Maternal prenatal depressive symptoms and risk for early-life psychopathology in offspring: genetic analyses in the Norwegian Mother and Child Birth Cohort Study

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Summary

Background **Maternal prenatal depression is a known risk factor for early-life psychopathology among offspring; however, potential risk transmission mechanisms need to be distinguished. We aimed to test the relative importance of passive genetic transmission, direct exposure, and indirect exposure in the association between maternal prenatal depressive symptoms and early-life internalising and externalising psychopathology in offspring.**

Methods **We used structural equation modelling of phenotypic data and genetically informative relationships from the families of participants in the Norwegian Mother and Child Birth Cohort Study (MoBa). The analytic subsample of MoBa used in the current study comprises 22 195 mothers and 35 299 children. We used mothers' self-reported depressive symptoms during pregnancy, as captured by the Symptom Checklist, and their reports of symptoms of psychopathology in their offspring during the first few years of life (measured at 18, 36, and 60 months using the Child Behavior Checklist).**

Findings **Maternal prenatal depressive symptoms were found to be associated with early-life psychopathology primarily via intergenerationally shared genetic factors, which explained 41% (95% CI 36–46) of variance in children's internalising problems and 37% (30–44) of variance in children's externalising problems. For internalising problems, phenotypic transmission also contributed significantly, accounting for 14% (95% CI 5–19) of the association, but this contribution was found to be explained by exposure to concurrent maternal depressive symptoms, rather than by direct exposure in utero.**

Interpretation **Associations between maternal prenatal depressive symptoms and offspring behavioural outcomes in early childhood are likely to be at least partially explained by shared genes. This genetic confounding should be considered when attempting to quantify risks posed by in-utero exposure to maternal depressive symptoms.**

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Introduction

Maternal prenatal depression is a risk factor for early-life psychopathology in children.[1,2] However, the nature of this link has not been comprehensively established, and several mechanisms are plausible.[3] First, maternal prenatal depression could have a direct effect on the intrauterine environment, influencing fetal development in ways that manifest behaviourally later in a child's life (figure 1).[4] This mechanism of direct exposure has been termed a fetal programming effect[3] and is supported by evidence from experimental studies with animal models.[5] Second, mothers who have depressive symptoms prenatally are also more likely to relapse during the child's early development (figure 1).[1] Therefore, the link between prenatal depressive symptoms and child psychopathology could arise from the child's direct, behavioural exposure to these later depressive symptoms.[6] Exposure to mothers' depressive symptoms in early childhood has been proposed as an environmental risk factor for both internalising and externalising problems in childhood,[7,8] and might involve a combination of social learning and attachment problems, and environmental-stress mechanisms, as well as reciprocal effects.[9] A third possible mechanism involves genetic confounding (figure 1).[10] If the same genes influence risk for prenatal depressive symptoms in mothers and internalising or externalising problems in young children, the link between them could be explained by genes shared intergenerationally.[11] Evidence that genetic influences on common disorders are highly pleiotropic (ie, affecting many different traits)[12] and largely stable across the lifespan supports this possibility.

Genetically informative designs are needed to separate the effects of these different mechanisms. Although the increasing availability of genomic data is enabling the development of new methods in this area (eg, Mendelian randomisation[13]), family-based designs remain the most powerful approaches available.[14]

Research in context

Evidence before this study

Prenatal depression among expectant mothers is known to be associated with a range of negative outcomes in offspring, including emotional and behavioural problems early in life. We did a systematic search of the scientific literature on the Ovid MEDLINE and PsycINFO databases, for articles published in English up to Jan 31, 2018, using the query ((prenatal or pregnan* or perinatal or antenatal) and depressi* and (maternal or mother* or women) and (offspring or child*) and (behav* or emotion* or internali* or externali* or temperament)), which revealed ten relevant empirical studies after deduplication and manual screening. Of these studies, only three investigated or accounted for genetic mechanisms in the association between maternal prenatal depression and offspring behavioural outcomes: one was a mouse model of an intervention for maternal stress, another was a candidate gene interaction study, and one a sibling comparison study. No study before the current study had explicitly modelled genetic transmission as a potential pathway for the association between maternal prenatal depressive symptoms and offspring internalising and externalising behaviours or psychopathology.

