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# Body mass index and depressive symptoms: instrumental-variables regression with genetic risk score

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**The causal role of obesity in the development of depression remains uncertain. We applied instrumental-variables regression (Mendelian randomization) to examine the association of adolescent and adult body mass index (BMI) with adult depressive symptoms. Participants were from the Young Finns prospective cohort study ($n = 1731$ persons, 2844 person-observations), with repeated measurements of BMI and depressive symptoms (modified Beck's Depression Inventory). Genetic risk score of 31 single nucleotide polymorphisms previously identified as robust genetic markers of body weight was used as a proxy for variation in BMI. In standard linear regression analysis, higher adult depressive symptoms were predicted by higher adolescent BMI ($B = 0.33$, CI = 0.06–0.60, $P = 0.017$) and adult BMI ($B = 0.47$, CI = 0.32–0.63, $P < 0.001$). These associations were replicated in instrumental-variables analysis with genetic risk score as instrument ($B = 1.96$, CI = 0.03–3.90, $P = 0.047$ for adolescent BMI; $B = 1.08$, CI = 0.11–2.04, $P = 0.030$ for adult BMI). The association for adolescent BMI was significantly stronger in the instrumented analysis compared to standard regression ($P = 0.04$). These findings provide additional evidence to support a causal role for high BMI in increasing symptoms of depression. However, the present analysis also demonstrates potential limitations of applying Mendelian randomization when using complex phenotypes.**

Keywords: Adolescence, adulthood, body mass index, depression, genetic risk score, instrumental variables, Mendelian randomization, obesity

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Despite the increasing public health importance of obesity, the role of excessive body weight in the etiology of mental health problems remains uncertain (Atlantis & Baker 2008, de Wit *et al*. 2010; Herva *et al*. 2006; Kivimäki *et al*. 2009; Kivimäki *et al*. 2011a; Kivimäki *et al*. 2011b; Luppino *et al*. 2010; Roberts *et al*. 2000; 2002). Some prospective longitudinal studies show that higher body mass index (BMI), the most commonly used marker of adiposity, increases the probability of developing depression several years later (Herva *et al*. 2006; Luppino *et al*. 2010; Roberts *et al*. 2000; Roberts *et al*. 2002). However, other studies have not observed such an association (Luppino *et al*. 2010) and some investigations have even reported an inverse relationship between BMI and depressive symptoms (Lawlor *et al*. 2007, 2011), supporting the so-called 'jolly fat' hypothesis. If obesity elevates depression risk, the ongoing secular increases in BMI would have major implications for mental health burden in the population.

Methodological limitations of observational data, such as residual confounding due to unobserved variables and bias resulting from reverse causality, may have contributed to inconsistencies between studies. Instrumental-variables analysis with genetic variants as instruments, or 'Mendelian randomization', has been advanced as a methodological tool to strengthen causal inferences in observational studies of modifiable risk factors with known genetic determinants (Bochud & Rousson 2010; Lawlor *et al*. 2008; Smith & Ebrahim 2004; Smith *et al*. 2007). The method takes advantage of the random allocation of genetic variants that already occurs between individuals before conception. The hypothesized health outcome is predicted only with the proportion of variance in the risk factor that is explained by genetic variants. These genetic variants are expected to be independent of factors that commonly confound associations between risk factors and health outcomes, such

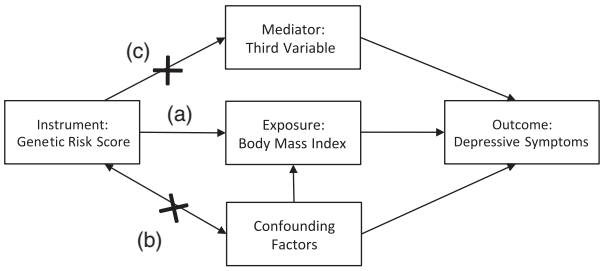


**Figure 1: Underlying assumptions of instrumental-variables analysis in the association between BMI and depressive symptoms using genetic risk score as an instrument for BMI**. (a) There should be a strong enough association between genetic risk score and body mass index for the risk score to be a valid instrument. (b) There should be no association between genetic risk score and confounding factors (including population stratification). (c) There should be no other pathway linking genetic risk score and depressive symptoms besides BMI.

as health behaviors or socioeconomic position. Assuming that the genetic variants affect the outcome only because they influence the risk factor, Mendelian randomization can provide estimates of the association that are free of confounding and reverse causation (Smith *et al*. 2007). Figure 1 outlines the assumptions of instrumental-variables regression in more detail.

