The causal effects of body mass index (BMI) on childhood symptoms of depression, anxiety disorder, and attention-deficit hyperactivity disorder: a within family Mendelian randomization study

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Abstract

**Objectives:** Higher BMI in childhood predicts neurodevelopmental and emotional problems, but it is unclear if these associations are causal. Previous genetic studies imply causal effects of childhood BMI on depression and attention-deficit hyperactivity disorder (ADHD), but these observations might also reflect effects of demography and the family environment. We used within-family Mendelian randomization, which accounts for familial effects by controlling for parental genotype, to investigate the impact of BMI on symptoms of depression, anxiety, and ADHD symptoms at age 8.

**Methods:** This study is based on the Norwegian Mother, Father and Child Cohort Study (MoBa) and uses data from the Medical Birth Registry of Norway (MBRN). Participants were 26,370 8-year-old children (48.7% female) born 1999-2009, together with their parents. We applied multivariable regression, classic Mendelian randomization (`classic MR`), and within-family Mendelian randomization (`within-family MR`). We report estimates of the effects of the child's own BMI, mother's BMI, and father's BMI on the child's depressive, anxiety, and ADHD symptoms, reported by mothers when the child was aged 8.

**Results:** In multivariable regression, higher BMI was marginally associated with more depressive and ADHD symptoms, and associated with fewer anxiety symptoms, in 8-year-old children. Classic MR models implied a causal effect of children's higher BMI on higher depressive and ADHD symptoms, and to a lesser degree, lower anxiety symptoms. In within-family MR models, there was less evidence that children's own BMI affected any of these symptoms. For example, a 5kg/m² increase in BMI was associated with 0.04 standard deviations (SD) higher depressive symptoms (95% CI -0.01 to 0.09) in multivariable regression, with corresponding effect estimates of 0.41 SD (95% CI 0.10 to 0.56) in classic MR and 0.08 SD (95% CI -0.25 to 0.42) in within-family MR. Within-family MR suggested that maternal but not paternal BMI was associated with children's depressive symptoms.

**Conclusions:** The influence of childhood BMI on depressive, anxiety and ADHD symptoms may have been overstated by MR approaches that do not account for parental genotype. Factors correlated with maternal BMI may influence offspring symptoms of depression.

**Keywords:** body mass index; BMI; depression; anxiety; attention-deficit hyperactivity disorder; ADHD; MoBa; MBRN
What is already known on this topic

- Children with high body mass index have been found to have more symptoms of depression, anxiety, and attention-deficit hyperactivity disorder.
- It is not known whether higher body weight increases risk of these symptoms, these symptoms increase body weight, or environmental or genetic factors cause both independently.
- Previous genetic studies have used samples of unrelated individuals to assess the causal impact of BMI on these symptoms, but these studies may have been biased by demographic and familial effects, for example the impact of risk factors correlated with parent’s BMI.

What this study adds

- When demographic and family-level effects were controlled for, we found less evidence of an effect of a child’s own BMI on depressive, anxiety, or ADHD symptoms, compared with classic MR approaches that do not account for parental genotype.
- We found evidence that demographic or familial factors correlated with parental BMI may independently impact children’s outcomes.
Introduction

Children with high body mass index (BMI) have been found to have greater risk of emotional and behavioural problems, including symptoms and diagnoses of depression(1–4), anxiety(1), and attention-deficit hyperactivity disorder (ADHD)(5,6). Prior to the COVID-19 pandemic, prevalence of childhood overweight and childhood obesity, respectively, was 21.3% and 5.7% in Europe(7) and 20.1% and 4.3% in Norway (8). The estimated prevalence in Europe of mid-childhood emotional disorders was around 4% (9,10), while global prevalence of child and adolescent ADHD was estimated at 5%(11). These rates may have increased considerably in the wake of the pandemic(12). In this context, there is a clear need to understand the relationship between these factors, but it is not known if child body weight causes emotional or behavioural problems.

High BMI in childhood could affect emotional symptoms through social mechanisms, for example bullying victimization(13). An impact on ADHD has been proposed via sleep disturbance and neurocognitive functioning(14). However, even if children with high BMI are more likely than normal weight children to experience these symptoms, associations may not be causal. Aspects of the family environment may independently affect children’s BMI and their likelihood of developing emotional and behavioural symptoms, for example socioeconomic disadvantage(15) or parental mental health(16,17). Some studies have suggested that prenatal maternal obesity may confound associations of childhood BMI with emotional and behavioural symptoms (18), although the evidence is mixed(19,20). Reverse causality is also plausible: depressive, anxiety or ADHD symptoms could cause higher BMI, for instance via disordered eating patterns or decreased physical activity(21,22). To avoid confounding and reverse causation, recent studies have applied Mendelian randomization (MR), a causal inference approach which uses genetic variants as instrumental variables for putative risk factors(23). Results, principally based on adult populations, are consistent with a causal influence of BMI on ADHD(22) and depression(24). They are inconclusive for anxiety, reporting both positive(25) and negative(26) predicted causal effects of body weight.

