

First investigation of two obesity-related loci (TMEM18, FTO) concerning their association with educational level as well as income: the MONICA/KORA study

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ABSTRACT

Background Strong evidence exists for an association between socioeconomic status and body mass index (BMI) as well as between genetic variants and BMI. The association of genetic variants with socioeconomic status has not yet been investigated. The aim of this study was to investigate two obesity-related loci—the transmembrane 18 (*TMEM18*) and the fat mass and obesity-associated (*FTO*) gene—for their association with educational level and per capita income, and to test whether the detected genotype–BMI association is mediated by these social factors.

Methods 12 425 adults from a large population-based study were genotyped for the polymorphism rs6548238 near *TMEM18* and rs9935401 within the *FTO* gene. Data on educational level and per capita income were based on standardised questionnaires.

Results High educational level and high per capita income were significantly associated with decreased BMI (-1.503 kg/m^2 , $p < 0.0001$ / -0.820 kg/m^2 , $p < 0.0001$). Neither the polymorphism rs6548238 nor rs9935401 nor their combination were significantly associated with educational level ($p = 0.773$ / $p = 0.827$ / $p = 0.755$) or income ($p = 0.751$ / $p = 0.991$ / $p = 0.820$). Adjustment for social factors did not change the association between rs6548238 or rs9935401 and BMI.

Conclusions As far as the authors know, this is the first study to investigate the association between polymorphisms and socioeconomic status. The polymorphisms rs6548238 and rs9935401 showed no association with educational level or income.

It is without controversy that genetic, environmental and lifestyle factors contribute to the development of obesity,^{1–3} a polygenic disorder with several genes involved.^{4–9} The fat mass and obesity associated (*FTO*) gene has the strongest effect on body mass index (BMI) followed by the transmembrane 18 (*TMEM18*) gene.^{4,6,7,10} Besides genetic variants, socioeconomic status is a well established risk factor for BMI. Epidemiological studies repeatedly show that obesity is more prevalent in individuals of low educational level and income.^{11–13} Furthermore, poor socioeconomic conditions in childhood lead to obesity risk in later life,^{14,15} and family socioeconomic status is inversely related to child obesity.¹⁶ No study has yet looked at the questions of whether there is an association between obesity-related genotypes and socioeconomic status

and whether the socioeconomic status modulates the genotype–BMI association. As far as we know, our study is the first to explore these issues, for which we investigated polymorphisms of the two strongest obesity-related loci (*TMEM18* and *FTO*) in a large population-based sample of 12 425 subjects.

SUBJECTS AND METHODS

Study population

The WHO Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project and the Cooperative Health Research in the Region of Augsburg (KORA) project conducted four independent cross-sectional population-based surveys (S1–S4). For the present study, genotype data were available from 12 425 participants (6251 men and 6174 women) aged 25–74 years from the surveys S2, S3 and S4 (conducted in 1989/90, 1994/5 and 1999/2001). The study was approved by the ethics committee of the Bavarian Medical Association. All participants gave written informed consent to genetic analysis. The potential of population stratification was small.¹⁷ Details of the study population have been described previously.^{18–20}

Body weight was measured in light clothing to the nearest 0.1 kg and height to the nearest 0.5 cm. BMI (kg/m^2) was calculated as body weight in kilograms divided by squared body height in square metres. Educational level was categorised according to the highest level attained: primary (in Germany called ‘Volksschule, Hauptschule’); secondary (‘Mittlere Reife, Realschule’) and tertiary (‘Abitur, Fachhochschule, Universität’) education. Dichotomisation was done into low (primary) and high (secondary or tertiary) educational group. Per capita income was based on the total household net income divided by the number of household members. Households with eight or more persons were excluded ($N = 37$).

Genotyping

Two single nucleotide polymorphisms (SNP) were genotyped: rs6548238 C>T near the *TMEM18* gene and rs9935401 G>A within the *FTO* gene with minor allele frequencies (MAF) of 17.5% or 41.0%, respectively. SNP selection was based on a previous analysis by the same investigators in the same study population, in which the minor alleles of rs6548238 and rs9935401 were significantly

associated with BMI, and on literature reporting the strongest effects on BMI for these two loci.^{6,7}

Samples were genotyped with the MassARRAY system using the iPLEX Gold chemistry (Sequenom, San Diego, California, USA) and were analysed in a matrix-assisted laser desorption ionisation time of flight mass spectrometer (Bruker Daltonik, Leipzig, Germany); 12.5% of samples were double-genotyped. Each SNP was tested for deviation from Hardy–Weinberg equilibrium by means of a χ^2 test. There was no violation of Hardy–Weinberg equilibrium ($p \geq 0.05$). The genotyping success rate represented 94.7% (rs9935401) and 94.6% (rs6548238).

