Education as a moderator of genetic risk for higher body mass index: Prospective cohort study from childhood to adulthood

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ABSTRACT

Objectives: The life-course development of body mass index (BMI) may be driven by interactions between genes and obesity-inducing social environments. We examined whether lower parental or own education accentuates the genetic risk for higher BMI over the life course, and whether diet and physical activity account for the educational differences in genetic associations with BMI.

Subjects/Methods: The study comprised 2441 participants (1319 women, 3-18 years at baseline) from the prospective, population-based Cardiovascular Risk in Young Finns Study. BMI (kg/m^2) trajectories were calculated from 18 to 49 years, using data from 6 time points spanning 31 years. A polygenic risk score for BMI was calculated as a weighted sum of risk alleles in 97 single nucleotide polymorphisms. Education was assessed via self-reports, measured prospectively from participants in adulthood and from parents when participants were children. Diet and physical activity were self-reported in adulthood.

Results Mean BMI increased from 22.6 to 26.6 kg/m^2 during the follow-up. In growth curve analyses, the genetic risk score was associated with faster BMI increase over time (b = 0.02, [95%CI, 0.01 to 0.02, $P < 0.001$]). The association between the genetic risk score and BMI was more pronounced among those with lower educational level in adulthood (b = -0.12 [95% CI, -0.23 to 0.01); $P = 0.036$]). No interaction effect was observed between the genetic risk score and parental education (b = 0.05 [95%CI, -0.09 to 0.18; $P = 0.51$]). Diet and physical activity explained little of the interaction effect between the genetic risk score and adulthood education.

Conclusions: In this prospective study, the association of a risk score of 97 genetic variants with BMI was stronger among those with low compared to high education. This suggests lower education in adulthood accentuates the risk of higher BMI in people at genetic risk.

INTRODUCTION

High body mass index (BMI) >25kg/m^2) increases the development of several chronic diseases and the risk of early mortality.[1–3] Individual differences in BMI reflect both genetic and environmental factors. A meta-analysis of twin studies estimated that genetic factors explain ~75% of BMI variation.[4] A recent genome-wide association study (GWAS) meta-analysis in 339,224 people from 125 cohorts identified 97 specific single nucleotide polymorphisms (SNP) explaining 2.7% of the phenotypic variance in BMI, with each risk allele increasing average BMI by 0.1 kg/m^2.[5]

Socioeconomic status (SES) is one of the established environmental factors associated with BMI. In high-income countries, disadvantaged SES is associated with higher BMI.[2,6,7] Recent evidence also suggests that there is an interaction between SES and genetic factors so that the genetic associations with BMI are contingent on socioeconomic context. For instance, a genetic risk score composed of 69 SNPs established in the European descent sample of the most recent GWAS meta-analysis[5] was more strongly associated with BMI in socioeconomically deprived people in the UK Biobank sample.[8] Similarly, cumulative socioeconomic disadvantage and downward social mobility over the lifespan were found to accentuate the association of the previously identified 32 SNP risk score[9] with BMI in the Health and Retirement Study.[10]

SES may interact with the genetic risk of higher BMI because it is related to various factors of the obesogenic environment. For instance, low SES may enhance genetic associations with BMI because of the links between low SES and lifestyle risks, such as unhealthy diet and sedentary behavior.[11–15] The 32 SNP risk score for BMI and the fat mass and obesity associated gene (*FTO*) variant have been found to associate with BMI more strongly among those with unhealthy behaviors, such as unhealthy diet and physical inactivity.[16–18] Further evidence for the implication that disadvantaged SES may strengthen the genetic associations with BMI has come from twin studies showing that the genetic variation of BMI is greater in people with disadvantaged SES.[19–21] Although disadvantaged SES seems to accentuate genetic risks for higher BMI, this issue has not been addressed in prospective follow-up studies using a genetic risk score for BMI. Studies following BMI trajectories over the course of adulthood would bring new insights into the long-term mechanisms as to how SES operates on genetic risk for BMI.

In addition to studies of the person's own adult SES, studies in life-course epidemiology have highlighted the importance of parental SES during childhood in influencing the development of BMI.[7,22–27] There is limited data, however, on whether childhood SES influences the association of genetic risk variants with BMI. Two previous studies with multilocus genetic risk scores reported no interaction effect between the 32 SNP risk score and childhood SES on BMI.[10,28] Understanding the role of SES at different life stages, in childhood and in adulthood, in shaping genetic associations with BMI is relevant for prevention; it can help direct interventions to at-risk individuals at most effective ages across life.

We used prospective data and the most recent 97 SNP genetic risk score for BMI[5] to test the hypothesis that lower SES over the life-course, in childhood and in adulthood, accentuates the genetic associations with BMI from early adulthood to midlife. We also examined whether an interaction effect would be explained by unhealthier diet and lower level of physical activity of people with lower SES. The participants were from a prospective Finnish cohort followed during 31 years from childhood to midlife. They were examined for the 97 risk variants for BMI,[5] parental and own education as proxies for childhood and adulthood SES, and the development of BMI over adulthood.

