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Maternal pre-pregnancy weight status and adolescent eating disorder behaviors: a longitudinal study of risk pathways

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Data are available following relevant procedures for data access from ALSPAC; computing code is available from Prof De Stavola upon request.

ABSTRACT

Background: Maternal characteristics and childhood growth have been identified as risk factors for eating disorders. Most studies to date have been unable to investigate these factors prospectively while accounting for their interdependencies. We address this by investigating whether the association of maternal pre-pregnancy body mass index (ppBMI) with adolescent eating disorder behaviors can be explained by childhood growth and/or a concurrent environmental pathway captured by maternal eating habits.

Methods: We analyzed data from girls participating in the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective UK cohort. The study had information on parentally and self-reported eating disorder behaviors at age 13/14 years (n=3,529), maternal ppBMI and eating habits at age 8, child's birth weight, BMI from age 7 to 12, pubertal development at 11, and relevant confounders. We quantified contributions of childhood growth and concomitant maternal eating habits to the association of maternal ppBMI with eating disorder behaviors in terms of interventional disparity effects for multiple mediators.

Results: Maternal pre-pregnancy underweight was negatively associated with eating disorder behaviors (-0.18; 95% confidence interval (CI): -0.29, -0.06) while overweight/obesity had the opposite relationship (0.25; 0.18, 0.32). Both were nearly fully explained by childhood growth.

Conclusions: Although maternal ppBMI is associated with developing eating disorders, its role needs to be understood in the context of childhood factors, in particular childhood growth. The relatively small size of the remaining associations, once growth factors are hypothetically equalized across levels of maternal ppBMI, suggests that childhood growth is a potential area for prevention.

Key words: ALSPAC, eating disorders, risk, mediation, interventional effects, disparity effects, maternal weight

Introduction

Eating disorders are chronic psychiatric illnesses comprising a range of conditions across the weight spectrum (anorexia nervosa, bulimia nervosa, binge eating disorder and other specified feeding and eating disorders). Eating disorders have a peak of onset in adolescence[1] and are prevalent amongst young people, affecting between 5%-10% of adolescent girls.[2-5] Eating disorder behaviors, mapping onto clinical diagnoses but not reaching thresholds for a clinical diagnosis in current diagnostic manuals, are common in young females and predict adverse consequences such as depression, anxiety disorders, and substance use.[2,4,6] Eating disorders are multifactorial in terms of their etiology.[7] However, efforts to understand developmental risk for eating disorders in the broader context of parental and child factors have been hampered by the lack of longitudinal studies that both cover the whole developmental period and adequately model the role of multiple risk factors and their interaction. Developmental risk factors do not exert their effect in a vacuum, but are often highly correlated and might operate through their effects on other factors. For instance, birth weight, childhood BMI, and early puberty have been suggested as risk factors for eating disorders and eating disorder behaviors.[8-11] Similarly, post-pregnancy maternal BMI has been found to be prospectively associated with eating disorder behaviors in adolescence and young adulthood.[12,13] An extensive body of literature has investigated maternal weight status in pregnancy in relation to mental health outcomes in childhood and adolescence;[14-16] however, no previous studies have sought to model the joint effects of maternal weight status, infant/childhood weight, and pubertal status on eating disorder behaviors. A further possible mechanism via which maternal factors may be associated with eating disorder behaviors involves childhood exposure to maternal eating and attitudes to food. The aim of this paper is to clarify these prospective associations and related risk pathways over time, as they may aid focusing preventative and early intervention efforts. We draw upon available longitudinal

data collected prospectively over a 15-year span as part of the Avon Longitudinal Study of Parents and Children (ALSPAC) on maternal weight status, child's birth weight, BMI childhood trajectories, pubertal development, maternal eating habits, and eating disorder behaviors in early adolescence. Eating disorder behaviors were reported separately by the participants and by their parents and thus allow an assessment of the robustness of findings to differential sources of reporting error. We focused the study on participating girls, due to the higher prevalence of eating disorder behaviors in early adolescence among girls and the differential patterns of these behaviors across genders.[17,18]

We investigated the extent to which the adjusted association between maternal pre-pregnancy weight status (underweight or overweight/obese) and adolescent eating disorder behaviors would remain if the distributions (conditionally on confounders) of selected childhood variables were made to be the same as those of children whose mothers were normal weight. The childhood variables were chosen to represent growth and environmental pathways of risk, with their contribution to the adjusted pre-pregnancy BMI (ppBMI)–eating disorder behaviors association quantified in terms of interventional disparity indirect effects.[19,20] This approach has the advantage of not demanding a causal interpretation with respect to the exposure, maternal ppBMI, (hence avoiding its related pitfalls[21]), while still investigating possible pathways of interventions involving intermediate variables, as has been done by VanderWeele and Robinson with race as the exposure.[22] As well as focusing on interventional effects for a single mediator (or a set of mediators considered as a group), we also make use of the extension to multiple mediator settings proposed by Vansteelandt and Daniel[20] that allows multiple mediator-specific pathways to be compared without requiring an assumption of no unmeasured common causes of one mediator with another.

Methods

Participants

ALSPAC is a longitudinal, population-based, prospective study of women and their children. All pregnant women living in the geographical area of Avon, UK, expected to deliver between 1 April 1991 and 31 December 1992 were invited to participate in the study. All participating women gave informed and written consent. The ALSPAC study website contains details of all the data that are available through a fully searchable data dictionary: http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary. A total of 14,541 pregnancies were enrolled, resulting in 14,062 live births and 13,617 singleton children who were alive at 1 year of age[23]. Additional 713 children enrolled in the cohort at age 7 years are not included in these analyses due to missing data on maternal BMI by design.[23] A total of 10,135 children from the initial cohort were still followed up at the age 13-year wave. Further exclusions were due to non-response at this wave, leaving 7,078 respondents with eating disorder behavior data, 3,529 of whom were girls (Figure 1).

