

ORIGINAL ARTICLE

Influence of maternal educational level on the association between the rs3809508 neuromedin B gene polymorphism and the risk of obesity in the HELENA study

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Objective: Neuromedin B (NMB) is a bombesin-like peptide, which inhibits food intake and modulates stress-related behaviour. An NMB gene polymorphism (P73T) has been earlier associated with obesity and abnormal eating behaviour in adults.

Methods: The association between four NMB polymorphisms and obesity-related phenotypes was investigated in the Healthy Lifestyle in Europe by Nutrition in Adolescence cross-sectional study ($n=1144$, 12–17-year-old European adolescents). This population was genotyped for the NMB rs1107179, rs17598561, rs3809508 and rs1051168 (P73T) polymorphisms. Obesity was defined according to Cole *et al.* (BMJ 2000; **320**: 1240–1243) criteria; eating behaviour was assessed by the Eating Behaviour and Weight Problems Inventory for Children (EWI-C) and the food choices and preferences questionnaires. Familial socioeconomic status (SES) was assessed through the parents' educational level.

Results: Only the genotype distribution of rs3809508 differed according to obesity status, as the TT genotype was more frequent in obese than in non-obese adolescents (8.6% vs 3.1%, $P=0.05$; adjusted odds ratio for obesity (95% confidence interval): 2.85 (1.11–7.31), $P=0.03$). Moreover, TT subjects had higher body mass index ($22.8 \pm 4.4 \text{ kg m}^{-2}$ vs $21.3 \pm 3.7 \text{ kg m}^{-2}$, $P=0.02$), waist circumference ($75.8 \pm 9.7 \text{ cm}$ vs $72.2 \pm 9.3 \text{ cm}$, $P=0.006$), waist-to-hip ratio (0.84 ± 0.14 vs 0.79 ± 0.07 , $P<0.0001$) and waist-to-height ratio (0.47 ± 0.06 vs 0.44 ± 0.55 , $P=0.002$) than C allele carriers. The effects of this single nucleotide polymorphism on all anthropometric values were influenced by the maternal SES, in that a low maternal educational level aggravated the phenotype of adolescents carrying the TT genotype (interactions: $P<0.02$). No association with EWI-C scores was found, although sweet craving was a more frequent cause of between-meal food intake in TT subjects than in C allele carriers (24.3% vs 9.2%, $P=0.01$).

Conclusion: In European adolescents, the TT genotype of the NMB rs3809508 polymorphism was associated with a higher risk of obesity. Moreover, the effects of this polymorphism on anthropometric values were influenced by the maternal educational level.

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Introduction

The prevalence of obesity and overweight in children and adolescents has markedly increased over the past few decades, even if the trends tend to stagnate in some countries, such as the United States,¹ Sweden² and France.³

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This increase is generally explained by the interaction between environmental and societal changes (promoting calorie intake and discouraging physical activity) and genetic susceptibility.⁴ In terms of environmental factors, associations between social factors and body weight have been extensively reported; unhealthy habits are seen more frequently in families with a low socioeconomic status (SES).^{5–8} In terms of genetic factors, several genes are associated with higher body weight and most of the attention has been paid to energy expenditure and fat storage as mechanisms underlying the genetic effects.⁹ However, genes could also affect body weight through appetite-related behavioural phenotypes¹⁰ existing great evidences for a genetic influence on the circulating peptides that affect appetite in human beings.¹¹ Several gene–environment interactions involving SES and single nucleotide polymorphisms (SNPs) in candidate genes for adiposity have been already reported in African- and European-American youth.¹²

