	1.21	[1.09;	1.36]
	High	1.34	[1.10;	1.53]	1.30	[1.07;	1.60]	1.17	[1.06;	1.30]
Beverages	Low	ref.			ref.			ref.		
	Medium	0.89	[0.74;	1.07]	0.88	[0.73;	1.07]	0.85	[0.68;	1.07]
	High	1.16	[0.96;	1.39]	1.12	[0.92;	1.36]	1.06	[0.84;	1.34]
Ready-to-eat savouries	Low	ref.			ref.			ref.		
	Medium	0.97	[0.80;	1.17]	0.97	[0.80;	1.17]	0.96	[0.77;	1.19]
	High	1.13	[0.94;	1.36]	1.03	[0.85;	1.26]	1.01	[0.81;	1.25]

Model A - crude model

Model B - adjusted for study region, maternal education, sex, age, pubertal status and energy intake from other food groups

Model C - additionally adjusted for the BMIs of the child and father

[a] Food groups were defined according to the Codex General Standard for Food Additives food category system (24);

[b] Defined using sex- and group-specific tertile cut-offs

Figure legend:

Figure 1 Relative risk ratios (RRR) for the associations between intake of food groups and mother's BMI. (A) crude, (B) adjusted for study region, maternal education, sex, age, pubertal status and energy intake from other food groups, (C) additionally adjusted for the BMIs of the child and father.

Figure 2 Relative risk ratios (RRR) for the associations between intake of food groups and mother's overweight. (A) crude, (B) adjusted for study region, maternal education, sex, age, pubertal status and energy intake from other food groups, (C) additionally adjusted for the BMIs of the child and father.

Figure 3 Linear regression coefficients for the association between mother's BMI and total energy intake in the total population and stratified by sex. (A) adjusted for study region, maternal education, age and pubertal status, (B) additionally adjusted for the BMIs of the child and father. Pooled models were additionally adjusted for sex.

