Higher adiposity and mental health: causal inference using Mendelian Randomisation

Francesco Casanova^[1], Jessica O'Loughlin^[1], Susan Martin[1], Robin N. Beaumont[1], Andrew R. Wood[1], Ed Watkins[2], Rachel Freathy[1], Saskia Hagenaars[3], Timothy M. Frayling[1], Hanieh Yaghootkar,[1], Jess Tyrrell[1]*

^These authors contributed equally

[1] Genetics of Complex Traits, The College of Medicine and Health, University of Exeter, The RILD Building, RD&E Hospital, Exeter, EX2 5DW

[2] School of Psychology, University of Exeter, United Kingdom

[3] Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

*Corresponding Author: Dr Jess Tyrrell, j.tyrrell@exeter.ac.uk

Abstract

Higher adiposity is an established risk factor for psychiatric diseases including depression and anxiety. The associations between adiposity and depression may be explained by the metabolic consequences and/or by the psychosocial impact of higher adiposity. We performed one- and two- sample Mendelian Randomisation(MR) in up to 145,668 European participants from the UK Biobank to test for a causal effect of higher adiposity on ten well-validated mental health and wellbeing outcomes derived using the Mental Health Questionnaire (MHQ). We used three sets of adiposity genetic instruments: a) a set of 72 BMI genetic variants, b) a set of 36 favourable adiposity variants and c) a set of 38 unfavourable adiposity variants. We additionally tested causal relationships (1) in men and women separately, (2) in a subset of individuals not taking antidepressants and (3) in non-linear MR models. Two-sample MR provided evidence that a genetically determined one standard deviation (1-SD) higher BMI (4.6 kg/m^2) was associated with higher odds of current depression [OR:1.50, 95%CI: 1.15, 1.95] and lower wellbeing [ß:-0.15, 95%CI:-0.26, -0.04]. Findings were similar when using the metabolically favourable and unfavourable adiposity variants, with higher adiposity associated with higher odds of depression and lower wellbeing scores. Our study provides further evidence that higher BMI causes higher odds of depression and lowers wellbeing. Using genetics to separate out metabolic and psychosocial effects, our study suggests that in the absence of adverse metabolic effects higher adiposity remains causal to depression and lowers wellbeing.

Introduction

Higher adiposity is an established risk factor for many psychiatric diseases including depression and anxiety. There is extensive evidence linking higher body mass index (BMI) to higher odds of depression(1) and anxiety(2, 3) in the adult population, especially in women(4). Understanding the complex relationships between adiposity and mental health outcomes is crucial to facilitate public health and medical intervention planning. Whilst several studies have attempted to test the directionality of associations between adiposity and mental health phenotypes including depression(5, 6) and anxiety(3, 7), determining causality in many studies is not trivial due to confounding or biases.

Mendelian randomisation (MR) is a genetic approach that has provided some evidence that higher BMI(8-12) and higher body fat percentage(13) cause depression. To date, there are no studies using MR to specifically test the role of adiposity on anxiety. MR relies on the fact that genetic variation is randomly allocated at conception and assumes that genetic variants associated with the exposure (e.g. BMI) represent unconfounded proxies. The majority of studies to date have tested the role of adiposity on depression using summary statistic data from genome-wide association studies (GWAS)(10, 11). These analyses are limited to the GWAS performed and leave several questions unanswered, for example, a) does higher BMI cause depression in men and women separately, b) are the relationships linear between BMI and depression and c) does antidepressant usage influence this relationship. Previous work by our group(12) attempted to address some of these questions in the UK Biobank, but was limited by the mental health variables at the time.

The observational associations between obesity and depression or anxiety, could be explained by a) the physiological consequences of obesity, including higher inflammation(14, 15)

and/or b) the psychological/social consequences of obesity. However, there is limited evidence about a) whether adiposity is a causal risk factor for psychiatric diseases and b) which component of higher adiposity (psychological/adverse social effect of excess weight, metabolic pathways or alternative pathways) cause the higher risk.

Here, we comprehensively test the relationship between higher BMI and well validated measures of depression and anxiety using data from the mental health questionnaire (MHQ) in up to 145,668 individuals of European ancestry in the UK Biobank. Firstly, we used three sets of genetic instruments in Mendelian randomisation analyses: a) 72 BMI genetic variants, b) a set of 36 favourable adiposity variants that associate with higher adiposity, but a more favourable metabolic profile (characterised by lower triglycerides, higher HDL and lower type 2 diabetes risk) and c) a set of 38 unfavourable adiposity variants that associate with higher adiposity and a less favourable metabolic profile (higher triglycerides, lower HDL and higher type 2 diabetes risk). We tested effects in men and women separately and explored non-linear relationships between BMI and mental health outcomes.

Results

Table 1 summarises the demographics of the 145,668 UK Biobank participants with valid genetic data, measured BMI and MHQ data available.

Higher BMI and body fat percentage are associated with adverse mental health outcomes in the UK Biobank

Observationally, higher BMI was associated with higher odds of depression and GAD (Table 2). For example, a 1-SD (4.6 kg/m^2) higher BMI was associated with 1.16 [95%CI:1.14, 1.17] higher odds of major depression, 1.56 [95%CI:1.51, 1.62] higher odds of current depression and 1.10 [95%CI:1.07, 1.13] higher odds of GAD. Following adjustment for GAD higher odds of depression were still observed per 1 SD higher BMI, but the GAD findings were attenuated to the null when the model was adjusted for depression (Supplementary table 1). Higher BMI was also associated with lower wellbeing (Table 2).

Observationally, higher BFP was associated with higher odds of depression and GAD (Table 2). A 1-SD (8.4%) higher BFP associated with 1.22 [95%CI:1.20, 1.24] higher odds of major depression, 1.75 [95%CI:1.66, 1.84] higher odds of current depression and 1.17 [95%CI:1.13, 1.21] higher odds of GAD. Higher BFP was associated with lower wellbeing, with a 1SD higher BFP was associated with lower wellbeing [ß:-0.27, 95%CI: -0.80, -0.26].

Observational associations were consistent when sex stratified analyses were performed (Table 2). Adjusting the observational analyses for type 2 diabetes, alcohol intake, physical activity, hypertension, LDL, HDL, CVD and CAD slightly attenuated the effect estimates toward the null. However, higher BMI/BFP remained associated with higher odds of

depression, anxiety and lower wellbeing although in females the confidence intervals for current GAD crossed the null (Supplementary Table 2).

Mendelian randomization analyses provided evidence that higher BMI causes depression and lowers wellbeing but is not associated with GAD

1-sample MR using unrelated indiviudals of European ancestry provided evidence for the causal role of higher BMI in depression. A genetically determined SD (4.6kg/m^2) higher BMI was associated with higher odds of major depression [OR:1.15, 95% CI:1.03, 1.29] and current depression [OR:1.57, 95% CI:1.11, 2.23] in all individuals. The points estimates were trending in the same direction in men and women separately, although in men the confidence intervals crossed the null (supplementary table 3).

