Investigating the association between body fat and depression via Mendelian randomization

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Abstract
Obesity and depression are major public health concerns that are both associated with substantial morbidity and mortality. There is a considerable body of literature linking obesity to the development of depression. Recent studies using Mendelian randomization indicate that this relationship is causal. Most studies of the obesity–depression association have used body mass index as a measure of obesity. Body mass index is defined as weight (measured in kilograms) divided by the square of height (meters) and therefore does not distinguish between the contributions of fat and nonfat to body weight. To better understand the obesity–depression association, we conduct a Mendelian randomization study of the relationship between fat mass, nonfat mass, height, and depression, using genome-wide association study results from the UK Biobank (n = 332,000) and the Psychiatric Genomics Consortium (n = 480,000).

Our findings suggest that both fat mass and height (short stature) are causal risk factors for depression, while nonfat mass is not. These results represent important new knowledge on the role of anthropometric measures in the etiology of depression. They also suggest that reducing fat mass will decrease the risk of depression, which lends further support to public health measures aimed at reducing the obesity epidemic.

Introduction
Obesity, defined as abnormal or excessive accumulation of body fat, is a major public health concern as an established risk factor for cardiovascular disease, type II diabetes, certain cancers, and overall decreased life expectancy. Furthermore, observational studies have shown an association between obesity and depression. For example, Luppino et al. found that obese individuals were 55% more likely to develop depression, while depressed individuals were 58% more likely to become obese.

To investigate the observed association between obesity and depression, prior studies have performed Mendelian randomization (MR), a method from genetic epidemiology which uses data from genome-wide association studies (GWAS) to determine whether a risk factor is causal for an outcome. MR studies have indicated that there is a causal relationship going from obesity to depression, but not vice versa. These MR studies measured obesity using body mass index (BMI), which is calculated as weight (measured in kilograms) divided by the square of height (meters).

Although BMI is the most common measure of obesity (for example, an obese individual is generally defined as someone with BMI ≥ 30), its use has been repeatedly criticized. Most notably, BMI does not distinguish between fat mass and nonfat mass. This distinction is very important from a physiological perspective, due to the fact that adipose tissue has very different properties compared to muscle and bone, the other major tissues contributing to body weight. In particular, adipose tissue is an endocrine organ that produces a range of adipokines and inflammatory proteins, which have been associated with negative systemic effects that may also affect the brain.

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Furthermore, BMI does not capture body fat location, and while upper-body and visceral fat, which are more common in men, contribute to the development of an unhealthy cardiometabolic profile, lower body fat, which is more common in women, seems to be protective of this. In addition, how much of an individual’s BMI is due to fat, and where this fat is located, might also be of importance, as these factors can influence body satisfaction and social stigma, with psychological consequences.

The aim of this study was to increase the understanding of the obesity–depression association by assessing the relationship between specific and biologically informative components of BMI (fat mass and nonfat mass, stratified on limbs and trunk) and depression via a MR study using results from large GWAS.

Materials and methods

In total, we consider 21 anthropometric measures: the first six are BMI, weight, height, whole-body fat percentage, whole-body fat mass, and whole-body nonfat mass; the remaining 15 are fat percentage, fat mass and nonfat mass for each of trunk, right arm, left arm, right leg, and left leg. Supplementary Fig. 1 reports the genetic correlations between the 21 measures. We use MR to test whether each measure is a causal risk factor for depression, then to test whether depression is a causal risk factor for each measure.

In order to use MR to test whether one phenotype is a causal risk factor for another, we require GWAS summary statistics for both phenotypes. For the anthropometric traits, we use genome-wide summary statistics provided by the Neale Lab (http://www.nealelab.is/uk-biobank/), who performed association analyses for over 2000 phenotypes from the UK Biobank (http://www.ukbiobank.ac.uk/). The UK Biobank is a population-based cohort of approximately 500,000 individuals; 54% are female, the average age is 57 (range 37–73), while 94% report as being White British. For the anthropometric GWAS, the average sample size is 331,910 (see Table 1 for exact numbers); the analysis was performed using linear regression including ten principal components and sex as covariates.