However, although MR studies avoid classical confounding and reverse causation, they can be vulnerable to other sources of bias. Specifically, estimates from ‘classic’ MR studies – those conducted on samples of unrelated individuals - may be affected by demographic and familial factors(27,28). Bias can firstly arise from uncontrolled population stratification, where systematic differences in genotype between individuals from different ancestral clusters correlates with differences in environmental or cultural factors. This is an example of gene-environment correlation, which can lead to biased associations of genotypes and phenotypes. Secondly, indirect genetic effects may exist whereby parental genotype influences a child’s phenotype via environmental pathways, termed ‘dynastic effects’ or ‘genetic nurture’(29). Thirdly, assortative mating in the parents’ generation, where parents are more (or less) similar to each other than expected by chance, may also distort genotype-phenotype associations in the child’s generation. Recent work has suggested that these biases may be especially pronounced for complex social and behavioural phenotypes(30,31). Previously reported MR estimates of the effect of BMI on emotional and behavioural problems may therefore partly reflect demographic or familial biases rather than a causal influence of BMI. To investigate this, we used a ‘within-family’ Mendelian randomization (within-family MR) design that uses genotype data from mother-father-child trios and are robust to these biases.
Figure 1: Bias in Mendelian randomization studies which do not account for parental genotype.

Caption: Adapted from Morris et al 2020 (28). Population stratification due to ancestral differences (yellow lines), dynastic effects (red lines), and assortative mating (green line). In within-family Mendelian randomization, parental genotype is controlled for, so effect estimates for the influence of child’s genotype on child phenotypes are unbiased by these processes.

Methods

Study population

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health(32,33). Participants were recruited from all over Norway from 1999-2008, with 41% of all pregnant women invited consenting to participate. The cohort now includes over 114,500 children, 95,200 mothers, and 75,200 fathers (for more details see Supplementary Methods 1: MoBa study details). The first child was born in October 1999 and the last in July 2009. As of April 2021, genotype data which had passed quality control filters was available for 26,370 complete mother-father-child trios.

The numbers of participants excluded are shown in the STROBE flow chart in Supplementary Figure S1. From all records in MoBa (N=114,717), participants were excluded if child sex was not known or if the parents had not completed any of the MoBa questionnaires. Of the 105,785 records remaining, there were 26,370 births for which genetic data were available and had passed QC filters for mother, father, and child (for details see Supplementary Methods 2: Genotyping and imputation and Supplementary Methods 3: Genetic quality control). Missing values in phenotypic information for these participants were estimated using multiple imputation (details in Supplementary Methods 4: Multiple imputation). Related participant were retained, but all models were clustered by genetic family ID derived using KING software(34). This genetic family ID groups first, second, and third-
degree relatives (i.e., siblings in the parental generation and their children as well as nuclear families), in this way accounting for non-independence of observations.

**Measures**

Children’s BMI was calculated from height and weight values reported by mothers when the children were 8 years old. Maternal pre-pregnancy BMI was calculated from height and weight reported at ~17 weeks gestation. Father’s BMI was calculated from self-reported height and weight at ~17 weeks gestation. This information was missing from around 60% of fathers, and in these cases the mother’s report of the father’s height and weight was used instead (observed values of BMI from the two sources were correlated at 0.98). Values of height and weight more than 4 standard-deviations from the mean were treated as outliers and coded to missing.

Depressive, anxiety, and ADHD symptoms were reported by the mother when the child was 8 years old using validated measures. For depressive symptoms, the 13-item Short Mood and Feelings Questionnaire (SMFQ) was used, for anxiety symptoms the 5-item Short Screen for Child Anxiety Related Disorders (SCARED)(35), and for ADHD symptoms the Parent/Teacher Rating Scale for Disruptive Behaviour Disorders (RS-DBD) (total score and subdomain scores for inattention and hyperactivity) (36). Full details of all questions asked in MoBa are available at https://mobawiki.fhi.no/mobawiki/index.php/Questionnaires.

Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth. Details of genotyping and genetic quality control are described in Supplementary Methods 2: Genotyping and imputation and Supplementary Methods 3: Genetic quality control. Polygenic scores (PGS) for BMI were calculated using SNPs previously associated in GWAS with BMI at p<5.0×10⁻⁸ and weighted using the individual SNP-coefficients from the GWAS. We first constructed a PGS based on the largest existing GWAS of BMI in adults(37). Since genetic influences on BMI in childhood and adulthood differ(38), we also constructed a PGS based on a GWAS of recalled BMI in childhood, as reported by adult participants of UK Biobank (hereafter “childhood BMI”) (39). These SNPs have been shown in external validation samples to predict BMI in childhood better than SNPs associated with adult BMI(39,40). From the full GWAS results, we excluded SNPs not available in MoBa, then used MRBase(41) to identify SNPs independently associated with BMI (with a clumping threshold of r=0.01, LD=10,000kb) at p<5.0×10⁻⁸. This left 961 SNPs associated with adult BMI, and 323 associated with childhood BMI. 33 and 9 SNPs respectively were excluded where alignment of the SNP could not be determined (see Supplementary Methods 5: Polygenic score construction), leaving 928 and 314 SNPs in the final PSGs. Full details of SNPs included in both PSGs are in Supplementary Tables 1 and 2. Equivalent PSGs were derived for depression and ADHD based on SNPs previously associated with these traits at p<5.0×10⁻⁸ in GWAS (42,43). This was not possible for anxiety, due to few known SNPs associated with these traits at p<0.05×10⁻⁸. Details of the SNPs in the depression and ADHD PSGs are provided in Supplementary Tables S3 and S4.

**Statistical analysis**

Among trios with genetic data, multiple imputation by chained equations was performed in STATAv16 to estimate missing phenotypic information (details in Supplementary Methods 4: Multiple imputation of phenotypes). We used multivariable linear regression, classic MR, and within-family MR to estimate the effects of the child’s BMI on the following outcomes: depressive, anxiety, and ADHD symptoms, and subdimensions of ADHD (inattention and hyperactivity). Multivariable linear regression models were adjusted for child’s sex and likely confounders of observational
associations: mother’s and father’s educational qualifications, mother’s and father’s depressive/anxiety symptoms (using selected items from the 25-item Hopkins Checklist(44)), and ADHD symptoms (from the 6-item adult ADHD self-report scale(45)), mother’s and father’s smoking status during pregnancy, and maternal parity. All MR models were performed i) using the PGS for adult BMI, and ii) using the PGS for childhood BMI. In classic MR models, which do not account for parental genotype, we used the child’s own PGS but not those of the parents to instrument the child’s BMI. Classic MR models were adjusted for the child’s sex, the child’s genotyping batch, and the child’s first 20 principal components of ancestry (for detailed information on principal components see Supplementary Methods 3: Genetic quality control). In within-family MR models, we used PGSs for all members of a child-mother-child trio to instrument the BMI of all three individuals. within-family MR models were adjusted for child’s sex, the genotyping batch of the child and both parents, and the first 20 principal components of ancestry for the child and both parents (model equations are provided in Supplementary Methods). Given skew in outcomes variables, all models used robust standard errors (Stata’s vce option) and thus made no assumptions about the distribution of outcomes. To assess the extent of assortative mating in the parental generation, we examined correlation between maternal and paternal polygenic scores for BMI, depression, and ADHD. We did not examine correlations with polygenic scores for anxiety, due to few known SNPs associated with these traits at p<0.05x10⁻⁸.

Sensitivity analyses

To check sensitivity of results to outliers, all analyses were repeated using log-transformed versions of outcome measures (as all symptoms scales began at 0, we added 1 to scores before log-transforming). Genetic studies designed to assess causation can be biased by horizontal pleiotropy(23). This is when genetic variants in a polygenic score influence the outcome via pathways which do not involve the exposure. Pleiotropic effects can inflate estimated associations, or bias estimates towards the null. Methods have been developed to test for the presence of horizontal pleiotropy by comparing SNP-specific associations of exposures and outcomes, although these tests themselves rest on assumptions(46). We therefore performed additional robustness checks based on associations of individual SNPs included in the polygenic scores with BMI in the GWAS, and associations of the same SNPs with each outcome in MoBa. It was not computationally feasible to include individual SNPs in the imputation models, so SNP-outcome associations in MoBa were calculated using unimputed SNP data with imputed outcome data. For robustness checks of classic MR models, SNP-outcome associations were adjusted for child’s sex, genotyping batch, and principal components. For robustness checks of within-family MR models, SNP-outcome associations were adjusted for child’s sex, mother’s and father’s genotype, and the child, mother, and father’s genotyping batch and principal components. We conducted inverse-variance weighted, MR-Median, MR-Mode, and MR-Egger regression in STATAv16 with the MRRobust package(47). A non-zero intercept from an MR-Egger model indicates presence of horizontal pleiotropy. We repeated main analyses without using imputed data in the sample of participants who had full genetic, exposure, outcome, and covariate data. To explore nonlinearities in associations of BMI with depression, anxiety, and ADHD symptoms, we ran multivariable regression models with the child’s BMI divided into quintiles.