To our knowledge, only two studies have examined the association between BMI and depressive symptoms using Mendelian randomization. In the British Whitehall II study, higher BMI increased common mental disorders when a genetic variant in the *FTO* gene was used as an instrument for BMI (Kivimäki *et al*. 2011a). In contrast, a more recent study in a large Danish cohort based on variants in the *FTO* and *MC4R* genes found that gene-instrumented BMI was associated with lower rather than higher mental distress (Lawlor *et al*. 2011), providing evidence for the 'jolly fat' hypothesis. A major limitation of these two studies is their reliance on single genetic variants that explain only a very limited proportion of the variance in BMI. Such weak instruments are open to bias (Pierce *et al*. 2011).

This study applied the Mendelian randomization approach to provide additional evidence on whether the association between BMI and depressive symptoms is causal or whether the association is more likely to be due to confounding. While Mendelian randomization is not free of methodological assumptions (Fig. 1; Glymour *et al*. 2012; Martens *et al*. 2006), it can provide further evidence for or against the hypothesis that obesity increases mental health problems. To advance previous research, we constructed a genetic risk score of BMI consisting of 31 single-nucleotide polymorphisms (SNP) that were identified as genetic markers for BMI in a recent multi-cohort genome-wide association studies (Speliotes *et al*. 2010). This score was then used as an instrument for adult and adolescent BMI in predicting adult depressive symptoms, providing a stronger instrument for BMI than single genetic variants (Sleiman & Grant 2010).

## Materials and methods

### *Participants*

The Cardiovascular Risk in Young Finns study is an ongoing, population-based prospective cohort study (Åkerblom *et al*. 1991; Raitakari *et al*. 2008). The original sample consists of 3596 healthy Finnish children and adolescents derived from six birth cohorts, aged 3, 6, 9, 12, 15 and 18 years at baseline in 1980. To select a broadly representative sample, Finland was divided into five areas according to locations of university cities with a medical school (Helsinki, Kuopio, Oulu, Tampere and Turku). In each area, urban and rural boys and girls were randomly selected on the basis of their unique personal social security number. The sample has been followed subsequently in seven data collection waves in 1983, 1986, 1989, 1992, 1997, 2001 and 2007. Despite study attrition, the sample has remained largely representative of the baseline sample, although men and younger participants have been more likely to drop out (Raitakari *et al*. 2008). The study was approved by local ethics committees, and all participants gave their written informed consent.

This study used data for adulthood depressive symptoms, BMI and covariates assessed in 2001 and 2007. Data for adolescent BMI were based on screenings in 1980, 1983 and 1986. The analytic sample included 1731 participants (989 women) with data on depressive symptoms and covariates in adulthood and BMI in childhood and adulthood.

### *Measures*

Both in 2001 and 2007, depressive symptoms were assessed using a modified version of Beck's Depression Inventory (BDI; Beck & Steer 1987) translated in Finnish and adapted for use in the Young Finns study (Jokela & Keltikangas-Järvinen 2011; Jokela *et al*. 2007). In the original version of the BDI, individuals are asked to choose one of the four alternative response statements in each of the 21 items, representing ascending levels of symptom severity. In the modified version used here, the 21 items of the scale were the second mildest statements of the original BDI items (e.g. 'I often feel sad'). Participants are asked to rate each of the 21 statement items on a five-point scale ranging from 'totally disagree' (1) to 'totally agree' (5). The depressive symptoms score was calculated as the sum of these 21 items. The second mildest statements of the original BDI items were selected for the modified scale because they were expected to best reflect individual differences in depressive symptoms in the general population. The modified BDI correlates with $r = 0.77$ ($P < 0.001$) with the original BDI-II (Beck *et al*. 1996) which was administered to the participants in 2007. We used the modified BDI to capture wider variation in depressive symptoms than assessed by the clinical screening instrument.