For depression, we use summary statistics from the most recent GWAS of major depressive disorder (MDD) by the Psychiatric Genomics Consortium (PGC), available at (https://www.med.unc.edu/pgc/results-and-downloads). This study recruited individuals from seven cohorts; they used a relatively liberal definition of MDD, based on self-reporting, clinical assessment, and examination of medical records, with an estimated population prevalence of 15%. The association analysis was performed using logistic regression, including significantly-associated principal components as covariates. The PGC provides two sets of summary statistics: from their main GWAS of 480,359 samples (135,458 cases, 344,901 controls) they report results for 10,000 of the most strongly-associated SNPs; whereas from a “sub-GWAS” of 173,005 samples (59,851 cases and 113,154 controls), they report results for all SNPs. Therefore, when testing whether depression is a causal risk factor for one of the anthropometric measures (which requires only results for significantly-associated SNPs), we use summary statistics from the main GWAS, whereas when testing whether an anthropometric measure is a causal risk factor for depression (which requires genome-wide results), we use summary statistics from the sub-GWAS.

In total, there are 6,568,396 SNPs common to the UK Biobank and PGC GWAS (we excluded SNPs with alleles A & T or C & G, or with info score < 0.9). We test whether an anthropometric measure is causally associated with depression using inverse-weighted regression, for which we use the R package Mendelian randomization. To decide which SNPs to use in this regression, we first identify which have \( P < 5 \times 10^{-8} \) for the measure, then thin these until no pair remains within 3 cM with correlation squared \( r^2 > 0.05 \). We use the same strategy to test whether depression is a causal risk factor for an anthropometric measure, except now we identify a set of independent, genome-wide significant SNPs for depression.

A key assumption of MR is no pleiotropy. For example, the SNPs we use when testing the relationship between BMI and depression should be causal for BMI, but not depression. This is difficult to test directly, so instead we perform three sensitivity analyses. Firstly, we repeat the inverse-weighted regression excluding SNPs showing evidence for pleiotropy (\( P < 0.05/N \), where \( N \) is the number of independent, genome-wide significant SNPs). Secondly, we instead assess causality using weighted-median regression, which gives unbiased estimates provided at least 50% of the information comes from non-pleiotropic SNPs. Thirdly, we estimate the intercept from Egger Regression; an intercept significantly different to zero (\( P < 0.05 \)) is an indication of directional pleiotropy.

Our primary analysis focuses on BMI, weight, height, whole-body fat mass, whole-body nonfat mass, and whole-body fat percentage; our secondary analysis considers the 15 location-specific measures of fat mass, nonfat mass and fat percentage. As we are performing a total of 42 tests, we set the (conservative) Bonferroni corrected significance threshold at \( P < 0.05/42 \) (this is satisfied when the regression slope is \( \geq 3.0 \) SDs from zero).

Results

Table 1 reports the number of independent, genome-wide significant SNPs for each of the 21 anthropometric measures, and how much of the phenotypic variation each set of SNPs explains. The results of our primary analysis are displayed in Figs. 1 and 2 and Table 2. Our main
conclusions are based on the results from inverse-variance regression using all SNPs (the red lines in each plot), while the remaining three regressions (the orange, green and blue lines) are sensitivity analyses. We note that each time the slope from inverse-variance regression using all SNPs is statistically significant, this finding is supported by the three sensitivity analyses (i.e., the slope remains significant when SNPs showing evidence for pleiotropy are excluded or when we use weighted-median regression, and Egger regression does not find significant directional pleiotropy).

Figure 1a confirms that BMI is a causal risk factor for depression. The estimated slope from inverse-weighted regression is 0.17 (SD 0.03), which is significantly greater than zero ($P = 1e^{-7}$) and indicates that a 1-SD increase in BMI corresponds to a 0.17 increase in the log-odds ratio (OR) for depression. Figure 1b indicates there is a causal relationship between weight and depression; however, the estimated slope (0.13, SD 0.03) is less than that for BMI, which supports the current preference to measure obesity using BMI rather than weight. Figure 1c suggests that height (short stature) is a causal risk factor for depression; the estimated slope is $-0.06$ (SD $0.02$), indicating that a 1-SD increase in height corresponds to a 0.06 decrease in the log-odds ratio (OR) for depression.