Results

To assess whether participants included in the analytic sample (N=26,370) differed from the rest of the MoBa sample (N=88,347), we conducted t-tests and chi-squared tests for key characteristics at birth, BMI, and outcomes using unimputed data. There were modest differences, described in Supplementary Results 1: Comparison of analytic sample and excluded participants. BMI differed for
fathers (mean=25.9 vs 25.8) but not for mothers or children. Children in the analytic sample had slightly lower depressive symptoms (mean SMFQ=1.79 vs 1.89) and anxiety symptoms (mean SCARED=1.04 vs 1.00) but did not differ on ADHD symptoms. Descriptive characteristics of the full MoBa sample are in Supplementary Table S5.

Descriptive statistics of the analytic sample after multiple imputation is presented in Table 1. The mean BMI for children was 16.3 (SD=2.0), for mothers 24.0 (SD=4.1), and for fathers 25.9 (SD=3.2). Corresponding descriptive characteristics from unimputed data are included in Supplementary Table S6. The polygenic score based on SNPs previously associated with BMI in adulthood explained 3.4% of the variance of BMI among children, 6.5% for mothers and 5.7% for fathers. These were strong instruments: first-stage F-statistics were 922.1, 1665.3, and 1396.0, for children, mothers, and fathers. The polygenic score based on SNPs previously associated with childhood BMI explained 5.1% of the variance of BMI among children, 4.0% for mothers and 3.2% for fathers. These were also strong instruments: first-stage F-statistics were 1397.3, 983.4 and 776.5 for children, mothers, and fathers. Correlation of the polygenic scores for adult BMI and for childhood BMI was 36.8% for children, 35.9% for mothers and 36.0% for fathers.
### Table 1: Descriptive Characteristics of Analytic Sample (N=26,370)$^a$

| Continuous variables | mean | SD  |
|----------------------|------|-----|
| Maternal age at child’s birth (years) | 30.0 | 4.4 |
| Paternal age at birth (years) | 32.5 | 5.2 |
| Maternal depressive/anxiety symptoms, based on 5 items from the Hopkins Symptoms Checklist-25 (SCL-25)$^b$ | 1.2 | 1.9 |
| Paternal depressive/anxiety symptoms, based on 8 items from the Hopkins Symptoms Checklist-25 (SCL-25)$^c$ | 1.1 | 2.1 |
| Maternal ADHD symptoms: adult ADHD self-report scale$^d$ | 8.3 | 3.2 |
| Paternal ADHD symptoms: adult ADHD self-report scale$^e$ | 6.7 | 3.3 |
| Maternal pre-pregnancy BMI (kg/m$^2$) | 24.0 | 4.1 |
| Paternal BMI (kg/m$^2$) | 25.9 | 3.2 |
| Child’s BMI at age 8 (kg/m$^2$) | 16.3 | 2.0 |
| Child depressive symptoms age 8: Short Mood and Feelings Questionnaire (SMFQ)$^f$ | 1.9 | 2.5 |
| Child anxiety symptoms age 8: Screen for Child Anxiety Related Disorders (SCARED)$^g$ | 1.0 | 1.2 |
| Child ADHD symptoms age 8: Parent/Teacher Rating Scale for Disruptive Behaviour Disorders (RS-DBD)$^h$ | 8.8 | 7.5 |
| Child ADHD symptoms (inattention) age 8: Parent/Teacher Rating Scale for Disruptive Behaviour Disorders (RS-DBD)$^i$ | 5.3 | 4.3 |
| Child ADHD symptoms (hyperactivity) age 8: Parent/Teacher Rating Scale for Disruptive Behaviour Disorders (RS-DBD)$^j$ | 3.7 | 4.1 |

| Categorical variables | Category | %  |
|----------------------|----------|----|
| Child’s sex          | Male     | 51.3 |
|                      | Female   | 48.7 |
| Maternal educational qualifications | Mandatory 9-year education only | 6.4 |
|                      | Further education: vocational | 12.8 |
|                      | Further education: general studies, sixth form | 14.2 |
|                      | Higher education: college/university, up to 4 years | 42.7 |
|                      | Higher education: college/university, over 4 years | 23.9 |
| Paternal educational qualifications | Mandatory 9-year education only | 10.0 |
|                      | Further education: vocational | 26.0 |
|                      | Further education: general studies, sixth form | 12.8 |
|                      | Higher education: college/university, up to 4 years | 28.0 |
|                      | Higher education: college/university, over 4 years | 23.7 |
| Maternal parity at child’s birth | 0 | 48.4 |
|                      | 1 | 34.4 |
|                      | 2 | 13.6 |
|                      | 3 | 2.7 |
|                      | 4+ | 0.7 |
| Mother’s marital status at birth | Married/registered partner | 97.4 |
|                      | single | 2.6 |
| Mother’s smoking status during pregnancy | never | 51.1 |
|                      | Stopped before week 17 | 41.7 |
|                      | Currently | 7.1 |

