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Abbreviations

BMI-GRS: combined obesity risk-allele score

SNP: single-nucleotide polymorphisms

Abstract

Background. Many genetic polymorphisms identified by genome wide association studies for adult BMI have been suggested to regulate food intake.

Objective. The objective was to study the associations between a genetic obesity risk score, appetitive traits and growth of children up to age 5 years, with a longitudinal design.

Methods. In 1,142 children from the EDEN birth cohort, a combined obesity risk-allele score (BMI-GRS) was related to appetitive traits (energy intake up to 12 months, a single item on appetite from 4 months to 3 years, a validated appetite score at 5 years) using Poisson regressions with robust standard errors. The potential mediation of appetitive traits on the association between BMI-GRS and growth was assessed by the Sobel test.

Results. Children with a high BMI-GRS were more likely to have high energy intake at 1 year and high appetite at 2 and 5 years. High energy intake in infancy and high appetite from 1 year were related to higher subsequent BMI. High 2-y appetite seemed to partially mediate the associations between BMI-GRS and BMI from 2 to 5 years (all $p<=0.05$).

Conclusions. Genetic susceptibility to childhood obesity seems to be partially explained by appetitive traits in infancy, followed by an early childhood rise in BMI.

Introduction

Genome-wide-association studies (GWAs) have identified several genes associated with an increased risk of obesity (1, 2). Time has now come to take advantage of these major findings in order to better understand the mechanisms of lifecourse obesity development from infancy to adulthood. Many birth cohorts have shown that scores of genetic susceptibility to obesity are associated with early growth, as early as 2 years in some of them, but not with foetal growth (3, 4, 5, 6).

A great part of the genes implicated by GWAs, and especially those from monogenic studies on severe childhood or early onset obesity, are purportedly involved in the central regulation of food intake (7). Furthermore, the genetic component of eating behavior has clearly been established through heritability studies, in adults (8) and also in children (9, 10). Eating behavior even in infancy may influence later adiposity development (11), which raises the question whether the association between the genetic score and adiposity is mediated by eating behaviour in childhood. Cross-sectional studies, conducted among 8-11 years children, have already shown that increased BMI of children homozygous for the at-risk allele of a FTO SNP may be partially mediated by appetitive traits (12, 13). Similarly, a cross-sectional analysis of the Twins Early Development Study highlighted that satiety responsiveness partially mediated the association between a polygenic risk score and adiposity in children aged 8-11 years(14). However, such a cross-sectional design is insufficient to establish a causal pathway. More recently, this causal pathway has been tested longitudinally within a Norwegian cohort following children from the age of 4 years to the age of 8 years (15). In that study, higher genetic risk for obesity was associated with appetitive traits at 6 years, but these appetitive traits were not related to BMI gain up to 8 years. As a previous study has shown that appetitive traits assessed at age 3 months predicted weight at 9 months, it would be important to test the potential mediating effect of infant or toddler's appetitive traits on

subsequent growth. A prospective design would also offer the opportunity to highlight a potential window of opportunity for this mediating effect.

In this context, we aimed at investigating within the French EDEN mother-child cohort, how genetic predisposition to obesity may influence eating behavior very early life and whether this relationship might explain the accelerated growth in children with higher genetic risk for obesity. In the present study, we focused on three aspects of child's eating behavior that could be assessed longitudinally, from 4 months to 5 years: energy intake and appetite.

Material and methods

Study population

The EDEN mother-child study is a prospective cohort whose aim is to assess pre- and post-natal determinants of child growth, development and health. It has been described in more detail elsewhere (16). In brief, 2002 pregnant women were recruited from 2003 to 2006 in two French university hospitals, before 24 weeks of amenorrhea. Exclusion criteria were multiple pregnancies, known diabetes prior to pregnancy, illiteracy, plan to move outside the region within the next three years. The study was approved by the Ethics Committee of the University Hospital of Kremlin-Bicêtre on December 12, 2002 and data files were declared to the National Committee for Processed Data and Freedom. Written consent was obtained from both parents.

The primary endpoints of the cohort were pre and post-natal growth, blood pressure, allergies, infectious diseases, mental health and cognitive development. Dietary behavior was initially collected as one of the main exposure factors in the cohort and was considered as a potential mediating factor in the present study.

Data collected during pregnancy and at birth, include sociodemographic variables, maternal smoking, gestational diabetes, parental anthropometric measurements, and newborn characteristics (sex, gestational age, birthweight) (17). At four, eight and twelve months after birth, mothers completed mailed questionnaires that provided detailed information on the feeding method (exclusive breast-feeding, exclusive formula-feeding or mixed-diet) between birth and four months, then at eight and twelve months as well as the date of breastfeeding cessation. Breastfeeding duration was derived from these data (18). Clinical exams were also conducted at birth, 1 year, 3 years and 5 years and were dedicated to collection of biological sample, cognitive assessments by psychologists and measurement of anthropometric and clinical parameters.