1-sample MR provided limited evidence for a relationship between higher genetically instrumented BMI and GAD or GAD severity (supplementary table 3).

1-sample MR provided evidence that higher BMI caused lower wellbeing scores in all individuals and in men and women separately (supplementary table 6). In all individuals, a 1SD higher genetically instrumented BMI was associated with a 0.22 reduction in wellbeing score [95%CI: -0.32, -0.13].

2-sample MR provided further evidence that higher genetically instrumented BMI is associated with depression outcomes (Figure 1 and Table 3). For example, a 1-SD higher BMI caused 1.50 [95%CI: 1.15, 1.95] and 1.09 [95%CI: 0.98, 1.21] higher odds of current depression and major depression respectively. Results also suggest that higher BMI is

associated with more severe depression (Figure 1 and Table 3). For example, a 1-SD higher BMI caused 1.81 [95%CI: 1.28, 2.56] higher odds of severe current depression and 1.27 [95%CI: 1.06, 1.53] higher odds of severe major depression. The effect estimates tended to be higher in women, but confidence intervals overlapped.

Genetically higher BMI was not associated with higher odds of GAD or GAD severity (Figure 1 and Table 3). Whilst, higher genetic BMI was associated with lower wellbeing scores in all individuals and women only (Figure 1 and Table 3). In all participants, a 1SD higher genetically instrumented BMI caused a 0.15 reduction in wellbeing score [95%CI: -0.26, -0.04].

The effects of higher BMI on mental health outcomes were directionally consistent when more pleiotropy robust 2-sample MR methods were utilised (Supplementary table 4). MR-Egger provided no evidence of horizontal pleiotropy.

Sensitivity analyses

Using one-sample MR approaches in the unrelated subset we repeated our analyses excluding individuals on antidepressant medications (supplementary table 5, supplementary figure 1A). Results were similar for depression and GAD outcomes when excluding individuals on antidepressants at recruitment to the UK Biobank study (supplementary table 5). For example, a one SD higher genetically instrumented BMI associating with 1.14 [95%CI 1.02, 1.29] higher odds of major depression and 1.65 [95%CI: 1.08, 2.52] higher odds of current depression.

We performed one-sample MR in the unrelated subset looking at a) atypical depression cases (n=2,632) only versus controls and b) major depression in the absence of atypical depression cases (n=29,379) versus controls. These analyses demonstrated that genetically instrumented higher BMI was robustly associated with atypical depression, with a one SD higher BMI causing 2.21 [95%CI: 1.59, 3.09] higher odds of atypical depression. This was consistent in sex stratified analyses (supplementary table 3). In our major depression analyses excluding atypical cases we observed an attenuation of the OR, with a one SD higher BMI associated with 1.09 higher odds of major depression [95%CI: 0.97, 1.23]. In sex stratified analyses the effect was attenuated to the null in men but tentatively remained in women (Supplementary table 3).

Favourable adiposity versus unfavourable adiposity and mental health

1-sample MR provided evidence that higher genetically instrumented favourable adiposity was associated with higher current depression in all indviduals [OR:2.48, 95% CI:1.27, 4.84] (supplementary table 3). In sex stratified analyses the effect estimates were directionally consistent although in women the confidence intervals crossed the null. MR using the unfavourable adiposity variants provided evidence for a causal role of higher unfavourable adiposity in depression. A genetically determined 1SD higher UFA was associated with 1.23 higher odds of major depression [95% CI:1.08, 1.41] and 2.10 higher odds of current depression [95% CI:1.37, 3.21]. The point estimates were consistent in men and women however the confidence intervals were much wider in men (supplementary table 3).

2-sample MR using both the favourable and unfavourable adiposity variants provided similar results. Higher favourable and unfavourable adiposity associated with higher odds of

depression, with stronger associations for more severe depression phenotypes (Figure 1 and Table 3).

Exclusion of individuals taking antidepressants at baseline did not alter our findings (supplementary table 5, supplementary figure 1B and 1C). Atypical depression was associated with higher favourable and unfavourable adiposity in all individuals (supplementary table 3) and exclusion of atypical depression cases from our major depression variable did not alter our findings in the one sample setting (supplementary table 3).

Neither 1- nor 2-sample MR provided evidence for a relationship between both favourable and unfavourable adiposity and GAD or GAD severity (supplementary table 3).

In contrast, both the favourable and unfavourable adiposity variants were associated with lower wellbeing scores (Table 3 and supplementary table 3). In sex stratified analyses the favourable and unfavourable adiposity variants were only associated with lower wellbeing in women (-0.31 [95%CI; -0.57, -0.05] in women and -0.068 [95%CI: -0.36, 0.23] in men).

For all 2-sample MR analyses, MR methods that are more robust to pleiotropy provided consistent results and MR-Egger provided no evidence of horizontal pleiotropy (Supplementary tables 6 and 7).

Non linear relationships

There was some evidence that both low and high BMI resulted in higher PHQ9 severity scores in males only (Figure 2, Supplementary table 8). For men, a unit lower BMI in the lowest BMI decile (<21.8kg/m^2) was associated with a higher PHQ9 severity score [ß:0.13,

95%CI: 0.03, 0.29], whilst in the highest BMI decile (>32.5kg/m^2) a unit higher BMI was associated with higher PHQ9 severity [ß:0.29, 95%CI:0.07, 0.51].

Non-linear MR provided tentative evidence for a non-linear relationship between higher BMI and current GAD in women but not in men (Figure 2, Supplementary table 8). For women in the lowest BMI decile (<21.8kg/m^2) a unit lower BMI was associated with 1.25 [95%CI:0.88, 1.75] higher odds of current GAD. For women in the highest BMI decile (32.6 to 67.4kg/m^2) a unit higher BMI was associated with 1.37 [95%CI:1.02, 1.83] higher odds of current GAD.

The strongest evidence of non-linear relationships was found between BMI and wellbeing, with both low and high BMI associated with lower wellbeing (Figure 2 and Supplementary table 8). For all individuals in the lowest BMI decile (<21.8kg/m2), lower BMI was associated with lower wellbeing [ß:-0.08, 95%CI:-0.14, 0.01], whilst individuals in the highest BMI decile (>32.5 kg/m^2) a unit higher BMI was also associated with lower wellbeing [ß:-0.12, 95%CI:-0.19, -0.05]. The same non-linear relationship was seen when stratified by sex although the confidence intervals in females crossed the null.

Discussion

Using Mendelian randomisation and well validated mental health measures in the UK Biobank, our study provides further evidence that higher BMI, and therefore obesity, leads to higher odds of depression(8-10, 12), higher depression severity and lowers wellbeing(26, 27). There was evidence that both high (>32.5 kg/m^2) and low BMI (<21.8 kg/m^2) may lead to lower wellbeing in both men and women. In addition, we tested which component of higher adiposity (psychological/adverse social effect of excess weight or metabolic pathways) cause the higher risk of mental health outcomes. Using this approach we provide evidence that higher adiposity in the absence of an adverse metabolic health profile causes depression and lowers wellbeing. In contrast, we found little evidence that higher adiposity in the presence or absence of adverse metabolic consequences causes generalised anxiety disorder.