Figure 1d and e shows that whole-body fat percentage and whole-body fat mass are both causal risk factors for depression; the estimated slopes are very similar (0.20, SD 0.04 and 0.19, SD 0.03, respectively) indicating that there is no advantage to normalizing (i.e., measuring fat percentage instead of fat mass). The estimated slope in Fig. 1f is 0.06 (SD 0.03), indicating that MR finds no evidence that whole-body nonfat is a causal risk factor for depression.

Figure 2 shows that, consistent with previous studies, there is no significant evidence that depression is a causal risk factor for any of the six anthropometric measures investigated here.

### Table 1 Sample characteristics for the traits of interest

| Trait (UK Biobank Code) | Mean (standard deviation) | Sample size | Independent genome-wide significant SNPs | Approximate variance explained (%) |
|-------------------------|--------------------------|-------------|------------------------------------------|-----------------------------------|
| Depression (N/A)        |                          | 480,359     | 35                                       | 0.3                               |
| BMI (21,001)            | 27.4 kg/m² (4.8)         | 336,107     | 420                                      | 6.4                               |
| Weight (21,002)         | 77.9 kg (15.9)           | 336,227     | 527                                      | 8.3                               |
| Height (50)             | 168.5 cm (9.3)           | 336,474     | 1304                                     | 29.2                              |
| Body fat percentage (23,099) | 31.4% (8.5)           | 331,117     | 336                                      | 4.9                               |
| Body fat mass (23,100)  | 24.8 kg (9.6)            | 330,762     | 387                                      | 5.8                               |
| Body nonfat mass (23,101) | 53.2 kg (11.5)         | 331,291     | 667                                      | 11.9                              |
| Trunk fat percentage (23,127) | 31.2% (8.0)           | 331,113     | 312                                      | 4.6                               |
| Arm fat percentage (right) (23,119) | 29.5% (10.2)        | 331,249     | 313                                      | 4.7                               |
| Arm fat percentage (left) (23,123) | 30.4% (10.3)        | 331,198     | 323                                      | 4.8                               |
| Leg fat percentage (right) (23,111) | 32.0% (10.7)        | 331,296     | 322                                      | 4.5                               |
| Leg fat percentage (left) (23,115) | 32.0% (10.6)        | 331,278     | 315                                      | 4.4                               |
| Trunk fat mass (23,128)  | 13.7 kg (5.2)           | 331,093     | 384                                      | 5.8                               |
| Arm fat mass (right) (23,120) | 1.2 kg (0.6)          | 331,226     | 373                                      | 5.7                               |
| Arm fat mass (left) (23,124) | 1.3 kg (0.7)          | 331,164     | 378                                      | 5.7                               |
| Leg fat mass (right) (23,112) | 4.3 kg (1.9)          | 331,293     | 363                                      | 5.5                               |
| Leg fat mass (left) (23,116) | 4.2 kg (1.9)          | 331,275     | 372                                      | 5.6                               |
| Trunk nonfat mass (23,129) | 29.6 kg (6.0)          | 331,030     | 659                                      | 12.1                              |
| Arm nonfat mass (right) (23,121) | 2.9 kg (0.8)          | 331,221     | 577                                      | 9.8                               |
| Arm nonfat mass (left) (23,125) | 2.9 kg (0.8)          | 331,159     | 565                                      | 9.6                               |
| Leg nonfat mass (right) (23,113) | 9.0 kg (2.0)          | 331,285     | 575                                      | 9.9                               |
| Leg nonfat mass (left) (23,117) | 8.9 kg (2.0)          | 331,258     | 558                                      | 9.6                               |

Mean, standard deviation, sample size, number of independent genome-wide significant SNPs, and approximate proportion of variance these explain for depression and the 21 anthropometric measures. #For depression the estimated variance is on the liability scale, assuming a prevalence of 15%.
Table 3 reports results from our secondary analysis. For each of the 15 location-specific anthropometric measures, the results are consistent with those from the whole-body version; i.e., regardless of whether we consider trunk, right arm, left arm, right leg, or left arm, we again find that fat percentage and fat mass are causally associated with depression, but that nonfat mass is not. For fat percentage and fat mass, we are interested in comparing slope estimates, as significant differences would indicate that risk of developing depression depends on fat location. The largest difference is observed for fat percentage, where the estimated slope for left leg (0.34, SD 0.06) is approximately twice that for trunk (0.16, SD 0.04); however, although this difference is nominally significance.
Discussion