Statistics

Means (\pm SD) or proportions for baseline characteristics of the study population were computed. We explored a mediator analysis according to surrogacy analyses,²¹ including the following criteria²²: first, genotype associated with outcome BMI (model 1); second, mediator (educational level, income) associated with outcome (model 2); third, genotype associated with mediator (model 3); and fourth, including mediator as covariate into the first model, genotype outcome association abolishes (model 4). The association of genotypes and mediators (model 3) was performed by logistic (education) or linear regression (income), assuming an additive genetic model and adjusting for age, sex and survey. The minor allele was defined as the risk or effect allele. Income was log-transformed and quintiles were built. Moreover, we conducted gender-specific analyses. All statistical analyses were performed using the statistical package SAS version 9.1.

RESULTS

Study population

Mean age (\pm SD) was 49 (\pm 14) years and mean BMI was 26.97 (\pm 4.49) kg/m²; 61% of the population attained primary school as the highest educational level. The median of per capita income was 1611.98 DM.

Association of genotypes with BMI (models 1 and 4)

There was a significant association between the polymorphisms rs6548238 and rs9935401 and BMI (model 1) (figure 1). The combination of SNPs showed an estimate of 0.335 kg/m² ($p=1.11 \times 10^{-15}$) per risk allele. Adjustment for educational level or log per capita income—as well as for both social factors together (model 4)—marginally changed beta estimates and p values. Sex-specific analyses showed similar results. The proportion of BMI variance explained by the two SNPs was 0.005%.

Association of social factors with BMI (model 2)

Higher educational and income level were associated with decreasing BMI (figure 1). Compared with the lowest quintile of per capita income, the effect size on BMI is gradually increasing from the second quintile with an estimate of -0.597 kg/m² to the fifth quintile with an estimate of -1.440 kg/m². Similar results were observed for sex-specific analyses. Adjustment for log per capita income did not change the significance of the association between educational level and BMI. Adjustment for educational level changed the association between log per capita income and BMI in men, in whom statistical significance was lost. The proportion of BMI variance explained by the two social factors was 0.050%.

Association of genotypes with socioeconomic status

There was no significant association (model 3) between polymorphisms rs6548238 and rs9935401 or their combination and educational level or log per capita income (figure 1). Sex-specific analyses showed similar results.

DISCUSSION

Our data replicate the result of an inverse association between educational level and BMI, both in men and women,^{23–25} but gender-specific differences were also reported in the literature.^{11,13,26,27}

Concerning income, our analyses also showed a negative association with BMI in both genders. In the Cardiovascular Health Study, lower income was not associated with higher body weight in men, but in women.²⁸ This finding for women was also reported in other studies.^{11,29} A positive association between income level and BMI was reported for men.^{13,25} Adjusting for educational level significantly changed the association between income and BMI in men, but adjustment for income hardly changed the association between educational level and BMI. This result indicates that for educational level the link is more direct than for income. One reason could be that for adults the educational level remains rather stable, whereas income can change more rapidly.

Our major finding is the lack of an association between polymorphisms rs6548238 (*TMEM18*) or rs9935401 (*FTO*) and educational level or income. Furthermore, these social factors are not mediators in the genotype–BMI association.

Neither *TMEM18* nor *FTO* showed a significant association with educational or income level (figure 1). Because this is the first study to investigate this association, our results cannot be directly compared with other studies.