Adult height and weight were measured during medical examinations in 2001 and 2007, and adult BMI was calculated using the standard formula (weight in kg/height in $m^2$). For adolescent BMI, we used the latest BMI measurement available between ages 9 and 18 from data collections in 1980, 1983 and 1986, adjusted for age at measurement.

Parental education (years of education of the more educated parent) was reported by the parents in 1980. Smoking (0 = non-smoker, 1 = smoker), physical activity (frequency of leisure-time physical activity; 0 = none, 1 = once monthly, 2 = once weekly, 3 = 2–3 times weekly, 4 = 4–6 times weekly, 5 = daily), education (years of education) and alcohol consumption (frequency of drinking six or more alcohol portions; 0 = never, 1 = 2–6 annually, 2 = once monthly, 3 = 2–3 times monthly, 4 = once weekly, 5 = twice or more weekly) were reported by the participants in 2001 and 2007.

### *Genetic risk score*

The genome wide SNP analyses (GWAS) for 2450 participants were performed in 2009 by using the 670 K Illumina platform (Sanger Institute, Cambridge, UK; for details see Smith *et al*. 2010). Variation in over 670 000 known SNPs was measured from 2450 study subjects. Data imputation for up to 2.5 million SNPs has been performed using information on Hapmap 2 by

using MACH (http://www.sph.umich.edu/csg/abecasis/mach/). We calculated multi-SNP ($P < 1 \times 10^{-7}$)m risk scores (m = number of SNPs) summarizing the impact of 31 SNPs for BMI (25). Using a set of m SNPs, for the *i*th SNP in the *j*th individual denote $x_{ij}$ as the 0/1/2 coded genotype (for directly genotyped markers) or expected allele count (which takes real values between 0.0 and 2.0 for imputed markers). The risk score for participant *j* is then defined to be: $s_j = x_{1j} + x_{2j} + \cdots + x_{mj}$.

The main analysis was based on a 31-SNP additive genetic risk score from the SNPs reported by Speliotes *et al*. (2010) The rs12444979 SNP identified by Speliotes *et al*. (2010) was not included due to missing data. Details of the SNPs are reported in Table S1. In addition, we created two variants of the risk score for supplementary analysis by (1) including only the 23 SNPs of these 31 SNPs which were associated with BMI in the total Young Finns cohort (details not shown), and (2) by weighting the 31-SNP genetic score (the risk score for participant *j* defined as: $S_j = w_1 x_{1j} + w_2 x_{2j} + \cdots + w_m x_{mj}$, where coefficients $w_1, w_2, \ldots, w_m$ are specified to be the effect sizes, in kg/m$^2$ per risk allele, estimated in single SNP analyses of BMI reported by Speliotes *et al*. (2010). Given that the results for the 31-SNP genetic score are most likely to be replicable across studies, the main results are shown for this genetic risk score. Results of the additional analyses are presented in Tables S2 and S3.

### *Statistical analysis*

Measurements from the two resurveys in adulthood in 2001 and 2007 were treated as separate observations in a multilevel data format, so that each participant contributed to 1 or 2 person-observations to the dataset ($n = 1731$ unique participants, 2844 person-observations). Adult BMI and other covariates assessed concurrently with depressive symptoms in 2001 and 2007 were treated as time-dependent covariates, so that these covariates could have different values for the two person-observations of the same participant. Adolescent BMI was treated as a time-invariant covariate having the same value for the same participant in both adult resurveys. Standard analyses were carried out using linear regression (for continuous outcomes) and logistic regression (for dichotomous outcomes). The effects of adjusting for BMI in the association between the genetic risk score and study covariates were quantified as the proportional attenuation of the unadjusted regression coefficient compared to the adjusted coefficient. The robust estimation method, which takes into account the non-independence of person-observations of the same participant, was used to calculate standard errors (Rogers 1994). The strength of the genetic risk score as a genetic instrument for BMI was assessed on the basis of the *F*-value derived from first-stage regression analysis. *F*-values higher than 10 indicate a sufficiently strong instrument to be used in instrumental-variables regression. Instrumental-variables analysis was performed with the ivreg2 package of STATA 12.1 for Mac.