The pathways from BMI to mental health could be biological or social. The biological pathways include the role of BMI as a risk factor for other negative health outcomes, such as diabetes and cardiovascular disease. In contrast societal influences, perceptions and stigma could cause individuals to associate negative health consequences with higher BMI and consequently report poorer mental health. To explore this further we used two sets of genetic variants – one which associates with higher adiposity but better metabolic health (favourable adiposity) and the second which associates with higher adiposity but poorer metabolic health (unfavourable adiposity). The effect estimates for depression and wellbeing were consistent for both sets of genetic variants, suggesting that the pathway from higher BMI to adverse mental health is not purely metabolic and to some extent may be driven by other factors (e.g. psychosocial factors). This may be partial explained by the relationship between higher BMI and lower socioeconomic position (SEP) and social contact as demonstrated by ourselves(28, 29) and others(30). Although, the associations between BMI and SEP may be predominantly

driven by familial effects(28, 31). In combination, with the evidence in UK populations that lower SEP associates with depression(32), this may mean that our results reflect a causal pathway from higher adiposity to lower SEP to higher depression. An alternative pathway which may explain the causal relationship between higher BMI and mental health is pain. Future work should look at multivariate approaches to tease apart these associations further.

The adiposity to depression findings in this study build on previous work by ourselves(12) and others(9, 11). Here, we were able to utilise the phenotypically rich MHQ in UK Biobank, which highlights a) a stronger relationship with current depression as defined by the PHQ-9 and b) the importance of atypical depression in the adiposity to major depression relationship using the CIDI-SF definition. Our findings were consistent with a recent study from Kappleman using the PHQ-9 data(33) which demonstrated that genetically instrumented BMI was associated with anhedonia, tiredness, appetite changes and feelings of inadequacy in the PHQ9. Atypical depression is characterised by weight gain and sleeping more than usual. This was robustly associated with BMI, favourable and unfavourable adiposity in our analyses. As atypical depression could result in unhealthy diets and lower physical activity levels reverse causal inference needs to be assessed.

This study provides further evidence of the adverse effects of higher BMI on wellbeing, which builds on previous work in the UK Biobank focused on subjective wellbeing(26). The previous work by Wooton *et al.*, highlighted that the relationship between higher BMI and subjective wellbeing was predominantly driven by the health satisfaction component included in their subjective wellbeing measure. Here, we have used the MHQ measure of subjective wellbeing which incorporates general happiness, general happiness with own health and belief that one's own life is meaningful. Our findings are similar to that of the previous study

with higher BMI lowering wellbeing, although our non-linear analyses provide evidence that both high and low BMI can have adverse effects on wellbeing.

Happiness is generally highly valued by individuals(34) and has the potential to act as a motivator in tackling the rising prevalence of obesity. Further work needs to explore whether emphasising the potential benefits to mental health and wellbeing that could be achieved by weight loss is a better motivator for weight loss than the well established adverse physical health consequences of obesity.

This study provided limited evidence for the causal role of adiposity in GAD. Previous observational studies have provided mixed evidence for the role of higher BMI in GAD, with some demonstrating positive associations(35, 36), whilst others provide no evidence of an association(2) or highlight age, sex and racial differences(37). Observationally, we observed strong associations with GAD, but not when we adjusted our observational models for depression or when we used MR, which provided limited evidence that higher adiposity causes GAD. Non-linear MR suggested high and low BMI in women may cause GAD and this fits with previous observational analyses where heterogenous associations with BMI were observed to be potentially influenced by demographic charateristics(37).

The adverse effects of low BMI on wellbeing suggested by our non-linear MR analyses were of similar magnitude to the adverse effects of higher BMI. However, the effects of higher BMI were seen across a wider range of BMIs, in larger numbers of people, and so, if real will have greater societal implications. The majority of individuals in the low BMI group were actually within the "recommended" range (18.5-24.9 kg/m^2). Only 2000 individuals in the UK Biobank with a BMI in the underweight category (BMI<18.5 kg/m^2), meaning we had

insufficient power to apply any MR to this subgroup. There was limited evidence for non-linear findings in other outcomes, although there was some evidence that males in the lowest BMI decile with lower BMI had higher PHQ9 scores and females in the lowest BMI decile with lower BMI were more likely to report GAD. Previous research has suggested a U-shaped relationship between BMI and GAD in women(37), which could be driven by eating disorders (e.g. anorexia nervosa).

The individual level data available in UK Biobank allowed us to stratify our analyses by sex and exclude individuals on antidepressant medication. In general our findings were similar when analyses were stratified by sex and when we excluded individuals taking antidepressant medication. The non-linear MR provided some suggested sex differences, with evidence of non-linear relationships between a) the PHQ-9 and higher BMI in men, but not in women and b) current GAD in women only. However, larger sample sizes are required to confirm these sex specific findings.

Strengths and limitations

The major strength of this study was the availability of individual level data in 145,668 individuals with well validated mental health outcomes available. This allowed us to perform several stratified analyses (e.g. sex and antidepressant usage stratified) and to run several sensitivity analyses including non-linear MR to test for non-linear causal relationships between adiposity and mental health outcomes. We acknowledge several limitations with this study. First, the UK Biobank is not population representive. However, our results were consistent with several other studies which use data from different age ranges and from different European countries. Second these analyses focused on a European population, so our findings our not generalisable to other populations. Third, the mental health questionnaire

was only available in a subset of Biobank participants and work by ourselves and others have suggested potential participation biases in this subset(38). Fourth, the favourable and unfavourable instruments only explain a small percentage of variation in body fat percentage, limiting our power, however the large numbers of individuals with mental health questionnaire data means that we had sufficient power to detect the OR reported in the observational analyses. Fifth, the sensitivity analyses were performed in the one-sample MR framework in the unrelated subset, which may not fully account for population structure. However, these findings were consistent with the 2-sample MR approaches. Finally, whilst the favourable adiposity variants associate with a more favourable metabolic profile, they do associate with higher C-reactive protein (CRP), which means in these analyses we cannot rule out the role of inflammation in linking adiposity to mental health outcomes.

Conculsion

In summary, using well validated mental health measures in up to 145,668 UK Biobank participants, we provide evidence that higher adiposity in the presence and absence of adverse metabolic effects, as estimated by genetics is causal to higher odds of depression and lower wellbeing scores. Our findings add to the evidence base to support the need to reduce obesity because of the adverse consequences on depression and wellbeing.

Materials and Methods

UK Biobank

The UK Biobank recruited over 500,000 adults aged between 37 and 73 years of age from 2006 to 2010. The study is extensively described elsewhere(16). Briefly, extensive phenotypic data (from questionnaires, anthropometric measures, etc.) were collected at baseline and subjects agreed to have their health followed over time and participate in

subsequent follow up activities. All participants were asked to provide blood, urine and saliva samples which were used for subsequent analyses. Genetic data were available for all participants and SNP genotypes were generated from the Affymetrix Axiom UK Biobank array (~450,000 individuals) and the UKBiLEVE array (~50,000 individuals). The genetic data underwent extensive centralised quality control(17). This study includes 145,668 individuals with mental health questionnaire data and measured BMI available, who were defined European using principal component analyses as previously described(12).