Figure 1 about here

Main Outcomes

Parentally –reported eating disorder behaviors (at p-ED: at mean child age 13.1 years (standard deviation, SD=0.2), data were collected via the Developmental and Well-being Assessment (DAWBA), a semi-structured validated interview that generates a range of psychiatric diagnoses in children and adolescents.[24] The eating disorders section of the DAWBA was given to parents and comprises 28 questions on eating disorder behaviors and cognitions. These were used to derive three disordered eating patterns: 1. binge eating/overeating; 2. shape and weight concern and weight control behaviors, and 3. food restriction, using exploratory structural equation modeling (as described in [17]). Data on these three patterns were available on 3,529 girls. Because these are latent factors derived from

structured questionnaires, they are standardized measures with mean 0 and standard deviation (SD) of 1.

Secondary Outcomes

Self-reported eating disorder behaviors were obtained from the children at mean age 14.0 years (SD=0.2) using validated questions adapted from the Youth Risk Behavior Surveillance System questionnaire[25] enquiring about the previous year; for details see [2]. We used two behaviors, binge eating and fasting, which map closely onto the first and third the p-ED patterns). These self-reported outcomes were available for 2,751 and 2,734 girls, respectively.

Exposure

Maternal ppBMI, (kg/m^2) was obtained from self-reported height and weight at enrollment during pregnancy, and used as an indicator of maternal weight status before the child's birth. It was categorized as: underweight (BMI<18.5), normal weight (18.5-24.9), overweight/obese (≥25) according to WHO criteria,[26] with normal weight treated as the reference category. Self-reported weight was highly correlated with maternal pregnancy objective weight in ALSPAC.[27]

Mediators

Birth weight (grams) was obtained from obstetric records. Childhood growth was quantified in terms of predicted random intercepts and slopes of the individual childhood trajectories of body mass index (BMI, kg/m^2). These were derived from the original measurements taken at around age 7.5, 8.6, 9.8, 10.6, 11.8, and 12.8 years using a linear mixed effects model after log-transformation to achieve near normality. Assuming that the timing and frequency of the observations were unrelated to actual BMI values, the best-fitting model had a linear and a quadratic term in age with random intercepts and random slopes for the linear age term only. Empirical Bayes predictions of the random intercepts and slopes were then saved and used to generate individual-level BMI at age 7.5 (thereafter labeled '*size'*) and BMI rate of increase

('*yearly velocity*') (details in eTable 1; http://links.lww.com/EDE/B349). Pubertal development was defined using Tanner's stage of breast development at mean child age 10.7 years,[28] based on parental reports. This was categorized as early (Tanner stage ≥2) or age appropriate (< 2). At child age 8 years, mothers were sent a questionnaire asking about their own eating habits. Factor analyses revealed two dimensions: (i) avoidance of new foods, and (ii) poor enjoyment of eating (Micali et al in preparation). These were correlated with maternal self-reported eating disorders at enrolment.

Covariates

We considered several potential confounders of the exposure–mediator, exposure–outcome and mediator–outcome relationships. These included maternal education, maternal age, and lowest parental social class, all obtained at enrollment.[23] At 12 weeks gestation women were asked about any recent or past history of: severe depression, schizophrenia, alcoholism, anorexia nervosa, bulimia nervosa, and other psychiatric disorders. Multiple answers were possible; therefore, women could report more than one disorder. This information was combined into a variable indicating presence of any pre-pregnancy psychopathology.

Statistical methods

Definitions of effects of interest

The aim of the study was to investigate the covariate-adjusted association between maternal pre-pregnancy weight status and offspring eating disorder behaviors, and to investigate the extent to which it is explained via a "growth pathway" and a "maternal environmental pathway" (Figure 2). The growth pathway comprises pathways from ppBMI to eating disorders that pass through birth weight, BMI size and velocity, and timing of puberty; the maternal environmental pathway comprises pathways that pass through the two latent dimensions measuring her eating habits.

Figure 2 about here

We defined the contributions of these pathways in terms of interventional disparity indirect effects, initially with all six mediators contributing to the growth and environmental pathways taken *en bloc*, then with the two groups of mediators taken separately. Interventional disparity indirect effects are a variant on interventional indirect effects;[19,20] they borrow an idea from the recent literature on counterfactual disparity measures,[22,29] and are described below.

In the setting with a vector of mediators, interventional indirect effects (as defined by VanderWeele et al.[19]) compare what, on average, would occur to the outcome had all individuals in the population had their mediators set to take random values from their joint distribution, conditional on confounders, among the exposed versus the corresponding distribution among the unexposed, conditional on confounders, while the exposure had been set to be exposed for all; thus it captures the effect of a hypothetical intervention that would shift the distribution of all mediators, while keeping the exposure set at exposed status. This definition is causal with respect to the effects of both the exposure and the mediators on the outcome, and thus a meaningful quantitative interpretation requires consideration of the nature of the entailed hypothetical interventions on the exposure and mediators. As has been widely discussed,[30,31] this is difficult (and would typically involve complex stochastic hypothetical interventions,[32-36]) especially for variables such as BMI. In this context, therefore, we do not seek a strict causal interpretation with respect to the exposure, and pursue an alternative specification following VanderWeele and Robinson[22,37] and Naimi et al.[29] The *interventional disparity measure* indirect effects we define here pertain to the extent by which eating disorder behaviors of girls whose mothers were underweight (or overweight/obese) before pregnancy would change, had the distributions of their mediators been changed to that of girls whose mothers were normal weight (conditional on confounders). Their complement, the direct effects, represent the covariate-adjusted

associations (between ppBMI and eating disorder behaviors) that would remain if all mediators were set to have the same joint distribution, given confounders, as is actually the case amongst girls whose mothers were normal weight.

