Interactions of genetic and environmental risk factors with respect to body fat mass in children: Results from the ALSPAC study

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Abbreviations: BMI- body mass index

ALSPAC-Avon Longitudinal Study of Parents and Children

GWA-genome-wide association

DXA-dual energy X-ray absorptiometry

FMI-fat mass index

CI-confidence interval

Abstract:

Background: Genetic risk factors for childhood obesity were found to have greater effects on children with a higher body fat mass. Similarly environmental and lifestyle risk factors for childhood obesity were found to have a stronger effect at high body mass index (BMI) percentiles. We hypothesized that these findings might reflect gene-environment interactions with respect to the development of overweight.

Methods: We analysed 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 clear 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. 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.

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) 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). We calculated fat mass index (FMI) for each child from DXA measurements at age 9 y by dividing fat mass (kg) by height squared (m^2).

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

115 complete genotype data at all eight variants were included in the analyses and only one
116 variant at each locus was chosen.

117 We selected environmental variables if they had shown a distribution dependent effect on
118 children's BMI [19, 20] or by a priori considerations. These were dichotomized in order to
119 compare FMI distributions in exposed and non-exposed children. Maternal smoking during
120 pregnancy and exclusive formula feeding are established priming factors for childhood
121 overweight [19, 20]. As factors associated with life-style, we chose low physical activity (defined
122 as child goes to special classes or clubs for some activity (e.g. dancing, judo, sports) less than
123 once a week), high TV consumption (defined as more than 2 hours per day), both at the age
124 of 9 y, and low parental education (i.e. neither father nor mother achieved O-level). Maternal
125 overweight defined as a BMI of at least 25 kg/m² was used as a proxy for both environmental
126 and unknown genetic risk factors. Finally, we defined the following nutritional factors
127 extracted from the 7-year food dietary records and dichotomized them as suggested by the
128 Institute of Medicine in 2005 [21]: high caloric intake (> 1 700 kcal / day in females; > 1 900
129 kcal / day in males), low intake of protein (< 10% of daily caloric intake), high intake of
130 carbohydrates (> 60% of daily caloric intake), high intake of saturated fatty acids (> 20% of
131 daily caloric intake) and low intake of mono- and polyunsaturated fatty acids (< 20% of daily
132 caloric intake).

133 Our analyses were restricted to white European children. In addition to all singletons, we
134 included one randomly selected child from each mother with more than one child in the study
135 (n = 7 146 children) in order to avoid potential intercorrelation in close family members. In
136 total, the dataset contained n = 4 616 observations with full information on FMI at the age of
137 9 y, of which n = 2 346 contained full information on all environmental variables (see **Table**
138 **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 3^{rd}, 10^{th}, 20^{th}, …, 90^{th} and 97^{th} 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 y. 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 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 children analyzed had a mean FMI of 4.1 kg/m² and a median FMI of 3.6 kg/m² at 9 years of age, whereby the distribution was right-skewed (**Table 1**). The prevalence of overweight (including obesity) according to 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 2,3).** For example, the estimated regression coefficients of maternal overweight were 0.46 [95% CI: 0.33; 0.59] at the 10^{th} percentile, 0.99 [0.84; 1.14] at the median, and 2.46 [2.07; 2.85] at the 90^{th} 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 90^{th} 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 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.

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 diet diary data allowing for detailed assessment of caloric intake etc. were collected at the age of 7 years, while fat mass was measured about two 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.

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The authors' responsibilities were as follows: AB developed the study hypothesis, performed data management and contributed to the first and final draft of the paper together with RvK. CR was responsible for statistical analyses and contributed to the first and final draft. ARN contributed to the final draft of the manuscript. NF contributed to the interpretation of the results and to subsequent drafts of the manuscript. KS made suggestions with respect to data analysis and variable selection.

Ethics approval

This study was conducted with the approval of the ALSPAC Ethics and Law Committee.

Competing interests

None of the authors had a conflict of interest.

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

Variable	**Mean (SD) / n (%)**
Fat mass index [kg/m²]	4.1 (2.2)
Overweight children *	n = 428 (18.2 %)
Obese children *	n = 83 (3.5 %)
Age [years]	9.8 (0.3)
Sex (female)	n = 1,146 (48.8 %)
Maternal overweight	n = 448 (19.1 %)
High TV consumption	n = 781 (33.3 %)
Low parental education	n = 1,016 (43.3 %)
Maternal smoking during pregnancy	n = 963 (41.0 %)
Exclusive formula feeding	n = 389 (16.6 %)
Low physical activity	n = 918 (39.1 %)
High caloric intake	n = 848 (36.1 %)
High intake of saturated fatty acids	n = 70 (3.0 %)
Low intake of unsaturated fatty acids	n = 1,934 (82.4 %)
Low protein intake	n = 126 (5.4 %)
High intake of carbohydrates	n = 333 (14.2 %)

* classified using IOTF cut-off values (20)

TABLE 2: Regression coefficients (±1.96 s.e. values) of risk factors as estimated by quantile regression at specific percentiles p. The effects of the factors obesity-risk-allele score and the environmental factors adjusted by age, height and sex were estimated.