## Results

Table 1 shows the descriptive statistics for the sample. In age- and sex-adjusted models, depressive symptoms were associated with several adulthood covariates, including education ($B = -0.24$; 95% CI = −0.38 to −0.09; $P = 0.002$), smoking ($B = 2.16$; CI = 1.03–3.29; $P < 0.001$), physical activity ($B = -1.98$; CI = −2.42 to −1.54; $P < 0.001$) and alcohol consumption ($B = 0.97$; CI = 0.58–1.36; $P < 0.001$).

### *Genetic risk score*

The *F*-value of the association between genetic instrument and adult BMI increased with increasing number of SNPs included in the score (Fig. 2), although after 22 SNPs the *F*-value started to decrease slightly. The total range of the 31-SNP risk score was associated with a approximately 4.1 units difference in adult BMI, so that the predicted adult BMI of individuals with the lowest and highest genetic risk score was 23.5 and 27.6 kg/m$^2$, respectively. The corresponding difference was 2.1 units range for adolescence BMI (18.9 vs. 21.0 kg/m$^2$). These findings support the status of genetic score as an instrument for BMI levels.

Table 2 shows the associations between genetic risk score and covariates. As well as predicting adolescent and adult BMI, the genetic risk score was also associated with a greater prevalence of depressive symptoms and higher probability

**Table 1:** Descriptive statistics ($n = 1731$ participants, 2844 person-observations)

| | Men | Women |
|---|---|---|
| Number of participants | 742 | 989 |
| Number of person-observations | 1198 | 1646 |
| Measurements in follow-ups in 1980, 1983, and 1986 | | |
| Age (years)† | 15.4 (3.3) | 15.2 (3.4) |
| Adolescent BMI (kg/m$^2$)† | 19.9 (3.1) | 19.8 (3.1) |
| Parental education (years) | 10.8 (3.6) | 10.7 (3.6) |
| Measurements across follow-ups in 2001 and 2007 | | |
| Age (years) | 34.8 (5.8) | 34.5 (5.9) |
| 31-SNP BMI genetic risk score | 27.5 (3.3) | 27.3 (3.3) |
| Adult BMI (kg/m$^2$) | 26.1 (4.0) | 24.8 (4.7) |
| Depressive symptoms (score)‡ | 41.2 (12.8) | 44.3 (14.4) |
| Smoking (% smokers) | 34.5 | 24.0 |
| Physical activity (0–5) | 2.2 (1.2) | 2.4 (1.1) |
| Alcohol consumption (0–5) | 2.1 (1.4) | 1.0 (1.2) |
| Education (years) | 15.1 (3.5) | 15.9 (3.4) |

Values are means (and SDs) or percentages calculated over two measurement times in 2001 and 2007.
†Data derived from the most recent follow-up in which data for the participant were available.
‡Modified Beck Depression Inventory (range from 21 to 105).

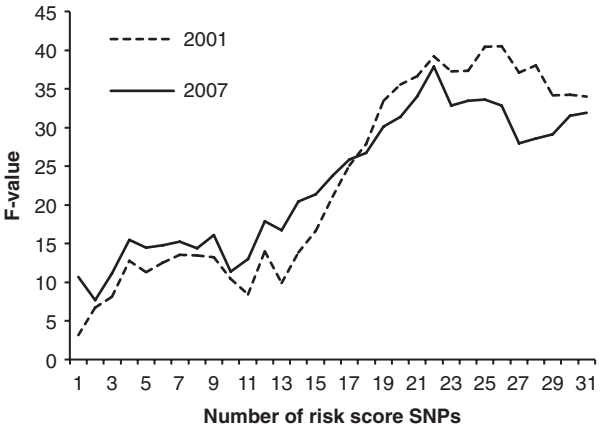


**Figure 2:** ***F*-value of the instrument indicating the strength of association between genetic risk score and BMI (in 2001 and 2007) when individual SNPs are added to the sum score one by one in order of the individual effect magnitudes of the SNPs (largest effects first)**.