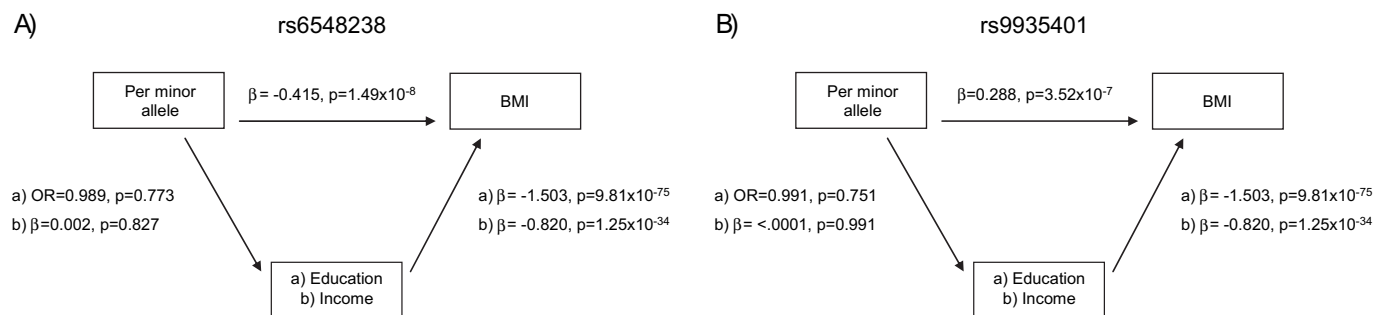


Figure 1 Association between polymorphism (genotype), body mass index (BMI) (outcome) and educational level or income (mediators). Beta estimates (β)/ORs and p values are shown for the association between minor allele and BMI (model 1), mediators (educational level (low = reference) (a) and income (b)) and BMI (model 2), and minor allele and mediators (model 3) for the whole study population; OR=0.989 corresponds to a β of -0.011 and OR=0.991 corresponds to a β of -0.009 ; results are shown separately for rs6548238 (A) and rs9935401 (B); all analyses were adjusted for age, sex and survey; an additive genetic model was assumed.

What is already known on this subject

- ▶ There is strong evidence from genome-wide association studies that genetic variants are associated with BMI and the risk of obesity. It is also known that low socioeconomic status is a risk factor for developing obesity.
- ▶ No study has been published investigating the association between obesity-related genetic variants and socioeconomic status as well as whether socioeconomic factors mediate the genotype–BMI association.

What this study adds

- ▶ The two strongest obesity-related loci (*TMEM18*, *FTO*) investigated here showed no evidence of an association with educational level or income, which is an important finding for public discussions concerning prevention strategies for obesity. Public health interventions should focus not on the genetic background, but lifestyle factors and living conditions.
- ▶ The genotype–BMI association was not modified by considering socioeconomic status.

There has already been some debate on the association between genetic predisposition on the one hand and social status and health inequalities on the other.^{30–31} Furthermore, twin studies indicate a genetic contribution to health status.^{32–33} The main objective for analysing the potential genetic contribution on health inequalities is the identification of target populations for prevention strategies. It might be argued that there is little reason to believe that social status is associated with genotype. It is important, though, to verify this argument by empirical analyses.

Our results are limited by the fact that we have analysed only two, albeit potentially important,^{6,7} genetic loci (*TMEM18*, *FTO*). Future studies should include genome-wide association analyses.

