

Interactions of Genetic and Environmental Risk Factors with Respect to Body Fat Mass in Children: Results from the ALSPAC Study

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Objective: To evaluate if percentile-specific effects of genetic, environmental and lifestyle obesity risk factors on body mass index (BMI) might reflect gene-environment interactions with respect to the development of overweight.

Design and Methods: Retrospective study with data of 2,346 children from the Avon Longitudinal Study of Parents and Children (ALSPAC), using quantile regression with body fat mass index (FMI) for children at the age of 9 years as outcome variable. We assessed interactions of an "obesity-risk-allele-score" with environmental and nutritional factors.

Results: There was no evidence of interactions between the obesity-risk-allele score and the environmental variables except for maternal overweight. However, we found a significant interaction with respect to intake of mono- and polyunsaturated fatty acids at the age of 7. In children with low intake, genetic risk was associated with increasing effect sizes by FMI percentile.

Conclusions: Our results suggest an interaction between a low dietary content of unsaturated fatty acids and genetic risk factors for overweight on FMI. This effect is likely to be stronger in children with higher FMI.

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Introduction

Genetic factors are likely to determine the risk of overweight in children. Evidence comes originally from adoption and twin studies (1,2) and has been confirmed in recent genome-wide association (GWA) studies, in which a number of risk alleles for overweight / obesity have been identified (3-7). Combining such genetic variants in a risk score appears to be an appropriate measurement of an individual's genetic predisposition for overweight (8,9). In a previous study, we found that such a genetic risk score was associated with differential effect sizes depending on children's body composition, with greatest effects on higher body mass index (BMI) percentiles (10).

Although the association of overweight/obesity with specific genetic predisposition is therefore well-established, the underlying mechanisms are still largely unknown. Recent studies suggest that interaction with environmental risk factors may be important (11-14). This might also help to explain why we had previously found similar

patterns of associations (i.e., different effect sizes by children's BMI) for environmental risk factors (15,16).

We therefore hypothesized that potential interactions with environmental risk factors might strengthen the effect of the "obesity-risk-allele score" in the upper body fat mass percentiles. In order to answer this question, we assessed interactions between the mentioned "obesity-risk-allele score" and a number of priming, life-style and nutritional factors with respect to body fat mass in children at primary school age using quantile regression.

Methods

Study Population and Data Sources

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing longitudinal birth cohort study that has been described in more detail elsewhere (17). A total of 14,541 pregnant women living in the former Avon Health Authority (South-West England)

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TABLE 1 Characteristics of the study population (*n* = 2,346)

Variable	Mean (SD)/ <i>n</i> (%)
Fat mass index [kg/m ²]	4.1 (2.2)
Overweight children ^a	<i>n</i> = 428 (18.2%)
Obese children ^a	<i>n</i> = 83 (3.5%)
Age [years]	9.8 (0.3)
Sex (female)	<i>n</i> = 1,146 (48.8%)
Maternal overweight	<i>n</i> = 448 (19.1%)
High TV consumption	<i>n</i> = 781 (33.3%)
Low parental education	<i>n</i> = 1,016 (43.3%)
Maternal smoking during pregnancy	<i>n</i> = 963 (41.0%)
Exclusive formula feeding	<i>n</i> = 389 (16.6%)
Low physical activity	<i>n</i> = 918 (39.1%)
High caloric intake	<i>n</i> = 848 (36.1%)
High intake of saturated fatty acids	<i>n</i> = 70 (3.0%)
Low intake of unsaturated fatty acids	<i>n</i> = 1,934 (82.4%)
Low protein intake	<i>n</i> = 126 (5.4%)
High intake of carbohydrates	<i>n</i> = 333 (14.2%)

^aclassified using IOTF cut-off values (26).

with an estimated date of delivery between April 1991 and December 1992 were enrolled, resulting in a cohort of 13,971 children at the age of 1 year. Information about demographic data, lifestyle habits, disease history, etc. was collected using self-administered questionnaires, data extraction from medical notes, and linkage to routine information systems and at research clinics. Dietary data were collected at the age of 7 years with the use of 3-day unweighed diet diaries (18). Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and Local Research Ethics Committees.