Genotyping and BMI Genetic Risk Score (BMI-GRS) generation

DNA was extracted from cord blood samples collected at birth. Genotypes at 16 single-nucleotide polymorphisms (SNPs) were measured at the Medical Research Council Epidemiology Unit, Cambridge (iPLEX platform; Sequenom), as previously described (19). Among the 32 loci identified by Speliotes et al. as having genome-wide significant associations with BMI in adults (2), we considered in the present study the 16 SNPs also showing associations with childhood BMI either in that original report (2) or in subsequent data (4); they lie in or near NRXN3 (rs10146997), SLC39A8 (rs13107325), TNNI3K (rs1514175), PTBP2 (rs1555543), MC4R (rs17782313), FLJ35779 (rs2112347), NEGR1 (rs2568958), RPL27A (rs4929949), TMEM18 (rs6548238), RBJ/POMC (rs713586), CADM2 (rs7640855), TRA2B/ETV5 (rs7647305), BDNF (rs925946), TFAP2B (rs987237), FTO (rs9941349), and ZNF608 (rs4836133). The summary of genotyped SNPs and allele frequencies in presented in **supplementary table S1**. All variants passed genotyping quality control criteria (call rate, >95%; Hardy-Weinberg equilibrium, $P > .01$).

Combined obesity risk-allele scores, indicating genetic susceptibility to obesity, were calculated for each participant as the sum of risk alleles (0, 1 or 2 at each locus) associated with higher BMI across the 16 SNP loci. The score ranged from 0 to 32. To minimize dropout due to missing genotype data, infants with missing genotype data at 4 (25%) or fewer loci were imputed with the mean number of susceptibility alleles in their cohort for each locus. In sensitivity analyses, we also computed a weighted BMI-GRS, where each risk allele was multiplied by the 'European only sex combined' effect estimate for the BMI-increasing allele reported by Locke and colleagues (1).

Child's eating behavior

Maternal perception of infant's appetite was assessed, at ages 4, 8 and 12 months, by one question, translated as follow: "Usually, you would say that your baby: 1/ is always hungry or demanding to feed 2/ demands to feed the same as other babies of the same age 3/ needs to be stimulated to eat", at ages 2 and 3 years, by one question: "Usually, you would say that your child: 1/ is always hungry or asking to eat 2/ has a normal appetite compared with other children of the same age 3/ is not often hungry", and at 5 years by the Low Appetite scale from the Children's Eating Difficulties Questionnaire (20). From 4 months to 4 years, a high appetite was defined as the category of children "always hungry or claiming to eat" and at 5 years as a Low Appetite score below the 10^{th} percentile.

Infant diet was assessed by food records on three non-consecutive days (two weekdays and one weekend day), when the infant was not sick, at 4, 8 and 12 months. Data were checked and computerized a posteriori by a dietician. Nutrient intake was then calculated based on two food composition databases, one specific to ready-prepared baby foods from the French baby foods industry group (SFAE 2005) and one for common foods from the French Observatory of Food Nutritional Quality (CIQUAL 2006) (21). Total nutrient intake was calculated only among infants who were not breastfed during the three days of the dietary records, given that

the amount of breast milk intake could not be measured in breastfed infants. At each age, high energy intake was defined as the highest quintile of energy intake. Unfortunately, energy intake was not available in 2-5-year-old children, as diet was collected from a 24-item food frequency questionnaire from 2 years instead of 3-d dietary records.

Child's growth

At each clinical examination, child's weight and height were measured. In between, weight and height data were collected from self-administered questionnaires and from measurements noted in the child's health booklet by health professionals. Children had on average 22 weight measurements (interquartile range 16–26) from birth to 5–6 years. Individual growth curves were obtained for weight and height using the Jenss-Bayley growth curve model (22). This model allows us to predict weight, length/height and then calculate BMI at any given age (22). We used these model-based values of weight, length/height and BMI at 1, 2, 3, 4 and 5 y. At each age, the WHO growth standards were used for the calculation of weight-for-age, length/height-for-age and BMI-for-age z-scores. The WHO Anthro SAS macro (WHO Anthro, SAS Macro, Geneva: World Health Organization; http://www.who.int/childgrowth/software/en/) was used for this calculation.

Sample selection

Of the 2002 women who were recruited, 76 women were excluded because they left the study before or at the time of delivery, 24 because of miscarriages, intra-uterine death, or discontinuation of pregnancy for medical reasons, and 9 because they delivered outside the study hospitals. Data on birthweight were available for 1899 newborns. Among them, genotyping data were available for 1324 children. Children without any data on eating behavior from 4 months to 5 years (n=123) as well as those with missing data on age, sex, growth, breastfeeding duration or maternal smoking (n=59) were excluded from the analyses. Among the 1899 newborns with data on birth weight, the 1142 participants included in our

139 analyses were quite similar to those excluded concerning gender (p=0.9) and maternal pre-
140 gestational BMI (p=0.12) but had older mothers (29.7 vs 29.1 years at delivery, p=0.007) and
141 were born with higher gestational age (39.4 vs. 39.0 weeks of amenorrhea, p<0.0001) and
142 higher birth weight (3324 g vs. 3210 g, p<0.0001).