Figure 1

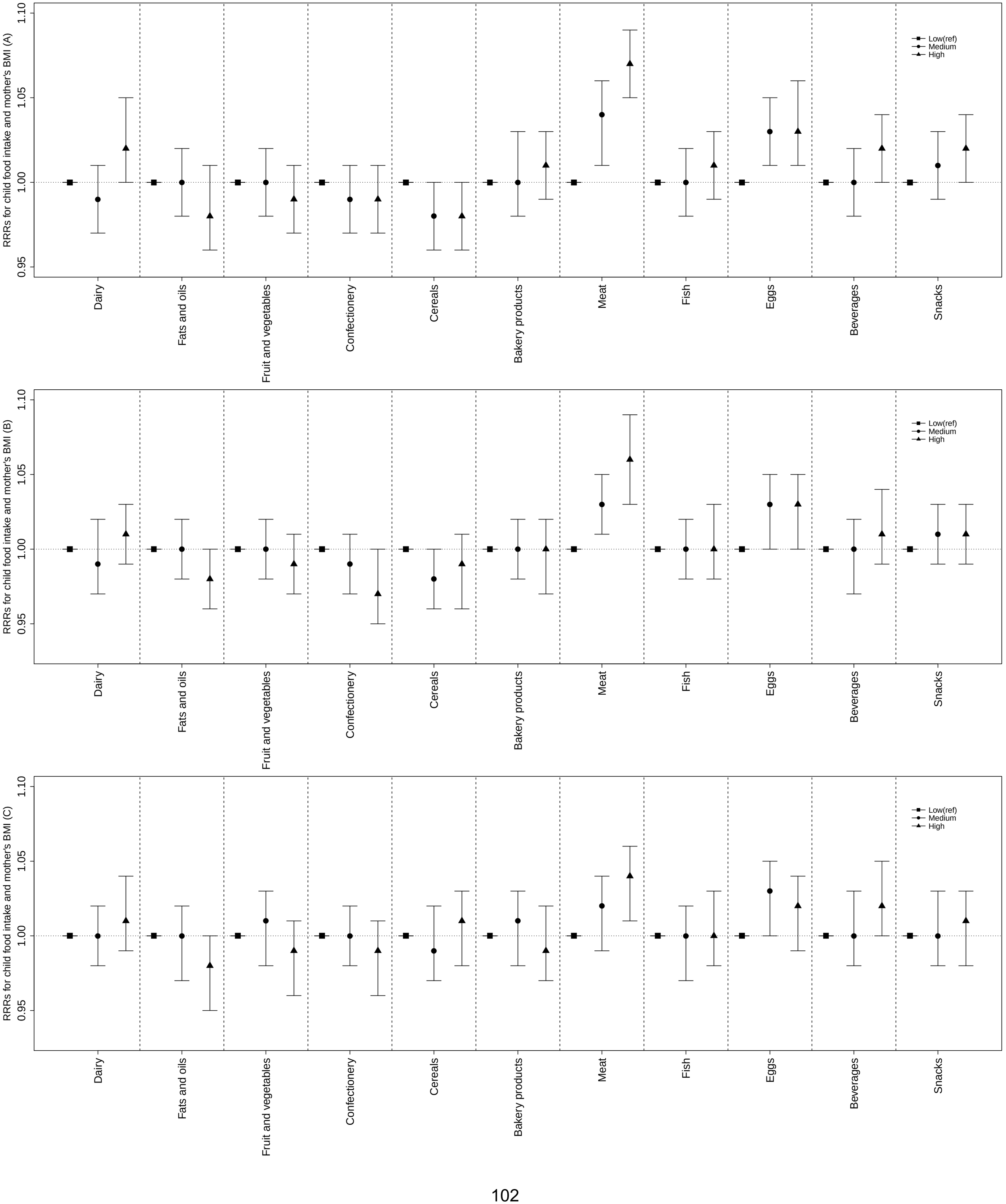

RRRs for child food intake and mother's BMI (A)
RRRs for child food intake and mother's BMI (B)
RRRs for child food intake and mother's BMI (C)
1.10
1.05
1.00
0.95
Low(ref)
Medium
High
Dairy
Fats and oils
Fruit and vegetables
Confectionery
Cereals
Bakery products
Meat
Fish
Eggs
Beverages
Snacks