SUBJECTS AND METHODS

Participants. The Cardiovascular Risk in Young Finns Study is an ongoing multicenter follow-up study on the determinants and risk factors of cardiovascular disease. At the study baseline in 1980, the sample comprised 3596 children and adolescents aged 3, 6, 9, 12, 15 and 18. They were enrolled from five geographical areas representing all parts of Finland using random-sampling from the national register to represent the population within each area. Follow-up studies have been carried

out in 1983, 1986, 1989, 1992, 1997, 2001, 2007 and 2011. We calculated BMI trajectories starting from age 18 or older and used all available data of BMI measured in 1980, 1983, 1986, 2001, 2007 and 2011. We included participants with data on the genetic risk score (genotyping in 2001), parental education in 1980, and trajectories of participant's own educational attendance in adulthood using all available data from 1986, 2001, 2007 and 2011. The age structure of the study is presented in the Supplementary table 1. The study was conducted in accordance with the Declaration of Helsinki and was approved by local ethics committees. All participants provided a written informed consent.

BMI. BMI was calculated at six time points as weight (kg) divided by height (m^2). Weight was measured in light clothing without shoes to the nearest 0.1 kg. Height was measured with a wall-mounted stadiometer to the nearest 0.5 cm.

Genetic risk. The genetic risk score for BMI was calculated as the sum of genotyped risk alleles (0/1/2) or imputed allele dosages of 97 SNPs, weighted by the effect sizes reported by Locke et al.[5] Genotyping was performed with the Illumina Bead Chip (Human 670K). Genotype imputation was performed in two stages: haplotype phasing was done using SHAPEIT v1 and genotype imputation using IMPUTE2 and 1000 Genomes Phase I Integrated Release Version 3 (March 2012 haplotypes) as a reference. There were 58 imputed and 39 directly genotyped SNPs. Average imputation quality for imputed SNPs was 0.9877 (range 0.8218-1). In genetic risk score formation effect allele dosages were calculated from imputed genotype probabilities to incorporate the degree of uncertainty of imputed SNPs. The genetic risk score was available for 2443 individuals. Standardized scores of the genetic risk score were used in all analyses. High and low genetic risk were defined at the 10^{th} and 90^{th} percentiles of the genetic risk score (mean ±1.28 standard deviations (SD)).

Education. Participants reported their highest level of educational attendance in 1986, 2001, 2007 and 2011. The responses were categorized into four groups: primary level (completion or attendance in upper elementary school or equivalent), secondary level (completion or attendance in high school, vocational school or equivalent), BA (attendance at a university or college, or a completed Bachelor's degree/equivalent), and MA or higher (a completed Master's Degree, Licentiate or Doctoral Degree or attendance in such program). Parental education (in full years) was obtained from parents prospectively in 1980 when the participants were children (mean age 10.5 years), categorized into primary (9 years or less), secondary (10-12 years), BA (13-15 years) and MA or higher (16 years or more).

Diet and physical activity. Diet and physical activity were measured via self-reports in 1986, 2001, 2007 and 2011.[29] We categorized the responses into ideal vs. non-ideal (1/0) levels following the American Heart Association (AHA) guidelines on ideal cardiovascular health as closely as possible.[29–31] In 2007 and 2011, diet was defined as ideal if it comprised 4 out of 5 dietary components scaled for caloric intake: ≥450 g/day of fruits and vegetables, ≥ two servings (100 g) of fish/week, ≥ three servings (30 g) of whole grain rye bread/day; <1500 mg of sodium/day; ≤450 kcal of sugar-sweetened beverages/week. In 1986 and 2001, diet was defined as ideal if it comprised 2 out of 3 dietary components: fruits and vegetables every day; fish ≥ 2 times a week; and soft drinks ≤ 2 times a week.[29] Physical activity was defined as ideal if the criteria of 120 min/week moderate-intensity or 60 min/week vigorous-intensity activity (or a combination) was met. In 1986, a criterion of ≥ 7 hours/week was used for participants under 20 years. We also ran the analyses using consistent criteria of diet and physical activity across all time-points. Diet was defined as ideal if the criterion of 2/3 ideal dietary components (fruits and vegetables every day; ≥ 2 times fish/week; and ≤450 kcal of sugar-sweetened beverages/week or ≤ 2 times soft drinks/week) was met. Adulthood criterion of ideal physical activity (120 min/week moderate-intensity, 60 min/week vigorous-intensity activity or a combination) was used for participants under 20 years.

Covariates. Sex and birth year were self-reported. All analyses were adjusted for sex, age and the year of follow-up.