143 ***Statistical analyses***

144 Student *t*-tests, χ^2-tests and 1-way ANOVA were used to test differences between included
145 and excluded populations.
146 Associations between the obesity risk-allele score (BMI-GRS) and child's eating behavior
147 were tested by Poisson regression models with robust standard errors, adjusted for recruitment
148 center, infant's gender, and age at eating behavior assessment. Additional analyses were
149 conducted to adjust further for breastfeeding duration and maternal smoking during
150 pregnancy.
151 Associations between infant/child eating behavior and predicted child's weight-for-age,
152 length/height-for age or BMI-for-age WHO z-scores were tested by linear regression models
153 adjusted for recruitment center, infant's sex, age at eating behavior assessment. Additional
154 analyses were conducted to adjust further for breastfeeding duration, maternal smoking during
155 pregnancy and parental height.
156 Associations between BMI-GRS and predicted child's weight, length/height or BMI z-scores
157 were tested by linear regression models adjusted for recruitment center and infant's sex.
158 If an eating behaviour was associated with both the independent variable (BMI-GRS, path a,
159 Supplementary Figure S1) and the dependent variable (WHO z-score, path b), we tested for
160 the presence of mediation. Mediation is said to occur when a third variable lies on the causal
161 pathway between an exposure (in this case, the BMI-GRS) and an outcome (in this case,
162 WHO z-scores). To test for mediation, the linear regression of genetic risk score on each
163 WHO z-score was adjusted for the considered eating behaviour. The presence of mediation

was established using the Sobel test (23, 24) and quantified by the mediation ratio ((β-β')/ β), where β is the initial coefficient for BMI from the model *WHO z-score ~ BMI-GRS* (path c) and β' is the coefficient for WHO z-score after the model is additionally adjusted for the eating behaviour (path c'). As high score on appetitive traits were considered as binary variables, we used the method adapted by Jasti et al. to calculate the Sobel test (25).

We conducted sensitivity analyses using a weighted genetic risk score for BMI (WtBMI-GRS) instead ot the crude genetic risk score. To calculate this weighted score, at each locus, the number of BMI increasing variants was multiplied by the effect estimate for the BMI-increasing variant from Speliotes et al (2).

All analyses were carried out using SAS V9.3 (SAS, Cary, NC).

Results

Among the 1142 mothers-child pairs with both genotyping data and eating behavior assessment, mothers were aged on average 29.7 (SD=4.8) years, had a pre-pregnancy BMI of 23.1 (SD=4.3) kg/m^2 and breastfed for 3.3 (SD=3.7) months. Children carried on average 13.7 (SD=2.5) obesity risk alleles, with a range of 5 to 22 obesity risk alleles. At 5 years, 6.6 % of children were considered overweight or obese using IOTF definition (26). Children's BMI and appetitive traits are described in **Supplementary table S2**.

BMI-GRS related to eating behaviours

BMI-GRS was not significantly related to high energy intake at 4 mo and 8 mo but was positively related to energy intake at 1 year (in infants who were not breastfed at time of energy intake assessment) (**Figure 1**). Among all children, BMI-GRS was positively related to maternal perception of high appetite between 8 months and 5 years, although not significant in the first year or at 3 years. Further adjustment for breastfeeding duration and maternal smoking during pregnancy did not substantially modify the associations (data not

188 shown). In sensitivity analyses, when considering the weighted BMI-GRS, results were
189 similar (data not shown).

190 ***Child's eating behavior and growth parameters***

191 Among children not breastfed during the 3-d dietary records, high energy intakes at 4 and 8
192 months were positively related to weight-for-age, length/ height-for-age and BMI-for-age z-
193 scores (**Table 1**) from 1 to 5 years. High energy intake at 12 months was positively related to
194 weight-for-age z-score from 3 to 5 years but was not related to length/ height-for-age or BMI-
195 for-age z-scores.

196 High appetite before 1 year was not clearly related to subsequent WHO's z-scores. High
197 appetite was not related to length/height-for-age z-score, whatever the age considered. High
198 appetite at 1 year was positively related to weight-for-age or BMI-for-age z-scores up to 5
199 years but the strength of the association decreased with age and was no more significant for
200 BMI-for-age at 5 years. High appetite at 2 or 3 years was positively related to child's
201 subsequent BMI-for-age z-score and, to a lesser extent, weight-for-age z-score. These
202 associations were mitigated by further adjustment for breastfeeding duration, maternal
203 smoking during pregnancy and parental height, the associations but remained significant,
204 except the association between high energy intake at 12 months and weight-for-age z-score
205 from 3 to 5 years (supplementary table S3)

206 ***Mediation analysis***

207 The association between BMI-GRS and child's size increased with age and became
208 significant from 3 years onwards for child's weight (**Figure 2A**) and 4 years onwards for
209 child's BMI (**Figure 2B**). High appetite at 2 years was the only eating behavior related to
210 both BMI-GRS and BMI, and therefore considered as a potential mediator in the association
211 between BMI-GRS and BMI. These associations were attenuated after adjustment for high
212 appetite at 2 years (Figure 2A and 2B). The Sobel test for mediation was significant but the

mediation was only partial with a mediation ratio decreasing with time from 47% for 2-y BMI z-score (p=0.03) and 35% for 3-y BMI z-score (p=0.03) to 28% for 4-y BMI z-score (p=0.05) and 24% for 5-y BMI (p=0.05). Similar results were found with the weighted BMI-GRS (data not shown).

Discussion

In our study, the score of genetic predisposition to develop obesity was association with a higher risk of high energy intake at 1 year, and high parental-perceived appetite at 2 and 5 years. The associations between the BMI-GRS and BMI-for-age or, to a lesser extent, weight-for-age z-scores were attenuated by further adjustment for high appetite at 2 years, whereas BMI-GRS was not related to length/height-for-age z-score up to 5 years. Finally, among infants not breastfed during the food records, energy intakes at 4 and 8 months were positively related to child's WHO z-scores until 5 years, but were not related to the BMI-GRS.