Added value of this study

In this analysis of a population-derived, longitudinal sample of adult sibling, half-sibling, and twin mothers and their young children, we found that associations between maternal prenatal depressive symptoms and early-life offspring internalising and externalising psychopathology were predominantly accounted for by genetic risk factors transmitted intergenerationally. These findings represent a new and important addition to the scientific literature because they indicate that studies treating maternal prenatal depression as an in-utero exposure for offspring risk overestimating its impact if they do not account for potential genetic transmission effects. An additional finding, that phenotypic transmission from maternal prenatal depressive symptoms to offspring internalising problems was accounted for by later exposure to maternal depressive symptoms, further emphasises the need for caution in interpreting apparent fetal programming effects associated with maternal prenatal depression.

Implications of all the available evidence

Although associations between prenatal depressive symptoms and later outcomes in children are widely found, they might not necessarily be indicative of in-utero exposure effects. Instead, passive genetic transmission and behavioural exposure to later maternal depressive symptoms might explain them. Evidence concerning specific mechanisms by which risks for children exposed to maternal prenatal depression are mediated is insufficient, and further efforts are needed to understand whether in-utero exposure effects are implicated. These efforts should involve rigorous control for genetic confounding intergenerationally.

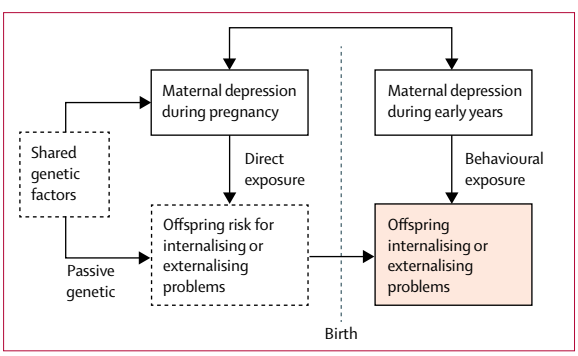

Figure 1: **Possible mechanisms for the transmission of risk for early-life internalising and externalising problems from maternal prenatal depressive symptoms**

Solid-line boxes indicate variables measured, in some form, in the current study; dashed boxes indicate indirectly measured variables.

One example of such a design is the prenatal cross-fostering design,[15] made possible in humans by in-vitro fertilisation (IVF). In this design, mothers are either genetically related or unrelated to their child but, in both cases, provide the prenatal environment. This design allows the effects of shared genes to be removed from the associations between prenatal factors and child outcomes. This approach has been used to show genetic confounding of associations between maternal smoking during pregnancy and childhood antisocial behaviour among offspring[16] and between mothers' self-reported prenatal stress and offspring attention-deficit hyperactivity disorder (ADHD; but no genetic confounding of the association with offspring anxiety).[17] However, the cross-fostering design has limitations in terms of the restricted availability, size, and representativeness of IVF-based samples.[14] An alternative design that is more widely applicable is the sibling control (or comparison) design.[15] When biologically related siblings are differentially exposed to a prenatal risk factor, the effect of that risk factor can be estimated without the effects of genetic confounding, even though mother and child only share 50% of their genes, because alleles from the mother and father are randomly distributed during gamete formation. Large-scale applications of this method have indicated a possible role for a genetic mechanism of risk transmission between maternal prenatal anxiety and offspring behavioural difficulties at 6 months and 36 months[18] and between maternal prenatal depressive symptoms and child psychopathology during early childhood.[19] These applications show the power of this method when it is combined with large samples of siblings, which, especially compared with IVF families, are relatively straightforward to obtain.[14]

