Original Article
EPIDEMIOLOGY/GENETICS

Obesity

The Genetic Architecture of Body Mass Index from Infancy to Adulthood Modified by Parental Education

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Objective: A higher prevalence of obesity in lower socioeconomic classes is common in Western societies. This study examined the role of gene–environment interactions in the association between parental education and body mass index (BMI) from infancy to the onset of adulthood.
Methods: Parentally reported BMI from 1 to 13 and self-reported BMI from 14 to 20 years of age were collected in 16,646 complete Dutch twin pairs and analyzed by genetic twin modeling.
Results: At 7 to 8 years of age, children whose parents had middle or low educational levels had more excess weight than the children of more highly educated parents, and the difference increased until 18 to 20 years of age. The major part of the BMI variation was explained by additive genetic factors ($a^2 = 0.55$–0.85), but environmental factors common for co-twins also played a significant role, especially from 3 to 7–8 years of age ($c^2 = 0.15$–0.29). The genetic variation in BMI was higher in children whose parents had middle or low educational levels compared with children whose parents had a high educational level.
Conclusions: The interaction between genetic factors and the childhood social environment may contribute to the formation of socioeconomic differences in obesity.

Obesity (2016) **24**, 2004–2011. doi:10.1002/oby.21588

Introduction

A higher prevalence of obesity in lower social classes is a common finding within Western societies (1,2). Overweight children have an increased risk of developing obesity in adulthood (3), and childhood can thus be an important phase of life for the development of later socioeconomic differences in obesity. Many childhood social factors, such as low parental education, occupational-based social position, low-income family, and deprivation, are associated with a higher risk of adiposity in childhood (4), and these factors are also closely associated with the later social position in adulthood (5). However, the major part of the variation in obesity and body mass index (BMI) is explained by genetic factors in both childhood (6) and adulthood (7). Genetic factors also largely underlie the continuity between BMI in childhood and adulthood (8). This raises the question of whether genetic factors may also contribute to the development of socioeconomic differences in adiposity.

Only a few studies have examined the interaction between socioeconomic and genetic factors in the development of obesity in children and adolescents. A Finnish twin study found that low parental education is associated with a stronger effect on BMI of environmental factors shared by co-twins at 11 to 12 and 14 years of age, but this effect disappeared at 17 years of age (9). Low parental socioeconomic position accentuated the effect of the FTO gene (10), the gene currently found to contribute most to the variance in BMI (11). Furthermore, maternal education limited the effect of the neuromedin B gene on obesity in European children and adolescents (12). The nitric oxide synthase-3 gene was more strongly associated with body fat percentage among those with a low socioeconomic background in a cohort of U.S. adolescents (13). The stronger effect of genes predisposing to obesity in an obesogenic environment is also indicated by twin studies finding that the genetic variation in BMI increased along with an increasing mean BMI in Denmark (14) and Sweden (15).

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Funding agencies: The study was supported by Spinozapremie (NWO/SPI56-464-14192); European Research Council Genetics of Mental Illness (ERC-230374); the Twin-Family Database for Behavior Genetics and Genomics Studies (NWO 480-04-004); a collaborative study of the genetics of DZ twinning (NIH R01 HD042157-01A1); Longitudinal Survey and Panel Funding Application 2008 (NWO-481-08-011); NARSAD; Brain & Behavior Research Foundation-18633; Genomics of Developmental Trajectories in Twins (1RC2MH089995-01) and Sport & Exercise: Determinants of Adolescent Exercise Behavior (NIH-1R01DK092127-01); Genetic and Family Influences on Adolescent Psychopathology and Wellness (NWO 463-06-001); A Twin-Sib Study of Adolescent Wellness (NWO VENI 451- 04-034); The Interplay of Genetic and Environmental Factors in the Development of Anxious Depression in Children and Adults (NWO-VENI grant 916-76-125); Genetic Influences on Stability and Change in Psychopathology From Childhood to Young Adulthood (ZonMW 912-10-020); ZonMW (31160008): Genetic determinants of risk behavior in relation to alcohol use and alcohol use disorder. KS was supported by the Academy of Finland (grant #266592).
Disclosure: The authors declared no conflict of interest.
Author contributions: CB, MB, GW and DB collected the data. KS conducted the analyses and wrote the first draft of the manuscript. CH helped in statistical analyses. All authors have commented on the manuscript and read and approved the final version.
Received: 17 March 2016; **Accepted:** 31 May 2016; **Published online 30 July 2016. doi:10.1002/oby.21588**

TABLE 1 Number of complete twin pairs and within-pair correlations of BMI by age, zygosity, and sex