The association between genetic susceptibility to obesity and appetitive traits has been previously examined in childhood but not so early in infancy. Within 8-11 years olds twins of the TEDS study, Llewellyn et al. (14) showed that a BMI-GRS (based on 28 SNPs) was related to both BMI and satiety sensitivity, and that the latter mediated the association with BMI. However, in a study conducted by Steinsbeckk et al. within Norwegian children aged from 4 to 6 years at inclusion (15), the BMI-GRS (based on 32 SNPs) was related to BMI from 4 to 8 years, to BMI change from 4 to 6 years and from 6 to 8 years, but was associated only with slowness in eating (negative association) at 6 years and not with other eating behaviours (i.e. food responsiveness, emotional overeating, enjoyment of food or satiety responsiveness). In that study, the association between the BMI-GRS and BMI was not mediated by any appetitive trait assessed at age 6 years.

If evidence of a mediating effect of appetitive traits on the association between the BMI-GRS and BMI remains scarce, many studies examined the influence of appetitive traits on BMI. The associations shown in EDEN are in agreement with previous studies in spite of the heterogeneity of ages and methods of investigation. In the GUSTO study (27), food responsiveness at 3 months was related to higher BMI up to 15 months, whereas appetitive traits assessed at 12 months were not related to BMI z-score in toddlers. Moreover, satiety responsiveness in early childhood was found related to lower subsequent BMI (28, 29). Similar results were found in the Gemini study (11), as all appetitive traits measured at 3 months of age were related to later weight, with stronger association for general appetite and satiety responsiveness. In that study, the possibility of reverse causality was suggested by the observation that weight at 9 months was also related to appetitive traits in toddlers, with stronger association for food responsiveness, satiety responsiveness and general appetite. Despite the positive associations between infant appetite and subsequent weight gain and also between infant size and subsequent, the prospective influence of appetite on weight appeared to be stronger than the reverse.

In our study, energy intake in the first months of life was related to growth throughout early childhood. High energy intake could probably be considered as an indicator of rapid growth during this period and rapid growth in infancy is related to higher risk of overweight later in childhood in this and other cohorts (30). The influence of high energy intake on child's 5-y BMI is similar to the influence of high genetic predisposition to obesity (data not shown). However, notably energy intake in infancy was not related to the BMI-GRS, and might be more explained by prenatal or early postnatal exposures. We have to acknowledge that energy intake was assessed only among infants who were not breastfed during the three days of the dietary records, given that the amount of breast milk intake could not be measured in

breastfed infants. Moreover, from 2 years onwards, the dietary data collection was unfortunately not designed to derive energy intake.

The main strength of this study is that eating behaviour and BMI were assessed repetitively and prospectively from very early in infancy (as early as birth for BMI and four months for eating behaviour), which permitted us to describe in detail the longitudinal patterns of associations between the BMI-GRS, eating behaviour and BMI. However, appetite was assessed only by one item, whereas other assessments, maybe based on more complex scales, would have allowed us to check for consistency for this trait. Moreover, we have to acknowledge that eating behaviour up to 3 years was not assessed by a validated tool up to 3 years as such tools were not developed when the EDEN study was designed. A validated tool became available and was introduced only at the 5-y follow-up. Concerning the item on appetite, a similar item was used by previous studies (10, 11) and associations with this item were similar to those with other appetitive traits, if not stronger. Moreover, in the EDEN study, we found similar associations at 5 years, when appetite was assessed by a validated scale (20). As appetitive traits were reported by parental questionnaires and not assessed by a laboratory tool, this measurement could be influenced by social desirability. Finally, because of the originality and the uniqueness of the collected data, our results yet rely on data from only one cohort. Further studies conducted in other birth cohorts would be necessary to confirm and demonstrate the generalizability of these findings. Ideally, these studies would be designed with repeated use of validated tools throughout early childhood to assess eating behaviour or energy intake and conducted in populations with higher prevalence of overweight. As previous studies have shown that these BMI variants could to be relevant also to other non-Caucasian populations (31, 32), it would be interesting to conduct similar analyses in non-Caucasian populations.

Conclusion

The study provides further support from a prospective study for a partial mediation by appetitive traits on the relationship between genetic susceptibility and BMI. In particular, in the EDEN birth cohort, genetic susceptibility to childhood and adult obesity seems to play a very precocious role by influencing appetitive traits in infants and preschool children and subsequently promote faster growth. Despite the more typically recognised concerns regarding infant feeding difficulties, many parents might benefit from counselling and support to manage high appetitive traits in their infants and young children to prevent later obesity risk.