$^a$The reasons for exclusions and numbers in each case are shown in supplementary Figure 1. Missing data in BMI, outcomes and covariates was imputed using multiple imputation by chained equations. Descriptive statistics for the unimputed data are shown in supplementary tables. $^b$Possible range: 0-15.
**Associations of BMI with depressive, anxiety and ADHD symptoms at age 8**

**Depressive symptoms (SMFQ)**

In multivariable linear regression models adjusted for child’s sex and parental covariates (Figure 2, Supplementary Table S7), children’s higher BMI at age 8 was associated with slightly higher depressive symptoms. Per 5kg/m² increase in BMI, SMFQ score was 0.04 standard deviations (SD) higher (95% CI: -0.01, 0.09). Classic MR using the adult BMI PGS suggested that for each 5kg/m² increase in BMI, the SMFQ score increased by 0.41 SD (95% CI: 0.18, 0.64). In contrast, within-family MR models using the adult BMI PGS provided weaker evidence for an effect (beta: 0.08 SD, 95% CI: -0.25, 0.42). However, estimates from within-family MR models were imprecise. From the ratio of standard errors, the within-family MR estimate for depressive symptoms was 68% as precise as the classic MR estimate, and only 15% as precise as the OLS estimates. Using the childhood BMI PGS (Figure 3, Supplementary Table S8) there was no strong evidence of an effect of a child’s own BMI from either classic MR (beta: 0.11 (95% CI: -0.08, 0.30) or within-family MR (beta: -0.14 (95%CI: -0.43, 0.14)).

**Anxiety symptoms (SCARED)**

In multivariable linear regression models (Figure 2, Supplementary Table S7), each 5kg/m² increase in BMI was associated with a 0.06 SD lower (95% CI: -0.11, -0.01) SCARED score. Estimates from the classic MR and within-family MR models using the adult BMI PGS were larger, but less precise (classic MR beta: -0.19, 95% CI: -0.42, 0.03, within-family MR beta: -0.16, 95% CI: -0.49, 0.17). Again, the ratio of standard errors indicated the within-family MR estimate for anxiety symptoms was 68% as precise as the classic MR estimate, and only 15% as precise as the OLS estimates. Using the childhood BMI PGS (Figure 3, Supplementary Table S8), MR estimates were similar (classic MR beta: -0.13, 95%: -0.32, 0.07, within-family MR beta: -0.15, 95%CI: -0.45, 0.15).

**ADHD symptoms (RS-DBD)**

Multivariable linear regression (Figure 2, Supplementary Table S7) found little evidence that children’s BMI was associated with increased ADHD symptoms after adjusting for confounders. Per 5kg/m² increase in BMI, ADHD symptoms from the RS-DBD were 0.04 SD lower (95% CI: -0.10, 0.01), with similar associations observed for the inattention or hyperactivity subscales (Figure 2, Supplementary Table S5). Using the adult BMI PGS there was in the classic MR model evidence of a positive association: with each 5kg/m² increase in BMI, ADHD symptoms were 0.33 SD higher (95% CI: 0.10, 0.56). As for depressive symptoms, this attenuated in the within-family MR model to 0.08 SD (95% CI: -0.25, 0.40). A similar pattern was seen with the inattention and hyperactivity subscales (Figure 2, Supplementary Table S5). From the ratio of standard errors, the within-family MR estimate for anxiety symptoms was 71% as precise as the classic MR estimate, and only 16% as precise as the OLS estimates. Using the childhood BMI PGS (Figure 3, Supplementary Table S8) there was little evidence of an association from either classic MR (beta: -0.03, 95%CI: -0.21, 0.15) or within-family MR models (beta: -0.10, 95%CI: -0.37, 0.16).

**Association of mother’s and father’s BMI with child’s symptoms**

Multivariable linear regression provided estimates of associations between mother’s and father’s BMI and child outcomes, conditional on the child’s own BMI. Mother’s BMI was associated with
slightly more depressive symptoms in the child: per 5kg/m² increase in maternal BMI, child SMFQ score was 0.06 S.D. higher (95%CI: 0.03,0.09). Maternal and paternal BMI were both associated with more ADHD symptoms in the child. Per 5kg/m² increase in maternal BMI, symptoms were 0.04 S.D. higher (95%CI: 0.02,0.07). Per 5kg/m² increase in paternal BMI, they were 0.03 S.D. higher (95%CI: 0.00,0.05). Similar associations were seen for inattention and hyperactivity subscales.