	Male MZ		Male DZ		Female MZ		Female DZ		Opposite-sex DZ	
	N	*r*	*N*	*r*	*N*	*r*	*N*	*r*	*N*	*r*
Age 1	1,717	0.83	1,948	0.47	1,948	0.83	1,801	0.49	3,624	0.43
Age 2	1,324	0.82	1,466	0.47	1,419	0.82	1,285	0.51	2,749	0.45
Age 3	1,176	0.81	1,338	0.50	1,394	0.84	1,270	0.49	2,574	0.47
Age 5	660	0.84	660	0.57	794	0.88	645	0.55	1,353	0.52
Age 7–8	1,220	0.86	1,434	0.57	1,247	0.88	1,159	0.55	2,337	0.52
Age 9–11	1,045	0.88	1,026	0.51	1,228	0.88	932	0.49	2,018	0.46
Age 12–13	921	0.88	856	0.54	1,038	0.89	820	0.54	1,657	0.46
Age 14–15	393	0.75	374	0.46	600	0.80	443	0.45	819	0.34
Age 16–17	314	0.76	271	0.46	445	0.80	332	0.43	456	0.22
Age 18–20	189	0.79	187	0.52	380	0.83	290	0.50	311	0.17

A limitation of these previous studies is that they started in early adolescence and did not cover the whole period from early childhood until the onset of adulthood. The results of twin studies, however, have suggested an increasing genetic variance after mid-childhood (6,16). This is in line with findings in molecular genetic studies that the effects of the FTO gene and other obesity candidate genes on BMI increase after 6 years of age (17-20). Therefore, in this study, we examined how parental education modifies the genetic architecture of BMI from infancy to the onset of adulthood in a large data set of Dutch twins, allowing the decomposition of variance into genetic and environmental factors. Our hypothesis is that the children of parents with a lower education experience more environmental exposures affecting their BMI. Based on the previous research, we assume that in early adolescence and probably also in childhood this is seen as the higher influence of common environmental factors. When the children grow up, we assume that genetic variation increases more in these children since the environmental exposures accentuate the effect of genes predisposing to obesity.

Methods

Data were derived from the Young Netherlands Twin Register (YNTR) (21). The database was started in 1987 and has been continuously updated. Weight and height between birth date and age 5 were reported by mothers in the data retrieved from a routine health care program in The Netherlands (Youth Health Services). In the surveys collected at the ages of 1, 2, 3, and 5 years, a parent was asked to report weights and heights. In the follow-up surveys at the ages of 7, 9/10, and 12 years, parents reported the current weight and height and the date of assessment. From age 14 onwards, weight and height were self-reported by the twins. BMI was calculated by dividing weight in kilograms by squared height in meters (kg/m^2). Zygosity classification in same-sex twin pairs was based on blood typing or DNA polymorphisms (15%) or on parental responses to validated questions of physical similarity and the substitution of one co-twin for another by relatives and nonrelatives (85%). The agreement between survey report and blood/DNA classification was found to be 93% in 618 same-sex twin pairs at 6 years of age and 97% in 869 adult same-sex twin pairs (22,23). In total, we had BMI measurements on 117,170 occasions from 33,338 twin individuals, including 16,646 complete twin pairs [33% monozygotic (MZ) twins, 50% female]. The number of complete twin pairs varied from 10,993 pairs at 1 year of age to 1,357 at 18 to 20 years of age (Table 1). The twin participants were born between 1986 and 2005. For the majority of them (91%), both parents were born in The Netherlands.

Parental education was assessed in surveys sent to both parents of the twins when the twins were 3, 7, and 10 years old, and was rated on a 13-point scale ranging from primary to postdoctoral education. The most recent measure was used and recoded into one of five educational categories: primary education (5% for mothers and 6% for fathers), prevocational secondary education (30% and 28%), secondary vocational education (42% and 35%), higher professional education (16% and 17%), and university education (7% and 13%). We reclassified parents who had secondary vocational education or less to have middle or low education and the parents who had higher professional or university education to have high education. We then classified the families into those where both parents have middle or low education (61%), those where one parent has middle or low and one high education (24%), and those where both parents have high education (15%).