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BLG and BH designed the research and wrote the manuscript. BLG, YAK, JB, AF and SC analysed the data. BH and MAC oversaw the EDEN study. BH, KC, VP, KKO and MAC were responsible for data collection and genotyping in EDEN. All authors reviewed drafts, provided critical feedback, approved the final manuscript and were responsible for the final content of the paper. BH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure 1. Association between obesity risk-allele score and child's eating behaviour, up to 5 years

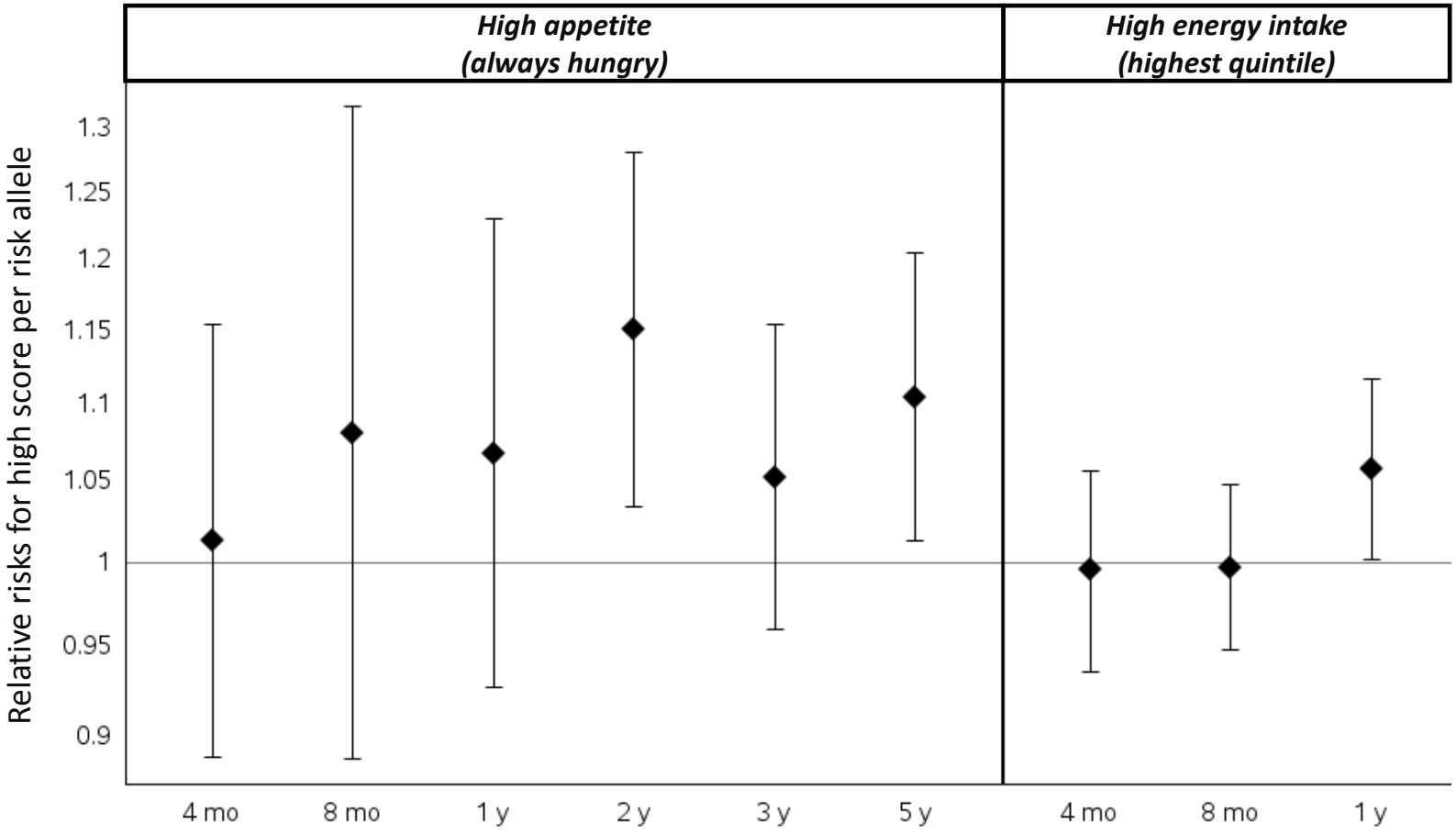

Figure legend. Results are RR [95% CI], adjusted for recruitment's center, child's age and sex (n=1081 at 4mo, 1072 at 8 mo, 1024 at 1 year, 940 at 2 years, 892 at 3 years and 790 at 5 years). Energy intake was assessed only on infants who were not breastfed during the 3-d dietary records. (679 at 4 mo, 861 at 8 mo and 822 at 12 mo)

Figure 2. Association between the obesity risk-allele score and child's WHO z-scores from 2 to 5 years