For completeness and clarity, we write the effects mathematically below. Let X be the exposure (ppBMI), **M** the vector of all six mediators, Y the outcome (eating disorder behavior score), and **C** the vector of four possible confounders. Write Y(**m**) to be the potential value that Y would take if **M** were intervened upon and set to level **m**. Let $\mathbf{M}^{x}_{\mathbf{C}}$ be a random draw from the joint distribution of **M** given **C** among those with X=*x*. The interventional disparity measure (IDM) direct and indirect effects, or *IDM-DE* and *IDM-IE*, are defined as follows, for categorical **C** (with corresponding integrals and densities for continuous **C**):

$$\textit{IDM-DE} = \Sigma_{\mathbf{c}} \left[E\{Y(\mathbf{M}^{0}_{\mathbf{C}})|X=1,\mathbf{C}=\mathbf{c}\} - E\{Y(\mathbf{M}^{0}_{\mathbf{C}})|X=0,\mathbf{C}=\mathbf{c}\}\right] \Pr(\mathbf{C}=\mathbf{c}),$$

$$\textit{IDM-IE} = \Sigma_{\mathbf{c}} \left[E\{Y(\mathbf{M}^{1}_{\mathbf{C}})|X=1,\mathbf{C}=\mathbf{c}\} - E\{Y(\mathbf{M}^{0}_{\mathbf{C}})|X=1,\mathbf{C}=\mathbf{c}\}\right] \Pr(\mathbf{C}=\mathbf{c}).$$

Note that these differ from the definitions given by VanderWeele[37] only to the extent that we marginalize over the distribution of covariates **C**.

Under the identifying assumptions described in the next section the sum of the *IDM-DE* and *IDM-IE* is the **C**-adjusted marginal association between X and Y expressed as a mean difference, which we label the adjusted total association, *Adj-TA*. That is,

$$\textit{IDM-DE} + \textit{IDM-IE} = \textit{Adj-TA} = \Sigma_{\mathbf{c}} \{E(Y|X=1,\mathbf{C}=\mathbf{c}) - E(Y|X=0,\mathbf{C}=\mathbf{c})\} \Pr(\mathbf{C}=\mathbf{c}).$$

Assumptions

The identification of the above effects relies on a number of assumptions, commonly referred to as 'no interference', consistency, and 'no unmeasured confounding'. Due to our focus on effects that avoid a causal interpretation with respect to the exposure (ppBMI), the precise nature of these assumptions is somewhat different (weaker) than usually stated (and furthermore do not require a cross-world independence or similar assumption). In the present

context, the assumption of no interference states that the eating disorder behavior of one girl is not influenced by the mediator levels of another; and the assumption of consistency states that within a group of girls, all of whom share the same mediator levels, **m** say, the same background confounder levels **c** and the same exposure level *x*, the mean eating disorder behavior level in this group were we hypothetically to intervene and set their mediator values to **m** would be the same as the actual mean eating disorder behavior level in this group; this should be true at all possible levels of confounders, exposure, and mediators. Written mathematically:

$E\{Y(\mathbf{m})|\mathbf{C=c},X=x,\mathbf{M=m}\} = E(Y|\mathbf{C=c},X=x,\mathbf{M=m})$, for all $\mathbf{c},x,\mathbf{m}$.

This version of the consistency assumption for mediation analysis is weaker than usually stated and still may not be met in applications, as expanded in the Discussion. Finally, assuming no unmeasured confounding in the present context implies that the potential eating disorder behavior score were the mediators set by hypothetical intervention to a particular set of levels are conditionally mean independent of the actual mediator levels, conditional on exposure and confounders; this should be true at all possible levels of confounders, exposure, and mediators. Hence, unmeasured exposure–mediators and exposure–outcome common causes are permitted (indicated by V and W in Figure 2). This is the rigorous way of saying that there can be no unmeasured mediator–outcome confounding; written mathematically:

$E\{Y(\mathbf{m})|\mathbf{C=c},X=x,\mathbf{M=m}\} = E(Y(\mathbf{m})|\mathbf{C=c},X=x)$, for all $\mathbf{c},x,\mathbf{m}$.

Vansteelandt and Daniel[20] extend the definition of interventional effects to multiple mediators, and allow for the partitioning of the indirect effect into effects that involve subsets of the mediators, plus an additional indirect effect representing the dependence between mediators. The mediators in Vansteelandt and Daniel's[20] formulation are permitted to be correlated via factors that are unmeasured (indicated by U in Figure 2); this, together with our focus again on disparity measure effects (in contrast to Vansteelandt and Daniel) means that

no additional assumptions from those stated above are needed for our investigation of separate indirect effects through subsets of multiple mediators. We adopted this approach when separating the mediators into growth and maternal environment subsets. The precise definitions of these interventional disparity measure multiple mediator effects can be found in the eAppendix; http://links.lww.com/EDE/B349 (equations (1)-(3) and (6)).

Note that if we additionally made assumptions that justified a causal interpretation of *Adj-TA*, then the sum of *IDM-DE* and *IDM-IE* would represent the total causal effect of X on Y expressed as a marginal mean difference: $E\{Y(1) - Y(0)\}$. Even without these additional assumptions, the decomposition of the adjusted total association is meaningful, as it allows the examination of alternative pathways.