Outcome and Explanatory Variables

Childhood height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, at dedicated ALSPAC Focus clinics by a trained research team. Fat mass was assessed at the 9-year visit using whole body dual energy X-ray absorptiometry (DXA) measurements (Prodigy scanner, Lunar Radiation Corp, Madison, Wisconsin, US). A fat mass index (FMI) was calculated for each child by dividing fat mass (kg) by height squared (m²).

In accordance with our previous studies (8,10), we calculated an "obesity-risk-allele score" by counting the total number of obesity risk alleles across the following eight genetic variants with known associations with BMI in children (3-6): rs9939609 (in/near to FTO), rs17782313 (MC4R), rs6548238 (TMEM18), rs10938397 (GNPDA2), rs368794 (KCTD15), rs2568958 (NEGR1), rs925946 (BDNF) and rs7647305 (ETV5). In doing so only individuals with complete genotype data at all eight variants were included in the analyses and only one variant at each locus was chosen (10).

We selected environmental variables if they had shown a distribution dependent effect on children's BMI (19,20) or by a priori considerations. These were dichotomized in order to compare FMI distributions in exposed and non-exposed children. Maternal smoking during pregnancy and exclusive formula feeding are

established priming factors for childhood overweight (19,20). As factors associated with life-style, we chose low physical activity (defined as child goes to special classes or clubs for some activity (e.g., dancing, judo, sports) less than once a week), high TV consumption (defined as more than 2 hours per day), both at the age of 9 years, and low parental education (i.e., neither father nor mother achieved O-level). Maternal overweight defined as a BMI of at least 25 kg/m² was used as a proxy for both environmental and unknown genetic risk factors. Finally, we defined the following nutritional factors extracted from the 7-year food dietary records and dichotomized them as suggested by the Institute of Medicine in 2005 (21): high caloric intake (> 1 700 kcal / day in females; > 1 900 kcal / day in males), low intake of protein (< 10% of daily caloric intake), high intake of carbohydrates (> 60% of daily caloric intake), high intake of saturated fatty acids (> 20% of daily caloric intake) and low intake of mono- and polyunsaturated fatty acids (< 20% of daily caloric intake).

Our analyses were restricted to white European children. In addition to all singletons, we included one randomly selected child from each mother with more than one child in the study (*n* = 7,146 children) in order to avoid potential intercorrelation in close family members. Full information on FMI at the age of 9 years was available from *n* = 4,616 children, whereas *n* = 2 346 children had full information on all environmental variables (see Table 1).

Statistical Analysis

Quantile regression is a statistical technique which has been applied in a wide research area (22-25). While traditional mean regression estimates the conditional mean of the outcome distribution, quantile regression estimates the conditional quantiles, i.e., sample percentiles, e.g., the 0.9 quantile / 90th percentile. In case of a binary risk factor, the quantile regression coefficient represents the difference of the particular conditional percentile in the estimated outcome distribution, e.g., FMI, in subjects that are exposed or not exposed, whereas all other explanatory variables remain constant. Thus, quantile regression gives a more complete picture of the response distribution than mean regression. Since it does not rely on distributional assumptions, it is even more adequate than mean regression when the outcome distribution is skewed, as in our case for FMI.

We calculated quantile regression models with the 3rd, 10th, 20th, ..., 90th and 97th percentiles of FMI as outcomes and the obesity-risk-allele score, maternal smoking during pregnancy, formula feeding, low physical activity, high TV consumption and low parental education as explanatory variables. We did not include the nutritional variables in these models, as these were not independent from each other (since the proportions of daily caloric intake were expected to sum up to 100% for each observation). These variables were assessed separately in additional models considering the other environmental factors as potential confounders. Bootstrap methods were used to calculate 95% confidence intervals (CIs) for the quantile regression effect estimates. We adjusted all models for sex, age, and height at the age of 9 years. If a specific predictor showed a distribution-dependent association with FMI, we additionally calculated separate models that included an interaction term between the obesity-risk-allele score and this factor adjusted for the other potential predictors. Thereby, an effect of the risk allele score was estimated separately for each level of the binary risk factors. If a significant interaction between the obesity-risk-allele-score and a specific risk factor was found, and if the risk factor was significant at