Exposure and outcome measures

Body mass index (BMI) and body fat percentage (BFP)

BMI was calculated for all participants from measured weight (kg)/height $(m)^2$. Body fat was calculated by impedance measurement (variable 23099). Both BMI and body fat percentage were inverse normalised prior to analysis.

Mental health outcomes

Mental health outcomes were defined using the definitions summarised in Davis et al.(18) and the R code which is freely available (https://data.mendeley.com/datasets/kv677c2th4/3). Here we focused on:

1. Major depression and major depression severity (CIDI severity)
2. Current depression and current depression severity (PHQ9 severity)
3. Generalised anxiety disorder (GAD) and anxiety severity
4. Current anxiety (Current GAD)
5. Wellbeing

More details of the coding and variables used is provided in the supplementary material.

Observational associations

Mental health outcomes were regressed against BMI and body fat percentage using logistic (major depression, severe major depression, current depression, severe current depression, GAD, current GAD) and linear regression (CIDI severity, PHQ9 severity, GAD severity, wellbeing score) models. All models were adjusted for age at baseline, sex and assessment centre, the Townsend Deprivation Index (TDI;variable 189) and smoking status then further adjusted for type 2 diabetes, alcohol intake, physical activity, hypertension, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), CardioVascular Disease (CVD) and Coronary Artery Disease (CAD). As depression and GAD are both highly heterogenous conditions and are often highly correlated we adjusted our analyses for depression with GAD and vice versa.

Genetic variants

Well imputed (INFO score$\geq$0.9) genetic variants were selected from the UK Biobank's imputation data for BMI, favourable adiposity and unfavourable adiposity (Supplementary table 9).

BMI

Genetic variants associated with BMI at genome-wide significance ($P<5x10^{-8}$) in the GIANT consortium of up to 339,224 people of European ancestry were selected(19). UK Biobank samples did not contribute to this meta-analysis. The full list of variants included are summarised in supplementary table 9. These variants explained 1.6% of the variance in BMI in the UK Biobank (supplementary table 10).

Favourable and unfavourable adiposity variants

We selected 36 favourable adiposity variants and 38 unfavourable adiposity variants (manuscript currently under review). These variants were associated (at $P<5x10^{-8}$) with body fat percentage and a composite metabolic phenotype consisting of: body fat percentage, HDL-cholesterol, triglycerides, sex hormone binding globulin (SHBG), alanine transaminase and aspartate transaminase. While both sets of variants are associated with higher adiposity, the unfavourable variants are associated with lower HDL-cholesterol, lower SHBG and higher triglycerides and liver enzymes; the favourable adiposity variants are paradoxically associated with higher HDL-cholesterol, higher SHBG, and lower triglycerides and liver enzymes. The favourable and unfavourable adiposity variants explained 0.2% and 0.6% variance in body fat percentage and 0.1% and 0.9% variance in BMI respectively in the UK Biobank (supplementary table 10).

One-sample Mendelian randomisation

We employed the two-stage least-squares regression estimator method which uses predicted levels of BMI/FA/UFA per genotype and regresses the mental health outcome against these predicted values. First, we calculated the association between the BMI, FA or UFA GRS and BMI or BFP, respectively. These predicted values were then used as the independent variable and the mental health and wellbeing measures as the dependent variables in a logistic (binary) or linear (continuous) regression model.

Two-sample Mendelian randomisation

Firstly, we performed GWAS of the 10 mental health outcomes, using BOLT-LMM(20) and adjusting for age, sex and genotyping platform.

Two-sample MR was performed in R (version 3.5.0), by extracting the genetic variants for a) BMI, b) favourable adiposity and c) unfavourable adiposity from BOLT-LMM(20) GWAS analyses for the 10 mental health outcomes. We next harmonised the direction of effects between the adiposity raising exposure and our mental health outcomes, where for each variant, the exposure allele was associated higher adiposity.

For each SNP individual effect-estimates were calculated using the Wald ratio, by dividing the SNP-outcome association by the SNP-exposure association. Random-effects inverse variance weighted (IVW) meta-analysis method was then used to combine the individual variants into a single instrument.

For binary outcomes we computed odds ratios (OR) which represent the change in odds of our outcome per SD higher genetically instrumented BMI (SD~4.6 kg/m^2) or body fat percentage (SD~8.4%).

In the absence of horizontal pleiotropy or when horizontal pleiotropy is balanced the IVW method provides an unbiased effect estimate(21). Several sensitivity analyses were performed to evaluate the potential for unbalanced (directional) horizontal pleiotropy. We calculated the proportion of variance explained and the F-statistic (an F-statistic of <10 is indicative of weak instrument bias). Three further MR methods were used and compared to account for directional pleiotropy: MR Egger(22), weighted median and penalised weighted median(23). The weighted median stipulates that at least 50% of the weight in the analysis stems from

variants that are valid instruments(23). The penalised weighted median is equivalent to the weighted median method but downweights the contribution to the analysis of heterogeneous genetic variants identified by Cochran's Q statistic (23).MR-Egger can provide unbiased estimates even when all SNPs violate the exclusion restriction assumption (i.e. they affect the outcome by means other than via the risk factor of interest). However, to use MR-Egger there must be negligible measurement error (NOME) in the genetic instrument and the Instrument Strength Independent of Direct Effect (InSIDE) assumption must be satisfied(22).

Non-linear Mendelian Randomisation

To explore non-linear relationships, we employed non-linear MR, using the *nlmr* package in R (https://github.com/jrs95/nlmr)(24). This package regresses the exposure (here, BMI) on the instrumental variable (genetic risk score for BMI) to generate the 'IV-free' exposure (non-genetic component of BMI). In strata of the IV-free exposure, the local average causal effect (LACE) of BMI on the outcome is estimated as a ratio of coefficients: the IV association with the outcome divided by the IV association with the exposure. This approach assumes a linear effect of the IV on the exposure. The *nlmr* package provides two options for estimating the non-linear effects of an exposure on an outcome; fractional polynomials and a piecewise linear function. Fractional polynomial methods can be unduly influenced by the extremes of a distribution, therefore we used the piecewise linear function only. The piecewise linear method estimates a continuous function, whereby a linear relationship is fitted within each stratum of the IV-free exposure distribution, constrained so that each segment begins where the previous one ended. Confidence intervals are estimated by bootstrapping. We a priori selected to run our analysis across deciles of IV-free BMI. Two statistical tests of non-linearity are presented: Cochran's Q statistic assesses whether heterogeneity of LACE estimates is greater than would be expected by chance, and a

quadratic test metaregresses the LACE estimates against the mean exposure value in each stratum (equivalent to fitting a quadratic exposure-outcome model). These analyses were performed in the unrelated subset only, as the *nlmr* package in R cannot account for relatedness.