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)

TABLE 3: Regression coefficients (±1.96 s.e. values) of risk factors as estimated by quantile regression at specific percentiles p. The effect of each nutrition factor was estimated separately considering the obesity-risk-allele score and the environmental factors adjusted by age, height and sex.

Risk factor	**3p**	**10p**	**30p**	**50p**	**70p**	**90p**	**97p**
high caloric intake	0.12 (± 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)	0.50 (± 0.28)	0.38 (± 0.46)	0.51 (± 0.48)
high intake of carbohydrates	-0.07 (± 0.08)	-0.13 (± 0.10)	-0.09 (± 0.07)	-0.33 (± 0.10)	-0.17 (± 0.20)	-0.22 (± 0.29)	-0.19 (± 0.51)

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.

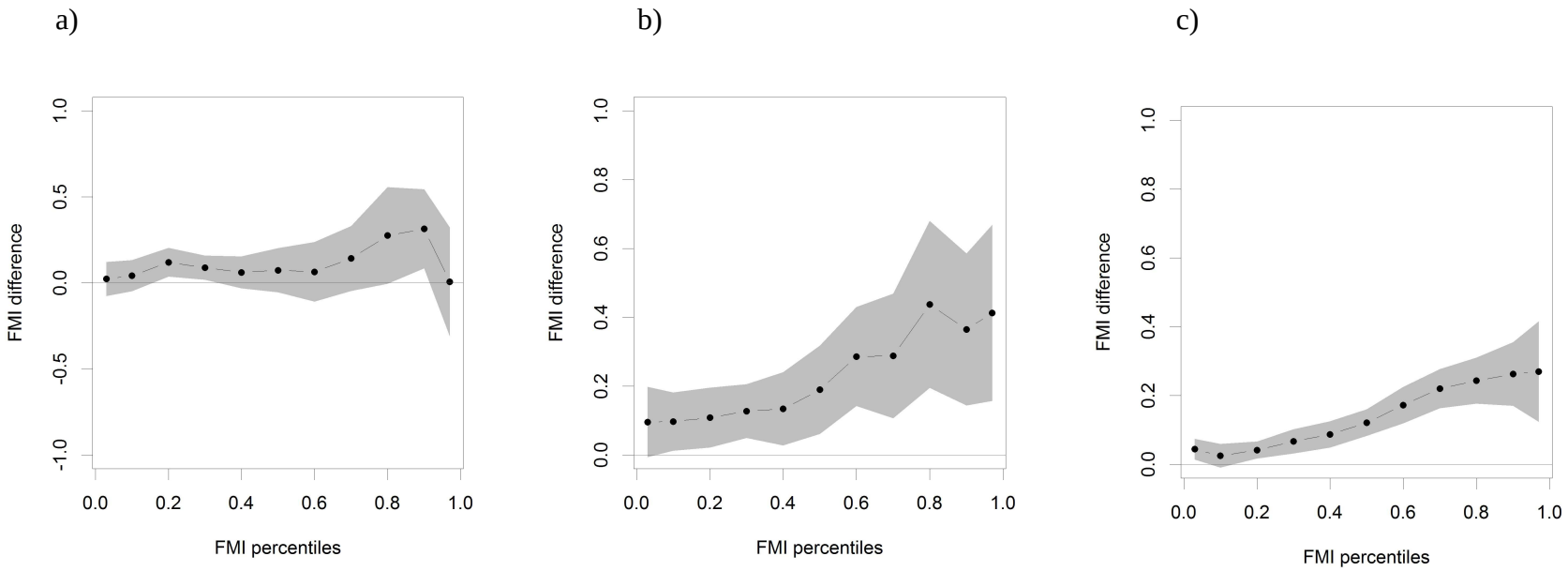

FIGURE 2: Point estimates and 95% confidence bounds (grey areas) for increase in fat mass index (FMI) at 9 years per obesity-risk-allele a) in interaction with low intake of mono- and polyunsaturated fatty acids, b) in children with low intake of mono- and polyunsaturated fatty acids and c) in children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