We have used MR to investigate the causal relationship between different anthropometric measures and depression. We first confirmed that BMI is a causal risk factor for depression, but found no significant evidence that depression causes increased BMI. These results are in line with recent MR studies reporting evidence that higher BMI causally increases the risk of depression, but not the reverse.5–8

Our main finding is that body fat mass is a causal risk factor for depression, but that body nonfat mass is not, therefore indicating that the BMI-depression causality is driven by fat. We note from Table 1 that the number of genome-wide associated SNPs for whole-body nonfat mass was significantly lower than for BMI, suggesting that BMI is driven by fat and not nonfat mass.
Table 2 Primary results of the Mendelian randomization analyses

| Trait               | Anthropometric measure → Depression | Depression → Anthropometric measure |
|---------------------|-------------------------------------|-------------------------------------|
|                     | Inverse-variance regression         | Pleiotropic SNPs excluded           | Weighted-median regression       | Significant (P < 0.05/42) | Inverse-variance regression | Pleiotropic SNPs excluded | Weighted-median regression | Significant (P < 0.05/42) |
| BMI                 | 0.17 (0.03) P = 1e−7                | 0.16 (0.03) P = 3e−7                | 0.22 (0.04) P = 1e−8 ✓            |                         | 0.08 (0.05) P = 0.08        | 0.04 (0.03) P = 0.18       | 0.11 (0.03) P = 4e−4 x    |
| Weight              | 0.13 (0.03) P = 7e−6                | 0.12 (0.03) P = 2e−5                | 0.16 (0.04) P = 1e−5 ✓            |                         | 0.07 (0.04) P = 0.08        | 0.02 (0.03) P = 0.053      | 0.07 (0.03) P = 0.007 x   |
| Height              | −0.06 (0.02) P = 9e−4               | −0.05 (0.02) P = 1e−3               | −0.04 (0.03) P = 0.16 ✓           |                         | −3e−3 (0.03) P = 0.91       | −0.03 (0.01) P = 0.05      | −0.02 (0.02) P = 0.20 x   |
| Body fat percentage | 0.20 (0.04) P = 7e−6                | 0.18 (0.05) P = 4e−5                | 0.20 (0.05) P = 2e−4 ✓            |                         | 0.05 (0.04) P = 0.15        | 0.03 (0.02) P = 0.22       | 0.09 (0.02) P = 1e−4 x    |
| Body fat mass       | 0.19 (0.03) P = 5e−9                | 0.18 (0.03) P = 8e−9                | 0.23 (0.04) P = 9e−9 ✓            |                         | 0.08 (0.05) P = 0.10        | 0.02 (0.03) P = 0.65       | 0.13 (0.03) P = 3e−5 x    |
| Body nonfat mass    | 0.06 (0.03) P = 009                 | 0.06 (0.03) P = 008                 | 0.07 (0.04) P = 010 x            |                         | 0.04 (0.02) P = 006         | 0.02 (0.02) P = 016        | 0.06 (0.02) P = 5e−4 x    |