The data were analyzed using classical genetic twin modeling based on linear structural equations. Genetic twin modeling is based on the fact that MZ twins share virtually the same DNA sequence, whereas dizygotic (DZ) twins share, on average, 50% of their genes identical by descent. In our data, DZ within-pair correlations of BMI were more than half of the MZ correlations, suggesting the presence of common environmental effects shared by co-twins (Table 1). Thus, we decomposed the trait variation into an additive genetic component (A), which is the sum of the effects of all alleles affecting the trait; a common environmental component (C), which includes all environmental factors making co-twins similar; and a unique environmental component (E), which includes all environmental effects making co-twins dissimilar, including measurement error. The correlation between additive genetic factors is 1 within MZ pairs and 0.5 within DZ pairs, whereas the correlation between the latent common environmental factors is 1 and between the unique environmental factors 0 within both MZ and DZ twin pairs.

To estimate the relative contribution of genetic (heritability) and environmental effects, we first calculated *z*-scores of BMI over ages

TABLE 2 Numbers and proportions of twin individuals and means and standard deviations (SD) of BMI (kg/m^2) by age, parental educational level, and sex

	Whole cohort			Middle or low education			Mixed education			High education		
	N	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD
Boys												
Age 1	11,044	17.1	1.31	62	17.0	1.32	24	17.1	1.32	14	17.1	1.24
Age 2	8,504	16.3	1.28	59	16.3	1.30	25	16.4	1.29	16	16.4	1.23
Age 3	7,768	15.7	1.19	59	15.7	1.20	25	15.7	1.20	16	15.8	1.15
Age 5	4,248	15.0	1.44	58	15.1	1.49	26	14.9	1.35	16	15.0	1.39
Age 7–8	7,320	15.3	1.61	58	15.3	1.70	26	15.3	1.56	16	15.1	1.39
Age 9–11	6,228	16.3	2.02	58	16.4	2.13	26	16.2	1.89	16	16.9	1.78
Age 12–13	5,308	17.3	2.33	58	17.5	2.50	26	17.1	2.09	16	17.0	1.96
Age 14–15	2,765	18.9	2.45	54	19.0	2.59	27	18.8	2.39	19	18.5	2.10
Age 16–17	2,088	20.3	2.45	52	20.5	2.59	28	20.1	2.33	20	20.0	2.19
Age 18–20	1,468	21.2	2.43	52	21.4	2.59	29	21.0	2.33	19	20.9	2.06
Girls												
Age 1	11,295	16.7	1.33	63	16.7	1.35	23	16.7	1.31	14	16.7	1.25
Age 2	8,327	16.0	1.30	61	16.0	1.31	24	16.0	1.31	15	16.1	1.23
Age 3	8,068	15.5	1.28	61	15.5	1.30	24	15.5	1.24	15	15.5	1.22
Age 5	4,335	14.9	1.53	57	15.0	1.60	26	14.9	1.48	17	14.9	1.33
Age 7–8	7,555	15.4	1.87	59	15.5	2.00	24	15.3	1.71	17	15.2	1.57
Age 9–11	6,422	16.5	2.26	59	16.7	2.40	26	16.3	2.05	15	16.1	1.91
Age 12–13	5,544	17.6	2.53	59	17.8	2.67	26	17.3	2.30	15	17.3	2.24
Age 14–15	3,490	19.3	2.69	57	19.6	2.89	26	19.0	2.27	17	18.8	2.49
Age 16–17	2,903	20.6	2.76	57	20.8	2.98	26	20.5	2.54	17	19.9	2.15
Age 18–20	2,490	21.4	2.94	58	21.8	3.27	26	21.0	2.34	16	20.9	2.35

by using the UK-WHO growth reference data with the Egen procedure for Stata software, version 13.1 for Windows. Further, we adjusted BMI for the remaining age effects within each age group separately in men and women by calculating regression residuals of age. The assumptions of twin modeling, the similarity of means and variances between MZ and DZ twins, were tested by comparing the results of an additive genetic/common environment/unique environment model with that of a saturated model. The fit of nested models was compared by calculating differences in −2 log-likelihood values (Δ−2LL) and degrees of freedom (Δ*df*). As reported earlier (24), there was only little evidence for the sex-specific expression of genetic effects; this effect was statistically significant at ages 7 to 8, 12 to 13, and 18 to 20 years ($P < 0.05$), but was only statistically significant at 18 to 20 years of age after Bonferroni correction for 10 tests ($P = 0.0023$). Thus, qualitative sex differences were not included into the model. Different means were allowed for men and women, but otherwise the mean parameters were fixed to be the same. At the ages of 2 and 18 to 20 years, the fit of the final additive genetic/common environment/unique environment model was somewhat poorer than in the saturated model ($P < 0.05$), but when multiple testing was taken into account by Bonferroni correction, the difference was not statistically significant at these ages either. The phenotypic variances differed in males and females at the ages of 1, 2, 5, and 7 to 8 years ($P < 0.0001$), and therefore the results were stratified by sex. Univariate models were then fitted in each age group stratified by parental education to analyze whether the genetic architecture of BMI differs according to parental education, indicating a parental education by genotype interaction.

