Depressive symptoms and obesity: Instrumental variable analysis using mother–offspring pairs in the 1970 British Cohort Study

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Abstract

Background: The extent to which depression and obesity are causally related remains to be determined. We utilised intergenerational data on mother – offspring pairs in an instrumental variable analysis to examine the longitudinal association between adolescent depressive symptoms and body mass index (BMI) in adulthood.

Methods: A total of 4,733 mother–offspring pairs were identified from the 1970 British Cohort study. Mothers completed the Malaise Inventory to assess depressive symptoms on three occasions across their offsprings childhood/adolescence (ages 5, 10, 16). Height and weight were recorded in mother and offspring (age 16). Measures of height, weight and the Malaise inventory were repeated in the participant at age 42.

Results: Maternal malaise score was associated with offspring malaise score, thus confirming the validity of the chosen instrumental variable. A higher mother's malaise score was associated with higher offspring BMI at follow up (B=0.043, 95% CI, 0.013, 0.072). There was a higher risk of adulthood offspring obesity in mothers with two or three episodes of depression compared with one or none (Odds ratio, 1.42, 95% CI, 1.14, 1.76). The maternal malaise – offspring BMI association remained (p=0.003) after adjustment for offspring malaise score, suggesting that maternal mental health influences offspring obesity through mechanisms other than depression. Results from standard and instrumental variable analyses did not support a causal pathway in a direction from BMI to depression.

Conclusions: Our data support a causal pathway linking adolescent depressive symptoms to adiposity in adulthood over 26 years follow up. The reverse direction, ie, adiposity to depression, was not supported.

Key words: Birth cohort; Epidemiology; Obesity; Depression

Introduction

Obesity and depression are both risk factors for morbidity and mortality,[1,2] but the extent to which these two conditions are causally related remains to be determined. In particular, understanding the direction of association is one of the problems with the contemporary literature on depression and obesity. There is evidence to suggest excess adiposity might lead to depressive symptoms,[3] although depressive symptoms may also precede the development of obesity.[4-6] Since co-occurrence of obesity and depressive symptoms is also possible, this raises difficulties in establishing direction of association in observational studies.

Investigators have taken various approaches in an attempt to resolve the direction of association. In studies with data collected across the life course, pre-morbid childhood obesity has been related to the subsequent occurrence of mental health problems.[7] Such an approach is, however, still subject to residual confounding. Using another technique, investigators have used Mendelian randomization, a form of instrumental variable analysis, to examine the association of obesity with mental health problems. This approach utilises adiposity-related genetic variants as an unconfounded instrument variable for obesity. With fat mass and obesity-associated (FTO) genotype representing a proxy or instrument for higher body mass index (BMI), the rationale is that as different FTO genotypes are randomly allocated at conception, the associations of FTO variants with depression should be free of confounding and reverse causation. This approach has, however, produced inconsistent findings with direct,[8,9] inverse[10] and null associations[11] reported between obesity and later risk of depressive symptoms. With robust genetic variants for depression presently unknown, it has not yet been possible to use Mendelian randomization approaches for assessing the role of depression in the aetiology of obesity.

An alternative instrumental variable analysis may be used in this context. It is well established that maternal (and paternal) BMI is related to offspring BMI,[12] and the same is known for the intergenerational correlation for mental health.[13] It is also the case that maternal–offspring

relationships are likely to be less biased and confounded than conventional analyses using exposure and outcome data from the same individual. For example, illnesses that lead to lower BMI could generate a spurious inverse association between BMI and depression but it is unlikely to bias the association between mother's BMI and offspring depression. Accordingly, to test the hypothesis that depression increases the risk of obesity, we used a novel instrumental variable analysis (the first of its kind in this area); maternal mental health was used as an instrument for offspring mental health to examine whether it predicted offspring's BMI in adulthood. Since both symptom severity and chronicity of exposure may be important in predicting outcomes, we modelled maternal depression using both absolute symptom scores and also as long term exposure from data on maternal depressive symptoms across three time points. In order to test the hypothesis of obesity leading to depression, we studied the associations of maternal BMI with offspring BMI and subsequent mental health.