Figure 2

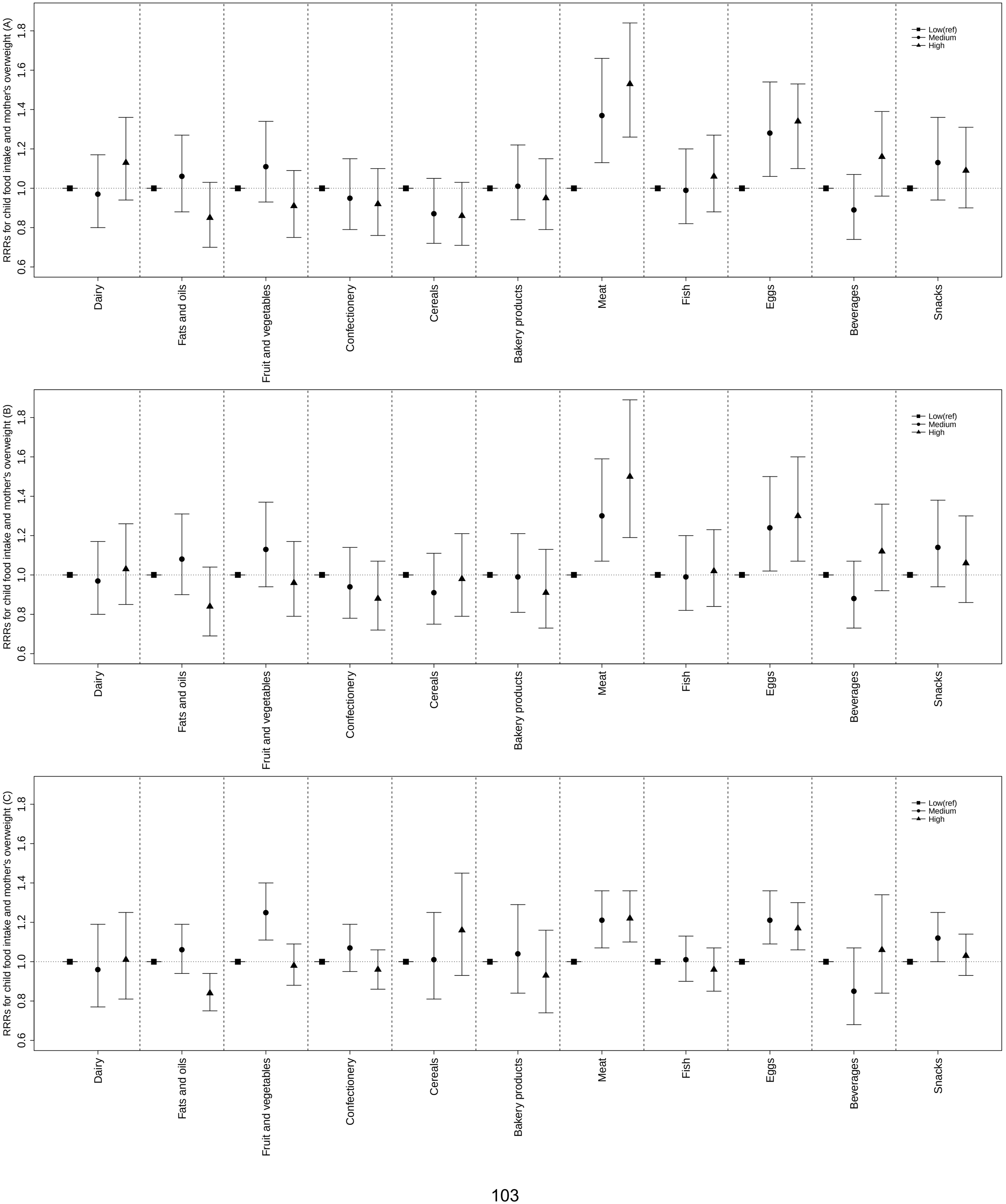
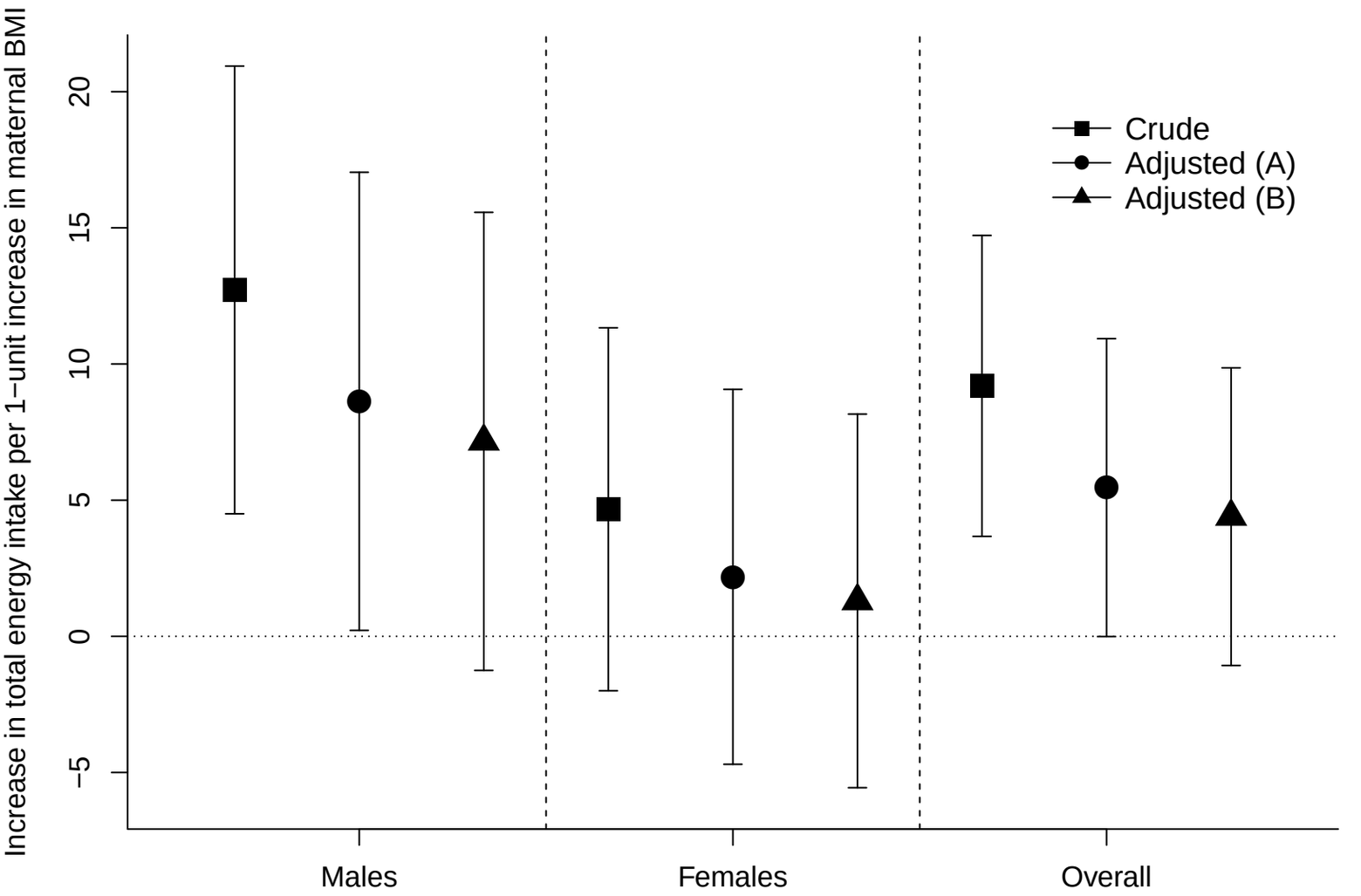