In a second series of analyses, age was included in the genetic model as a fixed effect and as a modifier of the genetic and environmental variance components stratified by sex. In addition to the linear effects of age, we also included quadratic age effects in the genetic and environmental variance components since they were highly statistically significant ($\Delta-2LL = 845$, $\Delta df = 6$, $P < 0.0001$). Models were fitted within each of the three categories of parental education to analyze how the change of genetic and environmental variation from 1 to 20 years of age differs between these categories. All genetic models were fitted in the OpenMx package, version 2.0.1, of R statistical software. All parameter estimates and 95% confidence intervals (95% CI) were calculated using the maximum likelihood method.

The NTR longitudinal survey study procedures were approved by the Medical Ethical Review Committee of the Vrije Universiteit Medical Center in Amsterdam on May 25, 2007 (approval number NTR_25052007).

Results

Table 2 presents the descriptive statistics from 1 to 18 years of age by parental education. Both in males and females, mean BMI

TABLE 3 Variance component estimates of BMI with 95% confidence intervals (CI) by age, and sex

	Males						Females					
	Additive genetic factors		Common environment		Specific environment		Additive genetic factors		Common environment		Specific environment	
	a^2	95% CI	c^2	95% CI	e^2	95% CI	a^2	95% CI	c^2	95% CI	e^2	95% CI
Age 1	0.78	0.74–0.81	0.05	0.02–0.09	0.17	0.16–0.18	0.62	0.56–0.69	0.20	0.13–0.26	0.18	0.17–0.19
Age 2	0.76	0.71–0.80	0.06	0.03–0.11	0.18	0.16–0.19	0.61	0.53–0.69	0.21	0.13–0.29	0.18	0.17–0.19
Age 3	0.62	0.57–0.67	0.21	0.17–0.26	0.17	0.16–0.18	0.54	0.48–0.60	0.29	0.23–0.35	0.17	0.17–0.18
Age 5	0.61	0.51–0.70	0.24	0.15–0.33	0.15	0.14–0.17	0.71	0.62–0.78	0.16	0.10–0.25	0.12	0.11–0.14
Age 7–8	0.59	0.51–0.67	0.27	0.19–0.34	0.14	0.13–0.16	0.73	0.66–0.78	0.15	0.10–0.22	0.12	0.11–0.13
Age 9–11	0.77	0.68–0.87	0.12	0.02–0.20	0.11	0.10–0.12	0.85	0.76–0.88	0.03	0.00–0.12	0.12	0.11–0.13
Age 12–13	0.70	0.61–0.85	0.19	0.03–0.27	0.12	0.11–0.13	0.84	0.68–0.88	0.05	0.01–0.21	0.11	0.10–0.12
Age 14–15	0.60	0.44–0.77	0.16	0.00–0.30	0.24	0.21–0.28	0.80	0.76–0.82	0.00	0.00–0.03	0.20	0.18–0.23
Age 16–17	0.62	0.45–0.75	0.14	0.03–0.30	0.24	0.20–0.28	0.71	0.57–0.80	0.08	0.00–0.22	0.21	0.18–0.24
Age 18–20	0.55	0.35–0.72	0.22	0.06–0.40	0.23	0.19–0.29	0.75	0.61–0.84	0.09	0.00–0.22	0.17	0.14–0.19

reached a nadir at 5 years of age and then started to increase. At the age of 1 year, both parents were highly educated in 14% of boys and girls, but this proportion increased to 19% in men and 16% in women at 18 to 20 years of age, mainly because of a lower dropout rate for this group. From 1 to 5 years of age, children of highly educated parents had the same or slightly higher BMI than children whose parents both had a middle or low education. After the age of 5, this association reversed, and higher parental education was associated with lower BMI in boys and girls: the difference increased from 0.18 (95% CI 0.07–0.29) kg/m^2 in boys and 0.28 (95% CI 0.15–0.41) kg/m^2 in girls at age 7 to 8 years to 0.48 (95% CI 0.12–0.84) kg/m^2 and 0.85 (95% CI 0.48–1.22) kg/m^2, respectively, at age 18 to 20 years. The mean BMI of children in families with mixed parental education was generally between these two categories. In all age groups, standard deviations were highest in the boys and girls whose parents both had middle or low education and lowest in those whose parents both had high education.