Methods

Design and participants

The 1970 British Cohort Study (BCS70) follows the lives of 17,284 people born in England, Scotland and Wales in a single week of 1970.[14] Since birth, participants have been followed up on multiple occasions across their life. The present analyses incorporated data from the age 16 and age 42 year surveys. The age 16 year survey (1986) contained a participant self-completion section on health-related behaviours in addition to questions completed by the mother of the participant. The age 42 survey (2012/13) comprised a 60 minute face-to-face computer-assisted-personal-interview, which included a vocabulary task and a self-completion section. At the age 16 survey 6898 participants completed the self-completion module although 9,842 took part in the age 42 survey. The lower response at age 16 arose because of a teachers' strike that resulted in many participants not

receiving the questionnaires. Participants provided informed consent and all data collection on BCS70 received full ethical approval (London Central REC).

Depressive symptoms and body mass index

Depressive symptoms were measured by the 24-item (age 16) and 9-item (age 42) Malaise Inventory[15] consisting of items on depressive mood, which has demonstrated acceptable psychometric properties.[16] The inventory has been validated against external criteria covering current or recent psychiatric morbidity and health service use.[17] A total symptom score, (ranging from 0 to 24 for the 24 item and 0 – 9 for the 9 item inventory), was derived from a count of the number of items eliciting a positive response, with higher scores indicating greater severity. At age 16 both the participant and mother completed the Malaise questions and at age 42 the questions were repeated in the participant. At age 16 height and weight were objectively collected in the participant but self-reported in the mother, and at age 42 self reported height and weight were collected in the participant. BMI was calculated using the standard formula (weight [kg] / height [m^2]).

Lifestyle and health measures

At age 16 respondents were asked questions on smoking (never; rarely; ≥ 1 cigarette/week), frequency of alcohol intake (daily; 4 -5 /week; 2-3/week; once a week; once a month; rarely; never), time spent in three types of screen based, sedentary activities (TV, video films, computer games) 'after school yesterday' (not at all; less than 1hr; > 1 hr; >2 hr; >3hr; >4hr; >5hr), and serious childhood illness/ accidents/ operations. Parents also provided information on their occupation, which were categorised using the 1970 and 1980 Office of Population Censuses and Surveys Classification of Occupations (managerial/ professional/ intermediate/ routine and manual).

Statistical analysis

We examined the distribution of offspring lifestyle and health variables according to tertiles of maternal Malaise score. We estimated coefficients for their association with maternal malaise score using logistic and linear regression. We performed an instrumental-variables regression analysis using two-stage least-squares regression "2SLS" command in SPSS to examine whether maternal Malaise score was associated with offspring BMI through its relationship with offspring Malaise. We compared results from the instrumental-variable estimates of the association between malaise measures and BMI with results from standard linear regression. In order to examine if the so-called exclusion restriction assumption may be violated we further adjusted the model for offspring malaise score (age 16). In addition, we used maternal BMI as an instrumental variable to explore the causal association between offspring's BMI and malaise score in adulthood. Standard linear regression models were adjusted for sex and mothers social status. In order to capture long term exposure, we incorporated measures of maternal malaise from two earlier survey points (age 5 and 10). A depressive case was defined as >80th centile distribution from malaise scores at each time point (ages 5, 10, 16), which was used to generate a grouped exposure variable (never depressed; one occasion; two or three occasions). Logistic regression was used to examine the association between episodes of maternal depression and risk of offspring obesity in adulthood. All analyses were conducted using SPSS version 22.