Sibling comparison studies, although powerful, do not typically model genetic and environmental transmission effects explicitly, instead basing conclusions about

transmission mechanisms on the effects of controlling for familiality. An alternative approach, which addresses this limitation, is the children of twins (CoT) design.[20] The CoT design works by applying the logic of classic twin studies, in which phenotypic variance is decomposed into genetic, shared environmental, and non-shared environmental components, to data drawn from samples of twin parents and their children. Differential genetic similarity among twin parents (100% for monozygotic twins; 50% for dizygotic twins) is mirrored elsewhere in the family structure, meaning that children with one parent who is a monozygotic twin are more related to their aunts, uncles, and cousins, than children in dizygotic families (ie, children with one parent who is a dizygotic twin) in systematic ways. Incorporation of these different genetic relatedness coefficients and the various phenotypic associations that arise in such a sample (eg, twin parents with one another, parents and their offspring, children and their aunts or uncles, and cousins) into a structural equation modelling framework allows for intergenerational transmission effects to be partitioned into passive genetic and direct phenotypic components. The CoT design is thus well suited to investigate the nature of links between aspects of maternal phenotypes and child outcomes and, indeed, has been widely used to do so.[21] However, despite the applicability of the CoT design to questions about the nature of the effects of prenatal exposures, only two have so far been studied with this design. The association between maternal prenatal smoking and birthweight was unconfounded by genetic effects,[20,22] whereas genetic factors were found, in one study, to be involved in the intergenerational link between maternal alcohol use prenatally and offspring ADHD.[23] To our knowledge, no CoT study has explored the link between maternal prenatal depressive symptoms and later offspring psychopathology.

In this study, we apply an adapted version of the standard CoT model to a large, population-derived sample of twins, siblings, and half-siblings, and their children. This approach allows us to investigate the relative importance of direct exposure (figure 1) and behavioural exposure to concurrent maternal depressive symptoms, and passive genetic mechanisms of risk transmission from maternal prenatal depressive symptoms and later internalising and externalising problems.

Methods

Sample

Data comprised a sample of twin, sibling, and half-sibling pairs of mothers and their children drawn from the larger Norwegian Mother and Child Birth Cohort Study (MoBa; described in detail elsewhere[24]). Briefly, recruitment into MoBa took place between 1999 and 2008 and was carried out in 50 of Norway's 52 hospitals with maternity units, with a participation rate of 42%. Individuals were recruited to the MoBa sample at routine ultrasound examinations, which are offered to all pregnant women in Norway at gestational weeks 17–18 (meaning that, in principle, all pregnant women in Norway during the recruitment period were eligible for inclusion). Data collection is ongoing at the time of writing, and the total sample now includes more than 114 500 children, more than 95 000 mothers, and more than 75 000 fathers. We used version 9 of the quality-assured MoBa data files, which were released in 2015.

Measures

Maternal depressive symptoms were assessed with a short form of the Symptom Checklist-90-R (SCL-90-R).[25] The performance of the short form of this questionnaire has been discussed in detail elsewhere (scores correlate with the full version of the scale at >0·9).[26] In MoBa, the five-item SCL-5 was used at gestational week 17 for mothers, and the eight-item SCL-8 was used at all subsequent measurement timepoints. Scores at the prenatal measurement occasions (gestational weeks 17 and 30) were combined to form a composite indexing prenatal depressive symptoms across this period of the pregnancy (ordinal Cronbach's alpha=0·93). A composite score derived from SCL-8 scores on subsequent measurement timepoints (when offspring were aged 18, 36, and 60 months) was used as a covariate in sensitivity analyses, to account for possible mediation of prenatal risk via concurrent depressive symptom exposure. Internalising and externalising problems were measured on three occasions, when offspring were 18, 36, and 60 months, with items included in the Child Behavior Checklist (CBCL)[27] for ages 1·5–5 years. Item-level scores across these three measurement occasions were combined to create composites for early-life internalising problems (ordinal Cronbach's alpha=0·84) and externalising problems (ordinal Cronbach's alpha=0·88).

Statistical analysis

Like the classic twin design, the CoT design derives its power to decompose variance into genetic and environmental components by leveraging differences in genetic relatedness among family members against their phenotypic similarity (appendix).[21]

See Online for appendix

Figure 2 shows a path diagram of the adapted multiple children of twins and siblings (MCoTS) model used in the current study. The MCoTS model decomposes variance in maternal prenatal depressive symptoms into genetic (A1), shared environmental (C1), and unique environmental (E1) components, and variance in child internalising or externalising problems similarly (A2, C2, and E2), with the intergenerational association accounted for by phenotypic (p) and genetic (A1′) transmission effects. The MCoTS model is well powered to distinguish such effects: the relative sample size requirements for the standard CoT model and the MCoTS model to detect small genetic transmission effects with 80% power are given in the appendix. More technical detail on the differences between this model and the standard CoT