RRRs for child food intake and mother's overweight (A)
RRRs for child food intake and mother's overweight (B)
RRRs for child food intake and mother's overweight (C)
0.6
0.8
1.0
1.2
1.4
1.6
1.8
Low(ref)
Medium
High
Dairy
Fats and oils
Fruit and vegetables
Confectionery
Cereals
Bakery products
Meat
Fish
Eggs
Beverages
Snacks

Figure 3


Increase in total energy intake per 1−unit increase in maternal BMI
−5
0
5
10
15
20
Crude
Adjusted (A)
Adjusted (B)
Males
Females
Overall

ZHENGCUN PEI

PHD student

Helmholtz Zentrum München

Institute of Epidemiology I

Germany

+49 89 3187 3257 (Voice)

+49 89 3187 3380 (Fax)

e-mail: zhengcun.pei@helmholtz-muenchen.de

EDUCATIONAL BACKGROUND

2011 – 2014 *Ludwig Maximilians University Munich* – Ph.D., Human biology

2009 – 2011 *Peking University* – M.Sc., Child, Adolescent and Women's Health

2004 – 2009 *Peking University* – Bachelor, Public health

RESEARCH EXPERIENCE

2011 – 2014 Helmholtz Zentrum München — Munich, Germany

Institute of Epidemiology

Research Advisor: Dr. Joachim Heinrich

Ph.D. research. Longitudinal modeling of growth in children from birth to adolescence and the potential influence of diet.

2009 – 2011 Peking University — Beijing, China

Institute of Child and Adolescent Health

Research Advisor: Prof. Dr. Jun Ma

M.Sc. research. Nutrition intervention, health promotion and childhood obesity in eight primary schools in Beijing.