We then calculated the relative proportions of BMI explained by additive genetic, common environmental, and unique environmental factors (Table 3). At all ages, the largest proportion of BMI variation was explained by additive genetic factors ($a^2 = 0.55$–0.85). In girls, the common environmental effects were largest from 1 to 7–8 years of age ($c^2 = 0.15$–0.29) and then largely disappeared. In boys, the age pattern was less clear: the common environmental effects were highest between 3 and 7 to 8 years of age ($c^2 = 0.21$–0.24), but were also present at later ages, though to a lesser extent. The proportion of BMI variance explained by unique environmental factors showed some variation across the age groups ($e^2 = 0.11$–0.24), but no clear age pattern was seen. In the analyses stratified by parental education, the additive genetic factors again contributed the most in all categories of parental education (Table 4). No systematic differences between the three categories of parental education were seen in the proportions of BMI variation explained by common environmental factors and unique environmental factors.

Finally, we studied how age modifies the absolute genetic and environmental variances of BMI in different categories of parental education (Figure 1). The most systematic result was the increase in additive genetic variation from 1 until 19 years of age. In the full data set, common environmental variation was seen in early adolescence, but it disappeared at the onset of adulthood. This was also the case in the analyses stratified by parental education, except in the boys whose parents had mixed education. The most systematic difference in the stratified analyses was, however, higher genetic variation in the group with middle or low parental education and lower genetic variation in the high parental education category. The differences in the parameter estimates between the parental educational categories were highly statistically significant ($\Delta -2LL = 1019$, $\Delta df = 56$, $P < 0.0001$).

Discussion

In this large study of Dutch twin children and adolescents, in agreement with our hypothesis the variation in BMI was larger in children whose parents had middle or low educational levels compared with children whose parents had a high educational level. This higher genetic variance suggests that a more obesogenic environment in lower socioeconomic families accentuates the effect of genes predisposing to adiposity, such as also found in previous molecular genetic studies (10,12,13). A Danish twin study using own education and adult BMI found that in women, but not in men, the genetic variation in BMI was higher in low educated as compared with highly educated individuals (25), and similar results were also found in a U.S. twin study where men and women were pooled (26). Thus, these previous adult studies partly support our results for childhood BMI and parental education. This finding is also consistent with the increasing genetic variation in BMI in Denmark (14) and Sweden (15), along with an increasing mean BMI. The differences between the parental educational categories emerged at 5 years of age and widened thereafter. This is well consistent with previous studies finding that the FTO gene and other obesity-related candidate genes have an increasing effect on BMI after 6 years of age (17-20). Thus, mid-childhood in particular seems to be a critical period when genes predisposing to obesity activate and start to increase the differences in genetic variation in children from families of different parental education.

TABLE 4 Variance component estimates of BMI with 95% confidence intervals (CI) by age, parental education, and sex