Statistical analyses. Given that BMI was approximately normally distributed, the associations of the genetic risk score, own attained education and parental education with BMI

trajectories were examined using mixed-effects linear regression. Each participant could contribute up to 6 repeated measurements of BMI and up to 4 repeated measurements of own education. The random intercept variance component of the regression model took into account the non-independence of within-individual measurements.[32] We first plotted curves for the BMI values from young adulthood (18 years old) to midlife (49 years) at each age by using age as a categorical variable, with adjustments for sex and study year. Fixed linear (age) and quadratic (age x age) time effects were included to account for non-linearity. Random-slope component was added for the linear effect of age to allow different individuals to follow more or less steep BMI trajectories. The models were fit using unstructured error covariance matrix, including covariances between the intercepts and the slopes. Age was centered so that the intercept referred to the average BMI at the age of 49 (the oldest in 2011). Participants' own education, ideal diet and physical activity were included in the models as time-varying predictors. We first examined the main effects and the age interactions of the genetic risk score with participant's own education and parental education on BMI trajectories in separate models. In the first model, we included an interaction effect between genetic risk score and the participant's education, and we also tested a three-way interaction between age, education, and the genetic risk score. We then fitted a similar model but replaced the participant's education with parental education. The three-way interactions with age (genetic risk score x education x age) were not significant ($P > 0.05$) in either model, so only the two-way interaction terms were included. The final models for both participant's own and parental education are written:

$$\mathrm{Y_{ij}} = \beta_0 + \beta_1\mathrm{AGE_{ij}} + \beta_2\mathrm{AGE_{ij}AGE_{ij}} + \beta_3\mathrm{PHASE_{ij}} + \beta_4\mathrm{SEX_i} + \beta_5\mathrm{GRS_i} + \beta_6\mathrm{EDUCATION_{ij}} + \beta_7\mathrm{GRS_iAGE_{ij}} + \beta_8\mathrm{EDUCATION_{ij}AGE_{ij}} + \beta_9\mathrm{GRS_iEDUCATION_{ij}} + (\varepsilon_{ij} + \zeta_{0i} + \zeta_{1i}\,\mathrm{AGE_{ij}})$$

in which *i* is the number of participants and *j* is the study phase. GRS refers to the genetic risk score.

Lastly, we adjusted the final models for the main effects of diet and physical activity and their interactions with the genetic risk score. A *P*-value of 0.05 was considered statistically significant in a two-tailed test. Power calculation for a cross-sectional analysis in 2001 indicated that with a sample size of 2210, we had 93% power to detect a variable that increased R^2 by 0.005 (i.e., from 0.05 in baseline model to 0.055 in full model), indicating that even with one measurement time we would have had sufficient statistical power to detect even a small effect. All analyses were performed using Stata version 13.1 (StataCorp LP, College Station, Texas).

Code availability. Stata (13.1) code is available from the first author.

RESULTS

The 2441 participants (1319 women) who had data on the genetic risk score and own or parental education contributed to 7790 person-observations of BMI measurements (Table 1). In 2011, the mean age was 41.9 (SD = 5.0) years; and women's mean BMI was 26.1 kg/m^2 (SD = 5.4) and men's 27.0 kg/m^2 (SD = 4.4). The distribution of the genetic risk score was not dependent on participant's own or parental education (Pearson's $r = 0.02$, $P = 0.14$; $r = 0.00$, $P = 0.83$ respectively). The correlation between parental education in 1980 and participant's own education in 2011 was 0.35 ($P < 0.001$).

Mean BMI increased from young adulthood to midlife following a quadratic curve, from 22.6 kg/m^2 (at 18 years) to 26.6 kg/m^2 (49 years) (B-coefficients for age b = 0.31; 95% CI, 0.25 to 0.37; $P < 0.001$ and age squared b = -0.003; 95% CI, -0.003 to -0.002; $P < 0.001$). The genetic risk score was associated with a more rapid increase in BMI (b = 0.02, 95% CI, 0.01 to 0.02, $P < 0.001$); participants with high genetic risk (at the 90th percentile of the genetic risk score) had 1.6, 2.2 and 2.8 kg/m^2 higher predicted BMI at ages of 20, 35 and 49 than those with low genetic risk (at the 10th percentile) (Figure 1, left panel, see also Table 2). Figure 1 (middle and right panel) shows that lower level of

