



Hannigan, L. J. , Eilertsen, E. M., Gjerde, L. C., Reichborn-Kjennerud, T., Eley, T. C., Rijdsdijk, F. V., Ystrom, E. and McAdams, T. A. (2018) Maternal prenatal depressive symptoms and risk for early-life psychopathology in offspring: results from a genetically-informative, population-based sample. *Lancet Psychiatry*, 5(10), pp. 808-815. (doi:[10.1016/S2215-0366\(18\)30225-6](https://doi.org/10.1016/S2215-0366(18)30225-6))

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Deposited on: 06 June 2018

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Manuscript title: Maternal prenatal depressive symptoms and risk for early-life psychopathology in offspring: results from a genetically-informative, population-based sample

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3,652 words; 2 tables; 4 figures; online-only supplement attached

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 behavioral problems early in life. A systematic search of the literature 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)), undertaken in February 2018 using the Ovid MEDLINE and PsycINFO databases revealed 10 relevant empirical studies after deduplication and manual screening. Of these, only three investigated or accounted for genetic mechanisms in the association between maternal prenatal depression and offspring behavioral 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 prior to the current study had explicitly modelled genetic transmission as a potential pathway for the association between maternal prenatal depressive symptoms and offspring internalizing and externalizing.

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 internalizing and externalizing psychopathology were predominantly accounted for by genetic risk factors transmitted intergenerationally. These findings represent a novel and important addition to the literature, as they indicate that studies treating maternal prenatal depression as an *in utero* exposure for offspring risk over-estimating 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 internalizing was accounted for by later exposure to maternal depressive symptoms, further emphasizes 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 child outcomes are widely found, they may not necessarily be indicative of *in utero* exposure effects. Instead, passive genetic transmission and behavioral exposure to later maternal depressive symptoms may explain them. The body of evidence concerning specific mechanisms by which risk for children exposed to maternal prenatal depression is mediated is currently 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.

Summary

Background. Maternal prenatal depression is a known risk factor for early-life psychopathology among offspring. However, it is necessary to distinguish between potential risk transmission mechanisms. 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 later internalizing and externalizing psychopathology.

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 sub-sample 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 (SCL), 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 [CBCL]).

Findings. Maternal prenatal depressive symptoms were found to be associated with both internalizing and externalizing problems in early childhood primarily via intergenerationally-shared genetic factors. For internalizing problems, phenotypic transmission also contributed significantly to the association, but was found to be explained by exposure to concurrent maternal depressive symptoms, rather than by direct exposure.

Interpretation. Associations between maternal prenatal depressive symptoms and offspring behavioral 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.

Funding. UK Economic and Social Research Council, Norwegian Research Council, Norwegian Ministries of Health & Care Services, and Education & Research, Wellcome Trust, Royal Society, and National Institute for Health Research.

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 plausible³. First, maternal prenatal depression could have a direct effect on the intrauterine environment, influencing fetal development in ways that manifest behaviorally later in a child's life⁴. This mechanism of direct exposure has been termed a 'fetal programming effect'³ and is supported by evidence from experimental studies using animal models⁵. Second, mothers who experience depressive symptoms prenatally are also more likely to relapse during the child's early development¹. The link between prenatal depressive symptoms and child psychopathology could thus arise from the child's direct, behavioral exposure to these later depressive symptoms⁶. Exposure to mothers' depressive symptoms in early childhood has been proposed as an environmental risk factor for both internalizing and externalizing problems in childhood^{7,8}, and may involve a combination of social learning, attachment problems, and environmental-stress mechanisms, as well as reciprocal effects⁹. A third possible mechanism involves genetic confounding¹⁰. If the same genes influence risk for prenatal depressive symptoms in mothers and internalizing or externalizing problems in young children, the link between them could be explained by genes shared intergenerationally¹¹. Evidence that genetic influences on common disorders are highly pleiotropic (influencing many different traits)¹² and largely stable across the lifespan lend support to this possibility. These three potential mechanisms which could underpin the link between maternal prenatal depressive symptoms and children's early-life psychopathology are shown schematically in **Figure 1**.