Estimation method

Estimation was via a series of richly specified regression models, combined using Monte Carlo simulation performed using Stata v14.2.[38] This required the specification of parametric models for the outcome given exposure, mediators, and confounders, and for the mediators given exposure and confounders, on a 1000-fold expanded dataset. By 'richly specified' we mean that many interactions and other higher-order terms were included, in an attempt to lessen the impact on the final estimates of incorrectly specified parametric models. Full details can be found in the eAppendix; http://links.lww.com/EDE/B349. Standard errors were estimated using the non-parametric bootstrap (with 1000 bootstrap samples) and used to calculate 95% confidence intervals. All mediated effects are expressed as mean differences, and thus when the outcome is binary (s-ED), these are risk differences.

Missing data

Data on exposure, confounders and mediators were affected by missingness. For this reason, single stochastic imputation using chained equations[39] with 10 burn-in iterations was implemented before the 1000-fold data expansion for the Monte Carlo estimation procedure

was carried out, under the assumption that missingness was at random (MAR).[40] In this instance, this implies that common drivers of missingness and the partially observed variables are included among the variables being conditioned upon in the imputation. The imputation models were all more general than the analytical models. Multiple imputation was not required since the bootstrap was used to estimate standard errors, and the imputation step was redone on each bootstrap sample.

Ethical approval

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Results

Data on p-ED behaviors were available on 3,529 girls (Figure 1). A comparison of baseline characteristics of these girls against those included in the ALSPAC study at birth shows some attrition linked to maternal education (eTable 2; http://links.lww.com/EDE/B349). Among the girls included in this study, and who represent 70% of those that were invited to participate at age 13 years (mothers of 1,562 girls--30% of those invited--did not return questionnaires), exposure, mediators, and confounders were affected by missingness, with 1,989 (56%) having complete information on all relevant variables. Missingness was associated with younger maternal age, lower education, parental manual social class, lower birth weight, and greater childhood BMI. The subset with complete records had slightly lower scores of p-ED behaviors and a slightly lower prevalence of s-ED behaviors (Table 1 and eTable 3; http://links.lww.com/EDE/B349).

Table 1 about here

Separate adjusted associations between each outcome and each of the exposure and mediators are shown in Table 2a (for parentally reported eating disorder behaviors) and Table 2b (for self-reported eating disorder behaviors). Maternal pre-pregnancy weight status and childhood

variables were in general strongly associated with parentally reported behaviors (Table 2a). Much weaker, but similar, associations are seen for self-reported behaviors (Table 2b). There was no evidence of associations between any of the outcomes and maternal eating habits.

Further exploration of associations between each potential mediator and the exposure shows strong and consistent relationships between each continuous mediator and maternal ppBMI, except for maternal avoidance of new foods (Table 3). The association with pubertal stage at age 12 year was also strong, with the OR of early pubertal development estimated to be about half in daughter of underweight mothers relative to those of normal weight mothers (OR=0.49; 0.27, 0.89) and the equivalent OR of daughters of overweight/obese mothers estimated to be 71% greater (OR=1.71; 1.35, 2.16).

Tables 2a and 2b and Table 3 about here

Table 4 reports the estimated adjusted total association between ppBMI and p-ED behaviors and their partitioning into interventional disparity direct and indirect effects, all expressed as mean differences in p-ED behavior scores and obtained using the full set of 3,529 girls. The estimated adjusted total association comparing maternal underweight vs normal on binge eating/overeating was negative (-0.18, 95% confidence interval (CI): -0.29, -0.06) and of similar magnitude to the estimated interventional indirect effect via the six mediators taken *en bloc* (-0.22, 95% CI: -0.32, -0.11).

The sum of the *IDM-DE* and *IDM-IE,* that we denote adjusted total association, Adj-TA, is estimated as-0.18 (95% CI: -0.29, -0.06) and represents the strength of association between maternal pre-pregnancy underweight and binge eating/overeating, estimated after adjusting for (and then standardizing by) the baseline covariates (maternal age, education, psychopathology, and parental social class). The estimated disparity measure-direct effects, *DM-DE,* is0.04 (95% CI: –0.09, 0.17) and represents the extent of this adjusted association that would remain if the six mediators were set to have the same distribution in girls whose

mothers were underweight before pregnancy, as that of girls whose mothers were normal weight (conditional on confounders). By complement, the estimated *DM-IE*=–0.22 (95% CI: –0.32, –0.11) represents the extent by which the eating disorder score of girls whose mothers were underweight before pregnancy would change, if the six mediators taken *en bloc* were set to have the same distribution as that of girls whose mothers were normal weight (conditional on confounders).

Similar estimates of the adjusted total associations and of the disparity measure- effects were found for weight concern/control weight and shape concern and for weight control behaviors and for food restriction.

The *Adj-TA* of maternal overweight/obesity vs. normal for each parentally reported eating disorder behavior was in the opposite direction to that for maternal underweight [binge eating/overeating: 0.25 (0.18, 0.32); weight and shape concern and weight control behaviors: 0.22 (0.15, 0.29); food restriction: 0.18 (0.11, 0.25); Table 4]. These effects were fully explained by the six mediators when taken as a group.

Table 4 about here

When the six mediators were split into a "growth pathway" (captured by birth weight, childhood growth and puberty status), and a "maternal environmental pathway" (captured by the two dimensions of maternal eating habits), we found that the first pathway explained most of the indirect effect of maternal ppBMI on eating disorder behaviors (Table 4).