The aim of this work is to explore neuromedin B (NMB), one of the most powerful anorexic substances acting on the hypothalamus.¹³ NMB is a member of the bombesin-like peptide family, which includes bombesin itself (an amphibian peptide) and its mammalian analogues (gastrin-releasing peptide (GRP) and NMB).^{14–16} These peptides exert their effects by binding to a range of G-protein-coupled receptors with varying affinity (NMB-preferring receptor, GRP-preferring receptor and the orphan receptor, bombesin receptor subtype 3).¹⁷ Bombesin peptides are widely expressed in the pituitary, brain, pancreas, adrenal glands, gastrointestinal tract¹⁷ and adipose tissue.¹⁸ They are initially released from the gastro-intestinal tract in response to food intake¹⁹ and their expression in adipose tissue is regulated by energy balance changes.¹⁸ The peptides have a broad spectrum of biological effects, including smooth muscle contraction and changes in gastro-intestinal motility, the release of gastro-intestinal hormones and neurotransmitters, regulation of circadian rhythm, thermoregulation, anxiety/fear responses and spinal sensory transmission.²⁰ Both NMB and GRP reduce food intake when infused into human subjects.^{21,22} When administered between meals, these peptides increase the amount of time until the next meal begins; that is they increase both satiety and satiation.²³ In particular, NMB has a number of direct and indirect effects on eating behaviour control.²⁴ First, NMB regulates thyrotropin secretion, which stimulates the release of thyroid hormones, known to increase food intake.²⁵ Second, NMB stimulates satiety gut hormones such as peptide YY²⁶ and can block the orexigenic effect of ghrelin.^{27,28} Third, NMB modulates the serotonergic (5-HT) system,²⁹ which has a function in the satiety processes through the melanocortin pathway.³⁰ Taken together, these suggest that NMB may act as a neurocrine bridge between the gut and the brain (and also between adipose tissue and the brain) to further inhibit food intake.²³

The decapeptide NMB is generated from a 121-amino-acid precursor encoded by a gene on chromosome 15q22.3–q23.

This chromosome region contains a gene involved in Bardet–Biedl syndrome type 4 (BBS4),³¹ a rare disease associated with severe obesity and congenital abnormalities.³² Oeffner *et al.*³³ detected in six Bardet–Biedl syndrome type 4 patients two sequence variants in *NMB*—a 253C>A transversion (creating a P73T substitution) and a 401G>A silent mutation at the stop codon. The authors studied these polymorphisms in German children and adolescents and found an association between these SNPs and obese and overweight status.³³ Bouchard *et al.*³⁴ found that *NMB* was a strong candidate gene for a link between eating behaviours and susceptibility to obesity in adults, as the P73T polymorphism was associated with disinhibition, susceptibility to hunger and changes over time in body fat. Hence, *NMB* polymorphisms seem to be associated with changes over time in adiposity by modulating eating patterns, which in turn could suggest an effect influenced by environmental factors.

The aims of the present study were to (i) assess the association between *NMB* polymorphisms and anthropometric parameters in adolescents and (ii) identify potential interactions between *NMB* polymorphisms, socioeconomic factors (such as parental educational level) and adiposity.

Materials and methods

Study subjects

Participants were recruited as part of the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) cross-sectional study (<http://www.helenastudy.com>) performed from 2006 to 2007 in 10 centres in 9 European countries (Athens and Heraklion in Greece, Dortmund in Germany, Ghent in Belgium, Lille in France, Pécs in Hungary, Rome in Italy, Västerås in Sweden, Vienna in Austria and Zaragoza in Spain). The complete description of the design and implementation of the study has been described elsewhere.^{35,36} The protocol was approved by an independent ethic committee in each centre. Written, informed consent was obtained from each subject and both of his/her parents or legal representatives. Complete description of ethical issues and good clinical practice within the HELENA study is described elsewhere.³⁷ Participation in the study was voluntary. The sample included a total of 3865 adolescents (mean \pm standard deviation age: 14.8 \pm 1.4 years) recruited through their schools; the latter were randomly selected according to a proportional cluster sampling methodology, which took account of the geographical distribution, age, private/public school ratio and number of classes per school.

An SES self-questionnaire and a case report form (in which clinical items were assessed during an examination) were recorded for each subject.³⁸ In the SES self-questionnaire, the parents' educational level was defined as one of four levels (elementary, lower secondary, higher secondary or tertiary education).

Anthropometric measurements (including weight, height and waist and hip circumferences) were taken by trained researchers with the participants barefoot and in their underwear. Waist and hip circumferences were measured three times consecutively to the nearest 0.1 cm with a non-elastic tape (the Seca 200 from Seca, Hamburg, Germany). The body mass index (BMI) was calculated; overweight and obesity were defined according to Cole *et al.*³⁹ criteria. The percentage of body fat (%BF) was estimated from skin-fold measurements, according to Slaughter *et al.*⁴⁰ Physical activity over a 1-week period was evaluated using accelerometers (Actigraph MTI, model GT1M, Manufacturing technology Inc., Fort Walton Beach, FL, USA), which are known to be objective measurement devices for assessing daily physical activity.⁴¹