	Males						Females					
	Additive genetic factors		Common environment		Specific environment		Additive genetic factors		Common environment		Specific environment	
	a^2	95% CI	c^2	95% CI	e^2	95% CI	a^2	95% CI	c^2	95% CI	e^2	95% CI
Age 1												
Middle or low	0.78	0.74–0.82	0.05	0.02–0.09	0.17	0.15–0.19	0.61	0.53–0.70	0.22	0.14–0.29	0.17	0.16–0.19
Mixed	0.60	0.48–0.80	0.21	0.02–0.33	0.18	0.16–0.21	0.76	0.51–0.82	0.07	0.01–0.31	0.17	0.15–0.20
High	0.73	0.56–0.86	0.11	0.00–0.27	0.17	0.14–0.20	0.77	0.53–0.81	0.00	0.00–0.24	0.22	0.19–0.27
Age 2												
Middle or low	0.76	0.70–0.81	0.06	0.02–0.12	0.18	0.16–0.19	0.61	0.51–0.71	0.21	0.11–0.30	0.18	0.16–0.20
Mixed	0.74	0.64–0.81	0.08	0.02–0.17	0.18	0.15–0.21	0.55	0.41–0.71	0.27	0.12–0.40	0.18	0.15–0.21
High	0.66	0.48–0.84	0.16	0.00–0.33	0.18	0.15–0.22	0.81	0.57–0.85	0.01	0.00–0.25	0.18	0.15–0.22
Age 3												
Middle or low	0.74	0.66–0.80	0.09	0.04–0.16	0.17	0.15–0.19	0.63	0.54–0.74	0.20	0.10–0.29	0.17	0.15–0.18
Mixed	0.44	0.29–0.62	0.31	0.14–0.44	0.25	0.21–0.30	0.74	0.65–0.81	0.08	0.02–0.17	0.17	0.15–0.20
High	0.71	0.54–0.86	0.15	0.00–0.31	0.14	0.11–0.17	0.77	0.61–0.86	0.08	0.00–0.23	0.15	0.13–0.19
Age 5												
Middle or low	0.65	0.54–0.75	0.21	0.11–0.32	0.14	0.12–0.16	0.70	0.59–0.79	0.18	0.09–0.29	0.12	0.11–0.14
Mixed	0.48	0.31–0.69	0.35	0.15–0.51	0.17	0.13–0.21	0.66	0.47–0.78	0.20	0.09–0.40	0.13	0.11–0.16
High	0.57	0.34–0.84	0.24	0.00–0.45	0.19	0.14–0.25	0.86	0.61–0.90	0.01	0.00–0.27	0.12	0.10–0.16
Age 7–8												
Middle or low	0.56	0.47–0.67	0.30	0.19–0.39	0.14	0.13–0.16	0.74	0.66–0.80	0.15	0.09–0.23	0.11	0.10–0.12
Mixed	0.31	0.23–0.40	0.53	0.46–0.60	0.16	0.13–0.19	0.35	0.27–0.43	0.50	0.43–0.57	0.15	0.12–0.18
High	0.72	0.55–0.82	0.14	0.05–0.29	0.14	0.12–0.18	0.55	0.39–0.75	0.32	0.12–0.47	0.14	0.11–0.17
Age 9–11												
Middle or low	0.87	0.71–0.90	0.02	0.00–0.17	0.11	0.10–0.13	0.80	0.69–0.90	0.09	0.00–0.20	0.11	0.10–0.12
Mixed	0.64	0.50–0.80	0.23	0.08–0.37	0.13	0.11–0.16	0.84	0.77–0.88	0.02	0.00–0.09	0.14	0.12–0.16
High	0.80	0.63–0.93	0.12	0.00–0.30	0.07	0.06–0.09	0.79	0.58–0.88	0.08	0.00–0.29	0.13	0.10–0.16
Age 12–13												
Middle or low	0.71	0.60–0.89	0.18	0.00–0.28	0.11	0.10–0.13	0.86	0.67–0.90	0.02	0.00–0.22	0.11	0.10–0.13
Mixed	0.66	0.51–0.86	0.20	0.01–0.35	0.13	0.11–0.16	0.88	0.72–0.92	0.04	0.00–0.20	0.08	0.07–0.10
High	0.37	0.26–0.48	0.50	0.40–0.60	0.13	0.10–0.17	0.25	0.14–0.36	0.61	0.51–0.70	0.14	0.10–0.18
Age 14–15												
Middle or low	0.49	0.28–0.73	0.25	0.02–0.43	0.27	0.22–0.32	0.78	0.71–0.82	0.01	0.00–0.08	0.20	0.17–0.24
Mixed	0.71	0.45–0.83	0.07	0.00–0.31	0.21	0.16–0.29	0.78	0.58–0.86	0.04	0.00–0.23	0.18	0.14–0.23
High	0.81	0.55–0.86	0.00	0.00–0.24	0.19	0.14–0.27	0.53	0.23–0.80	0.22	0.00–0.49	0.25	0.18–0.34
Age 16–17												
Middle or low	0.74	0.59–0.81	0.04	0.00–0.17	0.22	0.18–0.28	0.54	0.36–0.72	0.23	0.06–0.40	0.23	0.19–0.27
Mixed	0.39	0.12–0.69	0.34	0.05–0.57	0.27	0.20–0.37	0.81	0.73–0.86	0.00	0.00–0.07	0.19	0.14–0.25
High	0.32	0.00–0.69	0.42	0.08–0.70	0.26	0.17–0.40	0.81	0.56–0.88	0.02	0.00–0.27	0.17	0.12–0.25
Age 18–20												
Middle or low	0.50	0.22–0.73	0.23	0.03–0.47	0.27	0.20–0.36	0.76	0.59–0.85	0.07	0.00–0.24	0.17	0.14–0.21
Mixed	0.50	0.18–0.81	0.31	0.01–0.59	0.19	0.13–0.29	0.79	0.53–0.87	0.03	0.00–0.28	0.18	0.13–0.24
High	0.81	0.54–0.88	0.01	0.00–0.26	0.19	0.12–0.30	0.35	0.12–0.73	0.52	0.15–0.74	0.13	0.09–0.19