TABLE 2 Regression coefficients (± 1.96 S.E. values) of risk factors as estimated by quantile regression at specific percentiles p^a

Risk factor	3p	10p	30p	50p	70p	90p	97p
Obesity-risk-allele-score	0.04 (± 0.02)	0.03 (± 0.02)	0.09 (± 0.02)	0.13 (± 0.02)	0.23 (± 0.03)	0.30 (± 0.06)	0.32 (± 0.07)
Maternal BMI > 25	0.22 (± 0.09)	0.46 (± 0.13)	0.74 (± 0.10)	0.99 (± 0.15)	1.53 (± 0.22)	2.46 (± 0.39)	2.17 (± 0.33)
High TV consumption	0.19 (± 0.07)	0.19 (± 0.07)	0.21 (± 0.08)	0.30 (± 0.10)	0.30 (± 0.13)	0.62 (± 0.24)	0.72 (± 0.32)
Smoking during pregnancy	0.10 (± 0.07)	0.09 (± 0.07)	0.21 (± 0.06)	0.29 (± 0.09)	0.21 (± 0.12)	0.23 (± 0.24)	0.20 (± 0.30)
Formula feeding	0.04 (± 0.13)	0.22 (± 0.08)	0.25 (± 0.08)	0.24 (± 0.13)	0.33 (± 0.18)	0.17 (± 0.25)	0.07 (± 0.35)
Low physical activity	0.04 (± 0.07)	-0.03 (± 0.07)	0.08 (± 0.07)	0.03 (± 0.09)	-0.04 (± 0.12)	-0.02 (± 0.22)	0.13 (± 0.29)
Low parental education	-0.01 (± 0.06)	-0.09 (± 0.06)	-0.01 (± 0.07)	0.03 (± 0.10)	0.15 (± 0.13)	0.26 (± 0.22)	0.35 (± 0.29)

^aAll coefficients were adjusted for each other and for age, height and sex.

the 90th percentile, we stratified our analyses by exposure to this factor.

All calculations were carried out with the statistical software R 2.14.2 (<http://cran.r-project.org>), using the *quantreg* package.

Results

The analyzed children had a mean FMI of 4.1 kg/m² and a median FMI of 3.6 kg/m² at the age of 9 years, whereas the distribution was right-skewed (Table 1). The prevalence of overweight (including obesity) according to International Obesity Task Force (IOTF) criteria (26) based on BMI was 18.2%.

In the first model without interactions, increasing effect sizes by FMI percentile were found with respect to the obesity-risk-allele-score, maternal overweight, high TV consumption, maternal smoking during pregnancy, low parental education and low protein intake as well as decreasing effect sizes for low intake of unsaturated fatty acids (Table 2 and 3). For example, the estimated regression coefficients of maternal overweight were 0.46 (95% CI: 0.33; 0.59) at the 10th percentile, 0.99 (0.84; 1.14) at the median, and 2.46 (2.07; 2.85) at the 90th percentile.

Interaction with the Obesity-risk-allele-score

In the second model, there was no evidence for interactions between the obesity-risk-allele score and the environmental variables except for

maternal overweight at the 90th percentile of FMI (data not shown). Stratified analyses suggested that exposition to maternal overweight increased the effect of the genetic factors in the upper FMI percentiles, but not in the lower parts of the distribution (Figure 1).

With respect to the nutritional factors, the only significant interaction with the obesity-risk-allele-score was found with respect to intake of mono- and polyunsaturated fatty acids. In children with low intake, genetic risk was associated with continuously increasing effect sizes by FMI percentile, while in non-exposed children no such pattern occurred (Figure 2).