If the assumptions discussed in the Methods are deemed to be met, these estimates of indirect effects via the growth pathway quantify the extent by which the eating disorder scores of girls whose mothers were underweight (or overweight/obese) would change if the distributions of the childhood growth variables (but not those of maternal eating habits) were made to be the same as those of children whose mothers were normal weight (conditionally on confounders).

eTable 4; http://links.lww.com/EDE/B349 reports the estimated risk differences for the two self-reported eating disorder behaviors. The estimated effects for maternal overweight are in line with those from the parental reports although they are less precise. Those for the effects of maternal underweight on self-reported fasting instead indicate that the protective association is not explained by any of the mediators considered here. All the findings are consistent with the adjusted relationships observed in the data, in particular with the strength of association with the mediators belonging to the growth pathway.

Discussion

Parental and developmental risk factors for childhood disorders have often been studied independently; however, most developmental risk factors, especially weight, growth, and parental weight status are highly associated. Therefore, studying them independently might not provide a full account of risk pathways. We provide evidence of the importance of studying related intergenerational risk factors (in particular maternal weight status, child weight, growth, and pubertal development) for adolescent eating disorders using a causal inference framework. Existing evidence suggests that child weight, growth, and parental weight might be predictors of eating disorders.[8-13] However, few large, comprehensive prospective studies are available, therefore no studies (to our knowledge) have investigated how these factors might be related, nor relevant intergenerational risk pathways.

This study is the first to show a differential (protective vs. risk-conferring) adjusted association between pre-pregnancy maternal underweight vs normal and overweight/obesity vs normal and adolescent eating disorder behaviors. We found that these adjusted associations were almost fully explained by a growth pathway (with a strong biological component) involving the child's birth weight, growth, and early puberty. Shifting from the role of individual risk factors to a broader perspective which includes risk pathways has the potential not only to improve our understanding of the role of intergenerational risk for eating

disorders, but also, potentially, to target our prevention and early intervention efforts where they might be more effective. Secondly, given the increasing evidence of the importance of obesity genetic risk for eating behaviors and weight development,[42,43] new evidence on how biological risk pathways affect eating and eating disorders is likely to influence novel conceptualizations of the pathophysiology of eating disorders and eating development.

Our findings need to be understood in the context of the strengths and limitations. The data comprise information collected prospectively over 15 years as part of the ALSPAC Study. This birth cohort suffers from attrition linked to socio-economic status as also noted by Howe *et al.*[41]. These authors found that even an attrition of up to 50%, which was observed at age 15 years, did not affect the qualitative conclusions drawn from ALSPAC on the association between social inequalities and several outcomes when based on crude analyses of the complete records. We used ALSPAC data up to age 13 years and controlled in our analyses for the main drivers of attrition, namely socio-economic indicators. Furthermore, by imputing the variables affected by missingness, which pattern was found to be influenced by socio-economic factors, and by controlling for them in the analyses, the likely bias due to attrition and item-response missingness should be minimal, if the assumption that missingness and attrition are random is justified in this dataset.

The majority of data (i.e. child BMI, pubertal status, birth-weight) in this study were collected objectively. Moreover, we used novel approaches to mediation analysis to try and distinguish pathways along which maternal BMI may be associated with the outcome, distinguishing between a growth and a more environmental component that allowed for unmeasured common causes of their distributions. However, these analyses rely on strong unverifiable assumptions besides MAR, namely no unmeasured confounding of the mediator–outcome relationships, no interference, and consistency (again for the mediator–outcome relationships). To attempt to meet the first of these assumptions we have controlled

for likely confounders, including two indicators of socioeconomic position that may capture, at least in part, the effect of other unmeasured confounders. The assumption of no interference would not be satisfied, for example, if the eating habits of a girl's mother influenced the eating disorder of another girl, as might occur if they regularly socialized with each other's families. The ALSPAC participants, however, are located across a fairly wide geographic area so we can plausibly assume that this would affect only a minority. It is implausible that a single (simple) hypothetical intervention on the mediators exists that would lead to the consistency assumption being satisfied, especially for those involved in the growth pathway. For example, there are many different hypothetical ways of 'setting' the growth trajectory of girls, and each may lead to a different eating disorders behavior level; furthermore, our dataset will contain girls who attain their growth trajectory for many different reasons. The consistency assumption thus necessitates that we interpret our effects in terms of a complex hypothetical intervention, which randomly assigns girls to have their growth trajectory set in one of many different ways, such that the overall intervention is 'non-invasive' in the sense that it would not change the outcome for those whose mediators are being 'set' to the same value as was in fact attained. For further discussion of these issues, see [32,33,35].

Although our main analyses focused on parentally reported eating disorder behaviors, we also replicated our analyses on self-reported eating disorder behaviors, showing consistency of our results. The main limitations entail the nature of the sample, representative of a selected (by attrition and by design, as only pregnant women were included in the study) UK population, but limited in its generalizability to other populations. Our exposure, maternal ppBMI, was based on self-report; however, using questionnaires rather than objective measures is cost-effective in the context of large samples and maternal self-reported weight in this sample was highly correlated with objectively measured weight.[27] Maternal

underweight was not highly prevalent (~5%), leading to imprecision of our estimates of effects comparing maternal underweight versus normal weight. Although we were not able to study maternal eating disorders as an independent predictor, they were included among the confounders as a component in maternal pre-pregnancy mental health disorders; however, the overall prevalence was low and we acknowledge this is an imperfect measure of maternal psychopathology. It is plausible that a subset of women who were underweight might have suffered from restrictive eating disorders. In relation to our outcomes, our aim was to focus on eating disorder behaviors that are prevalent in the community,[2-4] rather than full-blown eating disorders (rarer at the developmental stage under investigation). However future studies will aim to determine whether similar risk mechanisms are at play in eating disorders. In conclusion, this study highlights the importance of examining intergenerational effects using comprehensive explanatory models that avoid focusing on specific variables in a vacuum. We confirmed our hypothesis that maternal ppBMI is conditionally associated with child eating behaviors, and that the majority of this adjusted association acts through a pathway driven by birth weight, growth and puberty. Future studies should extend this investigation to specific genetic or metabolic risk.