Table 1. Descriptive statistics

	Mean(SD)	No.(%)[a]	n
Sex (female)		1319 (54.0)	2441
Birth year			2441
1962		384 (15.7)	
1965		430 (17.6)	
1968		425 (17.4)	
1971		421 (17.2)	
1974		401 (16.4)	
1977		380 (15.6)	
BMI			
1980	21.4 (2.8)		384
1983	21.7 (2.8)		597
1986	22.0 (2.8)		823
2001	25.0 (4.4)		2221
2007	25.5 (4.8)		1989
2011	26.5 (5.0)		1776
Participant's own education in adulthood			
1986			821
Basic		53 (6.5)	
Secondary		704 (85.8)	
Bachelor		17 (2.1)	
Master or higher		47 (5.7)	
2001			2210
Basic		189 (8.6)	
Secondary		1425 (64.5)	
Bachelor		298 (13.5)	
Master or higher		298 (13.5)	
2007			1979
Basic		96 (4.9)	
Secondary		1156 (58.4)	
Bachelor		394 (19.9)	
Master or higher		333 (16.8)	
2011			1687
Basic		50 (3.0)	
Secondary		958 (56.8)	
Bachelor		366 (21.7)	
Master or higher		313 (18.6)	
Parental education in 1980			2405
Basic		1086 (45.2)	
Secondary		701 (29.2)	
Bachelor		312 (13.0)	
Master or higher		306 (12.7)	
Ideal diet[b,c]			
1986		184 (22.5)	817
2001		530 (25.4)	2088
2007		109 (6.2)	1773
2011		88 (6.7)	1271
Ideal physical activity[b]			
1986		273 (33.7)	811
2001		1143 (53.1)	2154
2007		1018 (52.1)	1018
2011		962 (58.2)	1953

Descriptive statistics are calculated for participants for whom the genetic risk score and parental or own education were available.

[a] All percentages do not add up to 100% because of rounding.

[b] Defined following the American Heart Association guidelines on ideal cardiovascular health.[29-31]

[c] Modified criteria for ideal diet (2/3 ideal components) were used in 1986 and 2001.[29]

Table 2. Associations of the genetic risk score, participant's own education and parental education with BMI between ages 18 and 49.

	B	95% CI	*P* Value	n
Genetic risk score[b]	1.09	0.84 to 1.34	**<0.001**	2441
Genetic risk score x age	0.02	0.01 to 0.02	**<0.001**	
Own education[b]	-0.59	-0.79 to -0.39	**<0.001**	2433
Own education x age	-0.02	-0.03 to -0.01	**<0.001**	
Parental education[b]	-0.65	-0.90 to -0.40	**<0.001**	2405
Parental education x age	-0.02	-0.02 to -0.01	**<0.001**	

[a] From separate models, all adjusted for age, age squared, sex and the year of follow-up.
[b] Main effects refer to effects at age 49.

participant's own and parental education were significantly associated with faster increases in BMI over time (Figure 1, b = -0.02; 95% CI, -0.03 to -0.01; $P < 0.001$; b = -0.02; 95% CI, -0.02 to -0.01, $P < 0.001$ for participant's own and parental education, respectively) (Table 2).

A significant two-way interaction between the genetic risk score and participant's own education (b = -0.12; 95% CI, -0.23 to -0.01; $P = 0.036$) showed that the association between genetic risk and BMI was more pronounced among those with lower education (Table 3). This finding is illustrated in Figure 2 defining low and high genetic risk at the 10th and 90th percentile scores (Figure 2). Compared to those with low genetic risk, high genetic risk was associated with 3.3 kg/m^2 higher BMI at age 49 among those with low education but only 2.4 kg/m^2 higher BMI among those with high education. The interaction effect between the genetic risk score and participant's own education was

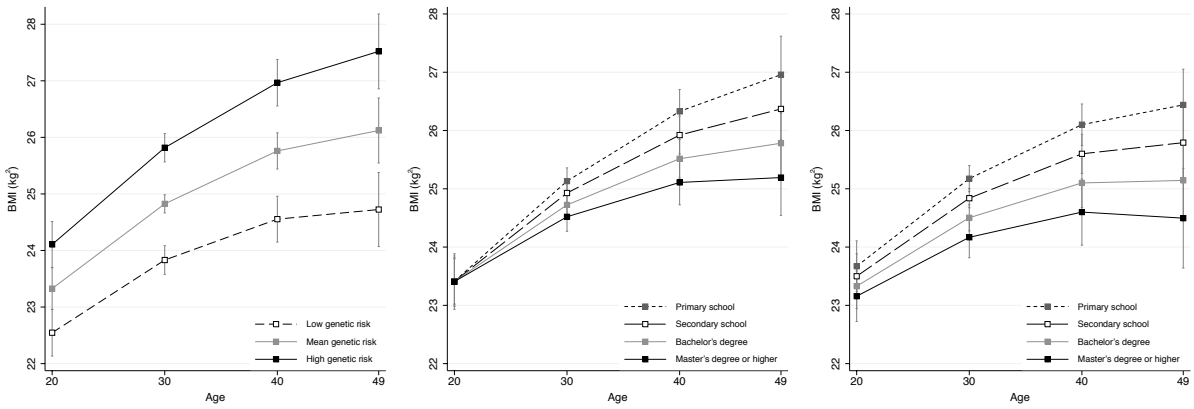

Figure 1. Model-predicted associations of the genetic risk score, participant's own education and parental education with BMI trajectories

Abbreviations: BMI, body mass index
Vertical lines represent the 95% confidence intervals.
The left panel presents the association of the genetic risk score with BMI trajectories (N = 7790 person-observations of 2441 persons across 6 measurement times). The middle panel presents the association of participant's own education with BMI trajectories (N = 7513 person-observations of 2433 persons across 6 measurement times). The right panel presents the association of parental education with BMI trajectories (N = 7648 person-observations of 2405 persons across 6 measurement times). Low genetic risk (left panel) was defined at the 10th percentile score and high genetic risk at the 90th percentile score of the 97 SNP genetic risk score.