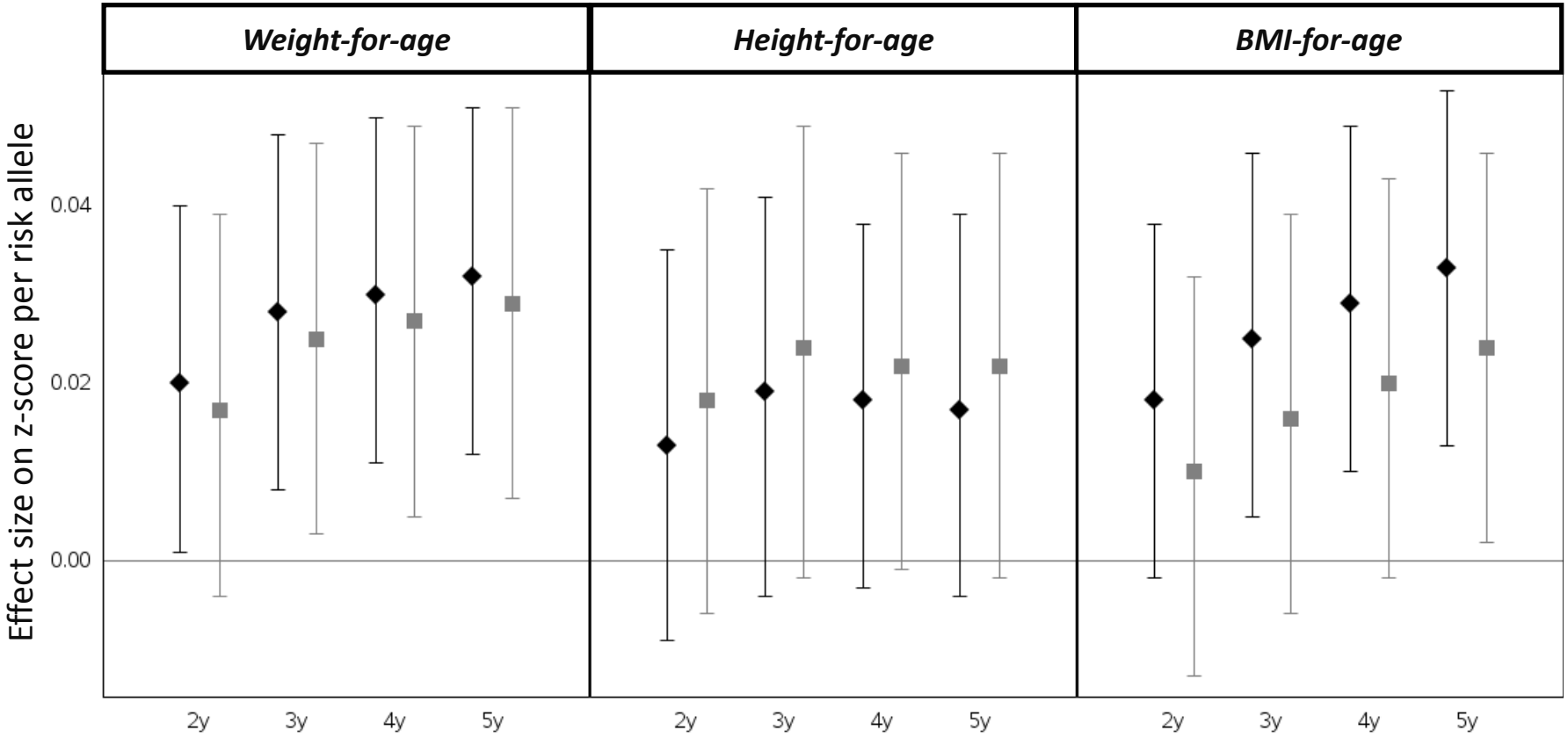

Figure legend. ◆ Results are effect size [95% CI], adjusted for recruitment center and infant's sex (n=1142). ■ Results are effect size [95% CI], adjusted for recruitment center, infant's sex, child's age and high appetite at 2 years (n=940).

SUPPORTING INFORMATION

Table S1. BMI and eating behaviour traits of children at different assessment steps

SNP	Locus	Effect allele	Other allele	SNP reported in GIANT	Evidence for association with childhood BMI	LD with GIANT SNP (r2)	EAF in EDEN
rs10146997	NRXN3	G	A	rs10150332	Reported in Speliotes et al.	1.0	0.18
rs13107325	SLC39A8	T	C	rs13107325	Reported in Elks et al.	-	0.08
rs1514175	TNNI3K	A	G	rs1514175	Reported in Speliotes et al.	-	0.38
rs1555543	PTBP2	C	A	rs1555543	Reported in Speliotes et al.	-	0.55
rs17782313	MC4R	C	T	rs571312	Reported in den Hoed et al.	0.96	0.21
rs2112347	FLJ35779	T	G	rs2112347	Reported in Elks et al.	-	0.61
rs2568958	NEGR1	A	G	rs2815752	Reported in den Hoed et al.	0.96	0.57
rs4836133	ZNF608	A	C/G	rs4836133	Reported in Elks et al.	-	0.40
rs4929949	RPL27A	C	T	rs4929949	Reported in Speliotes et al.	-	0.45
rs6548238	TMEM18	C	T	rs2867125	Reported in den Hoed et al.	1.0	0.81
rs713586	RBJ/POMC	C	T	rs713586	Reported in Speliotes et al.	-	0.44
rs7640855	CADM2	A	G	rs13078807	Reported in Speliotes et al.	1.0	0.17
rs7647305	TRA2B	C	T	rs9816226	Reported in den Hoed et al.	0.72	0.71
rs925946	BDNF	T	G	rs10767664	Reported in den Hoed et al.	1.0	0.25
rs987237	TFAP2B	G	A	rs987237	Reported in Elks et al.	-	0.15
rs9941349	FTO	T	C	rs1558902	Reported in den Hoed et al.	0.84	0.38

Effect allele refers to the allele associated with higher BMI in the Genetic Investigation of Anthropometric Traits (GIANT) consortium (Speliotes et al., Ref. 2).

EAF: Effect allele frequency.