To assess eating behaviour, a validated eating inventory questionnaire was adapted for the study, as described.^{42,43} Briefly, the Eating Behaviour and Weight Problems Inventory for Children (EWI-C) includes 60 items on 10 subscales measuring (1) hunger level and susceptibility to food cues, (2) importance and impact of eating on sense of well-being, (3) eating as a means of coping with emotional stress, (4) concerns about eating and weight, (5) dietary restraint, (6) attitude towards healthful nutrition, (7) attitude towards the obese, (8) pressures to eat from parents, (9) fear of weight gain and (10) figure dissatisfaction. To determine attitudes regarding food choices, a purpose-built food choices and preferences questionnaire was used, which includes three sections: (1) opinions about food choices, preferences, diet and health, (2) choices and preferences of snack foods and drinks and (3) important influences on food choices and preferences.

To investigate clinical biochemistry assays and genetic analyses, one third of the classes were randomly selected for blood collection, yielding a total of 1155 subjects. Blood samples were drawn at school in accordance with a standardized collection protocol (after a 10-h, overnight fast) and were sent to a central laboratory (the Analytical Laboratory at the University of Bonn (IEL), Germany) for subsequent biochemical measurements.⁴⁴ Blood for DNA extraction was collected in EDTA K3 tubes and sent to the Genomic Analysis Laboratory at the Institut Pasteur de Lille in Lille, France. DNA was extracted from white blood cells with the Puregene kit (QIAGEN, Courtaboeuf, France) and stored at -20°C . Data on the BMI was missing for 11 subjects, resulting in a final sample of 1144 subjects.

Genotyping

The HapMap database (chr 15: 82999005–83003166; release 24 November 2008) listed eight SNPs in the *NMB* gene with a minor allele frequency $\geq 5\%$, captured by four SNPs: rs1107179 (exon 3), rs17598561 (exon 3), rs3809508 (intron 2) and rs1051168 (exon 2). Genotyping of these four SNPs was performed on an Illumina system, using GoldenGate technology. The genotyping success rate was 99.9% for all SNPs. The distributions of rs1107179, rs17598561, rs3809508 and rs1051168 did not differ from the values expected for

Hardy–Weinberg equilibrium ($P=0.800$, 0.580 , 0.900 and 0.133 , respectively).

Statistical analyses

Statistical analyses were performed with SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Groups were compared in terms of genotype and allele distributions by using χ^2 tests. The association between the *NMB* polymorphism genotype and the risk of obesity (odds ratio (OR) and 95% confidence intervals) was calculated using logistic regression adjusted for age, gender and centre. Inter-group comparisons of quantitative variables were performed using a general linear model procedure. Reported P -values are nominal and were systematically adjusted for confounding variables (including age, gender and centre for anthropometric variables). Interaction between polymorphism and parental educational level for anthropometric variables was tested with a general linear model adjusted for age, gender and centre. When stratifying on maternal educational level groups, as the number of subjects was low in one of the groups, we first performed a rank transformation as described by Conover and Iman⁴⁵ and then used a general linear model procedure adjusted for age, gender and centre. To compare allele distributions and reasons for snacking, logistic regression adjusted for age, gender and centre was used. The threshold for statistical significance was set to $P \leq 0.05$. Power calculations were performed using Quanto v1.1.1.⁴⁶

Results

Association between NMB polymorphisms and the risk of obesity

In the HELENA study ($n=1144$), the frequencies of the rs1107179, rs17598561, rs3809508 and rs1051168 (P73T) minor alleles were 0.47, 0.06, 0.18 and 0.28, respectively. We compared the genotype distribution of these four polymorphisms in underweight ($n=66$), normal weight ($n=813$), overweight ($n=195$) and obese ($n=70$) individuals (Table 1). The genotype distributions of rs1107179, rs17598561 and rs1051168 were similar in all four BMI groups ($P \geq 0.19$), whereas that of rs3809508 differed significantly ($P=0.05$). Subjects carrying the TT genotype presented a higher risk of obesity (adjusted OR (95% confidence interval) = 2.85 (1.11–7.31), $P=0.03$) than C allele carriers. Further adjustment for physical activity level or Tanner stage did not alter the associations (data not shown).

Association between the NMB rs3809508 polymorphism and clinical variables

To better understand the observed association between the rs3809508 polymorphism and the risk of obesity, the

association between this polymorphism and anthropometric variables was first evaluated (Table 2). Significant associations between this polymorphism and BMI, waist circumference, waist-to-hip ratio and waist-to-height ratio were detected. Indeed, TT subjects had a higher BMI ($P=0.02$), higher waist circumference ($P=0.006$), higher waist-to-hip ratio ($P<0.0001$) and higher waist-to-height ratio ($P=0.002$) compared with CT+CC subjects (Table 2). Further adjustment for physical activity level or Tanner stage did not alter these associations (data not shown).