Table 3. Associations of the genetic risk score x education interactions with BMI between ages 18 and 49

Own education[a]			
	B	95% CI	*P* Value
Age	0.05	0.01 to 0.09	**0.010**
Age squared	0.00	0.00 to 0.00	**<0.001**
Sex	-1.02	-1.31 to -0.74	**<0.001**
Study phase	0.08	0.06 to 0.11	**<0.001**
GRS	1.28	0.97 to 1.60	**<0.001**
Participant's own education	-0.60	-0.80 to -0.40	**<0.001**
GRS * age	0.02	0.01 to 0.03	**<0.001**
Participant's own education * age	-0.02	-0.03 to -0.01	**<0.001**
GRS * participant's own education	-0.12	-0.23 to -0.01	**0.036**
Parental education[b]			
	B	95% CI	*P* Value
Age	0.02	-0.02 to 0.05	0.397
Age squared	0.00	0.00 to 0.00	**<0.001**
Sex	-0.94	-1.22 to -0.66	**<0.001**
Study phase	0.09	0.06 to 0.12	**<0.001**
GRS	1.04	0.75 to 1.33	**<0.001**
Parental education	-0.66	-0.91 to -0.41	**<0.001**
GRS * age	0.02	0.01 to 0.02	**<0.001**
Parental education * age	-0.02	-0.02 to -0.01	**<0.001**
GRS * parental education	0.05	-0.09 to 0.18	0.509

Abbreviations: GRS, genetic risk score.
Note: Main effects of the genetic risk score and education refer to associations with BMI at age 49. The GRS * education interaction terms refer to associations with the mean level of BMI across all ages. Three-way interactions between the GRS, education and age were omitted because they were not significant.
[a] N = 7513 person-observations of 2433 persons across 6 measurement times
[b] N = 7648 person-observations of 2405 persons across 6 measurement times

significant (n = 2210, b = -0.24, 95% CI, -0.46 to -0.02, *P* = 0.031) also in a cross-sectional analysis using data from 2001 (baseline in the complete sample) (Supplementary figure 1). We also tested a three-way interaction term between the genetic risk score, participant's own education, and age to examine whether the interaction effect between genetic risk and education changed with age, but this three-way interaction was not significant (*P* > 0.05).

In contrast to participant's own education, there was no interaction effect between parental education and the genetic risk score (b = 0.05; 95% CI -0.09 to 0.18, *P* = 0.51; Table 3). Additional age-stratified analyses showed that there was no interaction between parental education and the genetic risk score among those younger than 18 years (n = 2039, b = -0.01, 95% CI, -0.09 to 0.06, *P* = 0.780). A three-way interaction term between the genetic risk score, parental education and age was not significant (*P* > 0.05), indicating no age varying interaction effect between genetic risk and parental education.

When adjusted for diet and physical activity and their interactions with the genetic risk score, the interaction effect between participant's own education and the genetic risk score was somewhat attenuated (b= -0.10; 95% CI, -0.23 to 0.02, *P* = 0.10**)**. However, differences in BMI between high (90^{th} percentile) and low (10^{th} percentile) genetic risk at high and low levels of education remained virtually unchanged. The results were the same regardless of whether the criteria for diet and physical activity were inconsistent (following the AHA ideal health definition, which differs across ages) or consistent (similar for all ages) (a difference of 3.3 kg/m^2 at the lowest educational level; 2.5 kg/m^2 at the highest educational level).

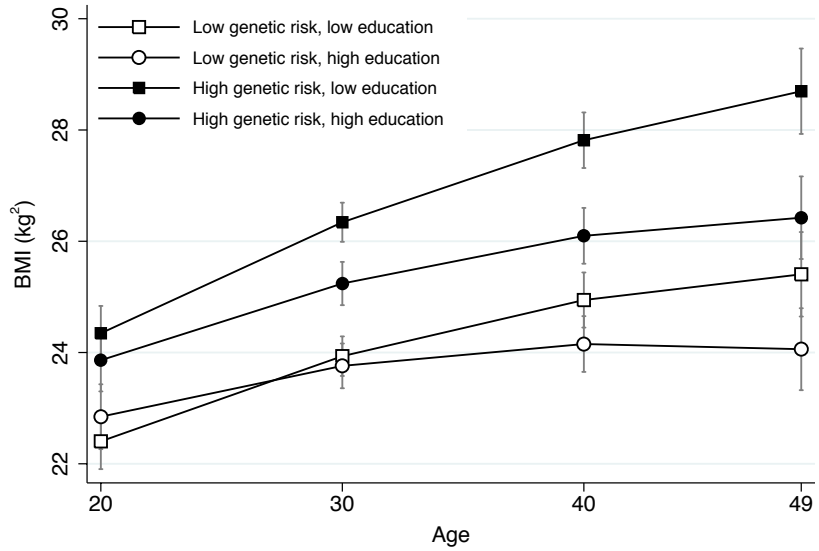

Figure 2. Model-predicted associations of the genetic risk score x participant's own education - interaction with BMI trajectories