Estimates of the slope (SD in brackets) and p-value from inverse-weighted regression, inverse-weighted regression with pleiotropic SNPs excluded and weighted-median regression, and whether the slope from inverse-weighted regression was significant (P < 0.05/42). Columns 6–9 examine whether depression is causally associated with each anthropometric measure. Significant tests (slope estimate P < 0.05/42) are marked in bold.
| Trait                  | Inverse-variance regression | Pleiotropic SNPs excluded | Weighted-median regression | Significant ($P < 0.05/42$) | Inverse-variance regression | Pleiotropic SNPs excluded | Weighted-median regression | Significant ($P < 0.05/42$) |
|------------------------|-----------------------------|---------------------------|-----------------------------|-------------------------------|-----------------------------|---------------------------|-----------------------------|----------------------------|
| Trunk fat percentage   | 0.16 (0.04) $P = 3e−5$     | 0.14 (0.04) $P = 1e−4$   | 0.18 (0.05) $P = 1e−4$      | ✓                             | 0.06 (0.03) $P = 0.16$    | 0.03 (0.03) $P = 0.34$   | 0.06 (0.03) $P = 0.04$   | x                          |
| Arm fat percentage (right) | 0.26 (0.05) $P = 5e−8$   | 0.23 (0.05) $P = 3e−7$   | 0.30 (0.06) $P = 3e−7$      | ✓                             | 0.05 (0.03) $P = 0.11$    | 0.02 (0.02) $P = 0.32$   | 0.10 (0.02) $P = 3e−5$   | x                          |
| Leg fat percentage (left) | 0.24 (0.05) $P = 2e−7$   | 0.23 (0.05) $P = 9e−7$   | 0.30 (0.06) $P = 1e−7$      | ✓                             | 0.06 (0.04) $P = 0.12$    | 4e−3 (0.02) $P = 0.86$   | 0.10 (0.02) $P = 6e−5$   | x                          |
| Leg fat percentage (right) | 0.33 (0.06) $P = 6e−9$   | 0.30 (0.05) $P = 4e−8$   | 0.36 (0.07) $P = 2e−7$      | ✓                             | 0.04 (0.03) $P = 0.24$    | 0.03 (0.02) $P = 0.06$   | 0.04 (0.02) $P = 0.03$   | x                          |
| Leg fat percentage (left) | 0.34 (0.06) $P = 2e−8$   | 0.30 (0.06) $P = 1e−7$   | 0.38 (0.07) $P = 2e−7$      | ✓                             | 0.04 (0.03) $P = 0.20$    | (0.02) $P = 0.06$        | 0.05 (0.02) $P = 7e−3$   | x                          |
| Trunk fat mass          | 0.17 (0.03) $P = 2e−8$   | 0.16 (0.03) $P = 1e−7$   | 0.20 (0.04) $P = 2e−7$      | ✓                             | 0.07 (0.05) $P = 0.12$    | −4e−3 (0.03) $P = 0.90$  | 0.09 (0.03) $P = 0.01$   | x                          |
| Arm fat mass (right)    | 0.19 (0.03) $P = 8e−9$   | 0.18 (0.03) $P = 2e−8$   | 0.25 (0.04) $P = 2e−9$      | ✓                             | 0.08 (0.05) $P = 0.08$    | 0.02 (0.03) $P = 0.63$   | 0.14 (0.03) $P = 4e−6$   | x                          |
| Arm fat mass (left)     | 0.19 (0.03) $P = 2e−8$   | 0.17 (0.03) $P = 3e−8$   | 0.25 (0.04) $P = 5e−9$      | ✓                             | 0.08 (0.05) $P = 0.08$    | 0.02 (0.03) $P = 0.47$   | 0.14 (0.03) $P = 9e−6$   | x                          |
| Leg fat mass (right)    | 0.27 (0.04) $P = 1e−10$  | 0.25 (0.04) $P = 2e−10$  | 0.33 (0.05) $P = 6e−10$     | ✓                             | 0.06 (0.04) $P = 0.14$    | 0.03 (0.02) $P = 0.25$   | 0.09 (0.02) $P = 2e−4$   | x                          |
| Leg fat mass (left)     | 0.27 (0.04) $P = 1e−10$  | 0.25 (0.04) $P = 3e−10$  | 0.33 (0.05) $P = 2e−10$     | ✓                             | 0.06 (0.04) $P = 0.13$    | 0.03 (0.02) $P = 0.22$   | 0.10 (0.03) $P = 6e−05$  | x                          |
| Trunk nonfat mass       | 0.03 (0.03) $P = 0.28$   | 0.03 (0.03) $P = 0.28$   | 0.05 (0.04) $P = 0.27$      | X                             | 0.03 (0.02) $P = 0.09$    | 0.03 (0.02) $P = 0.10$   | 0.05 (0.02) $P = 2e−03$  | x                          |
| Arm nonfat mass (right) | 0.04 (0.04) $P = 0.33$   | 0.04 (0.04) $P = 0.29$   | 0.03 (0.05) $P = 0.54$      | X                             | 0.04 (0.02) $P = 0.05$    | 0.01 (0.02) $P = 0.43$   | 0.06 (0.02) $P = 5e−4$   | x                          |
| Arm nonfat mass (left)  | 0.06 (0.04) $P = 0.13$   | 0.06 (0.04) $P = 0.11$   | 0.07 (0.05) $P = 0.15$      | X                             | 0.04 (0.02) $P = 0.05$    | 9e−3 (0.02) $P = 0.60$   | 0.05 (0.02) $P = 2e−3$   | x                          |
| Leg nonfat mass (right) | 0.06 (0.04) $P = 0.11$   | 0.06 (0.03) $P = 0.09$   | 0.08 (0.05) $P = 0.08$      | X                             | 0.05 (0.02) $P = 0.05$    | 0.03 (0.02) $P = 0.13$   | 0.06 (0.02) $P = 9e−4$   | x                          |
| Leg nonfat mass (left)  | 0.08 (0.04) $P = 0.04$   | 0.07 (0.04) $P = 0.03$   | 0.09 (0.05) $P = 0.05$      | X                             | 0.05 (0.03) $P = 0.07$    | 0.03 (0.02) $P = 0.06$   | 0.05 (0.02) $P = 2e−3$   | x                          |