LD: Linkage Disequilibrium; calculated based on 1000 Genomes pilot 1 data using SNAP (https://www.broadinstitute.org/mpg/snap/).

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Table S2. BMI and eating behaviour traits of children at different assessment steps

	4 months	8 months	1 year	2 years	3 years	5 years
N	1081	1072	1024	940	892	790
Age (months)	4.3 (1.0)	8.3 (0.8)	12.1 (0.7)	24.4 (1.3)	37.9 (0.9)	67.7 (1.9)
Predicted BMI (kg/m^2)	16.9 (1.3)	17.1 (1.3)	16.8 (1.2)	16.2 (1.2)	15.9 (1.2)	15.4 (1.3)
High appetite (always hungry)[a]	3.7% (40)	1.9% (20)	3.1% (32)	5.1% (48)	7.2% (64)	9.0% (71)
Energy intake (kcal)						
among children not receiving	n=680	n=861	n=822			
breastmilk during the 3-d record	589 (104)	716 (135)	809 (135)			

Values are means (sd) or % (n).

[a] at 5 years, high appetite was defined as a Low Appetite Score below the 10^{th} percentile.

Table S3. Association between eating behaviour and child's WHO z-scores after further adjustment on parental height, maternal smoking during pregnancy and breastfeeding duration

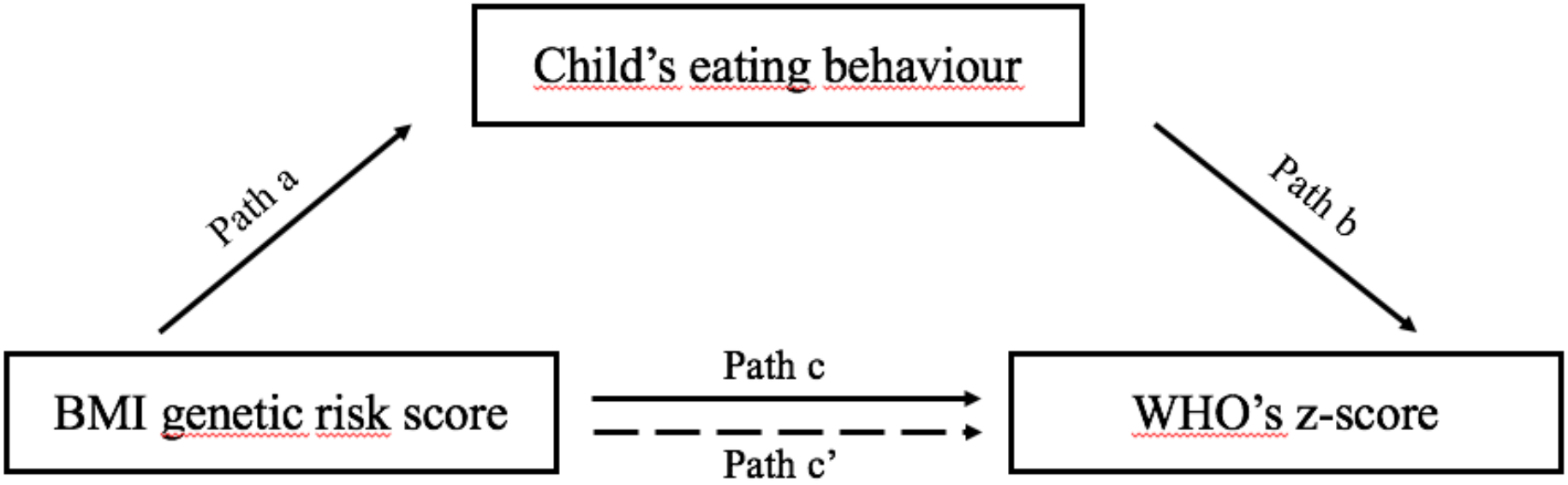
	N	Age at WHO z-score assessment				
		1 year	2 years	3 years	4 years	5 years
Outcome: Weight-for-age z-score						
High energy intake (highest quintile)						
4 months	629	**0.39 [0.23 ; 0.55]**	**0.31 [0.15 ; 0.46]**	**0.25 [0.09 ; 0.41]**	**0.21 [0.05 ; 0.36]**	**0.18 [0.02 ; 0.33]**
8 months	791	**0.33 [0.19 ; 0.47]**	**0.29 [0.15 ; 0.43]**	**0.24 [0.10 ; 0.38]**	**0.19 [0.05 ; 0.33]**	**0.15 [0.02 ; 0.29]**
12 months	767	0.04 [-0.10 ; 0.19]	0.07 [-0.07 ; 0.22]	0.09 [-0.06 ; 0.23]	0.09 [-0.05 ; 0.23]	0.09 [-0.05 ; 0.23]
High appetite (always hungry)						
4 months	993	**0.32 [0.04 ; 0.59]**	0.21 [-0.07 ; 0.48]	0.14 [-0.14 ; 0.42]	0.09 [-0.18 ; 0.37]	0.06 [-0.21 ; 0.34]
8 months	987	0.28 [-0.10 ; 0.66]	0.23 [-0.14 ; 0.61]	0.17 [-0.21 ; 0.55]	0.11 [-0.26 ; 0.49]	0.08 [-0.3 ; 0.45]
1 year	945	0.21 [-0.10 ; 0.51]	0.23 [-0.08 ; 0.53]	0.20 [-0.11 ; 0.51]	0.16 [-0.14 ; 0.47]	0.14 [-0.17 ; 0.44]
2 years	868		**0.32 [0.08 ; 0.56]**	**0.28 [0.04 ; 0.53]**	**0.24 [0.00 ; 0.48]**	0.20 [-0.04 ; 0.44]
3 years	826			**0.28 [0.06 ; 0.50]**	**0.24 [0.02 ; 0.46]**	0.21 [-0.01 ; 0.43]
5 years	738					**0.41 [0.20 ; 0.61]**
Outcome : Length/Height-for-age z-score						
High energy intake (highest quintile)						
4 months	629	**0.25 [0.08 ; 0.42]**	0.13 [-0.04 ; 0.29]	0.11 [-0.06 ; 0.28]	0.10 [-0.06 ; 0.26]	0.11 [-0.05 ; 0.27]
8 months	791	**0.21 [0.06 ; 0.35]**	**0.20 [0.05 ; 0.34]**	**0.18 [0.03 ; 0.33]**	**0.13 [0.00 ; 0.27]**	0.11 [-0.03 ; 0.25]
12 months	767	0.11 [-0.05 ; 0.26]	0.09 [-0.05 ; 0.24]	0.10 [-0.06 ; 0.25]	0.09 [-0.06 ; 0.23]	0.08 [-0.06 ; 0.23]
High appetite (always hungry)						
4 months	993	0.07 [-0.23 ; 0.37]	0.03 [-0.26 ; 0.32]	0.04 [-0.26 ; 0.34]	0.05 [-0.22 ; 0.33]	0.07 [-0.21 ; 0.35]
8 months	987	0.15 [-0.25 ; 0.55]	0.11 [-0.28 ; 0.50]	0.08 [-0.33 ; 0.48]	0.05 [-0.33 ; 0.42]	0.02 [-0.36 ; 0.40]
1 year	945	-0.27 [-0.59 ; 0.06]	-0.22 [-0.53 ; 0.09]	-0.18 [-0.50 ; 0.15]	-0.12 [-0.42 ; 0.18]	-0.07 [-0.38 ; 0.23]
2 years	868		-0.20 [-0.45 ; 0.05]	-0.20 [-0.46 ; 0.07]	-0.17 [-0.41 ; 0.07]	-0.16 [-0.41 ; 0.08]
3 years	826			0.11 [-0.12 ; 0.34]	0.09 [-0.13 ; 0.30]	0.07 [-0.15 ; 0.29]