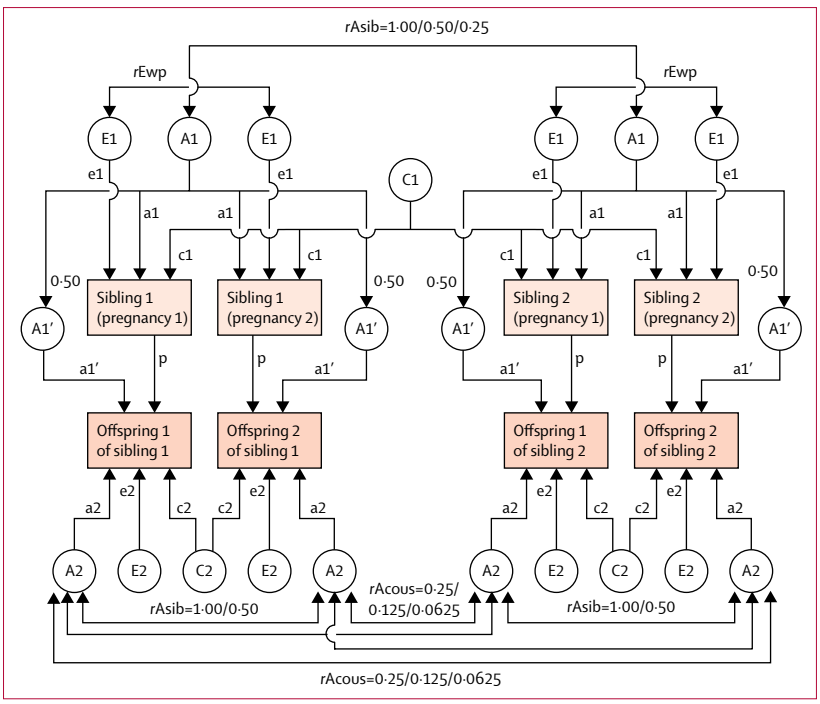

Figure 2: **Structural equation model path diagram from the multiple children of twins and siblings model**
For genetic correlation paths (ie, rAsib and rAcous), multiple values are given, which correspond to the strength of the genetic relationship between, respectively: monozygotic, full sibling or dizygotic, and half-sibling dyads (eg, rAsib=1·00/0·50/0·25). These values are set based on the genetic relationship at the parent level in all cases apart from rAsib between A2 variance components, which refers to the genetic relationship between siblings within a nuclear family (no half-siblings are included at this level, hence only two values are given). Monozygotic twin children share a single A1p parameter. Upper case letters represent variance component and lower case letters represent path. Within-person correlation between maternal unique environmental factors (rEwp) is fixed to 1 when children are twins of either zygosity. A1 and a1=maternal genetic factors. C1 and c1=maternal common environmental factors. E1 and e1=maternal unique environmental factors. A1′ and a1′=child genetic factors associated with A1. A2 and a2=child-generation-specific genetic factors. C2 and c2=child common environmental factors. E2 and e2=child unique environmental factors. p=phenotypic transmission path.

	Total children (n=35 299)	Monozygotic (n=722)	Dizygotic (n=2432)	Full sibling (n=23 094)	Singleton (n=9043)
Monozygotic mothers (n=178)	229	..	..	108	121
Dizygotic mothers (n=104)	135	..	..	64	71
Full sibling mothers (n=10 524)	12 814	86	272	4250	8206
Maternal half-sibling mothers (n=338)	391	..	..	126	265
Paternal half-sibling mothers (n=460)	516	..	..	136	380
Singleton mothers (n=10 591)	21 206	636	2160	18 410	..

Half-siblings in the offspring generation were not included in the analyses. Child generation twins were retained only in groups large enough to support analysis (full sibling and singleton families); singleton children of singleton parents were not included.