In conclusion, our data provide some evidence for the association of genetic factors (*TMEM18*, *FTO*) with BMI. There is no evidence that the polymorphisms are associated with the socioeconomic factors investigated here or that the socioeconomic factors modulate the genotype–BMI association.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Bavarian Medical Association/Bavarian commissioner for data protection and privacy.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Galgani J**, Ravussin E. Energy metabolism, fuel selection and body weight regulation. *Int J Obes (Lond)* 2008;**32**(Suppl 7):S109–19.
2. **Eckel RH**. Obesity research in the next decade. *Int J Obes (Lond)* 2008;**32**(Suppl 7):S143–51.
3. **Kopelman PG**. Obesity as a medical problem. *Nature* 2000;**404**:635–43.
4. **Frayling TM**, Timpson NJ, Weedon MN, *et al*. A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007;**316**:889–94.
5. **Loos RJ**, Lindgren CM, Li S, *et al*. Common variants near *MC4R* are associated with fat mass, weight and risk of obesity. *Nat Genet* 2008;**40**:768–75.
6. **Willer CJ**, Speliotes EK, Loos RJ, *et al*. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* 2009;**41**:25–34.
7. **Thorleifsson G**, Walters GB, Gudbjartsson DF, *et al*. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet* 2009;**41**:18–24.
8. **Meyre D**, Delplanque J, Chevre JC, *et al*. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet* 2009;**41**:157–9.
9. **Hofker M**, Wijmenga C. A supersized list of obesity genes. *Nat Genet* 2009;**41**:139–40.
10. **Hotta K**, Nakamura M, Nakamura T, *et al*. Association between obesity and polymorphisms in *SEC16B*, *TMEM18*, *GNPDA2*, *BDNF*, *FAIM2* and *MC4R* in a Japanese population. *J Hum Genet* 2009;**54**:727–31.
11. **Flegal KM**, Harlan WR, Landis JR. Secular trends in body mass index and skinfold thickness with socioeconomic factors in young adult women. *Am J Clin Nutr* 1988;**48**:535–43.
12. **Sonne-Holm S**, Sorensen TI. Prospective study of attainment of social class of severely obese subjects in relation to parental social class, intelligence, and education. *BMJ (Clin Res Ed)* 1986;**292**:586–9.
13. **Flegal KM**, Harlan WR, Landis JR. Secular trends in body mass index and skinfold thickness with socioeconomic factors in young adult men. *Am J Clin Nutr* 1988;**48**:544–51.
14. **Parsons TJ**, Power C, Logan S, *et al*. Childhood predictors of adult obesity: a systematic review. *Int J Obes Relat Metab Disord* 1999;**23**(Suppl 8):S1–107.
15. **Senese LC**, Almeida ND, Fath AK, *et al*. Associations between childhood socioeconomic position and adulthood obesity. *Epidemiol Rev* 2009;**31**:21–51.
16. **Murasko JE**. Socioeconomic status, height, and obesity in children. *Econ Hum Biol* 2009;**7**:376–86.
17. **Steffens M**, Lamina C, Illig T, *et al*. SNP-based analysis of genetic substructure in the German population. *Hum Hered* 2006;**62**:20–9.
18. **Loewel H**, Doering A, Schneider A, *et al*. The MONICA Augsburg surveys—basis for prospective cohort studies. *Gesundheitswesen* 2005;**67**(Suppl 1):S13–18.
19. **Wichmann HE**, Gieger C, Illig T. KORA-gen—resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* 2005;**67**(Suppl 1):S26–30.
20. **Holle R**, Happich M, Lowel H, *et al*. KORA—a research platform for population based health research. *Gesundheitswesen* 2005;**67**(Suppl 1):S19–25.
21. **Prentice RL**. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med* 1989;**8**:431–40.
22. **Heid IM**, Vollmert C, Kronenberg F, *et al*. Association of the *MC4R V103I* polymorphism with the metabolic syndrome: the KORA Study. *Obesity (Silver Spring)* 2008;**16**:369–76.
23. **Baecke JA**, Burema J, Frijters JE, *et al*. Obesity in young Dutch adults: I. Socio-demographic variables and body mass index. *Int J Obes* 1983;**7**:1–12.
24. **Rissanen AM**, Heliovaara M, Knekt P, *et al*. Determinants of weight gain and overweight in adult Finns. *Eur J Clin Nutr* 1991;**45**:419–30.
25. **van Lenthe FJ**, Droomers M, Schrijvers CT, *et al*. Socio-demographic variables and 6 year change in body mass index: longitudinal results from the GLOBE study. *Int J Obes Relat Metab Disord* 2000;**24**:1077–84.
26. **Sundquist J**, Johansson SE. The influence of socioeconomic status, ethnicity and lifestyle on body mass index in a longitudinal study. *Int J Epidemiol* 1998;**27**:57–63.
27. **Garn SM**, Bailey SM, Cole PE, *et al*. Level of education, level of income, and level of fatness in adults. *Am J Clin Nutr* 1977;**30**:721–5.
28. **Harris TB**, Savage PJ, Tell GS, *et al*. Carrying the burden of cardiovascular risk in old age: associations of weight and weight change with prevalent cardiovascular disease, risk factors, and health status in the Cardiovascular Health Study. *Am J Clin Nutr* 1997;**66**:837–44.
29. **Kahn HS**, Williamson DF, Stevens JA. Race and weight change in US women: the roles of socioeconomic and marital status. *Am J Public Health* 1991;**81**:319–23.
30. **Holtzman NA**. Genetics and social class. *J Epidemiol Community Health* 2002;**56**:529–35.
31. **Mackenbach JP**. Genetics and health inequalities: hypotheses and controversies. *J Epidemiol Community Health* 2005;**59**:268–73.
32. **Osler M**, McGue M, Christensen K. Socioeconomic position and twins' health: a life-course analysis of 1266 pairs of middle-aged Danish twins. *Int J Epidemiol* 2007;**36**:77–83.
33. **Fujiwara T**, Kawachi I. Is education causally related to better health? A twin fixed-effect study in the USA. *Int J Epidemiol* 2009;**38**:1310–22.