Exploring eating attitudes as a function of rs3809508 genotype, significant association between genotype groups

Table 1 Genotype distribution of NMB polymorphisms in underweight, normal weight, overweight or obese subjects in the HELENA study

	rs3809508			P
	CC (n=764)	CT (n=341)	TT (n=39)	
Underweight (n=66)	51 (0.77)	14 (0.21)	1 (0.02)	0.05
Normal weight (n=813)	534 (0.66)	256 (0.31)	23 (0.03)	
Overweight (n=195)	135 (0.69)	51 (0.26)	9 (0.05)	
Obese (n=70)	44 (0.62)	20 (0.29)	6 (0.09)	
	rs1107179			P
	AA (n=322)	AC (n=578)	CC (n=251)	
Underweight (n=66)	16 (0.24)	36 (0.55)	14 (0.21)	0.99
Normal weight (n=813)	229 (0.28)	409 (0.50)	175 (0.22)	
Overweight (n=195)	55 (0.28)	96 (0.49)	44 (0.23)	
Obese (n=70)	21 (0.30)	13 (0.47)	16 (0.23)	
	rs17598561			P
	GG (n=1010)	GA (n=130)	AA (n=3)	
Underweight (n=66)	63 (0.95)	3 (0.05)	0 (0.00)	0.19
Normal weight (n=812)	712 (0.88)	99 (0.12)	1 (0.001)	
Overweight (n=195)	173 (0.89)	21 (0.11)	1 (0.005)	
Obese (n=70)	62 (0.89)	7 (0.10)	1 (0.01)	
	rs1051168 (P73T)			P
	CC (n=600)	CA (n=442)	AA (n=101)	
Underweight (n=66)	29 (0.44)	27 (0.41)	10 (0.15)	0.24
Normal weight (n=813)	436 (0.53)	306 (0.38)	71 (0.09)	
Overweight (n=195)	94 (0.48)	85 (0.44)	16 (0.08)	
Obese (n=69)	41 (0.59)	24 (0.35)	4 (0.06)	

Data are n (frequency).

Table 2 Association between NMB rs3809508 and anthropometric variables in the HELENA study

	CC (n=764)	CT (n=341)	TT (n=39)	P	P (TT vs CT+CC)
BMI (kg m ⁻²)	21.3 ± 3.8	21.3 ± 3.5	22.8 ± 4.4	0.07	0.02
Body fat (%)	23.9 ± 9.9	23.1 ± 9.1	27.6 ± 11.2	0.04	0.11
Waist circumference (cm)	72.2 ± 9.5	72.3 ± 8.9	75.8 ± 9.7	0.02	0.006
Waist/hip ratio	0.79 ± 0.07	0.79 ± 0.06	0.84 ± 0.14	< 0.0001	< 0.0001
Waist/height ratio	0.44 ± 0.06	0.44 ± 0.05	0.47 ± 0.06	0.007	0.002

Data are means ± s.d. P-values are adjusted for age, gender and centre.

and the EWI-C subscale scores was not found (data not shown). However, when analysing the main reasons for between-meal snacking (assessed by the question 'What would you say is your main reason for snacking?') as a function of rs3809508 genotype, it was observed that 'sweet cravings' was more frequently cited by TT subjects than by CT+CC subjects ($P=0.01$) (Table 3).

Interaction between parental SES and NMB rs3809508 polymorphism on anthropometric traits

The possible influence of parental SES status (as assessed by the mother's and father's respective educational levels) on the association between rs3809508 and adiposity was investigated. We searched for an interaction between maternal and paternal educational level and the rs3809508 polymorphism with regard to BMI, %BF, waist circumference, waist-to-hip ratio and waist-to-height ratio. No significant interaction with the paternal educational level was found, whereas significant interactions between the maternal educational level, rs3809508 and all anthropometric variables were detected (all $P<0.05$; Table 4). When the sample was stratified according to the maternal educational level, there were 102, 273, 356 and 351 adolescents whose mother had an elementary, lower secondary, higher secondary and tertiary educational level, respectively (Figure 1). The association between the rs3809508 and anthropometric variables remained significant only for the lowest educational level. The mean of all anthropometric variables was much higher for TT subjects whose mother had an elementary educational level, than for those carrying the C allele (all $P<0.05$). But these differences were not observed in subjects whose mother had a higher educational level.