Abbreviations: BMI, body mass index
Vertical lines represent the 95% confidence intervals.
N = 7513 person-observations of 2433 persons across 6 measurement times
At age 49, compared to those with low genetic risk, high genetic risk was associated with 3.3 units higher BMI among those with low education (empty squares vs. filled squares), and 2.4 units higher BMI among those with high education (empty circles vs. filled circles) (both $p < 0.001$).
Low genetic risk was defined at the 10th percentile score and high genetic risk at the 90th percentile score of the 97 SNP genetic risk score. Low education refers to primary school; high education refers to a Master's degree or higher.

To adjust for possible underlying population substructures, we also conducted all analyses including the genetic risk score adding first four principal components calculated from GWAS data. This adjustment did not affect the results.

DISCUSSION

In this 31-year prospective study, the association of a genetic risk score of 97 SNPs was stronger with BMI among people with lower compared to higher educational level. These findings suggest that low education in adulthood accentuates the genetic risk for higher BMI; the difference at age 49 between high and low genetic risk was 3.3 BMI units among those with low education but only 2.4 among those with high education. Parental education in participant's childhood did not modify the genetic associations with adulthood BMI.

Higher genetic susceptibility to obesity, measured by 97 SNPs across the genome, has previously been shown to predict modestly accelerated time-dependent increase in BMI over a 10-year follow up.[33] Although twin studies have suggested that education might be a critical adult SES indicator to interact with the genetic predisposition to high BMI,[20,34] previous studies with 29 SNP and 69 SNP risk scores have not found evidence for education modifying the effects of the genetic risk.[8,35] With the genetic measure composed of 97 identified SNPs across the genome, we demonstrate that the genetically influenced development of BMI from early adulthood to midlife may be sensitive to adulthood educational attainment.

Contrary to participant's own education in adulthood, parental education did not modify the expression of the genetic risk in our study. This finding is in line with two previous studies, which

showed no interaction effect between the 32 SNP risk score and parental SES.[10,28] By contrast, a recent twin study conducted among children and youth found a gene-environment interaction suggesting that low parental education accentuates the genetic risk for higher BMI[21]. We tested the possibility that parental education would interact with the genetic risk score in a subsample consisting of participants less than 18 years of age, but found no interaction effect. While parental education was associated with participant's own education, the correlation in our data was only moderate. Together with previous molecular genetic results,[10,28] our findings suggest that parental education may not be as important moderator variable to the genetic risk for higher BMI as a person's own education.

Explanations as to why lower education in adulthood may increase vulnerability to the expression of genetic risk of higher BMI are hypothetical. Education may affect BMI via several routes, such as money and prestige, cognitive and emotional skills, factual knowledge, or social environment.[36,37] Low education can manifest in more obesogenic lifestyles due to healthy food expenses, neighborhood food environment, limited knowledge on nutritional recommendations or psychosocial stress in response to socioeconomic adversity. Previous research has shown that unhealthy lifestyles, such as sedentary behaviors, intake of sugar-sweetened beverages or high-fat foods, may accentuate the genetic predisposition to adiposity.[16–18] Although we expected that diet and physical activity might account for the interaction effect between the genetic risk score and education, they explained little of this effect in our data. This result is in agreement with the recent findings of Tyrrell et al,[8] suggesting that no single aspect of environment or behavior, such as diet and physical activity, may exhaustively explain socioeconomic differences in genetic associations with BMI. Following the arguments of Tyrrell et al,[8] we assume that education serves a proxy measure for a cumulative burden of obesogenic exposures and environmental adversities, including material deprivation (e.g., living in low-income neighborhood), behavioral factors (e.g., lifestyle choices), and psychosocial deficits (i.e., social isolation).[15] The accumulation of multiple risk exposures may add up to higher environmental stress-burden,[38–41] which could explain the educational differences in genetic associations we observed. Measures of accumulative disadvantage and obesogenic exposures are required to explore this explanatory pathway.