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Figure 1: Flow-diagram of ALSPAC participants

Figure 2: Assumed causal relationships among exposures, mediators, confounders, and outcome. U, V, and W indicate unaccounted confounders.

Table 1 - Means and standard deviations, or frequencies and percentages (*italics*), of main variables in the whole study and in the complete records [a] subset

	Overall			Complete records		
	N	Mean/Freq	SD/%	N	Mean/Freq	SD/%
Outcomes						
Parental report						
Binge eating/ overeating (SD) [b]	3,529	0.00	1.00	1,989	-0.04	0.98
Weight concern/control (SD) [b]	3,529	0.00	1.00	1,989	-0.03	0.99
Food restriction (SD) [b]	3,529	0.00	1.00	1,989	-0.03	0.97
Self-report [a]						
Binge eating	2,751			1,679		
Yes		188	*6.8*		99	*5.9*
No		2,563	*93.2*		1,580	*94.1*
Fasting	2,734			1,662		
Yes		247	*9.0*		130	*5.9*
No		2,487	*91.0*		1,532	*92.2*
Exposure						
PP-maternal weight status	3,088			1,989		
Underweight		*154*	*5.0*		*92*	*4.6*
Normal weight (reference group)		*2,344*	*75.9*		*1,529*	*76.9*
Overweight/Obese		*590*	*19.1*		*368*	*18.5*
Mediators						
Birth weight (SD) [b]	3,330	0.06	0.96	1,989	0.09	0.90
BMI size at age 7y (SD) [b,c]	3,238	0.00	1.00	1,989	-0.05	0.97
BMI yearly velocity (age 7-12y) (SD) [b,c]	3,238	0.00	1.00	1,989	0.03	1.00
Pubertal development at age 12y	2,776			1,989		
Age appropriate		2,138	*77.0*		1,529	*76.9*
Early		638	*23.0*		460	*23.1*
Maternal avoidance of new foods (age 8y) (SD)	2,942	-0.02	0.99	1,989	-0.03	0.99
Poor enjoyment of eating (age 8y) (SD)	2,942	-0.02	1.00	1,989	-0.05	0.97
Confounders						
Maternal age (y)	3,369			1,989		
<25		521	*15.4*		239	*12.0*
25-29		1,336	*39.7*		811	*40.8*
≥30		1,512	*44.9*		939	*45.2*
Parental social class	3,091			1,989		
Manual/low		428	*13.9*		234	*11.8*
Non-manual/high		2,663	*86.1*		1,755	*88.2*
Maternal education	3,185			1,989		
Up to secondary		1,772	*55.6*		1,019	*48.9*
Secondary or higher		1,413	*44.4*		970	*51.2*
Maternal lifetime psychopathology reported in pregnancy	3,250			1,989		
None reported		2,880	*88.6*		1,801	*90.6*
Any		370	*11.4*		188	*9.5*

N: records with information; Freq: frequency; SD: standard deviation; y: years.

a: The definition of complete records did not include self-reported ED

b: Internally standardized (before exclusions), with units expressed in terms of SDs.

c: Predicted values from a mixed effects model fitted to the repeated childhood BMI measures.

Table 2 – Estimated regression coefficients (β) or odds ratios (ORs) for associations between ED behaviors (dependent variable, internally standardized) and, separately, exposure and mediators, adjusted for relevant confounders [a]

ED behaviors (parentally reported)		Binge eating /overeating[b]		Weight and shape concern & weight control behaviors[b]		Food restriction[b]	
	N	β	95% CI	β	95% CI	β	95% CI
Exposure							
Pp-maternal weight status	2,874						
Underweight		-0.14	-0.31, 0.03	-0.20	-0.37, -0.03	-0.19	-0.36, -0.02
Normal weight (ref. group)		0		0	-	0	-
Overweight/Obese		0.31	0.22, 0.40	0.26	0.17, 0.35	0.22	0.13, 0.31
Linear trend (p-value)		*<0.001*		*<0.001*		*<0.001*	
Mediators							
Birth weight (SD)[b]	2,840	0.06	0.02, 0.10	0.05	0.01, 0.10	0.04	0.00, 0.08
BMI size at age 7y (SD)[b,c]	2,675	0.33	0.29, 0.36	0.33	0.29, 0.36	0.27	0.23, 0.31
BMI yearly velocity (7-12y) (SD)[b,c]	2,675	0.11	0.07, 0.15	0.15	0.11, 0.18	0.13	0.09, 0.17
Pubertal development (age 12y)	2,330						
Age-appropriate		Ref		Ref		Ref	
Early		0.37	0.28, 0.46	0.44	0.34, 0.53	0.44	0.34, 0.53
Maternal avoidance of new foods (age 8y) (SD)	2,499	0.01	-0.03, 0.05	0.02	-0.02, 0.06	0.02	-0.02, 0.06
Maternal poor enjoyment of eating (age 8y)(SD)	2,499	-0.01	-0.04, 0.04	0.01	-0.03, 0.05	0.02	-0.02, 0.06