Results

Depression and BMI in adulthood

A total of 4733 mother–offspring pairs were identified. There were small differences between mothers of offspring included and excluded from these analyses. For example, mothers excluded were more likely to come from lower social occupational classes (39.8% vs. 36.1%, p=0.001) compared to the analytic sample, although there were no differences in age of mother (p=0.56). On

97 average mothers were aged 26.2 ± 5.4 yrs at the age 5 survey although mothers' age was not
98 associated with Malaise scores or chronic depressive episodes. At follow-up 42.3%, 36.2%, 21.5% of
99 offspring were categorised as normal weight, overweight, and obese, respectively. Table 1 shows
100 that maternal malaise score was associated with offspring malaise score, thus confirming the validity
101 of the chosen instrumental variable (F-value = 18.68, p<0.001). Maternal malaise was also associated
102 with several potential confounders including offspring smoking and sedentary behaviour.
103 Nevertheless, stronger associations were observed between offspring malaise score and these
104 confounders, in particular for smoking; participants with Malaise scores in the upper tertile
105 compared with lower tertile had 1.8 (95% CI, 1.5, 2.1) higher odds of smoking, whereas the
106 respective association using mother's Malaise score was weaker (OR= 1.4, 95% CI, 1.2, 1.7).

107 We found a linear association between episodes of depression and mothers' own BMI in models
108 adjusted for social status and age, such that higher BMI was observed in mothers with one (B=0.33,
109 95% CI, 0.08, 0.58 Kg/m^2) and two or more episodes (B=0.68, 95% CI, 0.40, 0.96 Kg/m^2) compared to
110 mothers never depressed. In longitudinal analysis examining associations between malaise and
111 offspring BMI at follow up, associations using offspring malaise age 16 were attenuated to the null
112 after adjustment for mother's social class. A higher mother's malaise score, however, remained
113 associated with higher offspring BMI at follow up (Table 2). More robust effect estimates were
114 observed in the instrumental variable analysis. In analyses to explore the so-called exclusion
115 restriction assumption adjustment for offspring malaise score age 16 did not alter the maternal
116 malaise – offspring BMI association (B=0.063, 95% CI, 0.021, 0.105, p=0.003). In view of the findings
117 showing associations between our instrumental variable and possible confounders we also
118 conducted a further analysis that controlled for offspring smoking and sedentary behaviours (at age
119 16) although this did not influence the association between maternal depression and offspring BMI
120 (B=0.065, 95% CI, 0.015, 0.115, p=0.01).

In analyses to examine the association between episodes of maternal depression and risk of offspring obesity in adulthood we observed a dose-response association, with a higher risk of offspring obesity in mothers with two or three episodes of depression compared with one or none (Table 3).

BMI and depression in adulthood

We also used maternal BMI as an instrumental variable to explore the causal association between offspring's BMI and malaise score in adulthood. Maternal BMI was strongly associated with offspring BMI (F-value = 58.7, p<0.001), supporting the use of maternal BMI as a valid instrument for offspring BMI. However, maternal BMI was also associated with several potential confounders including offspring smoking (OR per unit increase = 1.03, 95% CI, 1.01 – 1.06, p=0.015) and sedentary behaviour (OR = 1.05, 95% CI, 1.02 – 1.08, p=0.001). Results from standard and instrumental variable analyses did not support a causal pathway in a direction from BMI to depression (Table 4). In further analysis that controlled for offspring smoking and sedentary behaviours (at age 16) the association between BMI and depression was unchanged (B=0.013, 95% CI, -0.008, 0.035, p=0.23).

Discussion

The aim of this study was to examine associations between depressive symptoms and obesity across the life course using an instrumental variable approach. Existing instrumental variable analyses in this field have used the FTO and other genotypes as an unconfounded measure of obesity. However, as robust genetic variants for depression are presently unknown, we chose to adopt a novel approach utilising intergenerational data on mother – offspring pairs for assessing the role of depression in the aetiology of obesity. We found evidence to support a causal pathway linking adolescent depressive symptoms to BMI in adulthood over 26 years follow up. The reverse direction, ie, BMI to depression, was not supported.