The major strengths of this study include the repeated BMI measurements over 31 years, molecular data on a comprehensive, most recent polygenic risk score for BMI, and a prospective assessment of own education in adulthood and parental education when the participants were children. The primary limitations involve attrition over the follow-up (Supplementary tables 2 and 3), which is typical for long-standing cohort studies, and a homogeneous sample from a European population. We did not limit our analysis to the SNPs identified in the European-descent GWAS meta-analysis sample only, but used the total of 97 SNPs identified in European, African and east Asian descents – the common BMI-associated variants have been found to show comparable effects across ancestries[5] and additional SNPs may thus be expected to increase the variance explained in BMI. However, some independent risk-associated SNPs may differ in these populations.[5] Also it is not known whether our findings generalize to other ethnicities. BMI alone may not be the best indicator of adiposity; combining BMI with measures that assess body fat, such as waist circumference, might better indicate adiposity-related disease risk in adults.[42] Also the AHA cutoffs we used for diet and physical activity are relatively crude, and may not have captured relevant components of these lifestyles in sufficient detail.

In this prospective cohort, the association of BMI and the genetic risk score for higher BMI was stronger among those with low education compared to those with high education. This suggests that low education in adulthood accentuates the risk of higher BMI in people at genetic risk. More research is needed on the exact mechanisms whereby environmental factors may increase genetic susceptibility to higher BMI.

Supplementary information is available at the *International Journal of Obesity's* website.

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The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest
The authors declare no conflict of interest.

Author Contributions
Ms Komulainen and Dr. Pulkki-Råback had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; study concept and design: Komulainen, Pulkki-Råback, Jokela, Keltikangas-Järvinen; acquisition, analysis and interpretation of data: all authors; drafting of the manuscript: Komulainen, Pulkki-Råback, Jokela; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: Komulainen, Jokela; obtained funding: Keltikangas-Järvinen, Elovainio, Hintsanen, Lehtimäki; study supervision: Raitakari, Lehtimäki, Keltikangas-Järvinen.

All authors have given final approval of the submitted manuscript.
All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
The corresponding author (Pulkki-Råback) confirms to have the final responsibility for the decision to submit for publication.

Data availability
The data that support the findings of this study are available from the corresponding author upon request and with the permission of Prof. Olli Raitakari.

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Supplementary Online Content

Supplementary table 1. The cohort structure of the Young Finns Study.

	Study phase					
Birth year	1980	1983	1986	2001	2007	2011
1977	3	6	9	24	30	34
1974	6	9	12	27	33	37
1971	9	12	15	30	36	40
1968	12	15	18	33	39	43
1965	15	18	21	36	42	46
1962	18	21	23	39	45	49

The cells present the ages of the participants of the Young Finns Study at each study phase. The grey-shaded cells indicate the person-observations that were included in the present analysis.

Supplementary table 2. Differences between included and excluded study participants.

A. Participant's own education x genetic risk score -interaction analysis (N = 2433)

		1980	1983	1986	2001	2007	2011
Sex (female)	Included	54.5	**55.7**	**56.3**	**55.1**	**54.4**	**55.7**
	Excluded	49.2	**49.4**	**47.7**	**44.3**	**46.8**	**46.8**
Ideal diet	Included			22.5	25.4	6.2	6.9
	Excluded			18.0	22.5	5.4	5.8
Ideal physical activity	Included			**33.7**	53.1	52.2	58.3
	Excluded			**25.1**	49.9	45.9	53.6
BMI†	Included	21.5	21.6	22.0	25.1	26.0	26.5
	Excluded	21.2	21.8	22.1	25.1	26.3	26.8
Genetic risk score (z-score)†	Included	0.0	0.0	0.0	0.0	0.0	0.0
	Excluded	0.0	0.0	0.0	-0.1	0.0	0.0
Participant's own education†	Included			1.1	**1.3**	1.5	1.6
	Excluded			1.0	**1.2**	1.5	1.5
Parental education†	Included	0.6	0.7	0.7	0.9	0.9	0.9
	Excluded	0.7	0.6	0.7	0.9	0.9	0.9
Age†	Included	18.0	19.3	20.8	**31.6**	**37.7**	**41.9**
	Excluded	18.0	19.5	20.8	**31.2**	**37.1**	**41.0**

Values are percentages unless otherwise noted. † Values are means. Bolded values differ at $P < 0.05$.

B. Parental education x genetic risk score -interaction analysis (N = 2405)

		1980	1983	1986	2001	2007	2011
Sex (female)	Included	53.6	54.5	**56.0**	**55.0**	**54.4**	**55.0**
	Excluded	49.1	49.9	**48.1**	**44.7**	**46.8**	**47.1**
Ideal diet	Included			22.4	25.2	6.0	6.8
	Excluded			18.7	23.5	6.5	6.0
Ideal physical activity	Included			**33.8**	53.2	52.1	58.2
	Excluded			**25.2**	49.3	47.2	54.3
BMI†	Included	21.4	21.7	22.0	25.0	26.0	26.5
	Excluded	21.3	21.8	22.1	25.1	26.3	26.8
Genetic risk score (z-score)†	Included	0.0	0.0	0.0	0.0	0.0	0.0
	Excluded	-0.1	-0.1	0.0	-0.1	0.0	0.0
Participant's own education†	Included			1.1	**1.3**	1.5	**1.6**
	Excluded			1.0	**1.1**	1.5	**1.4**
Parental education†	Included	0.6	0.7	0.7	0.9	0.9	0.9
	Excluded	0.7	0.6	0.7	0.9	0.9	0.9
Age†	Included	18.0	**19.3**	20.8	31.5	**37.7**	**41.9**
	Excluded	18.0	**19.5**	20.9	31.3	**37.2**	**41.0**