Teasing apart the effects of these different mechanisms requires genetically-informative designs. Although the increasing availability of genomic data is allowing for the development of new methods in this area (e.g., Mendelian randomization¹³), family-based designs remain the most powerful approaches available¹⁴. One example of such a design is the 'pre-natal cross-fostering' design¹⁵, made possible in humans by *in vitro* fertilization (IVF). In this design, mothers are either genetically related or unrelated to their child but, in both cases, provide the prenatal environment. This allows the effects of shared genes to be parceled out of 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 behavior among offspring¹⁶ and between mothers' self-reported prenatal stress and offspring ADHD (but no genetic confounding of the association with offspring anxiety)¹⁷. However, there are limitations to this approach, in terms of the restricted availability, size, and representativeness of IVF-based samples¹⁴. An alternative design that is more widely applicable is the sibling control (or comparison) design¹⁵. 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. This is because alleles from the mother and father are randomly distributed during gamete formation. Large-scale applications of this method have recently indicated a likely role for a genetic mechanism of risk transmission between maternal prenatal anxiety and offspring behavioral difficulties at 6 and 36 months¹⁸ and between maternal prenatal depressive symptoms and child psychopathology during early childhood¹⁹. These applications show the power of this method when combined with large samples of siblings – which, especially when compared to IVF families, are relatively straightforward to obtain¹⁴.

Sibling comparison studies, while powerful, do not typically model genetic and environmental transmission effects explicitly, instead basing conclusions about transmission mechanisms on the effects of controlling for familiarity. An alternative approach, which addresses this limitation, is the Children-of-Twins (CoT) design²⁰. The CoT design works by applying the logic of classical 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 [MZ] twins; 50% for dizygotic [DZ] twins) is mirrored elsewhere in the family structure, meaning that children whose parent is an MZ twin are more related to their aunt/uncle, and to their cousins, than children in DZ

families (i.e., children whose parent is a DZ twin) in systematic ways. Incorporating these different genetic relatedness coefficients and the various phenotypic associations that arise in such a sample (e.g., twin parents with one another; parents and their offspring; children and their aunts/uncles; cousins) into a structural equation modelling (SEM) framework allows for intergenerational transmission effects to be partitioned into passive genetic and direct phenotypic components. The CoT design is thus well-placed to investigate the nature of links between aspects of maternal phenotypes and child outcomes; and, indeed, has been widely employed to do so²¹. 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 using this design. The association between maternal prenatal smoking and birth weight have been found to be unconfounded by genetic effects^{20,22}, while genetic factors were found, in one study, to be involved in the intergenerational link between maternal alcohol use prenatally and offspring ADHD²³. 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 allows us to investigate the relative importance of direct exposure (*dE* in **Figure 1**), behavioral exposure (*bE*) to concurrent maternal depressive symptoms, and passive genetic (*pG*) mechanisms of risk transmission from maternal prenatal depressive symptoms and later internalizing and externalizing problems respectively.

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 elsewhere²⁴). Recruitment to the MoBa sample was made at routine ultrasound examinations offered to all pregnant women in Norway at gestational week 17-18. The total sample now includes >114,500 children, >95,000 mothers, and >75,000 fathers. Version 9 of the quality-assured MoBa data files, released in 2015, were used. Written informed consent was obtained from all participants upon recruitment. The MoBa study has been granted a license from the Norwegian Data Inspectorate, and the present study was approved by the Regional Committee for Medical Research Ethics.

Mothers with at least one child 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, 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 female. **Table 1** presents an overview of the study sample, broken down by family type.