Table 1: **Study sample size as stratified by maternal sibship**

model is provided in the appendix, and a detailed methodological description of the extension of the CoT model to incorporate multiple children per parent is available elsewhere.[28]

We ran MCoTS models on prenatal depressive symptoms with child internalising and externalising problems separately. The best-fitting models for internalising and externalising problems were retained and the composition of the intergenerational association was inspected. If the p path remained significant in the best-fitting model, indicating an exposure effect, we ran a further model incorporating concurrent maternal depressive symptoms as a covariate on the child phenotype. This model tested whether the exposure effect was accounted for by concurrent maternal depressive symptoms, which would be indicated by a significant β value for the effect of the covariate on the child phenotype. If the central p path remained significant in this model, it would be interpreted as evidence for the direct exposure mechanism. If no exposure effect was found in the best-fitting version of the original model, we did not run the additional model with concurrent maternal depressive symptoms as a covariate. Further details of the modelling procedure are included in the appendix. We used R version 3.1.2 (the OpenMx package [version 2.9.6]) for analyses.[29]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 1999 and 2014, data were collected from 22 195 mothers who were eligible for inclusion in the MoBa study and their children (35 299) (table 1). Mothers were predominantly cohabiting (48%) or married (44%), with married status slightly more common among those with two or more children (55%). Of all mothers, at least 74% were educated up to high school level (typically completed by the age of 19 years in Norway) with 62% having received some further education beyond this point. The mean age for mothers in the sample was 30·16 years (SD 4·24), and 49% of the children included were girls. An overview of the study sample, separated into family type, is shown in table 1.

Descriptive statistics for the main study variables are presented in the appendix. There was some evidence of selective attrition in the sample, such that mothers who provided data on offspring psychopathology scored significantly lower on prenatal depressive symptoms than those who did not [t(8202)=–10·19, p<0·001]. Variables with excessively skewed distributions (maternal prenatal depressive symptoms and offspring internalising behaviours) were transformed using Box-Cox transformation. Because structural equation models applied to large samples are generally robust to violations of distributional assumptions, we did the genetic modelling on raw data, with all analyses re-run using transformed data to check the sensitivity of the estimates to non-normality in the variables. With conclusions relating to the main hypotheses remaining unchanged whether raw or transformed data were used, we present the results for

the raw data here, with the results of the sensitivity analyses included in the appendix.

Correlation coefficients derived from the best-fitting MCoTS models of the intergenerational transmission of risk from maternal prenatal depressive symptoms to early childhood internalising and externalising problems are presented in table 2. To the extent that phenotypic similarity changed in line with genetic relatedness for the different dyads, variance and covariance was attributed to genetic effects in the models. For example, in the internalising model, monozygotic mothers correlated at 0·33 for prenatal depressive symptoms, full-sibling and dizygotic mothers at 0·17, and half-sibling mothers at 0·08, indicating genetic influence on maternal prenatal depressive symptoms (table 2).

Parameter estimates from the best-fitting model for internalising problems in early childhood are shown in figure 3A. This model was selected by removing non-significant parameters (C1 and A2) from the full model and formally comparing the model fits. The more parsimonious model did not fit the data significantly worse than the full model (p>0·05; model fit statistics for all internalising models are presented in the appendix), and so was retained. In this model, the influence of genetic factors on maternal prenatal depressive symptoms (A1) was estimated at 33% (95% CI 29–38; figure 3). Genetic factors associated with these symptoms (A1′) were also significant in explaining variance (41% [95% CI 36–46]) in early childhood internalising problems in the offspring generation (figure 3). These factors accounted entirely for the heritability of early childhood internalising problems. Shared environmental factors (C2; 27% [95% CI 25–30] variance explained) and unique environmental factors (E2; 31% [27–34] variance explained) also accounted for variation in offspring internalising problems (figure 3).

The significance of the path from A1′ to offspring internalising symptoms (figure 3) indicated that the passive genetic mechanism was involved in the transmission of risk from maternal prenatal depressive symptoms. An exposure-based route of transmission was also found to be significant, with the central p path being estimated at 0·03 (95% CI 0·01–0·04; figure 3). To ascertain the relative roles of passive genetic transmission and phenotypic exposure in this model, it is necessary to divide the contribution of each route by the total mother–offspring phenotypic covariance (r=0·21). Passive genetic transmission, calculated by multiplying the paths connecting maternal prenatal depressive symptoms to A1 (√0·33), A1 to A1′ (0·5), and A1′ to offspring internalising symptoms (√0·41), thus accounted for 86% of the association between maternal prenatal depressive symptoms and child internalising behaviours. The remaining 14% (95% CI 5–19) was accounted for, in this model, by phenotypic exposure (0·03).