ED behaviors (self-reported)		Binge eating			Fasting	
	N	OR	95% CI	N	OR	95% CI
Exposure						
PP-maternal weight status	2,279			2,236		
Underweight		0.68	0.27, 1.71		0.94	0.46, 1.91
Normal weight (ref. group)		1	-		1	-
Overweight/obese		1.08	0.71, 1.47		1.37	0.96, 1.96
Linear trend (p-value)		*0.45*			*0.10*	
Mediators						
Birth weight (SD)[b]	2,230	1.10	0.90, 1.33	2,210	0.93	0.79, 1.09
BMI size at 7y (SD) [b,c]	2,147	1.49	1.25, 1.77	2,110	1.67	1.43, 1.59
BMI yearly velocity (7-12y) (SD) [b,c]	2,147	0.98	0.82, 1.16	2,110	0.97	0.83, 1.13
Pubertal development at 12y	2,037			1,997		
Age-appropriate		Ref	-		Ref	-
Early		1.27	0.85, 1.89		1.86	1.32, 2.61
Maternal avoidance of new foods (8y) (SD)	2,036	0.77	0.63, 0.94	2,001	0.84	0.71, 1.00
Maternal poor enjoyment of eating (8y) (SD)	2,036	0.84	0.67, 1.04	2,001	1.12	0.96, 1.30

ED indicates eating disorder.

[a] Estimates were adjusted as follows:

- For the exposure: parental social class, maternal education, age and psychopathology
- For the mediators: as above plus pp-BMI

[b] Internally standardized (before exclusions), with units expressed in terms of SDs.

[c] Predicted values from a mixed effects model fitted to the repeated childhood BMI measures.

Table 3 – Estimated regression coefficients or odds ratios (OR, *in italics)* for the association between each mediator (dependent variable) and pp-BMI

		Pre-pregnancy maternal weight status (pp-BMI)					
		Underweight		Normal weight	Overweight/obese		*Trend (p-value)*
	N	Regression coeff./OR	95% CI		Regression coeff./ OR	95% CI	
Mediators							
Birth weight (SD)[a]	2,840	-0.33	-0.49, -0.18	Ref.	0.24	0.16, 0.33	<0.001
BMI size at 7y (SD) [a,b]	2,675	-0.30	-0.47, -0.13	Ref.	0.51	0.42, 0.61	<0.001
BMI yearly velocity (7-12y) (SD)[a,b]	2,675	-0.19	-0.36, -0.01	Ref.	0.12	0.02, 0.21	0.001
Pubertal stage at age 12y[c]	2,330	*0.49*	*0.27, 0.89*	Ref.	*1.71*	*1.35, 2.16*	<0.001
Maternal avoidance of new foods (8y) (SD)	2,499	0.06	-0.13, 0.24	Ref.	-0.03	-0.13, 0.07	0.43
Maternal poor enjoyment of eating (8y) (SD)	2,499	0.41	0.23, 0.59	Ref.	-0.16	-0.25, -0.06	<0.001

OR indicates odds ratio, SD standard deviation, CI confidence interval, BMI body mass index.
[a] Estimates were adjusted for parental social class, maternal education, age and psychopathology
[b] Internally standardized (before exclusions), with units expressed in terms of SDs.
[c] Predicted values from a mixed effects model fitted to the repeated childhood BMI measures (details in eTable 1).

Table 4– Adjusted total association of maternal pre-pregnancy body mass index and eating disorder (ED) behaviors and interventional disparity direct and indirect effects estimated by Monte Carlo simulation and imputation of missing values (standard errors estimated using 1000 bootstrap samples); N=3,529; Monte Carlo sample of 3,529,000.

Outcome	Effect (all direct and indirect effects are IDM)	*Maternal weight status (pp-BMI; reference: normal weight)* Underweight Mean difference	95% CI	Overweight/Obese Mean difference	95% CI
Binge eating /Overeating	**Adjusted total association**	-0.18	-0.29, -0.06	0.25	0.18, 0.32
	Direct	0.04	-0.09, 0.17	-0.02	-0.08, 0.05
	Indirect via all six mediators	-0.22	-0.32, -0.11	0.26	0.21, 0.32
	Indirect via "growth pathway" [a]	-0.22	-0.32, -0.11	0.28	0.23, 0.33
	Indirect via "maternal environment pathway" [a]	-0.01	-0.04, 0.03	-0.02	-0.04, -0.01
	Indirect via dependence of growth/puberty on maternal eating habits [b]	0.00	-0.01, 0.01	0.00	-0.01, 0.01
Weight-control behaviors and concern with weight and shape	**Adjusted total association**	**-0.20**	-0.32, -0.07	**0.22**	0.15, 0.29
	Direct	0.08	-0.06, 0.22	-0.03	-0.10, 0.04
	Indirect via all six mediators	-0.28	-0.39, -0.17	0.25	0.20, 0.30
	Indirect via "growth pathway" [a]	-0.28	-0.39, -0.17	0.26	0.22, 0.31
	Indirect via "maternal environment pathway" [a]	0.00	-0.04, 0.04	-0.02	-0.03, 0.00
	Indirect via dependence of growth/puberty on maternal eating habits [b]	0.00	-0.01, 0.01	0.00	-0.01, 0.01
Food Restriction	**Adjusted total association**	**-0.21**	-0.33, -0.09	**0.18**	0.11, 0.25
	Direct	0.01	-0.12, 0.15	-0.03	-0.10, 0.05
	Indirect via all six mediators	-0.22	-0.33, -0.11	0.20	0.16, 0.25
	Indirect via "growth pathway" [a]	-0.23	-0.33,-0.11	0.20	0.16, 0.25
	Indirect via "maternal environment pathway" [a]	-0.01	-0.03, 0.04	-0.01	-0.02, 0.01
	Indirect via dependence of growth/puberty on maternal eating habits [b]	0.00	-0.01, 0.01	0.01	-0.002, 0.01

IDM: Interventional disparity measure

[a] The "growth pathway" involves birth weight, growth and puberty; the "maternal environment pathway" involves the two latent classes measuring attitude to food when the child was 8 year old.