Measures. Symptoms of maternal depressive symptoms were assessed by a short form of the Symptom Checklist (SCL²⁵). The performance of the short form of this questionnaire has been discussed in detail elsewhere²⁶. In MoBa, the five-item SCL-5 was used at the 17th week of gestation for mothers, and the eight-item SCL-8 was used at all subsequent measurement occasions. Scores at the prenatal measurement occasions (17th and 30th week of gestation) 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 occasions (when offspring were aged 18, 36, and 60 months respectively) was used as a covariate in sensitivity analyses, to account for possible mediation of prenatal risk via concurrent depressive symptoms exposure. Internalizing and externalizing problems were measured on three occasions,

when offspring were 18, 36, and 60 months, using items included in the Child Behavior Checklist (CBCL²⁷) for preschool children. Item-level scores across these three measurement occasions were combined to create composites for early-life internalizing (ordinal Cronbach's alpha = 0.84) and externalizing problems (ordinal Cronbach's alpha = 0.88).

Statistical analyses

Genetic models. Like the classical 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 similarity²¹. Full details of the logic underlying the CoT approach are included in **eAppendix 1**.

Figure 2 shows a path diagram of the adapted multiple children-of-twins/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 internalizing or externalizing similarly (A2, C2, 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, as illustrated in **eFigure 2**, which shows the relative sample size requirements for the standard CoT model and the MCoTS model to detect small genetic transmission effects with 80% power. More technical detail on the differences between this model and the standard CoT model is provided in **eAppendix 2**, and a detailed methodological description of the extension of the CoT model to incorporate multiple children-per-parent is available elsewhere²⁸.

Modelling procedure. We ran MCoTS models on prenatal depressive symptoms with child internalizing and externalizing separately. The best-fitting models for internalizing and externalizing respectively were retained and the composition of the intergenerational association 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 beta value for the effect of the covariate on the child phenotype. If the central p path remained significant in this model, this 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, the additional model with concurrent maternal depressive symptoms as a covariate was not run. Further details of the modelling procedure are included in **eAppendix 3**.

Results

Descriptive statistics for the main study variables are presented in **eTable 1**. Variables with excessively skewed distributions (maternal prenatal depressive symptoms and offspring internalizing) were transformed using Box-Cox transformation. Because SEMs with large samples are generally robust to violations of distributional assumptions, we performed 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 using raw or transformed data, we present the results for the raw data here, with the results of the sensitivity analyses included in **eFigures 3 & 4**.

Correlation coefficients derived from the best-fitting MCoTS models of the intergenerational transmission of risk from maternal prenatal depressive symptoms to early childhood internalizing

and externalizing problems are presented in **Table 2**. To the extent that phenotypic similarity changed in line with genetic relatedness for the different dyads, variance/covariance was attributed to genetic effects in the models. For example, in the internalizing model, MZ mothers correlated at 0.33 for prenatal depressive symptoms; full sibling/DZ mothers at 0.17; and half-sibling mothers at 0.08, indicating genetic influence on maternal prenatal depressive symptoms. Estimates for the genetic, shared and non-shared environmental parameters that are derived from these correlations are presented below.

Parameter estimates from the best-fitting model for internalizing problems in early childhood are shown in **Figure 3, panel A**. This model was selected by dropping non-significant parameters (*C1*, *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 internalizing models are presented in **eTable 2**), and so was retained. In this model, the influence of genetic factors on maternal prenatal depressive symptoms (*A1*) was estimated at 33% (95% CIs: 29-38%). Genetic factors associated with these (*A1'*) were also significant in explaining variance (41% [36-46%]) in early-childhood internalizing problems in the offspring generation. These factors accounted entirely for the heritability of early-childhood internalizing problems. Shared environmental factors (*C2*; 27% [25-30%] variance explained) and unique environmental factors (*E2*; 31% [27-34%] variance explained) also accounted for variation in offspring internalizing.