Sensitivity analyses

We repeated our analyses in an unrelated subset using 1-sample MR approaches to firstly confirm findings between BMI and depression and GAD outcomes in individuals not taking antidepressant medication. We excluded individuals on antidepressants to test whether the BMI-depression association was driven by their usage. The unrelated subset was defined using the KING Kinship matrix to separate out related individuals (up to third degree) and included 123,923 individuals with MHQ data available. Antidepressant medication was coded using 82 relevant medication codes in UK Biobank (Supplementary table 11 and field 20003, http://biobank.ndph.ox.ac.uk/showcase/coding.cgi?id=4&nl=1) from the study interview undertaken by a trained nurse(18). This variable represents treatment at baseline interview and not lifetime treatment.

We also tested the causal relationship between adiposity and depression in atypical depression cases, to test whether any adiposity association with depression is solely driven by atypical depression cases, which by definition involves weight gain. Atypical depression was coded from our major depression variable and was defined as depression with weight gain (field 20526) and sleeping too much (field 20534)(25).

Acknowledgement: This research has been conducted using the UK Biobank resource under application number 9072.

Conflict of interest: None declared.

Funding: JO, FC and JT are supported by an Academy of Medical Sciences (AMS) Springboard award, which is supported by the AMS, the Wellcome Trust, GCRF, the Government Department of Business, Energy and Industrial strategy, the British Heart Foundation and Diabetes UK [SBF004\1079]. R.M.F. is funded by a Wellcome Senior Research Fellowship (WT220390). H.Y. is funded by a Diabetes UK RD Lawrence fellowship (17/0005594).

References

1 Onyike, C.U., Crum, R.M., Lee, H.B., Lyketsos, C.G. and Eaton, W.W. (2003) Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol*, **158**, 1139-1147.

2 Scott, K.M., McGee, M.A., Wells, J.E. and Oakley Browne, M.A. (2008) Obesity and mental disorders in the adult general population. *J Psychosom Res*, **64**, 97-105.

3 Gariepy, G., Nitka, D. and Schmitz, N. (2010) The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. *Int J Obes (Lond)*, **34**, 407-419.

4 McCrea, R.L., Berger, Y.G. and King, M.B. (2012) Body mass index and common mental disorders: exploring the shape of the association and its moderation by age, gender and education. *Int J Obes (Lond)*, **36**, 414-421.

5 Blaine, B. (2008) Does depression cause obesity?: A meta-analysis of longitudinal studies of depression and weight control. *J Health Psychol*, **13**, 1190-1197.

6 Luppino, F.S., de Wit, L.M., Bouvy, P.F., Stijnen, T., Cuijpers, P., Penninx, B.W. and Zitman, F.G. (2010) Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*, **67**, 220-229.

7 Anderson, S.E., Cohen, P., Naumova, E.N., Jacques, P.F. and Must, A. (2007) Adolescent obesity and risk for subsequent major depressive disorder and anxiety disorder: prospective evidence. *Psychosom Med*, **69**, 740-747.

8 Kivimaki, M., Jokela, M., Hamer, M., Geddes, J., Ebmeier, K., Kumari, M., Singh-Manoux, A., Hingorani, A. and Batty, G.D. (2011) Examining overweight and obesity as risk factors for common mental disorders using fat mass and obesity-associated (FTO) genotype-instrumented analysis: The Whitehall II Study, 1985-2004. *Am J Epidemiol*, **173**, 421-429.

9 Hung, C.F., Rivera, M., Craddock, N., Owen, M.J., Gill, M., Korszun, A., Maier, W., Mors, O., Preisig, M., Rice, J.P. *et al.* (2014) Relationship between obesity and the risk of clinically significant depression: Mendelian randomisation study. *Br J Psychiatry*, **205**, 24-28.

10 Hartwig, F.P., Bowden, J., Loret de Mola, C., Tovo-Rodrigues, L., Davey Smith, G. and Horta, B.L. (2016) Body mass index and psychiatric disorders: a Mendelian randomization study. *Sci Rep*, **6**, 32730.

11 Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J., Agerbo, E., Air, T.M., Andlauer, T.M.F. *et al.* (2018) Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet*, **50**, 668-681.

12 Tyrrell, J., Mulugeta, A., Wood, A.R., Zhou, A., Beaumont, R.N., Tuke, M.A., Jones, S.E., Ruth, K.S., Yaghootkar, H., Sharp, S. *et al.* (2019) Using genetics to understand the causal influence of higher BMI on depression. *Int J Epidemiol*, **48**, 834-848.

13 Speed, M.S., Jefsen, O.H., Borglum, A.D., Speed, D. and Ostergaard, S.D. (2019) Investigating the association between body fat and depression via Mendelian randomization. *Transl Psychiatry*, **9**, 184.

14 Lawlor, D.A., Smith, G.D., Ebrahim, S., British Women's, H. and Health, S. (2003) Association of insulin resistance with depression: cross sectional findings from the British Women's Heart and Health Study. *BMJ*, **327**, 1383-1384.

15 Miller, A.H. and Raison, C.L. (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*, **16**, 22-34.
16 Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M. *et al.* (2015) UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*, **12**, e1001779.
17 Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L.T., Sharp, K., Motyer, A., Vukcevic, D., Delaneau, O., O'Connell, J. *et al.* (2018) The UK Biobank resource with deep phenotyping and genomic data. *Nature*, **562**, 203-209.
18 Davis, K.A.S., Coleman, J.R.I., Adams, M., Allen, N., Breen, G., Cullen, B., Dickens, C., Fox, E., Graham, N., Holliday, J. *et al.* (2020) Mental health in UK Biobank - development, implementation and results from an online questionnaire completed by 157 366 participants: a reanalysis. *BJPsych Open*, **6**, e18.
19 Locke, A.E., Kahali, B., Berndt, S.I., Justice, A.E., Pers, T.H., Day, F.R., Powell, C., Vedantam, S., Buchkovich, M.L., Yang, J. *et al.* (2015) Genetic studies of body mass index yield new insights for obesity biology. *Nature*, **518**, 197-206.
20 Loh, P.R., Kichaev, G., Gazal, S., Schoech, A.P. and Price, A.L. (2018) Mixed-model association for biobank-scale datasets. *Nat Genet*, **50**, 906-908.
21 Hemani, G., Bowden, J. and Davey Smith, G. (2018) Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Hum Mol Genet*, **27**, R195-R208.
22 Bowden, J., Davey Smith, G. and Burgess, S. (2015) Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*, **44**, 512-525.
23 Bowden, J., Davey Smith, G., Haycock, P.C. and Burgess, S. (2016) Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol*, **40**, 304-314.
24 Staley, J.R. and Burgess, S. (2017) Semiparametric methods for estimation of a nonlinear exposure-outcome relationship using instrumental variables with application to Mendelian randomization. *Genet Epidemiol*, **41**, 341-352.
25 Brailean, A., Curtis, J., Davis, K., Dregan, A. and Hotopf, M. (2020) Characteristics, comorbidities, and correlates of atypical depression: evidence from the UK Biobank Mental Health Survey. *Psychol Med*, **50**, 1129-1138.
26 Wootton, R.E., Lawn, R.B., Millard, L.A.C., Davies, N.M., Taylor, A.E., Munafo, M.R., Timpson, N.J., Davis, O.S.P., Davey Smith, G. and Haworth, C.M.A. (2018) Evaluation of the causal effects between subjective wellbeing and cardiometabolic health: mendelian randomisation study. *BMJ*, **362**, k3788.
27 van den Broek, N., Treur, J.L., Larsen, J.K., Verhagen, M., Verweij, K.J.H. and Vink, J.M. (2018) Causal associations between body mass index and mental health: a Mendelian randomisation study. *J Epidemiol Community Health*, **72**, 708-710.
28 Howe, L.D., Kanayalal, R., Harrison, S., Beaumont, R.N., Davies, A.R., Frayling, T.M., Davies, N.M., Hughes, A., Jones, S.E., Sassi, F. *et al.* (2019) Effects of body mass index on relationship status, social contact and socio-economic position: Mendelian randomization and within-sibling study in UK Biobank. *Int J Epidemiol*, in press.
29 Tyrrell, J., Jones, S.E., Beaumont, R., Astley, C.M., Lovell, R., Yaghootkar, H., Tuke, M., Ruth, K.S., Freathy, R.M., Hirschhorn, J.N. *et al.* (2016) Height, body mass index, and socioeconomic status: mendelian randomisation study in UK Biobank. *BMJ*, **352**, i582.