[b] This component represents the dependence between the two multivariate pathways in their indirect effects.

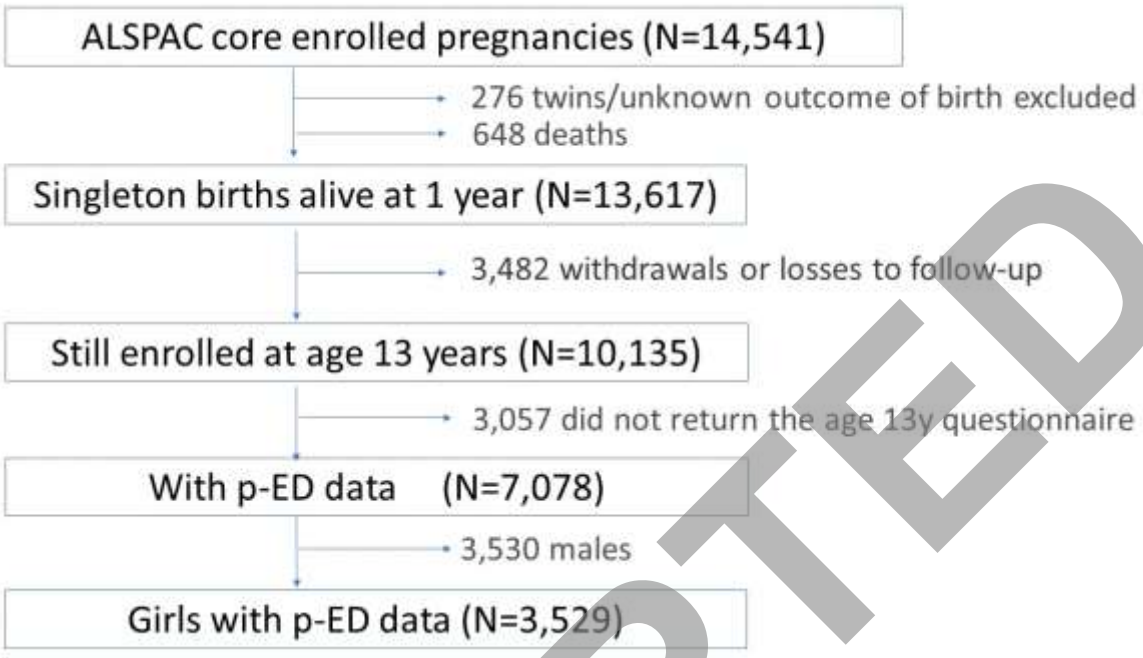

Figure 1: The study flow diagram

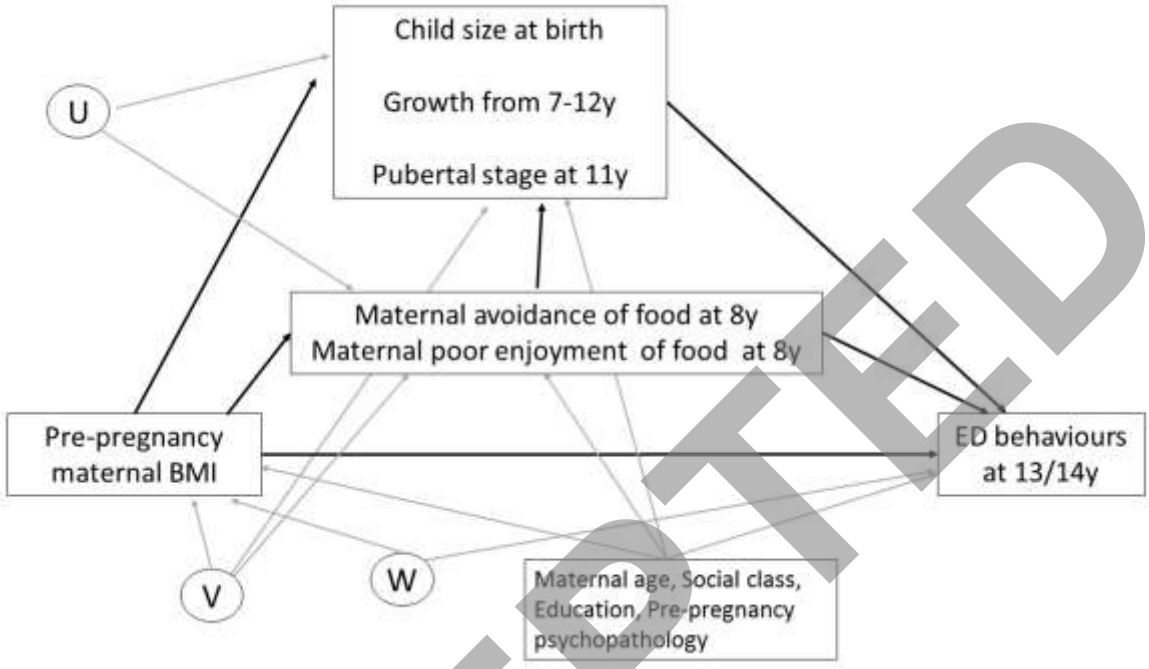

Figure 2: Presumed causal model