Within-family MR models also provide estimates for the effect of familial and demographic factors linked to parental genotypes on child outcomes, conditional on the child’s own BMI (Figure 2, Supplementary Table S5). Specifically, the predicted causal effect in within-family MR models of each parent’s BMI with the child’s depression, anxiety, and ADHD symptoms captures impact of that parent’s BMI on the outcome, but also reflects the impact of residual population stratification and assortative mating. In within-family MR models, there was a predicted causal effect of higher maternal BMI on more depressive symptoms in the child, regardless of the genetic instrument used. Using the adult BMI PGS, SMFQ score was 0.16 SD higher (95% CI: 0.06,0.26) per a 5kg/m² increase in maternal BMI. Using the childhood BMI PGS, SFMQ score 0.13 S.D. higher (95%CI: 0.00,0.26) per 5kg/m² increase in mother’s BMI. Only in within-family MR models using the adult BMI PGS was there a predicted causal effect of paternal BMI on higher ADHD-hyperactivity symptoms in the child (0.14 SD higher (95% CI: 0.01,0.27) per 5kg/m² increase in paternal BMI), but not full ADHD symptoms or the inattention subscale. There was little evidence of other maternal or paternal effects from within-family MR models.

There was little evidence in the parent’s generation of correlation of either BMI PGS with depression or ADHD PGSs. Absolute correlations between maternal BMI PGSs and paternal depression and ADHD PGSs, and vice versa, were all <0.02 (Supplementary Table S7). In regression models adjusted for mother’s and father’s genotyping batch and principal components of ancestry, there was a positive association of the maternal childhood BMI PGS and the paternal depression PGS (beta: 0.02, 95%CI: 0.00,0.03), but little evidence of other associations (Supplementary Table S9). This suggests assortative mating is unlikely to explain our results using the adult BMI PGS.

Sensitivity analyses

Analyses using log-transformed versions of the outcomes (Supplementary Tables S10 and S11) were consistent with main results. Robustness checks based on comparing associations of individual SNPs with BMI in the GWAS and with children’s outcomes in MoBa (Supplementary Tables S12 and S13) were consistent with the main results, and MR-Egger estimates found no evidence of horizontal pleiotropy. Results of analyses using the complete-case sample were qualitatively similar to results of main analyses using imputed data (Supplementary Tables S14 and S15). In multivariable regression models where the child’s BMI was divided into quintiles (Supplementary Tables S16), there was little evidence of nonlinear associations.
Figure 2: BMI and child’s depressive, anxiety, and ADHD symptoms, using a polygenic score for adult BMI in Mendelian randomization models.

Caption: Coefficients represent standard-deviation change in outcomes per 5kg/m$^2$ increase in BMI. Multivariable adjusted (phenotypic) models adjust for child’s sex, maternal parity, and mother’s and father’s: educational qualifications, depressive/anxiety symptoms, ADHD symptoms, and smoking status. Classic MR models adjust for child’s sex, genotyping batch, and the first 20 principal components of ancestry. Within-families MR models adjust for child’s sex and child’s, mother’s, and father’s genotyping batch and first 20 principal components of ancestry.
Figure 3: BMI and child’s depressive, anxiety, and ADHD symptoms, using a polygenic score for childhood BMI in MR models.

Caption: Coefficients represent standard-deviation change in outcomes per 5kg/m² increase in BMI. Phenotypic models adjust for child’s sex, maternal parity, and mother’s and father’s: educational qualifications, depressive/anxiety symptoms, ADHD symptoms, and smoking status. Classic MR models adjust for child’s sex, genotyping batch, and the first 20 principal components of ancestry. Within-families MR models adjust for child’s sex and child’s, mother’s, and father’s genotyping batch and first 20 principal components of ancestry.
Discussion

In a large cohort of Norwegian 8-year-olds, multivariable regression suggested that higher BMI was associated with more depressive symptoms but fewer anxiety symptoms and ADHD symptoms. Classic MR models using a PGS of SNPs associated with adult BMI, and which did not adjust for parental genotype, suggested that higher BMI in childhood increased symptoms of depression and ADHD, and to a lesser degree, decreased anxiety symptoms. Effect sizes from classic MR analyses were larger than associations from multivariable regression models. Within-family MR estimates were similar to estimates from multivariable regression models, although much less precise. When BMI was instrumented using a PGS of SNPs associated with childhood BMI, there was no strong evidence from any MR model that the child’s BMI influenced any outcome. In within-family MR models using both PGSs, there was a predicted causal effect of higher maternal BMI on children’s higher depressive symptoms.