Discussion

We found no evidence for a potential interaction of genetic disposition for overweight with a number of established environmental risk factors such as high TV consumption, low physical activity, maternal smoking during pregnancy, formula feeding or low parental education as well as for high caloric intake, high intake of saturated fatty acids, low protein intake or high intake of carbohydrates. However, there was a weak interaction with maternal overweight and a clear interaction with intake of unsaturated fatty acids.

The interaction of genetic disposition with unsaturated fatty acids is particularly interesting. We were able to demonstrate that the effect of genetic disposition was weight status dependent in children with low intake of unsaturated fatty acids, while there was virtually no

TABLE 3 Regression coefficients (± 1.96 S.E. values) of risk factors as estimated by quantile regression at specific percentiles p^a

Risk factor	3p	10p	30p	50p	70p	90p	97p
High caloric intake	0.13 (± 0.07)	0.15 (± 0.07)	0.09 (± 0.07)	0.21 (± 0.11)	0.23 (± 0.13)	0.03 (± 0.23)	0.04 (± 0.32)
High intake of saturated fatty acids	0.40 (± 0.18)	0.27 (± 0.11)	0.01 (± 0.17)	-0.18 (± 0.38)	0.35 (± 0.39)	-0.20 (± 0.69)	1.52 (± 1.22)
Low intake of unsaturated fatty acids	0.02 (± 0.10)	-0.02 (± 0.09)	-0.09 (± 0.10)	-0.16 (± 0.13)	-0.37 (± 0.20)	-0.61 (± 0.27)	-0.59 (± 0.39)
Low protein intake	-0.07 (± 0.09)	-0.18 (± 0.14)	0.02 (± 0.17)	0.20 (± 0.24)	0.48 (± 0.28)	0.38 (± 0.46)	0.51 (± 0.48)
High intake of carbohydrates	-0.07 (± 0.08)	-0.13 (± 0.10)	-0.08 (± 0.07)	-0.33 (± 0.10)	-0.17 (± 0.20)	-0.23 (± 0.29)	-0.19 (± 0.51)

^aThe effect of each nutrition factor was estimated separately and adjusted for the obesity-risk-allele score, environmental factors, age, height and sex.

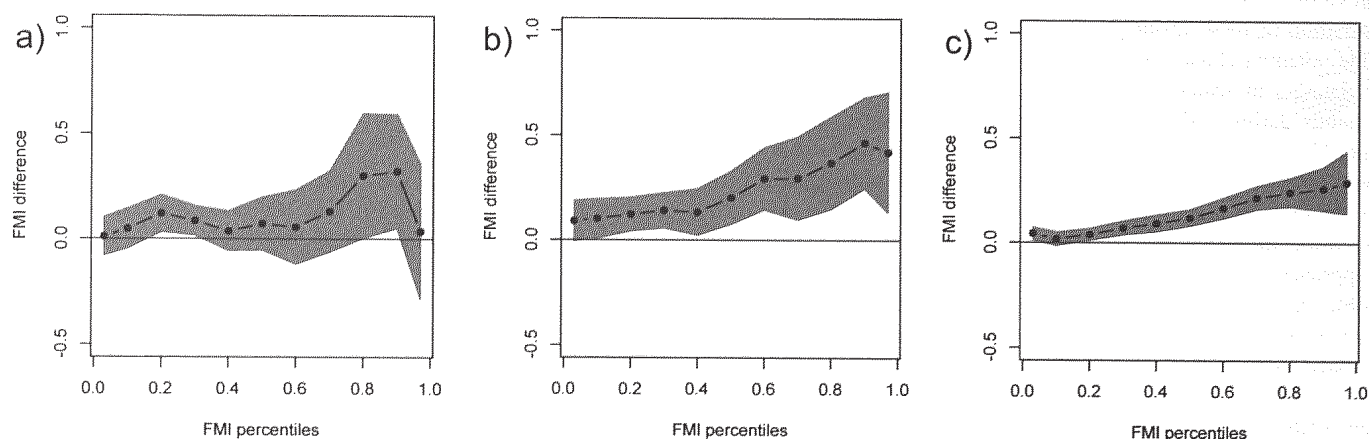


FIGURE 1 Point estimates and 95% confidence bounds (grey areas) for increase in fat mass index (FMI) at 9 years per obesity-risk-allele (a) in interaction with maternal overweight, (b) in children of overweight mothers and (c) in children of non-overweight mothers.