To establish whether the small, but significant phenotypic exposure effect found could be accounted for by behavioural exposure, maternal depressive symptoms measured concurrently with offspring internalising problems were added to the model as a covariate. The estimates from the reduced version of this model, which again fit the data no worse than the full version (p>0·05; appendix), are shown in figure 3B. In this model, controlling for the effects of

	Monozygotic	Full sibling or dizygotic	Half sibling
Early childhood internalising problems			
Mother, within person*	0·64	0·64	0·64
Mother, across siblings†	0·33	0·17	0·08
Mother–offspring‡	0·21	0·21	0·21
Avuncular	0·19	0·10	0·05
Child across siblings§	0·69	0·38	NA
Child cousin	0·11	0·06	0·03
Early childhood externalising problems			
Mother, within person*	0·65	0·65	0·65
Mother, across siblings†	0·32	0·16	0·08
Mother–offspring‡	0·17	0·17	0·17
Avuncular	0·17	0·08	0·04
Child across siblings§	0·83	0·43	NA
Child cousin	0·16	0·08	0·04

Correlations derived by standardising covariances from best-fitting multiple children of twins and siblings models indicated in the appendix. NA=not applicable. *Mothers' depressive symptom scores for first pregnancies correlated with scores for second pregnancies. †Mothers' depressive symptoms scores for a pregnancy correlated with their sister's score for the equivalent (first or second) pregnancy. ‡Mothers' depressive symptom scores correlated with offspring internalising or externalising scores. §Columns here denote child sibship type.

Table 2: **Model-derived phenotypic associations within different family structures**

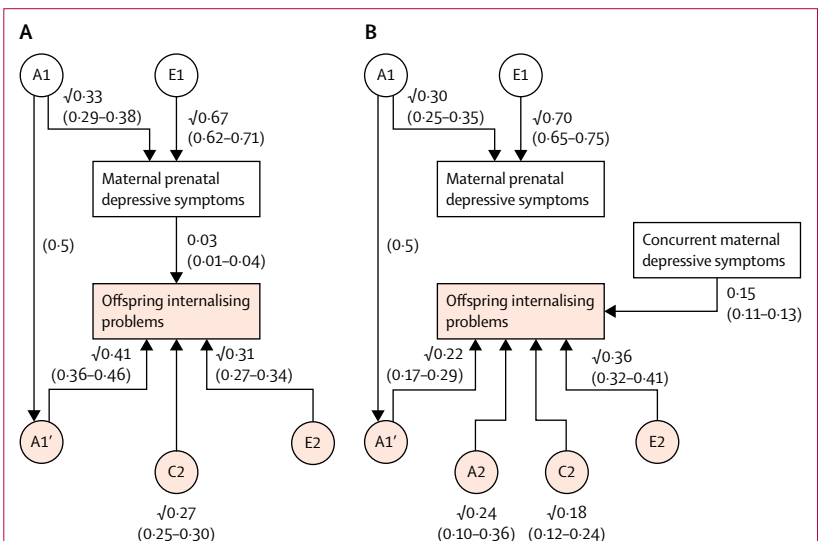

Figure 3: **Parameter estimates from the best-fitting model for the association between maternal prenatal depressive symptoms and offspring early childhood internalising problems (A) and the same model including concurrent maternal depressive symptoms as a covariate (B)**
Data are parameter values (95% CI). A1=maternal genetic factors. E1=maternal unique environmental factors. A1′=child genetic factors associated with A1. A2=child-generation-specific genetic factors. C2=child common environmental factors. E2=child unique environmental factors.