Despite of different absolute variances, the relative proportions of genetic and environmental variance components were largely similar between the categories of parental education. These results are different from a previous Finnish twin study finding that environmental factors common for co-twins are less important in children whose parents have a high level of education (9). The current data set is considerably larger than in the Finnish study, and thus a lack of power is not likely to explain these different results. However, one explanation can be that in the Dutch cohort only 5% of mothers and 6% of fathers had only a primary education, whereas in the Finnish cohort these proportions were 28% and 47%, respectively (unpublished data). Thus, the effect of common environmental factors on BMI may be specific to low parental education. However, it is also noteworthy that the prevalence of obesity both in children and adults

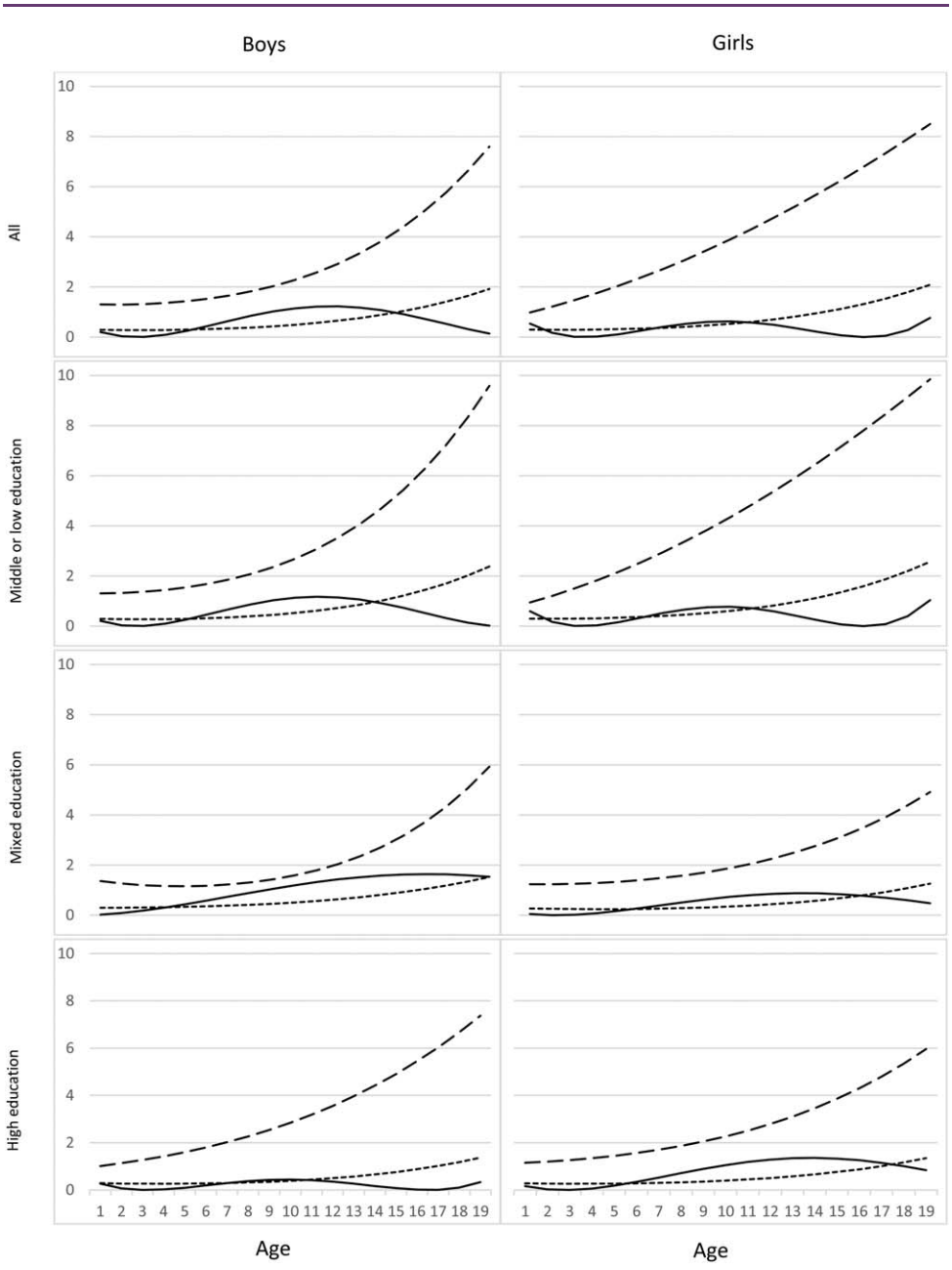

Figure 1 Changes of additive genetic (dash line), common environmental (solid line), and unique environmental (dotted line) variance with increasing age in the quadratic gene–environment interaction model.

is much higher in Finland than in The Netherlands (27). It is possible that the more obesogenic environment in Finland especially affects the children of parents with a lower education. This underlines the importance of replicating this finding in different populations.