Discussion

This study reports for the first time an association between the NMB rs3809508 polymorphism and obesity risk (OR=2.85) in adolescents. The OR for obesity associated with rs3809508 is higher than the ones detected by genome wide association studies (GWAS) in children and adolescents for the established *FTO* (OR~1.30) or *MC4R* (OR ~1.20) polymorphisms. These GWAS on extreme obesity have not

Table 3 Main reasons for snacking according to genotype of NMB rs3809508 in the HELENA study

	CC (n = 647)	CT (n = 286)	TT (n = 37)	P (TT vs CT+CC)
Craving something salty	29 (0.04)	12 (0.04)	4 (0.11)	0.07
Craving something sweet	65 (0.10)	24 (0.08)	9 (0.24)	0.01
Socializing with friends	12 (0.02)	9 (0.03)	1 (0.03)	0.82
Feeling alone	2 (0.01)	0	0	0.97
Feeling bored	60 (0.09)	28 (0.10)	2 (0.05)	0.42
Feeling happy	12 (0.02)	5 (0.02)	0	0.98
Feeling hungry	283 (0.43)	121 (0.41)	14 (0.38)	0.98
Feeling sad	11 (0.02)	8 (0.03)	0	0.97
Feeling stressed	8 (0.01)	8 (0.03)	2 (0.05)	0.19
Feeling tired	6 (0.01)	2 (0.01)	0	0.98
Need some energy	64 (0.10)	27 (0.09)	1 (0.03)	0.19
Miss a meal	17 (0.03)	5 (0.02)	0	0.97
For a treat	18 (0.03)	9 (0.03)	2 (0.05)	0.57
Out of habit	31 (0.05)	12 (0.04)	0	0.97
Other reason	12 (0.02)	10 (0.03)	2 (0.05)	0.32
Not snack	29 (0.04)	14 (0.05)	0	0.97

Data are n (frequency). P-values are calculated with a logistic regression adjusted for age, gender and center.

Table 4 P-values for the interaction between maternal educational level and NMB rs3809508 in terms of anthropometric variables in the HELENA study

	Maternal educational level	P	P (TT vs CT+CC)
BMI (kg m ⁻²)	Elementary (n = 102)	0.03	0.01
	Lower secondary (n = 273)		
	Higher secondary (n = 356)		
	Tertiary (n = 351)		
Body fat (%)	Elementary (n = 96)	0.07	0.03
	Lower secondary (n = 253)		
	Higher secondary (n = 344)		
	Tertiary (n = 338)		
Waist circumference (cm)	Elementary (n = 101)	0.05	0.02
	Lower secondary (n = 265)		
	Higher secondary (n = 354)		
	Tertiary (n = 349)		
Waist/hip ratio	Elementary (n = 99)	0.007	0.0007
	Lower secondary (n = 261)		
	Higher secondary (n = 354)		
	Tertiary (n = 349)		
Waist/height ratio	Elementary (n = 101)	0.06	0.01
	Lower secondary (n = 265)		
	Higher secondary (n = 354)		
	Tertiary (n = 349)		

P-values are adjusted for age, gender and centre.

linked NMB SNPs to obesity suggesting that NMB variability is not a major determinant of obesity risk.^{47,48} Other reasons may explain the lack of association with NMB. First, it is possible that no NMB SNP was present on the chips or could be imputed from other SNPs. In this study, some NMB SNPs were not associated with obesity so, if the associated haplotype block was not appropriately tagged by genotyping or imputation, the association with obesity could have been missed. Second, the GWAS were performed in children with extreme obesity who may suffer from different genetic defects than adolescents with mild obesity.⁴⁷ Finally, in the GWAS including <700 obese children, the P-value of the association between NMB SNPs and obesity might not reach

the required P-value threshold in GWAS (at least $P < 10^{-7}$), and thus NMB associations could have been missed.