effect in children with appropriate intake. This finding might potentially indicate that a genetic disposition for overweight might only have an effect in subjects who have a relatively low intake of unsaturated fatty acids (which might e.g., due to a low proportion of vegetarian food or fish), while an appropriate intake seemed to be protective against the effects of genetic obesity risk factors. Interestingly, this finding would confirm the result of a recent study which showed an interaction between the ratio of polyunsaturated and saturated acids in the diet with the FTO gene (27): A allele carriers with an intake ratio of lower than 0.43 had a higher risk for becoming obese than TT carriers irrespective of their intake ratio. However, this finding was based on a relatively small dataset ($n=354$). With respect to other genetic settings, similar findings had been reported before (28,29).

Our results did not confirm, however, other observational studies reporting interactions between genetic disposition and intake of carbohydrates (30,31), total fat (28,29,32,33), or total energy (34,35). Unfortunately, we were not able to assess whether this was due to

lack of statistical power, as, to our knowledge, no methods exist for power estimation in quantile regression.

Maternal overweight may represent the outcome of the effects of nutrition, life-style and genetic disposition and is therefore likely to be a risk factor for overweight especially in younger children. Therefore, its observed interaction with genetic disposition for overweight may at least partially reflect the effect of polyunsaturated fatty acids mentioned above. An alternative explanation might be that the effects of identified genetic risk factors are modified by other (unknown) obesity risk genes which may also be part of the impact of maternal overweight on offspring's body composition.

The prospective design of the ALSPAC data set constitutes a strength of our analyses because reverse causation is not likely to be an issue. Furthermore, the use of quantile regression enabled us to examine differential effect sizes of explanatory variables and their interactions with respect to FMI in children.

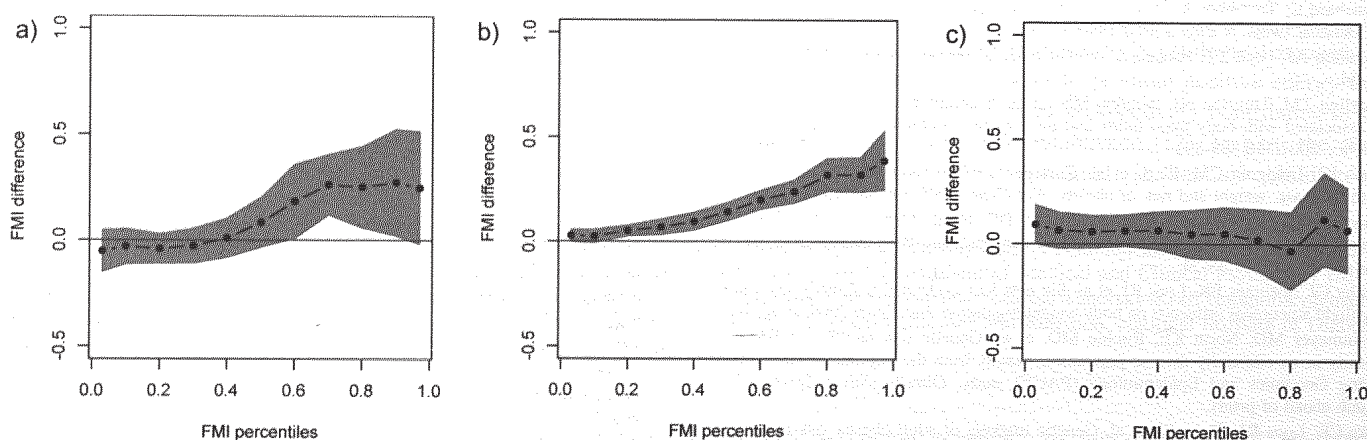


FIGURE 2 Point estimates and 95% confidence bounds (grey areas) for increase in fat mass index (FMI) at 9 years per obesity-risk-allele (a) in interaction with low intake of mono- and polyunsaturated fatty acids, (b) in children with low intake of mono- and polyunsaturated fatty acids and (c) in children with appropriate intake of mono- and polyunsaturated fatty acids.