**Table 2:** Associations between the 31-SNP genetic risk score and study covariates

| Outcome | *B* (95% CI) | $\beta$ | *F*-value | $R^2$ (%) | *P*-value |
|---|---|---|---|---|---|
| Sex[†] | 0.00 (−0.01, 0.01) | 0.03 | 1.3 | 0.1 | 0.252 |
| Age (years)[†] | 0.00 (−0.08, 0.08) | 0.00 | 0.0 | 0.0 | 0.991 |
| Measurements in follow-ups of 1980, 1983, and 1986 | | | | | |
| Adolescent BMI (kg/m$^2$)[†] | 0.10 (0.05, 0.14) | 0.10 | 19.1 | 1.1 | <0.001 |
| Parental education (years)[†] | −0.02 (−0.07, 0.03) | −0.02 | 0.5 | 0.0 | 0.466 |
| Measurements across follow-ups of 2001 and 2007 | | | | | |
| Adult BMI (kg/m$^2$) | 0.18 (0.12, 0.24) | 0.14 | 34.2 | 1.9 | <0.001 |
| Depressive symptoms (score) | 0.18 (0.01, 0.36) | 0.04 | 4.0 | 0.2 | 0.044 |
| Smoking (0 = no, 1 = yes)[‡] | 1.04 (1.01, 1.07) | 1.14 | – | 0.2 | 0.012 |
| Physical activity (0–5) | 0.01 (−0.01, 0.02) | 0.02 | 0.7 | 0.0 | 0.404 |
| Alcohol consumption (0–5) | 0.01 (−0.01, 0.03) | 0.02 | 0.9 | 0.0 | 0.347 |
| Education (years) | −0.04 (−0.10, 0.01) | −0.04 | 2.8 | 0.2 | 0.096 |

$\beta$, standardized linear regression coefficient; *B*, unstandardized linear regression coefficient; CI, confidence interval; $R^2$, fraction of explained variance (%).
Models are fitted with two measurement times ($n = 1731$ participants, 2844 person-observations) unless otherwise noted.
[†]Models fitted with one measurement time ($n = 1731$).
[‡]Regression coefficient expressed as odds ratios.

of smoking; the association with education was weaker. These findings suggest that instrumental-variables analyses on the association between BMI and depressive symptoms should be adjusted for adulthood covariates. However, these associations were much weaker than those with BMI, as indicated by the *F*-values (Table 2).

The association between genetic risk score and depressive symptoms ($B = 0.18$, CI = 0.01–0.36; $P = 0.044$; Table 2) attenuated by 41% when adjusted for adult BMI ($B = 0.11$, CI = −0.06 to 0.28; $P = 0.212$) and by 14% when adjusted for adolescent BMI ($B = 0.16$, CI = −0.01 to 0.34; $P = 0.068$). Thus, a large proportion of the association between genetic risk score and depressive symptoms was not accounted for by adolescent or adult BMI. The association between genetic risk score and smoking was little affected by adjustments for adult BMI (OR = 1.04, CI = 1.01–1.07, $P = 0.022$; 3% attenuation) and adolescent BMI (OR = 1.04, CI = 1.01–1.07, $P = 0.23$; 4% attenuation).

### *Instrumental-variables regression*

The standard and instrumented regression models are compared in Table 3. Both adult and adolescent BMI were associated with depressive symptoms in the standard regression analysis, and these associations strengthened and were statistically significant when instrumented by the genetic risk score. The effect of adult BMI on depressive symptoms was 2.3-fold stronger and the effect of adolescent BMI was 5.8-fold stronger in the instrumental-variables regression model compared to those in the corresponding standard regression models. On the basis of the predicted values of the regression models, the level of adult depressive symptoms was 0.39 standard deviations (SD) higher in obese adults compared to normal weight adults (depressive symptoms scores of 46.9 vs. 41.6), which increased to 0.88 SD (52.0 vs. 39.8) in the instrumented analysis. The corresponding difference for adolescent BMI was 0.26 SD higher depressive symptoms in obese adolescents compared to normal weight adolescents (46.4 vs. 42.8), which increased to 1.52 SD (63.0 vs. 42.0), in the instrumental-variables analysis.