The higher BMI in the children of parents with a middle or low level of education emerged in mid-childhood and became stronger until the onset of adulthood. The inverse association between childhood BMI and parental education is a common feature of Western societies (4). However, according to this study, this association changes over childhood and adolescence. Since no differences in BMI by parental education were found before age 5, it is unlikely that the association is because of genetic correlation. Our results showing both higher genetic variance and higher mean BMI in children of parents with a lower education thus suggest that genetic factors interacting with family background can contribute to socioeconomic differences in childhood obesity.

Health behavioral factors could contribute to the higher genetic variation and higher mean BMI in the children whose parents have a lower education. Many of the common risk variants for obesity are

expressed particularly in the hypothalamus, which has a central role in the regulation of appetite and satiety (28). There is clear evidence that the FTO gene and the MC4R gene are associated with increased energy intake and less healthy eating habits in children and affect BMI through these behavioral factors (29). Further, low physical activity and sedentary behavior may predispose to obesity in childhood (30), and these behaviors are more common in children with a lower socioeconomic background (31,32). Previous twin studies have also found that genetic factors affect physical activity, leisure time physical activity, and sedentary behavior in childhood (33). A large Dutch twin study that made use of the same YNTR database, however, found no relationship between voluntary exercise behavior in leisure time and BMI throughout childhood and adolescence (34). Common environmental factors affect nutritional intake in childhood (35), but disappear in adulthood when genetic factors become more important (36,37). This may reflect the increasing independence of children from their parents and is well consistent with the findings of two meta-analyses that the common environmental variance disappears before the onset of adulthood (6,16). Our results somewhat challenge this and rather suggest that family background interacts with genetic factors and thus increases genetic variation. In sum, in families where parents have a middle or low level of education, the environment may promote the energy intake and possible low energy expenditure of children and can further activate genes predisposing to obesity, explaining the greater genetic variance and higher mean BMI in the offspring of these parents.

Our study has both strengths and weaknesses. Our major strength is the very large sample size: the YNTR cohort is the largest twin cohort of children in the world, and our data set included more than 100,000 BMI measurements. Furthermore, BMI was available from infancy until the onset of adulthood, which allowed us to study the development of educational differences in BMI during this very important phase of human life. The BMI of twins in this data set was somewhat lower at 5 years of age than in the general population (38), but this difference was no longer present at 18 years of age (39). Thus, at least after mid-childhood, the twins are largely representative of the general population. Although a study in the YNTR showed the mothers of DZ twins to have a higher BMI than mothers of MZ twins (40), in this study, we did not find evidence for any mean or variance differences between MZ and DZ twins in their own BMI. One limitation of the study is that parents were responsible for copying and reporting height and weight measures, followed by self-reported data on BMI in adolescence and young adulthood. This may have decreased the accuracy of BMI measures, thus increasing unique environmental variation, which also includes measurement error. However, there were no systematic differences in the unique environmental variance components between the categories of parental education, suggesting that the accuracy of the measurements was not dependent on parental education. We also found that the proportion of children with highly educated parents increased from 1 to 18–20 years of age, suggesting a higher dropout rate of children whose parents had middle or low educational levels. This may have made this group more selected after childhood. However, if this had an effect on our results, it probably would have decreased rather than increased the differences between the categories of parental education. For example, we found that both the mean BMI and the variation of BMI increased more in the middle or low as opposed to the high parental education categories. It is not likely that this was caused by the selective dropout of children whose parents had a middle or low level of education, but if it had an effect, it has made the results rather more conservative. Finally, despite our large sample size, the confidence intervals were wide for common environmental factors in our parental educational categories. Our results are, however, different than in a previous Finnish twin study (9), and thus pooling twin data from different countries would not increase the power. However, these somewhat contrasting results underline the need for international comparisons to shed more light on this question.

In conclusion, we found that high parental education was associated with lower BMI. This association emerged in mid-childhood and became stronger until the onset of adulthood. More variation in BMI occurred among children whose parents had a middle or low educational level compared with those children whose parents had a high level of education. This difference was caused by the lower genetic variance of BMI in the category of high parental education. Our results suggest that a more obesogenic environment in lower socioeconomic families accentuates the effect of genes predisposing to obesity. Interaction between the family environment and genetic factors may play an important role in the formation of socioeconomic differences in obesity. O

Acknowledgments

We thank Professor Jaakko Kaprio, the head of the Finnish Twin cohort, for offering us the distributions of parental education in the FinnTwin12 data.

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