30 Norris, T., Bann, D., Hardy, R. and Johnson, W. (2020) Socioeconomic inequalities in childhood-to-adulthood BMI tracking in three British birth cohorts. *Int J Obes (Lond)*, **44**, 388-398.
31 Brumpton, B., Sanderson, E., Heilbron, K., Hartwig, F.P., Harrison, S., Vie, G.A., Cho, Y., Howe, L.D., Hughes, A., Boomsma, D.I. *et al.* (2020) Avoiding dynastic, assortative mating, and population stratification biases in Mendelian randomization through within-family analyses. *Nat Commun*, **11**, 3519.
32 Lorant, V., Deliege, D., Eaton, W., Robert, A., Philippot, P. and Ansseau, M. (2003) Socioeconomic inequalities in depression: a meta-analysis. *Am J Epidemiol*, **157**, 98-112.
33 Kappelmann, N., Arloth, J., Georgakis, M.K., Czamara, D., Rost, N., Ligthart, S., Khandaker, G.M. and Binder, E.B. (2020) Dissecting the Association Between Inflammation, Metabolic Dysregulation, and Specific Depressive Symptoms: A Genetic Correlation and 2-Sample Mendelian Randomization Study. *JAMA Psychiatry*, in press.
34 Diener, E. (2000) Subjective well-being. The science of happiness and a proposal for a national index. *Am Psychol*, **55**, 34-43.
35 Barry, D., Pietrzak, R.H. and Petry, N.M. (2008) Gender differences in associations between body mass index and DSM-IV mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Ann Epidemiol*, **18**, 458-466.
36 Kasen, S., Cohen, P., Chen, H. and Must, A. (2008) Obesity and psychopathology in women: a three decade prospective study. *Int J Obes (Lond)*, **32**, 558-566.
37 DeJesus, R.S., Breitkopf, C.R., Ebbert, J.O., Rutten, L.J., Jacobson, R.M., Jacobson, D.J., Fan, C. and St Sauver, J. (2016) Associations Between Anxiety Disorder Diagnoses and Body Mass Index Differ by Age, Sex and Race: A Population Based Study. *Clin Pract Epidemiol Ment Health*, **12**, 67-74.
38 Tyrrell, J., Zheng, J., Beaumont, R., Hinton, K., Richardson, T.G., Wood, A.R., Davey Smith, G., Frayling, T.M. and Tilling, K. (2021) Genetic predictors of participation in optional components of UK Biobank. *Nat Commun*, **12**, 886.

Figure Legends

Figure 1. 2 sample Mendelian randomization IVW results for BMI, favourable and unfavourable adiposity in UK Biobank representing A) odds of the binary mental health outcome per standard deviation change in genetically determined BMI, 95% confidence interval in brackets and B) betas representing standard deviation change in the continuous mental health outcome per standard deviation change in genetically determined BMI, 95% confidence interval in brackets.

Figure 2: Summary of the results from the non-linear Mendelian randomization for (a) PHQ9 severity, (b) current GAD, and (c) wellbeing score. Betas (continuous) and odds ratios (binary) represent the difference in mental health outcome per unit higher BMI. Results are presented for all individuals and male and females separately.

Table 1: Demographics of participants with mental health questionnaire data available

	All	Male	Female	P^{I}
N	145,668	63,462	82,206	
Age (SD)	56.6 (7.7)	57.2 (7.7)	56.1 (7.6)	<1.00E-15
BMI (SD)	26.8 (4.6)	27.3 (4.0)	26.4 (4.9)	<1.00E-15
TDI (SD)	-1.79 (2.8)	-1.83 (2.8)	-1.76 (2.8)	7.60E-14
Body fat % (SD)	30.8 (8.4)	24.5 (5.7)	35.6 (6.8)	<1.00E-15
Smoking status				<1.00E-15
Never (%)	83,335 (57.2)	33,275 (52.4)	50,060 (60.9)	
Former (%)	51,720 (35.5)	24,752 (39.0)	26,968 (32.8)	
Current (%)	9,036 (6.2)	4,590 (7.2)	4,446 (5.4)	
Missing (%)	1,577 (1.1)	845 (1.3)	732 (0.9)	
Major depression[II] (%)	34,739 (23.9)	10,808 (17.4)	23,931 (29.1)	<1.00E-15
Severe major depression[III] (%)	5,483 (3.8)	1,441 (2.3)	4,042 (4.9)	<1.00E-15
Current depression[IV] (%)	2,641 (1.8)	962 (1.5)	1,679 (2.0)	6.70E-15
Severe current depression[V] (%)	1,787 (1.2)	662 (1.0)	1,125 (1.4)	1.40E-08
Atypical depression[VI] (%)	2,892 (2.0)	748 (1.2)	2,144 (2.6)	<1.00E-15
GAD[VII] (%)	7,218 (7.5)	2,533 (5.5)	4,685 (9.3)	<1.00E-15
Current GAD[VIII] (%)	1,844 (1.9)	646 (1.4)	1,198 (2.4)	<1.00E-15
Mean CIDI severity (SD)	2.97 (3.0)	2.26 (2.8)	3.51 (3.0)	<1.00E-15
Mean PHQ9 severity (SD)	2.79 (3.7)	2.45 (3.5)	3.05 (3.8)	<1.00E-15
Mean GAD severity (SD)	2.15 (3.4)	1.75 (3.1)	2.45 (3.6)	<1.00E-15
Mean Wellbeing score (SD)	12.7 (2.0)	12.7 (2.0)	12.7 (2.0)	1.60E-05