The association between the NMB rs3809508 polymorphism and obesity was reinforced by further relationships with body composition indices. Indeed, the TT genotype was associated with a higher waist circumference (~3 cm), waist-to-hip ratio (~0.05) and higher frequency of sweet cravings as a reason for snacking, in comparison with CT and CC genotypes. The rs3809508 is located in intron 2 and so the T allele may be associated with lower NMB mRNA levels. This polymorphism may modulate the serotonergic response to stress and thus influence eating patterns and food choice. This was shown in an earlier work in which NMBR knockout

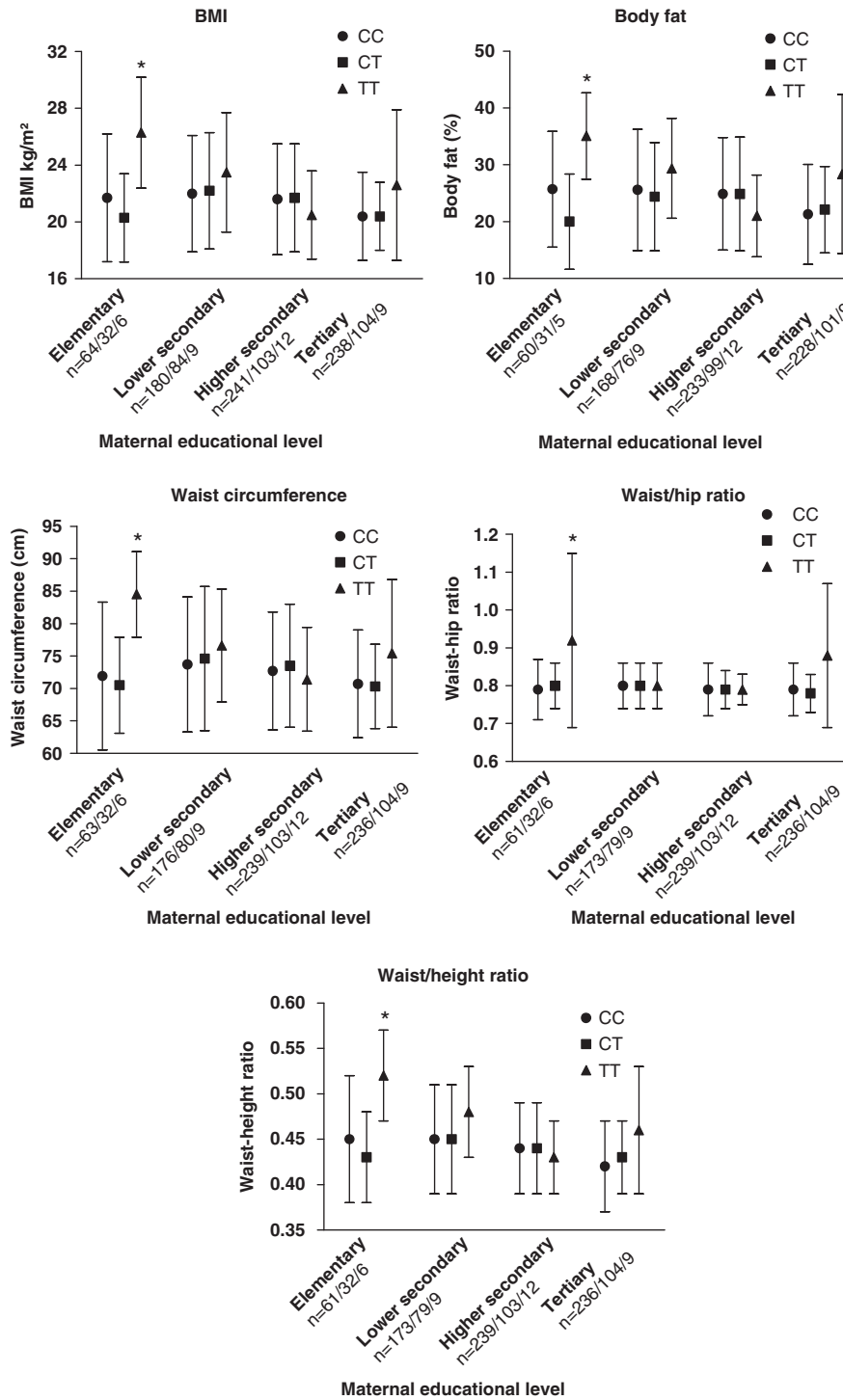


Figure 1 CC, CT and TT subjects are represented by circles, squares and triangles, respectively. Values shown are means and s.d. The NMB × maternal educational level interactions were significant with all *P*-values < 0.05. *Comparison between TT genotype and the other genotype groups for each maternal educational level, *P*-value < 0.05.