5 years	738					**0.30 [0.09 ; 0.50]**
Outcome: BMI-for-age z-score						
High energy intake (highest quintile)						
4 months	629	**0.35 [0.18 ; 0.52]**	**0.33 [0.16 ; 0.51]**	**0.28 [0.11 ; 0.45]**	**0.21 [0.04 ; 0.38]**	0.16 [-0.01 ; 0.33]
8 months	791	**0.29 [0.14 ; 0.44]**	**0.25 [0.10 ; 0.40]**	**0.21 [0.05 ; 0.36]**	**0.16 [0.02 ; 0.31]**	0.14 [-0.01 ; 0.28]
12 months	767	-0.02 [-0.18 ; 0.13]	0.03 [-0.13 ; 0.18]	0.05 [-0.11 ; 0.20]	0.06 [-0.10 ; 0.21]	0.06 [-0.09 ; 0.21]
High appetite (always hungry)						
4 months	993	**0.37 [0.08 ; 0.66]**	0.27 [-0.03 ; 0.57]	0.17 [-0.13 ; 0.47]	0.09 [-0.20 ; 0.38]	0.03 [-0.26 ; 0.33]
8 months	987	0.27 [-0.13 ; 0.67]	0.25 [-0.16 ; 0.66]	0.19 [-0.22 ; 0.60]	0.14 [-0.26 ; 0.54]	0.11 [-0.29 ; 0.51]
1 year	945	**0.49 [0.17 ; 0.81]**	**0.52 [0.20 ; 0.85]**	**0.45 [0.12 ; 0.78]**	**0.35 [0.02 ; 0.67]**	0.27 [-0.05 ; 0.59]
2 years	868		**0.64 [0.38 ; 0.90]**	**0.60 [0.34 ; 0.86]**	**0.52 [0.26 ; 0.78]**	**0.46 [0.20 ; 0.72]**
3 years	826			**0.32 [0.08 ; 0.56]**	**0.29 [0.05 ; 0.52]**	**0.27 [0.03 ; 0.50]**
5 years	738					**0.35 [0.13 ; 0.57]**

Results are effect size [95% CI] of high level of the considered appetitive trait on WHO z-score, adjusted for recruitment centre, infant's sex, age at eating behaviour assessment, parental height, maternal smoking during pregnancy and breastfeeding duration. Significant results are highlighted in bold.

[a] at 5 years, high appetite was defined as a Low Appetite Score below the 10^{th} percentile.

Figure S1. Figure depicting the mediation analyses.



Path a shows the association between the BMI genetic risk score and eating behaviour

Path b shows the association between eating behaviour and WHO's z-score

Path c shows the relationship between the BMI genetic risk score and WHO's z-score

Path c' shows the relationship between the BMI genetic risk score and WHO's z-score, adjusted for the considered eating behaviour