As previous evidence with respect to our findings is relatively scarce, confirmation of these results in another dataset would be desirable to exclude potential chance findings. Unfortunately, we had no access to other datasets in which both detailed genotyping and assessment of food habits during childhood had been collected. Further, our dataset was not big enough to allow dividing it into a "training" and a "validation" sample. Another potential weakness of our study might constitute in the fact that dietary data were collected at the age of 7 years, while fat mass was measured about 2 years later. However, this approach has been used previously on these data and yielded plausible results (18). Furthermore, there was at least reasonable agreement between general food patterns at the ages of 7 and 9 years, as assessed by food frequency questionnaires (36).

In conclusion, our analyses suggest potential interactions between a diet with a low content of unsaturated fatty acids and genetic risk factors for overweight on FMI. This effect is likely to be stronger in children with higher FMI. Apart from maternal overweight, which might also reflect unknown genetic factors, we found no evidence for interactions of genetic disposition with other environmental or nutritional factors. **O**

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References

- Bouchard C, Tremblay A, Despres JP, et al. The response to long-term overfeeding in identical twins. *N Engl J Med* 1990;322:1477-1482.
- Stunkard AJ, Foch TT, Hrubec Z. A twin study of human obesity. *JAMA* 1986;256:51-54.
- Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007;316:889-894.
- Loos RJ, Lindgren CM, Li S, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat Genet* 2008;40:768-775.
- Thorleifsson G, Walters GB, Gudbjartsson DF, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet* 2009;41:18-24.
- Willer CJ, Speliotes EK, Loos RJ, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* 2009;41:25-34.
- Fesinmeyer MD, North KE, Ritchie MD, et al. Genetic risk factors for BMI and obesity in an ethnically diverse population: results from the Population Architecture Using Genomics and Epidemiology (PAGE) study. *Obesity (Silver Spring)* 2012 [Epub ahead of print].
- Elks CE, Loos RJ, Sharp SJ, et al. Genetic markers of adult obesity risk are associated with greater early infancy weight gain and growth. *PLoS Med* 2010;7:e1000284.
- Peterson RE, Maes HH, Holmans P, et al. Genetic risk sum score comprised of common polygenic variation is associated with body mass index. *Hum Genet* 2011; 129:221-230.
- Beyerlein A, von Kries R, Ness AR, et al. Genetic markers of obesity risk: stronger associations with body composition in overweight compared to normal-weight children. *PLoS One* 2011;6:e19057.
- Reinehr T, Hebebrand J, Friedel S, et al. Lifestyle intervention in obese children with variations in the melanocortin-4 receptor gene. *Obesity (Silver Spring)* 2009;17:382-389.
- Edwards TL, Velez Edwards DR, Villegas R, et al. HTR1B, ADIPOR1, PPARGC1A, and CYP19A1 and obesity in a cohort of Caucasians and African Americans: an evaluation of gene-environment interactions and candidate genes. *American journal of epidemiology* 2012;175:11-21.
- Hiroi M, Nagahara Y, Miyauchi R, et al. The combination of genetic variations in the PRDX3 gene and dietary fat intake contribute to obesity risk. *Obesity (Silver Spring)* 2011;19:882-887.
- Qi Q, Chu AY, Kang JH, et al. Sugar-sweetened beverages and genetic risk of obesity. *N Engl J Med* 2012.