The positive association between BMI and depressive symptoms in multivariable regression models accords with previous observational studies (1–4). The inverse association between BMI and anxiety symptoms contrasts with results of a recent study, in which Swedish 6-17 year olds receiving treatment for obesity had a greater likelihood of a diagnosis or prescription for anxiety disorder compared to controls (1). The discrepancy may reflect confounding (we adjusted for more factors, including parental BMI), age of the participants (children in our study were younger) or differences in the outcome or exposure, since we considered anxiety symptoms rather than diagnosis, and a continuous BMI measure rather than obesity. However, anxiety symptoms in our sample were not raised in the top BMI quintile. Another difference concerns the population: children receiving obesity treatment may be more likely than other children with obesity to experience anxiety symptoms or to receive a diagnosis. On the other hand, our results accord with genetic evidence for an inverse association of anxiety and BMI in adults (26). The inverse association between BMI and ADHD symptoms in multivariable regression models contrasts with previous reports of positive or null associations with obesity, which typically adjusted for fewer confounders (5,48). Since previous studies have found more evidence of an association in adults than children, and often considered ADHD diagnoses rather than symptoms, the discrepancy may also point to age-varying associations, or to different influences on likelihood of diagnosis compared to parent-reported symptoms (5,48).

Classic MR estimates were larger than estimates from multivariable regression. Horizontal pleiotropy, which we could not rule out, could have inflated MR estimates using the adult BMI PGS, but we found little evidence of pleiotropy using MR-Egger. Importantly, classic MR does not adjust for parental genotype, and estimates may therefore be inflated by demographic and familial factors. The within-family MR estimates for effects of a child’s own BMI are robust to these factors, and within-family MR estimates using the adult BMI PGS were closer than classic MR estimates were to the multivariable regression estimates. This may suggest that classic MR estimates using the adult BMI PGS are substantially biased by demographic and familial factors. Of note, the childhood BMI PGS explained more variation in children’s BMI, while the adult BMI PGS explained more variation in parental BMI, consistent with other studies (39,49). Using the childhood BMI PGS, even classic MR models found little evidence of effects of child’s own BMI on any of the outcomes studied. Again, this may point to an influence of demographic and familial factors: if associations in classic MR models in part reflect indirect processes - including effects of parent’s BMI - then models which use better instruments for adult BMI may be more likely to capture these effects. However, estimates from within-family MR models were imprecise, and were also consistent with more modest effects of children’s BMI than suggested by classic MR models. Our within-family MR estimates accord with
a recent study which accounted for family effects by using dizygotic twin pairs and found a 0.07 S.D. increase in ADHD symptoms at age 8 per S.D. increase in BMI PGS (50).

Attenuation of effects in within-family MR models accords with earlier evidence of familial effects for BMI and ADHD(51–53). Our results may be explained by several sources of genetic familial bias. Firstly, frequencies of BMI-associated variants may differ between sub-populations in a similar manner to environmental influences on emotional or behavioural functioning (population stratification). Such gene-environment correlation can inflate estimates from classic MR models, but not within-family MR models, where ancestry is fully controlled for via parental genotypes. Although we included principal components of ancestry in classic MR models, residual population stratification may nevertheless have influenced results. Secondly, smaller estimates in within-family MR models may reflect the presence of indirect effects of parental BMI via the family environment (dynastic effects, or genetic nurture). This could explain the associations in within-family MR models of maternal BMI with children’s depressive symptoms, conditional on child genotype. In observational studies, maternal pre-pregnancy obesity is linked with children’s risk of emotional disorders and ADHD(18). Although mechanisms are not well understood, an in utero effect on children’s neurodevelopment of metabolic correlates of obesity has been proposed(54).

Additionally, our results may reflect an impact of maternal BMI later in the child’s life. A well-documented ‘wage penalty’ exists for high BMI(55), especially for women(56), reflecting social consequences of obesity being a stigmatized condition(51). High BMI in adulthood is also linked to worse mental health, with stronger associations for women again pointing to gendered social processes(57). Maternal BMI may therefore influence children’s emotional and behavioural problems via economic consequences, or via maternal mental health, throughout childhood. However, while our results are consistent with an influence of maternal BMI on child’s depressive symptoms, predicted causal effects of maternal and paternal BMI in within-family MR models should be interpreted with caution, as they may themselves have been impacted by familial biases in previous generations. Thirdly, people with high BMI may be more likely to partner with people with emotional or behavioural conditions (assortative mating). Over generations, this would induce an association of not only the phenotypes but of associated genetic variants. However, low correlations between the BMI, depression, and ADHD PGSs within mother-father pairs suggest that such assortment is unlikely to substantively explain our results.