**Table 3:** Linear and instrumental variables regression models predicting adult depressive symptoms by adult and adolescent BMI ($n = 1731$ participants, 2844 person-observations)

| | *B* coefficients (95% CI) for adult depressive symptoms | | *P* for difference between models[‡] |
|---|---|---|---|
| | Linear regression | Instrumental variables regression[†] | |
| Adult BMI (kg/m$^2$) | 0.47 (0.32, 0.63); $P < 0.001$ | 1.08 (0.11, 2.04); $P = 0.030$ | 0.15 |
| Adolescent BMI (kg/m$^2$) | 0.33 (0.06, 0.60); $P = 0.017$ | 1.96 (0.03, 3.90); $P = 0.047$ | 0.04 |

All models adjust for sex, age, measurement time, parental education, education, smoking, alcohol consumption and physical activity.
[†]In the instrumental variables regression, the 31-SNP genetic risk score of BMI is used as an instrument for BMI.
[‡]Durbin–Wu–Hausman test.

### *Supplementary analysis*

When the instrumental-variables regression models were repeated with the 23-SNP genetic risk score, all the results were substantially similar to those in the main analyses (Tables S2 and S3). When the weighted 31-SNP score was used as the instrument, the regression coefficients for the instrumented associations between BMI and depressive symptoms were again higher than those in standard regression, but they were imprecisely estimated and did not reach statistical significance at conventional levels ($P = 0.24$ and 0.25, respectively; Tables S1 and S2).

The differences in estimates between the instrumented and standard regressions were not statistically significant ($P = 0.80$ and 0.35).

## Discussion

In this population-based study, we applied Mendelian randomization approach with 31 genetic variants to provide further evidence on the causal vs. non-causal association between BMI and depressive symptoms. Our data offer novel evidence to support the possibility of a causal association, as genetic variance in adolescent and adult BMI predicted adult depressive symptoms. While the relationship between total BMI variance and depressive symptoms may be biased by reverse causality and confounding by unmeasured third variables, the more restricted genetic variance in BMI is expected to be less confounded (Lawlor *et al*. 2008; Smith *et al*. 2007). Our results also imply that conventional observational studies may underestimate the association between BMI and symptoms of depression, particularly with respect to adolescent BMI. However, the instrumented effects had lower precision than standard analysis, and therefore only the effect of adolescent BMI was significantly stronger in the instrumented analysis compared with the association estimated by standard regression.

### *Comparison with other studies*

The present results are in agreement with a previous Mendelian randomization study in the Whitehall II cohort, in which higher body weight related to *FTO* genotype predicted increased psychological distress in men (Kivimäki *et al*. 2011a). On the other hand, our findings contradict the other Mendelian randomization study in a Danish cohort (Lawlor *et al*. 2011) in which lower rather than higher BMI was associated with increased risk of distress in analyses instrumented by the *FTO* and *MC4R* genotypes. The genetic risk score used in this study provided a much stronger genetic instrument and a much wider BMI range was explained by the genetic instrument than the single genotypes used in these two previous studies. A further advantage of this study is the measurement of BMI in medical examinations in both adolescence and adulthood. This allowed us to examine both longitudinal and cross-sectional relationships between instrumented BMI and adult depressive symptoms.

### *Plausible mechanisms*

Several plausible psychological and social mechanisms have been suggested to mediate the effects of obesity on depressive symptoms, including social stigma and discrimination, negative self-image, low health-related quality of life and poorer health behaviors (Markowitz *et al*. 2008). Some recent studies have suggested that obesity and mood disorders may share common biological pathways, including the HPA axis (Björntorp 2001) and immuno-inflammatory reactions (Miller *et al*. 2003; Soczynska *et al*. 2011). Thus, obesity and mood disorders may be linked by common underlying pathophysiological mechanisms instead of, or in addition to, psychological and social factors.