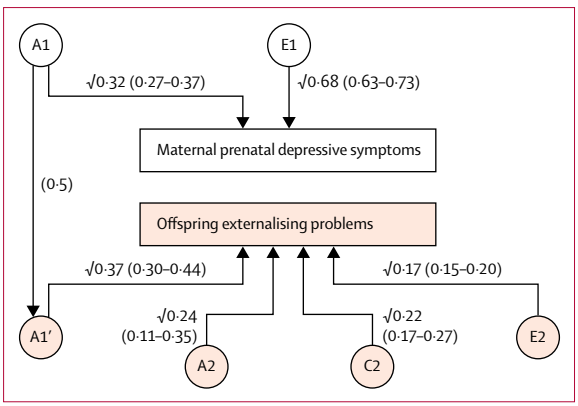

Figure 4: **Parameter estimates from the best-fitting model for the association between maternal prenatal depressive symptoms and offspring early childhood externalising problems**

Data are parameter values (95% CI). A1=maternal genetic factors. E1=maternal unique environmental factors. A1′=child genetic factors associated with A1. A2=child-generation-specific genetic factors. C2=child common environmental factors. E2=child unique environmental factors.

concurrent maternal depressive symptoms on early-life internalising problems in offspring (β=0·15 [95% CI 0·11–0·13]) reduces the phenotypic association between prenatal depressive symptoms and offspring internalising behaviours to *r*=0·13. Moreover, the phenotypic exposure effect (the central p path) from the previous model is rendered non-significant (and thus excluded from the model), indicating that this effect was accounted for by concurrent depressive symptoms. The passive genetic transmission route was also attenuated (with A1′ now accounting for 22% [95% CI 17–29] residual variance in offspring internalising problems; figure 3B).

Parameters from the best-fitting model of the intergenerational transmission of risk from maternal prenatal depressive symptoms to early childhood externalising problems are shown in figure 4. This model was selected by removing non-significant parameters (C1 and p) from the full model and formally comparing the model fits. The more parsimonious model did not fit the data significantly worse than the full model (p>0·05; model fit statistics for all externalising models are presented in the appendix), and so was retained. In this model, genetic factors that explained 32% (95% CI 27–37) variance in maternal prenatal depressive symptoms (A1) were again associated with those explaining significant variation in the child generation (A1′; figure 4). These influences accounted for 37% (95% CI 30–44) of the variance in offspring externalising problems (figure 4). Child-generation-specific genetic factors (A2) also contributed to the heritability of offspring externalising problems, explaining a further 24% (95% CI 11–35) variance (figure 4). Shared environmental factors (C2; 22% [95% CI 17–27] variance explained) and unique environmental factors (E2; 17% [15–20] variance explained) accounted for the remaining variation in offspring externalising problems (figure 4).

With the estimate of the phenotypic exposure effect (p) not included in the best-fitting model, the intergenerational association (*r*=0·17) between maternal prenatal depressive symptoms could be entirely explained by passive genetic transmission (ie, via A1 and A1′). With no exposure effect to investigate further, we did not run the additional model (ie, the model including concurrent maternal depressive symptoms as a covariate).

Discussion

In this study, we showed that shared genetic factors account for most of the association between maternal prenatal depressive symptoms and both internalising and externalising problems in offspring early in life. For internalising problems, genetic risk in children was entirely accounted for by genes also associated with their mothers' prenatal depressive symptoms. In addition to genetic transmission, a small effect of behavioural exposure to concurrent maternal depressive symptoms was identified for internalising problems.

This study is, to our knowledge, the first to apply genetically informed structural equation modelling to explain how the link between maternal prenatal depressive symptoms and early-life psychopathology among offspring arises. However, our results do broadly accord with those of a sibling comparison study on the same sample[19] and with results from other genetically sensitive studies of similar prenatal exposures.[17,18] Nonetheless, replication is needed. The fetal programming hypothesis has both biological plausibility and empirical support from animal models,[8] wherein genetic confounding is controlled. However, our results suggest that caution is needed in assuming its applicability in humans, especially for links between complex behavioural traits, for which genetic influences are likely to be highly pleiotropic.[12] Attempts should be made to control for genetic confounding wherever possible in studies aiming to test for fetal programming effects in humans. With the cost of collecting genomic data continually decreasing, control of genetic confounding is now a realistic proposition even in samples that do not contain individuals with known genetic relationships.