Estimates of the slope (SD in brackets) and p-value from inverse-weighted regression, inverse-weighted regression with pleiotropic SNPs excluded and weighted-median regression, and whether the slope from inverse-weighted regression was significant ($P < 0.05/42$). Columns 2–5 examine whether each anthropometric measure is a causal risk factor for depression. Columns 6–9 examine whether depression is causally associated with each anthropometric measure. Significant tests (slope estimate $P < 0.05/42$) are marked in bold.
psychological consequences of adiposity and not by its adverse metabolic effects. This conclusion resonates well with the results of our study.

In addition to the results on the impact of body fat on the risk of depression, we also found evidence suggesting that height (short stature) is a causal risk factor for depression. Several large observational studies have found short stature to be associated with poorer mental health,25, lower health-related quality of life,26 depressive symptoms in adolescents27 and adults28,29, and suicide in men30. Other studies have found no association between height and depression or suicide31 or negligible effects of height on mental health32. The association between short stature and poor mental health may be explained by confounding factors, such as socioeconomic status, prenatal development, or childhood factors, or by a causal effect of height on depression risk33,34. Our results indicate that at least part of the association between short stature and depression is indeed due to a direct causal effect.

Finally, we note some limitations of our work. Firstly, the MR estimates rely on three key assumptions: (i) the SNPs used as genetic predictors for a trait are causal for that trait; (ii) these SNPs are not associated with confounders of the trait-outcome association; (iii) these SNPs only affect the outcome through the causal relationship (i.e., there is no pleiotropy). We can be confident of (i) because our genetic predictors only used SNPs robustly-associated (P < 5e−8) with the trait, while (ii) should be true due to the fact an individual’s genotypes are randomly allocated during gamete formation. It is hard to explicitly test (iii), however, our sensitivity analyses indicate that our conclusions are not the consequence of pleiotropy.

Secondly, the UK Biobank measured fat and nonfat mass via bioelectrical impedance analysis (using a Tanita BC418MA body composition analyzer), which is considered less accurate than techniques such as dual-energy x-ray absorptiometry. However, we would expect measurement error to cause the estimates for fat and nonfat to become more similar, so the fact that we observed a significant difference indicates that the UK Biobank measurements were sufficiently accurate for our purpose.

Thirdly, we note that some samples were common to both the anthropometric and MDD GWAS (the PGC GWAS used approximately 30,000 individuals from the UK Biobank). Although this overlap is likely to have only a small impact, ideally, our analysis would be repeated using summary statistics from completely independent GWAS.

Fourthly, while we found only suggestive evidence that location of fat affects risk of depression, we recognize that the high correlations between measurements taken in the trunk, arms, and legs (Supplementary Fig. 1) would have reduced our power to detect significant differences.

Fifthly, there may be sex-specific psychological and physiological factors affecting the obesity–depression relationship. While we were not able to test sex differences, because the PGC did not release results from male-only and female-only GWAS of depression, this is worthy of further study.

In conclusion, the present study provides evidence that the causal relationship between BMI and depression is driven by fat mass and height, and not by nonfat mass. These results represent important new knowledge on the role of anthropometric measures in the etiology of depression. They also suggest that reducing fat mass will decrease the risk of depression, which lends further support to public health measures aimed at reducing the obesity epidemic.

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Conflict of interest
The authors declare that they have no conflict of interest.

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