Despite a high participation rate, MoBa is not perfectly representative, and selection biases linked to participation could have affected our results. The current analyses were restricted to families with complete genetic data and at least some questionnaire data. These families were found to have slightly more years of education than the wider MoBa sample, and the children to score slightly lower for depressive and anxiety symptoms. Reflecting the requirement of genetic data for fathers, single mothers were under-represented. Outcomes were based on mother-reported symptoms of depression, anxiety disorders and ADHD, and estimates based on diagnoses may have differed. However, a child’s sociodemographic characteristics can influence their likelihood of diagnosis independently of symptoms(58), indicating that such an approach is not always preferable. BMI measurements were based on reported height and weight, so reporting bias may have influenced relationships. In many families, fathers’ BMI was based on height and weight reported by the mothers. However, these measures were very highly correlated with father’s self-reports, so additional measurement error is unlikely to have greatly affected our results for father’s BMI. Effects of parental BMI may be time-varying, for example a parent’s own BMI during childhood could influence their child independent of the parent’s later BMI. We could not explore these effects because information on parent’s childhood BMI was not available. Within-family MR may still be affected by horizontal pleiotropy, and recent genetic work points to genetic overlap between BMI
and psychiatric disorders including major depression(59). While robustness checks found little evidence of pleiotropy, these methods rely on assumptions, and pleiotropy cannot be ruled out. However, pleiotropy normally biases estimates away from the null, and is unlikely to explain our null findings between child BMI and the outcomes. The Mendelian randomization methods employed here assume any causal impact of BMI is linear – that a kg/m² increase in BMI will have the same impact regardless of the child’s initial BMI. There is substantial evidence for a ‘J-shaped’ phenotypic association of BMI with common mental disorders, consistent with an impact of both high and low BMI on risk of depression or anxiety(3,60,61). Genetic methods exist for exposures with nonlinear effects, but require much larger samples(62). If there exist nonlinear effects of BMI on mental health, rather than vice versa, our results may underestimate the effects of high BMI. Finally, effects of BMI on emotional and behavioural functioning likely differ by age, and relationships may be substantially different for older children or adolescents. In particular, depressive symptoms do not tend to occur until the teenage years(63), and observational associations of BMI and ADHD become clearer with age(48). Work in larger samples will be needed to precisely estimate the influence of a child’s BMI on their emotional and behavioural outcomes. Meanwhile, studies with extensive intergenerational information will be needed to fully explore mechanisms linking child outcomes to maternal BMI.

Conclusion

Our results suggest that any effect of a child’s own BMI on their depressive, anxiety, and ADHD symptoms in this age group is likely to be small. Previous genetic studies using a PGS for adult BMI may have overestimated causal effects of a child’s own BMI. Demographic or familial factors linked to parental BMI may independently influence a child’s depressive, anxiety, and ADHD symptoms.
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Author contributions:

AMH conducted all statistical analysis and wrote the manuscript. TM assisted with interpretation of results and made critical revisions to the manuscript. ZA assisted with preparation of phenotype data and interpretation of results. MT made critical revisions to the manuscript. HA made critical revisions to the manuscript. TR-K was involved in acquisition of data, securing funding, and made critical revisions to the manuscript. OAA was involved in acquisition of data and made critical revisions to the manuscript. PM was involved in acquisition of data and made critical revisions to the manuscript. ØH made critical revisions to the manuscript. SJ made critical revisions to the manuscript. PN was involved in acquisition of data and made critical revisions to the manuscript. GDS made critical revisions to the manuscript. AH was involved with securing funding, acquisition of data, study design, interpretation of results, and made critical revisions to the manuscript. LDH was involved with securing funding, study design, interpretation of results, and made critical revisions to the manuscript. NMD was involved with securing funding, study design, interpretation of results, and made critical revisions to the manuscript. All authors have approved the manuscript.

Conflicts of interest:

OAA has received speaker’s honorarium from Sunovion and Lundbeck and is a consultant for HealthLytix.
Data availability:

The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should submit an application to datatilgang@fhi.no. Access to data sets requires approval from The Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa.

Code availability:

Code used to generate these results is available at https://github.com/ammhughes/BMI-depressive-anxiety-and-ADHD-symptoms-in-MoBa

Ethical approval:

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and The Regional Committees (REC) for Medical and Health Research Ethics. The REC South East Norway, one of four in Norway, was the ethical committee that evaluated the ethics of this study. Approval from the REC was granted (2016/1702). Informed consent was obtained from each MoBa participant upon recruitment, which included consent to link to the Medical Birth Registry of Norway (MBRN). The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act.

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