The stronger association between BMI and depressive symptoms in the instrumented compared to standard regression implies that there may be some environmental confounders that attenuate this association in observational data. Given the imprecision of estimation in the instrumental-variables approach, the point estimates from these analyses need to be interpreted with caution. Mendelian randomization studies might be used to strengthen the evidence for various plausible mechanisms by examining whether genetic instruments for body weight are related to these intermediate outcomes. The positive association between BMI genetic risk score and smoking observed here provides one piece of such evidence by suggesting that body weight might also be related to smoking initiation, which, in turn, has been associated with increased depression risk (Chaiton *et al*. 2009).

### *Methodological considerations*

BMI is a complex phenotype influenced by several genes, and these genes may influence various other phenotypes besides BMI. One of the assumptions of instrumental-variables analysis is that the instrument should affect the outcome only via the exposure of interest. If the instrument has (1) a direct effect on the outcome or (2) an effect mediated via other factors besides the exposure of interest, the instrumented analysis may overestimate for the effect of the exposure. This methodological assumption is empirically unverifiable (Hernan & Robins 2006; Martens *et al*. 2006). The genetic risk score for BMI was associated with smoking, and to some extent with lower education, suggesting that the genetic risk score could be associated with depressive symptoms via other pathways besides BMI. This would violate the assumptions of instrumental-variables analysis, and the instrumented association would thereby overestimate the causal association between BMI and depressive symptoms. However, it is also possible that smoking lies on the causal pathway between BMI and depressive symptoms, as it is sometimes used as a means to control weight.

Furthermore, the association between BMI and depressive symptoms might arise directly due to pleiotropic genetic effects that affect both the tendency to gain weight and risk of becoming depressed (Glymour *et al*. 2012). There is some evidence suggesting that BMI and psychological distress may share familial origins (Afari *et al*. 2010), although another study concluded exactly the opposite (Choy *et al*. 2009). There may also be common psychological traits that influence BMI, depressive symptoms and smoking initiation, which account for their clustering with the genetic risk score (Gale *et al*. 2008; von Stumm *et al*. 2009). The shared genetics of obesity and mental health problems thus remain to be examined more thoroughly.

The present sample included only native Finnish individuals, so the results are unlikely to be confounded by population heterogeneity. However, the genetic risk score might be differently associated with BMI in different ethnic groups, so the present findings may not generalize to other ethnic groups directly. Depressive symptoms were assessed using a modified version of the BDI, which has not been psychometrically

validated. Although the modified instrument is strongly correlated with the original version of the BDI that was developed as a screening instrument for depression (Beck & Steer 1987), it taps into less severe symptoms of depression. A meta-analysis of 15 prospective longitudinal studies indicated that obesity is more strongly associated with clinically diagnosed depression than with self-rated depressive symptoms (Luppino *et al*. 2010). Results derived from studies using self-reported symptoms of depression may therefore underestimate the clinical significance of the association between BMI and depression.

## Conclusions

The present results provide supportive evidence for a causal association between excessive body weight and increased risk of depressive symptoms, although this evidence needs to be considered bearing in mind the methodological limitations of Mendelian randomization. The observed association between BMI genetic risk score and smoking also indicates that the assumptions of Mendelian randomization may be difficult to meet when the exposure of interest is a complex phenotype (rather than a specific biochemical or neurobiological factors produced by specific genes). Thus, our findings also emphasize the need to assess confounding in Mendelian randomization studies. Furthermore, the present results do not exclude the possibility of a bidirectional association between body weight and depressive symptoms (Luppino *et al*. 2010). Finally, with few exceptions (Afari *et al*. 2010; Choy *et al*. 2009), previous studies have examined associations between BMI and mental health using only phenotypic data. The current findings suggest that more attention needs to be given to genetic analysis of the bidirectional association between BMI and mental health problems.

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## Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

**Table S1:** Details of the 31 SNPs used for the genetic risk score of BMI.

**Table S2:** Associations between 23-SNP and weighted 31-SNP genetic risk scores and covariates.

**Table S3:** Linear and instrumental-variables regression models predicting adult depressive symptoms by adult and adolescent BMI ($n = 1731$ participants, 2844 person-observations).

**Figure S1:** *F*-value indicating the strength of association between weighted genetic risk score and body mass index (in 2001 and 2007) when individual SNPs are added to the sum score one by one in order of the individual effect magnitudes of the SNPs (largest effects first).