mice are not obese, but have elevated neuronal 5-HT expression levels and plasma corticosterone levels (compared with wild-type mice) in response to restraint stress.²⁹

Moreover, stress has an effect on eating behaviour by leading to decreased or increased food intake, which is related to severity and chronic nature of the applied stress.⁴⁹ Chronic

stress elicits a more passive response driven by the hypothalamus–pituitary–adrenal axis, with increased cortisol secretion,⁵⁰ increasing food intake through neuropeptide-Y secretion and augmenting abdominal fat mass through adipose tissue lipoprotein lipase activation.⁵¹ In contrast, increases in cortisol prompt people to consume hedonic, highly palatable foods that are energy dense and potentially contribute to weight gain.⁵²

As eating patterns can be influenced by social factors; we studied the interaction between *NMB* rs3809508 and the familial educational level with respect to anthropometric variables. Interestingly, we found that a low maternal educational level accentuated the association between the SNP and anthropometric values. These data reflect a gene–social environment interaction and suggest that adolescents exposed to an unfavourable environment will develop more severe obesity if they present an unfavourable genetic background. Childhood obesity has been unambiguously linked to lower educational levels and low parental social class,^{53,54} and the influence of social factors can seem very early in life.⁵⁵ Unhealthy habits—such as high-fat diets, low levels of physical activity and exposure to chronic stress—are seen more frequently in families with a low SES.^{5–8} This was also reported by MacFarlane *et al.*⁵⁶ explaining that adolescents with a low SES were more likely to report that they were allowed to watch television during meal times and that unhealthy foods were usually available at home.

In our study, the familial SES was assessed in terms of the parental educational level. Many studies have found a significant inverse association between adiposity and multiple SES indicators. Moreover, these studies revealed that parental education was more consistently inversely associated with adiposity than indicators such as parental occupation or income; this could be explained by the relative stability of parental education levels, whereas parental occupation and income are more liable to change.⁵³ Moreover, in studies that included both maternal and paternal education, the inverse association persisted for the former only, suggesting that mothers have more influence than fathers on the children's behaviour.⁵³ Our results are consistent with these earlier studies. Each SES indicator may influence the development of adiposity through a different mechanism. Education influences knowledge and beliefs, whereas occupation influences lifestyle and shared peer values and income is related to access to resources.⁵⁷ It is possible that knowledge and beliefs are more important for healthy lifestyles than are access to resources or shared values.⁵⁸

In a sample of 660 adults in the Québec Study Family, Bouchard *et al.*³⁴ showed that *NMB* T73T homozygotes had higher %BF and were more disinhibited and susceptible to hunger (as evaluated by the Three-Factor Eating Questionnaire) than P73 allele carriers. Moreover, after an average follow-up period of 6 years, the amount of body fat gain over time in T73T subjects was greater than in P73P homozygotes.³⁴ In the HELENA-CSS study, the association between the rs1051168 (P73T) SNP and %BF was not detected. This

lack of association could be due to a lack of power, as our sample had 80% power to identify effects of at least 3%BF (or 1.2 kg m⁻²) and of 2.8 OR when considering rs1051168 with a recessive model. Spalova *et al.*⁵⁹ found no association between the P73T polymorphism and obesity or overweight in 447 subjects. However, they also showed gender-specific associations of the *NMB* P73T polymorphism with eating behaviour and weight changes over time. In fact, obese or overweight male P73 allele carriers showed a more favourable response to weight management at the follow-up point of 2.5 years, as they exhibited a significant reduction in waist circumference, energy intake and depression score as well as a significant increase in dietary restraint. In contrast to these reported *NMB* association studies in adults, our study was conducted in an adolescent sample. It is known that genetic studies in children and adolescents are less susceptible to confounding, complex environmental factors because of the young age of the subjects.⁶⁰

Conclusion

In European adolescents, the TT genotype of the *NMB* rs3809508 polymorphism was associated with a higher risk of obesity, a higher BMI, waist circumference, waist-to-hip ratio and waist-to-height ratio. Moreover, the effects of this polymorphism on anthropometric parameters were influenced by maternal social status; finding that a low maternal educational level aggravated the anthropometric phenotypes of adolescents carrying the TT genotype.

Conflict of interest

The authors declare no conflict of interest.

Disclaimer

The writing group takes sole responsibility for the content of this article. The content of this paper reflects only the authors' views, and the European Community is not liable for any use that may be made of the information contained therein.

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