Our instrumental variable, maternal depressive symptoms, met the majority of assumptions required for an instrumental variables analysis. Firstly, in our study and other published studies,[13] maternal depressive symptoms were positively associated with offspring depressive symptoms. Second, an offspring's body mass index in adulthood (outcome) cannot plausibly affect variation in maternal depressive symptoms. Thus, our instrumental variable analysis was more protected from reverse causality than conventional analysis. The final assumption postulates that except from its association with the risk factor of interest, there is no other pathway linking the instrumental variable with the outcome of interest. This assumption was only partly met, as both maternal mental health and BMI was associated with several factors (offspring sedentary behaviour and smoking status) which might be associated with the respective outcomes in offspring. However, the maternal influence on these confounding factors is likely to be weaker than that of participant's, as confirmed in the present study. Maternal depressive symptoms might contribute to an environment that may have long lasting effects on offspring BMI. However, given that participants were followed into midlife over a 26 year follow-up period these potential environmental influences in childhood are likely to be diluted.

After adjustment for offspring malaise score, the maternal malaise–BMI association persisted, thus providing further evidence for violation of the exclusion restriction assumption and suggesting that maternal mental health may influence offspring obesity through mechanisms other than depression. For example, genetic vulnerability to depression may be associated with pleiotropic effects reflecting unknown biological pathways driving BMI of offspring in later life. In addition, children with depressed mothers may be exposed to more environmental and family risk factors, than families without depression,[13] although we attempted to control for this by adjusting for mother's social status.

A direct pathway from depression to obesity seems biologically plausible. One of the driving factors might be disturbances in key stress axes including the hypothalamic pituitary adrenal axis and sympathetic nervous system. Disturbances in these axes have been associated with depressive symptoms[18] and are linked to insulin resistance and the cascade of events in the metabolic syndrome, including deposition of adiposity.[19-21] Furthermore, depression is associated with reduced physical activity,[22] which may also contribute to increased weight gain. These direct and indirect underlying mechanisms may conceivably operate over a prolonged period, thus studies with sufficient follow up would be required to detect the effects and may therefore explain the equivocal nature of the literature.

The main strength of this study is the use of intergenerational, longitudinal data to reduce confounding and bias. In addition we utilised data on maternal depressive symptoms across three time points during their offspring's childhood/adolescence in order to better capture long term exposure. The limitations included the use of self-reported weight and height. Previous studies, however, have demonstrated the validity of using self-reported weight.[23] Furthermore, errors in self-reported weight are often systematic instead of random, reflecting both rounding to the nearest point of heaping and a tendency to report weights closer to ideal weight.[24] Although well validated, the instrument used to assess depressive symptoms could not capture clinical diagnosis. The Malaise Inventory is essentially a measure of 'negative affect' since it covers an array of items relating to anxiety disorder, psychological and somatic symptoms. Although the Malaise inventory has not been commonly used in the past, a wide variety of psychometric instruments have been employed to assess negative affect (commonly termed as 'depressive symptoms') in this area. Depressive symptoms were measured using different versions (24-item and 9-item) of the Malaise Inventory at various stages of the survey although the full 24 item version is known to be more reliable. In addition, different subtypes of depression may be more strongly associated with obesity.[25] Missing

data may have introduced bias as excluded participants were more disadvantaged. Nevertheless, given that this may have slightly constrained variation in depressive symptoms and BMI our results are likely to reflect conservative estimates. Over 95% of the cohort was 'British white' thus it was not possible to investigate possible interactions by ethnicity. Although our study does not provide a definitive answer to the complexities in the relationships between depression and obesity, it adds a novel component to the cumulating evidence on depression as a long-term risk factor for increased body mass.

In summary, to our knowledge this is the first study to adopt a novel approach utilising intergenerational data on mother – offspring pairs to examine a causal pathway linking adolescent depressive symptoms to BMI in adulthood.

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Author contributions

MH had full access to the data, and takes responsibility for the integrity and accuracy of the results. All authors contributed to the concept and design of study, drafting and critical revision of the manuscript.

Conflict of interest

None of the authors have any competing interests to declare.

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