PUBLICATIONS

1. Zhengcun Pei, Claudia Flexeder, Elaine Fuertes, *et al.* Early life risk factors of being overweight at 10 years of age. Results of the German birth cohorts GINIplus and LISAplus. *Eur J Clin Nutr*. 2013 Aug;67(8):855-62. (Journal Impact Factor: 2.756).

2. Zhengcun Pei, Joachim Heinrich, Elaine Fuertes, *et al.* Cesarean Delivery and Risk of Childhood Obesity. *J Pediatr*. 2014 Feb 5. (Journal Impact Factor: 4.035) [Epub ahead of print]

3. Zhengcun Pei, Claudia Flexeder, Elaine Fuertes, et al. Food intake and overweight in school-aged children in Germany. Results of the GINIplus and LISAplus studies. In press (Ann Nutr Metab, Journal Impact Factor: 1.661).

4. Zhengcun Pei, Claudia Flexeder, Elaine Fuertes, et al. Maternal body mass index and food intake in school-aged children. Results of the GINIplus and the LISAplus studies. In press (Eur J Clin Nutr, Journal Impact Factor: 2.756).

CONFERENCES

ESPGHAN (the European Society for Paediatric Gastroenterology, Hepatology and Nutrition) Annual Meeting 2013&2014.

2013 Oral presentation: Caesarean section and risk of obesity in childhood: Results from the longitudinal LISAplus birth cohort. (Plenary Session)

2014 Poster presentation: Maternal body mass index and food intake in school-aged children. Results of the GINIplus and LISAplus studies.

DAG (Deutsches Adiposity Gesellschaft - German Obesity Society) Annual Meeting 2013.

Poster presentation: Caesarean section and risk of obesity in childhood: results from the longitudinal LISAplus birth cohort.

9 Acknowledgements

Firstly, I would like to express my gratitude to my advisor Dr. Joachim Heinrich, Director of the Institute of Epidemiology I at Helmholtz Zentrum München - German Research Center for Environmental Health for his constant support and belief in me. He operated his institute excellently and offered me the opportunity to do my PhD dissertation in his working group. He supported me in every aspects of my research. He helped scheduling my study topics, guided the interpretation of the results of my analyses, critically reviewed and revised my papers and manuscripts. He also has been very supportive when I was interested in participating extra courses and international conferences. He introduced many of his professional research partners to me, from whom I've learned so much in my research field.

I'm very grateful to Prof. Dr. Dr. H-Erich Wichmann, Chair of Epidemiology Institute of Medical Information Processing, Biometry and Epidemiology of the Ludwig-Maximilians-University of Munich (emeritus), who agreed to accept me as a PhD candidate in LMU, and who had been supportive throughout my thesis. He provided many valuable comments on my work progress reports, which substantially helped to improve my papers as well as my dissertation.

I would also like to thank Prof. Dr. Dr. Berthold Koletzko, Head of Division of Metabolic and Nutritional Medicine of Dr. von Hauner Children's Hospital and Medical Centre of LMU for his critical and very helpful comments on my study topics.

I must also thank all the co-authors that contributed to my papers and manuscripts. Especially, thanks to Prof. Dr. Sibylle Koletzko, who substantially improved the C-section paper and recommended me to the ESPGHAN annual meetings. Also thanks to Dr. Anette Buyken for sharing a lot of expertise in her research field, which substantially improved my diet manuscripts.

Then I wish to express my appreciation to all my lovely colleagues in EPI I who create this joyful working environment, and who are always willing to answer all my questions. Special thanks to Claudia Flexeder and Elaine Fuertes for being extremely helpful in my first year.

Thanks to everything here I experienced in Germany, I really appreciate it.

Thanks to all my friends for supporting me as always. Last but not least, my deepest love and gratitude goes to my family for all the support, dedication and love.

Eidesstattliche Versicherung

Zhengcun Pei

Name, Vorname

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Thema

Longitudinal modeling of growth in children from birth to adolescence and the potential influence of diet

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Ort, Datum

Unterschrift Doktorandin/Doktorand