- Beyerlein A, Toschke AM, Schaffrath Rosario A, et al. Risk factors for obesity: further evidence for stronger effects on overweight children and adolescents compared to normal-weight subjects. *PLoS One* 2011;6:e15739.
- Beyerlein A, Toschke AM, von Kries R. Risk factors for childhood overweight: shift of the mean body mass index and shift of the upper percentiles: results from a cross-sectional study. *Int J Obes (Lond)* 2010;34:642-648.
- Golding J. The Avon Longitudinal Study of Parents and Children (ALSPAC) - study design and collaborative opportunities. *Eur J Endocrinol* 2004;151(Suppl 3): U119-U123.
- Johnson L, Mander AP, Jones LR, et al. Energy-dense, low-fiber, high-fat dietary pattern is associated with increased fatness in childhood. *Am J Clin Nutr* 2008;87: 846-854.
- Beyerlein A, Toschke AM, von Kries R. Breastfeeding and childhood obesity: shift of the entire BMI distribution or only the upper parts? *Obesity (Silver Spring)* 2008; 16:2730-2733.
- Beyerlein A, Ruckinger S, Toschke AM, et al. Is low birth weight in the causal pathway of the association between maternal smoking in pregnancy and higher BMI in the offspring? *Eur J Epidemiol* 2011;26:413-420.
- Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. The National Academies Press: Washington, D.C.; 2005.
- Koenker R. *Quantile Regression*. 1st ed. New York: Cambridge University Press; 2005.
- Cade BS, Noon BR. A gentle introduction to quantile regression for ecologists. *Front Ecol Environ* 2003;1:412-420.
- Koenker R, Hallock KF. Quantile regression. *J Econ Perspec* 2001;15:143-156.
- Redden DT, Fernandez JR, Allison DB. A simple significance test for quantile regression. *Stat Med* 2004;23:2587-2597.
- Cole TJ, Bellizzi MC, Flegal KM, et al. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000;320:1240-1243.
- Moleres A, Ochoa MC, Rendo-Uribeaga T, et al. Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case-control study of children. *Br J Nutr* 2012; 107:533-538.
- Luan J, Browne PO, Harding AH, et al. Evidence for gene-nutrient interaction at the PPARGgamma locus. *Diabetes* 2001;50:686-689.
- Memisoglu A, Hu FB, Hankinson SE, et al. Interaction between a peroxisome proliferator-activated receptor gamma gene polymorphism and dietary fat intake in relation to body mass. *Hum Mol Genet* 2003;12:2923-2929.
- Ochoa MC, Marti A, Azcona C, et al. Gene-gene interaction between PPAR gamma 2 and ADR beta 3 increases obesity risk in children and adolescents. *Int J Obes Relat Metab Disord* 2004;28(Suppl 3):S37-S41.
- Martinez JA, Corbalan MS, Sanchez-Villegas A, et al. Obesity risk is associated with carbohydrate intake in women carrying the Gln27Glu beta2-adrenoceptor polymorphism. *J Nutr* 2003;133:2549-2554.
- Robitaille J, Brouillette C, Houde A, et al. Association between the PPARGalpha-L162V polymorphism and components of the metabolic syndrome. *J Hum Genet* 2004;49:482-489.
- Robitaille J, Despres JP, Perusse L, et al. The PPAR-gamma P12A polymorphism modulates the relationship between dietary fat intake and components of the metabolic syndrome: results from the Quebec Family Study. *Clin Genet* 2003;63:109-116.
- Miyaki K, Sutani S, Kikuchi H, et al. Increased risk of obesity resulting from the interaction between high energy intake and the Trp64Arg polymorphism of the beta3-adrenergic receptor gene in healthy Japanese men. *J Epidemiol* 2005;15: 203-210.
- Song Y, Miyaki K, Araki J, Zhang L, Omai K, Muramatsu M. The interaction between the interleukin 6 receptor gene genotype and dietary energy intake on abdominal obesity in Japanese men. *Metabolism* 2007;56:925-930.
- Northstone K, Emmett PM. Are dietary patterns stable throughout early and mid-childhood? A birth cohort study. *Br J Nutr* 2008;100:1069-1076.