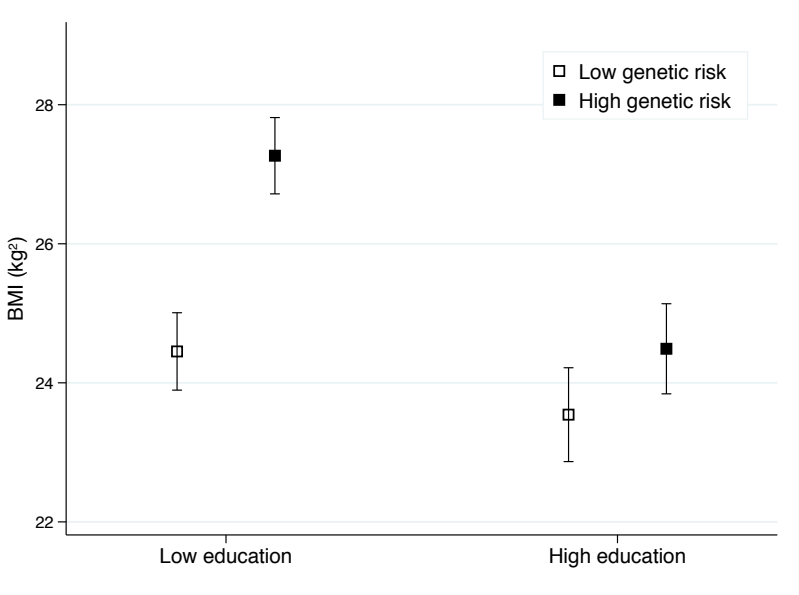
Values are percentages unless otherwise noted. † Values are means. Bolded values differ at $P < 0.05$.

Supplementary table 3. Selective attrition from BMI follow-up.

Value in previous study wave	Drop-out year[a]	OR	95% CI	*P*-value
BMI	1983	0.96	0.89 to 1.04	0.389
	1986	1.04	0.97 to 1.10	0.279
	2001	0.99	0.89 to 1.10	0.895
	2007	1.03	1.00 to 1.05	**0.020**
	2011	1.01	0.99 to 1.03	0.474
Genetic risk score	1983	0.94	0.80 to 1.09	0.475
	1986	1.06	0.94 to 1.19	0.310
	2001	0.93	0.80 to 1.06	0.287
	2007	0.99	0.89 to 1.09	0.901
	2011	0.97	0.88 to 1.05	0.476
Participant's own education[b]	1983			
	1986			
	2001	0.80	0.43 to 1.18	0.359
	2007	0.89	0.77 to 1.01	0.078
	2011	0.95	0.82 to 1.08	0.453
Parental education	1983	0.99	0.82 to 1.15	0.876
	1986	0.99	0.86 to 1.11	0.829
	2001	1.06	0.93 to 1.20	0.349
	2007	1.04	0.94 to 1.14	0.423
	2011	1.01	0.92 to 1.09	0.883
Ideal diet[b]	1983			
	1986			
	2001	0.98	0.27 to 1.68	0.955
	2007	1.07	0.81 to 1.33	0.597
	2011	0.75	0.35 to 1.14	0.283
Ideal physical activity[b]	1983			
	1986			
	2001	1.10	0.41 to 1.79	0.772
	2007	0.97	0.76 to 1.17	0.745
	2011	1.07	0.83 to 1.31	0.548
Age	1983	1.15	1.03 to 1.27	**0.008**
	1986	1.05	1.00 to 1.10	0.065
	2001	0.98	0.95 to 1.00	0.096
	2007	0.96	0.94 to 0.98	**<0.000**
	2011	0.95	0.93 to 0.96	**<0.000**
Sex	1983	0.81	0.56 to 1.07	0.191
	1986	0.80	0.61 to 0.98	0.059
	2001	0.63	0.46 to 0.81	**0.001**
	2007	0.93	0.74 to 1.12	0.511
	2011	0.87	0.71 to 1.02	0.113

Abbreviations: OR, odds ratio; CI, confidence interval
[a] Drop-out year indicates the study wave for dropping out from the BMI measurement.
[b] Measured in 1986, 2001, 2007 and 2011.

Supplementary figure 1. Association of the genetic risk score x participant's own education interaction with BMI cross-sectionally in 2001.



Abbreviations: BMI, body mass index
Vertical lines represent the 95% confidence intervals.

Low genetic risk was defined at the 10th percentile score and high genetic risk at the 90th percentile score of the 97 SNP genetic risk score. Low education refers to primary school; high education refers to a Master's degree or higher.