P^{I} comparison males and females

[II] N_{total}=145,583 N_{male}=63,423 N_{female}=82,160

[III] N_{total}=145,583 N_{male}=63,423 N_{female}=82,160

[IV] N_{total}=145,667 N_{male}=63,462 N_{female}=82,205

[V] N_{total}=145,667 N_{male}=63,462 N_{female}=82,205

[VI] N_{total}=145,583 N_{male}=63,423 N_{female}=82,160

[VII] N_{total}=96,658 N_{male}=46,272 N_{female}=50,386

[VIII] N_{total}=96,642 N_{male}=46,268 N_{female}=50,374

Table 2: Observational associations between higher adiposity (using BMI and body fat percentage) and 10 mental health outcomes

		BMI			Body fat percentage		
Mental health outcome	**Strata**	**N cases (controls)**	**OR (95% CI) per SD higher BMI**	**P[I]**	**N cases (controls)**	**OR (95% CI) per SD higher body fat %**	**P[I]**
Major depression	All	34,739 (110,844)	1.16 (1.14, 1.17)	<1.00E-15	34,338 (109,526)	1.22 (1.20, 1.24)	<1.00E-15
	Males only	10,808 (52,615)	1.16 (1.13, 1.19)	<1.00E-15	10,655 (51,889)	1.22 (1.18, 1.26)	<1.00E-15
	Females only	23,931 (58,229)	1.16 (1.14, 1.18)	<1.00E-15	23,683 (57,637)	1.22 (1.19, 1.24)	<1.00E-15
Severe major depression	All	5,483 (140,100)	1.32 (1.28, 1.35)	<1.00E-15	5,412 (138,452)	1.43 (1.38, 1.48)	<1.00E-15
	Males only	1,441 (61,982)	1.50 (1.41, 1.60)	<1.00E-15	1,416 (61,128)	1.62 (1.50, 1.76)	<1.00E-15
	Females only	4,042 (78,118)	1.28 (1.24, 1.32)	<1.00E-15	3,996 (77,324)	1.38 (1.33, 1.44)	<1.00E-15
Current depression	All	2,641 (143,026)	1.56 (1.51, 1.62)	<1.00E-15	2,601 (141,347)	1.75 (1.66, 1.84)	<1.00E-15
	Males only	962 (62,500)	1.67 (1.55, 1.80)	<1.00E-15	948 (61,635)	1.78 (1.61, 1.96)	<1.00E-15
	Females only	1,679 (80,526)	1.53 (1.47, 1.60)	<1.00E-15	1,653 (79,712)	1.74 (1.63, 1.84)	<1.00E-15
Severe current depression	All	1,787 (143,880)	1.62 (1.55, 1.70)	<1.00E-15	1,760 (142,188)	1.83 (1.73, 1.95)	<1.00E-15
	Males only	662 (62,800)	1.77 (1.62, 1.93)	<1.00E-15	653 (61,930)	1.91 (1.70, 2.14)	<1.00E-15
	Females only	1,125 (81,080)	1.58 (1.49, 1.66)	<1.00E-15	1,107 (80,258)	1.81 (1.68, 1.94)	<1.00E-15
Atypical depression	All	2,892 (142,691)	2.15 (2.08, 2.23)	<1.00E-15	2,860 (141,004)	2.61 (2.48, 2.74)	<1.00E-15
	Males only	748 (62,675)	2.47 (2.27, 2.69)	<1.00E-15	740 (61,804)	2.87 (2.56, 3.22)	<1.00E-15

	Females only	2,144 (80,016)	2.09 (2.01, 2.18)	<1.00E-15	2,120 (79,200)	2.56 (2.42, 2.70)	<1.00E-15
Major depression without atypical depression	All	32,631 (110,060)	1.13 (1.12, 1.15)	<1.00E-15	32,254 (108,750)	1.19 (1.17, 1.20)	<1.00E-15
	Males only	10,294 (52,381)	1.14 (1.12, 1.17)	<1.00E-15	10,147 (51,657)	1.21 (1.17, 1.24)	<1.00E-15
	Females only	22,337 (57,679)	1.13 (1.11, 1.15)	<1.00E-15	22,107 (57,093)	1.18 (1.15, 1.20)	<1.00E-15
GAD	All	7,218 (89,440)	1.10 (1.07, 1.13)	4.60E-14	7,132 (88,403)	1.17 (1.13, 1.21)	<1.00E-15
	Males only	2,533 (43,739)	1.14 (1.09, 1.20)	9.80E-08	2,501 (43,143)	1.22 (1.15, 1.29)	1.70E-10
	Females only	4,685 (45,701)	1.09 (1.05, 1.12)	2.60E-08	4,631 (45,260)	1.15 (1.11, 1.20)	2.80E-12
Current GAD	All	1,844 (94,798)	1.17 (1.11, 1.22)	6.70E-11	1,817 (93,960)	1.22 (1.15, 1.30)	2.50E-10
	Males only	646 (45,622)	1.31 (1.20, 1.44)	6.10E-09	635 (45,000)	1.30 (1.16, 1.46)	1.20E-05
	Females only	1,198 (49,176)	1.12 (1.06, 1.18)	4.60E-05	1,182 (48,690)	1.19 (1.11, 1.28)	3.30E-06
Mental health outcome	**Strata**	**N total**	**β (95% CI) per SD higher BMI**	**P[I]**	**N total**	**β (95% CI) per SD higher body fat %**	**P[I]**
CIDI severity[II]	All	145,668	0.21 (0.20, 0.23)	<1.00E-15	143,949	0.27 (0.25, 0.29)	<1.00E-15
	Males only	63,462	0.19 (0.16, 0.21)	<1.00E-15	62,583	0.22 (0.19, 0.25)	<1.00E-15
	Females only	82,206	0.23 (0.21, 0.25)	<1.00E-15	81,366	0.30 (0.27, 0.33)	<1.00E-15
PHQ9 severity[II]	All	145,668	0.49 (0.47, 0.51)	<1.00E-15	143,949	0.61 (0.58, 0.63)	<1.00E-15
	Males only	63,462	0.45 (0.42, 0.49)	<1.00E-15	62,583	0.51 (0.47, 0.55)	<1.00E-15
	Females only	82,206	0.51 (0.48, 0.53)	<1.00E-15	81,366	0.67 (0.63, 0.70)	<1.00E-15
GAD severity[II]	All	145,069	0.11 (0.10, 0.13)	<1.00E-15	143,363	0.16 (0.13, 0.18)	<1.00E-15

	Males only	63,246	0.16 (0.14, 0.19)	<1.00E-15	62,371	0.20 (0.16, 0.23)	<1.00E-15
	Females only	81,823	0.09 (0.06, 0.11)	1.30E-13	80,992	0.13 (0.10, 0.16)	<1.00E-15
Wellbeing Score[II]	All	141,447	-0.21 (-0.22, -0.20)	<1.00E-15	139,780	-0.27 (-0.28, -0.26)	<1.00E-15
	Males only	61,423	-0.18 (-0.20, -0.16)	<1.00E-15	60,570	-0.22 (-0.24, -0.20)	<1.00E-15
	Females only	80,024	-0.22 (-0.23, -0.21)	<1.00E-15	79,210	-0.30 (-0.32, -0.28)	<1.00E-15

[I]adjusted for age, sex, centre, TDI and smoking status

[II]Severity scores used linear regression

Table 3: 2-sample Mendelian Randomization results in UK Biobank. Results from the inverse variance weighted instrumental variable analysis (IVW).