Another mechanism often discussed in terms of the fetal programming hypothesis is intergenerational epigenetic transmission.[30] Notably, for the interpretation of the results of the current study, epigenetic changes are most usefully conceptualised as an intermediate phenotype between genes or environments and outcomes of interest. Specifically, this conceptualisation means that any epigenetic pathways by which maternal prenatal depressive symptoms relate to offspring behavioural and emotional problems early in life will appear, in our models, in the intergenerational pathway that corresponds to their origin. That is, if epigenetic changes associated with the mother's environment affect her child's development, these changes would be captured in the

phenotypic transmission pathway, and similar changes associated with maternal genes that are transmitted to children would be captured in the passive genetic transmission pathway. As such, although the results of the current study cannot be used to rule epigenetic inheritance in or out, they do indicate a genetic, rather than environmental, origin for any epigenetic factors involved in contributing to the intergenerational association.

The finding that genetic factors shared between mother and child explain most of the association between maternal prenatal depressive symptoms and early-life psychopathology in offspring should not be interpreted to mean that treatment of prenatal depressive symptoms will have no secondary protective benefits for children. The behavioural exposure pathway that was found in the current study for internalising problems might be disrupted by the earlier treatment of maternal depressive symptoms.[7] As far as treatment of prenatal depressive symptoms reduces a woman's risk of further depressive episodes throughout the child's life, implications for child psychopathology could be substantial, especially in view of evidence that behavioural exposure effects might predominantly explain links between maternal depressive symptoms and child psychopathology later in development.[11] Furthermore, the finding that genetic factors associated with prenatal maternal depression account entirely for the heritability of internalising symptoms in their offspring might also have considerable clinical implications, because it implies that any translational insights from genome-wide studies of depression (done primarily in adult populations) should be equally applicable to emotional problems early in life.

Despite the strengths of the adapted MCoTS design applied in the current study, some limitations remain. First, the potential effects of assortative mating are not modelled in the current design. Although assortative mating for depressive symptoms is lower than for other psychiatric traits,[31] the occurrence of depressive symptoms in fathers is moderately correlated with the occurrence of maternal depressive symptoms around the perinatal period[32] and the potential effects in the current design have not been fully explored. Future work to incorporate phenotypic information from fathers into these models should help to quantify the impact of assortative mating. A second limitation concerns shared method variance, since maternal reports were used for both prenatal depressive symptoms and offspring outcomes. Although this approach might have led to an inflation of the association between the variables, it is unlikely to have done so in a way that favours either genetic or phenotypic transmission (ie, factors influencing mothers' general reporting behaviour might be both genetic and environmental). Furthermore, maternal ratings are generally considered a good indicator of early-life behaviour among children. Nonetheless, future analyses using prenatal depression symptom scores derived from clinical interviews would be valuable. Third, selective attrition was evident in the sample, with participation in later waves linked to mothers' depressive symptoms at baseline. This selective attrition might have reduced our coverage of the high end of the distribution of maternal prenatal depressive symptoms scores. The impact of this limitation depends on the extent to which mechanisms of risk differed in particularly severe cases. Previous studies[33,34] of the causes of the extremes of distributions of psychological traits have found them to be highly similar to those underpinning so-called normal variation, so there is no specific reason to expect this to be the case. Nonetheless, the possibility remains and could be explored further in clinical samples. Finally, the absence of a specific measure of postnatal depression (ie, earlier than 1·5 years after birth) could be considered a limitation, because it might have specific effects on child outcomes. However, such effects could only account for the proportion of the intergenerational association that is established as phenotypic in the baseline models. In the event, phenotypic transmission was only significant (and still considerably smaller than the genetic portion) in one set of analyses, largely mitigating this potential limitation.

In summary, the evidence presented here suggests that shared genes might play an important part in underpinning associations between maternal prenatal depressive symptoms and subsequent internalising and externalising problems in offspring early in childhood. In the case of internalising problems, behavioural exposure to later maternal depressive symptoms might also be influential. The results of this study emphasise the importance of rigorous control for genetic confounding when investigating potential effects of prenatal exposures.

Contributors

LJH, TAM, and EY conceived of the investigation. LJH EME, FVR, and TAM developed models for use in the analyses. LJH and EME prepared and analysed the data, and all authors discussed results. LJH drafted and revised the manuscript, and all authors critically reviewed the manuscript.

Declaration of interests

We declare no competing interests.

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