			BMI		FAVOURABLE ADIPOSITY		UNFAVOURABLE ADIPOSITY	
Mental health outcome	**Strata**	**N cases (controls)**	**OR (95% CI) per SD higher BMI**	**P**	**OR (95% CI) per SD higher FA**	**P**	**OR (95% CI) per SD higher UFA**	**P**
Major depression	All	34,739 (110,844)	1.09 (0.98, 1.21)	1.12E-01	1.15 (0.86, 1.53)	3.52E-01	1.34 (1.12, 1.60)	2.95E-03
	Males only	10,808 (52,615)	1.04 (0.89, 1.21)	6.36E-01	1.15 (0.73, 1.81)	5.50E-01	1.41 (1.04, 1.91)	3.25E-02
	Females only	23,931 (58,229)	1.12 (0.99, 1.27)	7.89E-02	1.14 (0.80, 1.63)	4.83E-01	1.32 (1.09, 1.59)	6.93E-03
Severe major depression	All	5,483 (140,100)	1.27 (1.06, 1.53)	1.35E-02	1.43 (0.76, 2.67)	2.73E-01	1.58 (1.12, 2.22)	1.21E-02
	Males only	1,441 (61,982)	1.38 (0.96, 1.98)	8.96E-02	2.31 (0.88, 6.06)	9.63E-02	1.94 (1.02, 3.69)	5.05E-02
	Females only	4,042 (78,118)	1.23 (1.00, 1.52)	5.92E-02	1.23 (0.58, 2.58)	5.93E-01	1.48 (1.00, 2.21)	5.98E-02
Current depression	All	2,641 (143,026)	1.50 (1.15, 1.95)	3.81E-03	2.85 (1.38, 5.89)	7.68E-03	2.59 (1.60, 4.21)	4.49E-04
	Males only	962 (62,500)	1.35 (0.89, 2.06)	1.67E-01	6.41 (1.94, 21.14)	4.33E-03	1.60 (0.72, 3.54)	2.56E-01
	Females only	1,679 (80,526)	1.56 (1.10, 2.21)	1.59E-02	1.77 (0.71, 4.40)	2.29E-01	3.33 (1.70, 6.54)	1.25E-03
Severe current depression	All	1,787 (143,880)	1.81 (1.28, 2.56)	1.23E-03	3.05 (1.27, 7.36)	1.78E-02	3.42 (1.84, 6.34)	3.86E-04
	Males only	662 (62,800)	1.92 (1.15, 3.19)	1.49E-02	6.98 (1.65, 29.50)	1.23E-02	2.36 (0.90, 6.21)	9.09E-02
	Females only	1,125 (81,080)	1.75 (1.14, 2.68)	1.20E-02	1.87 (0.61, 5.68)	2.79E-01	4.29 (2.01, 9.19)	6.01E-04

	All	7,218 (89,440)	0.99 (0.83, 1.18)	9.04E-01	1.10 (0.64, 1.89)	7.23E-01	1.06 (0.78, 1.44)	7.30E-01
GAD	Males only	2,533 (43,739)	1.01 (1.00, 1.02)	1.74E-01	1.03 (0.99, 1.08)	1.74E-01	1.00 (0.98, 1.03)	8.11E-01
	Females only	4,685 (45,701)	0.88 (0.72, 1.08)	2.13E-01	0.89 (0.45, 1.74)	7.26E-01	1.08 (0.74, 1.57)	7.02E-01
	All	1,844 (94,798)	1.22 (0.89, 1.65)	2.17E-01	0.86 (0.36, 2.04)	7.27E-01	1.49 (0.84, 2.67)	1.84E-01
Current GAD	Males only	646 (45,622)	1.65 (0.99, 2.76)	6.01E-02	1.39 (0.32, 5.93)	6.63E-01	1.60 (0.60, 4.21)	3.51E-01
	Females only	1,198 (49,176)	1.02 (0.69, 1.49)	9.32E-01	0.60 (0.20, 1.77)	3.59E-01	1.41 (0.68, 2.94)	3.64E-01
Mental health outcome	**Strata**	**N total**	**β (95% CI) per SD higher BMI**	**P**	**β (95% CI) per SD higher FA**	**P**	**β (95% CI) per SD higher UFA**	**P**
	All	145,668	0.100 (0.070)	1.56E-01	0.141 (0.148)	3.48E-01	0.249 (0.110)	2.94E-02
CIDI severity	Males only	63,462	0.052 (0.079)	5.13E-01	-0.050 (0.230)	8.30E-01	0.101 (0.152)	5.11E-01
	Females only	82,206	0.139 (0.093)	1.40E-01	0.293 (0.205)	1.60E-01	0.366 (0.130)	7.84E-03
	All	145,668	0.355 (0.091)	2.06E-04	0.505 (0.181)	8.49E-03	0.566 (0.143)	3.23E-04
PHQ9 severity	Males only	63,462	0.245 (0.109)	2.73E-02	0.534 (0.263)	5.01E-02	0.169 (0.202)	4.09E-01
	Females only	82,206	0.432 (0.117)	4.31E-04	0.508 (0.249)	4.86E-02	0.865 (0.173)	1.43E-05
	All	145,069	0.041 (0.075)	5.85E-01	0.150 (0.166)	3.71E-01	0.002 (0.125)	9.86E-01
GAD severity	Males only	63,246	0.074 (0.083)	3.80E-01	0.309 (0.230)	1.89E-01	-0.070 (0.166)	6.74E-01
	Females only	81,823	0.009 (0.103)	9.33E-01	0.042 (0.234)	8.60E-01	0.043 (0.162)	7.94E-01
Wellbeing score	All	141,447	-0.152 (0.057)	9.18E-03	-0.202 (0.100)	5.07E-02	-0.192 (0.100)	6.11E-02
	Males only	61,423	-0.084 (0.072)	2.49E-01	-0.068 (0.150)	6.56E-01	0.017 (0.148)	9.08E-01

Females only	80,024	-0.204 (0.068)	3.54E-03	-0.312 (0.133)	2.53E-02	-0.349 (0.097)	9.33E-04

BMI=body mass index, FA= favourable adiposity, UFA=unfavourable adiposity. β represent standard deviation change in mental health outcome for standard deviation change in genetically determined adiposity trait, 95% confidence interval in brackets.