The significance of the path from *A1'* to offspring internalizing symptoms in **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 (0.01-0.04). 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 (running via *A1*, the 0.5 correlation path, and *A1'*) thus accounted for 86% [$(\sqrt{0.33} * 0.5 * \sqrt{0.41}) / .21 = 0.86$] of the association between maternal prenatal depressive symptoms and child internalizing. The remaining 14% [$0.03/0.21 = 0.14$] was accounted for, in this model, by phenotypic exposure.

To establish whether the small, but significant phenotypic exposure effect found could be accounted for by *behavioral* exposure, maternal depressive symptoms measured concurrently with offspring internalizing problems was 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 ($p > 0.05$; see **eTable 2**), are shown in **Figure 3, right-hand panel**. In this model, controlling for the effects of concurrent maternal depressive symptoms on early life internalizing problems in offspring reduces the phenotypic association between prenatal depressive symptoms and offspring internalizing to $r = 0.13$. Moreover, the phenotypic exposure effect (the central p path) from the previous model is rendered non-significant (and thus dropped 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% [17-29%] residual variance in offspring internalizing).

Parameters from the best-fitting model of the intergenerational transmission of risk from maternal prenatal depressive symptoms to early childhood externalizing problems are shown in **Figure 4**. This model was selected by dropping non-significant parameters (*C1*, 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 externalizing models are presented in **eTable 3**), and so was retained. In this model, genetic factors that explained 32% (27-37%) variance in maternal prenatal depressive symptoms (*A1*) were again associated with those explaining significant variation in the child generation (*A1'*). These influences accounted for 37% (30-44%) of the variance in offspring externalizing problems. Child-generation-specific genetic factors (*A2*) also contributed to

the heritability of offspring externalizing problems, explaining a further 24% (11-35%) variance. Shared environmental factors ($C2$; 22% [17-27%] variance explained) and unique environmental factors ($E2$; 17% [15-20%] variance explained) accounted for the remaining variation in offspring externalizing.

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 (i.e., via $A1$ and $A1'$). With no exposure effect to investigate further, we did not run the additional model (i.e., the model including concurrent maternal depressive symptoms as a covariate).

Discussion

In this study, we sought to investigate different mechanisms by which maternal prenatal depressive symptoms could be linked to offspring psychopathology early in life: via direct (*in utero*) exposure, via behavioral exposure (to later maternal depressive symptoms), or via confounding due to shared genetic influences. Our results indicate that this latter mechanism of genetic transmission accounts for most of the association between maternal prenatal depressive symptoms and both internalizing and externalizing problems in offspring. Indeed, for internalizing 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 behavioral exposure to concurrent maternal depressive symptoms was also identified for internalizing symptoms.

This is the first application of a genetically-informed SEM 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 recent sibling comparison study on the same sample¹⁹ 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 models⁸, wherein genetic confounding is controlled. However, our results suggest that caution is needed in *assuming* its applicability in humans – especially for links between complex behavioral traits, for which genetic influences are likely to be highly pleiotropic¹². Attempts should be made to control for genetic confounding wherever possible in studies aiming to test for fetal programming effects in humans. The increasing availability of genomic data may facilitate this 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 transmission²⁹. It should be noted, for the interpretation of the results of the current study, that epigenetic changes are most usefully conceptualized as an *intermediate phenotype* between genes or environments and outcomes of interest. Specifically, this means that any epigenetic pathways by which maternal prenatal depressive symptoms relate to offspring behavioral 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 influence her child's development, these 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, while 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 on offspring should not be interpreted to mean that treatment of prenatal depressive symptoms will have no secondary protective benefits to children. The behavioral exposure pathway that was found in the current study for internalizing problems may be disrupted by the earlier treatment of maternal depressive symptoms⁷. As far as treating prenatal depressive symptoms reduces a woman's risk of further depressive episodes throughout the child's life, implications for child psychopathology may be substantial – especially given evidence that behavioral exposure effects may predominantly explain links between maternal depressive symptoms and child psychopathology later in development¹¹. Furthermore, the finding that genetic factors associated with prenatal maternal depression account entirely for the heritability of internalizing symptoms in their offspring may also have considerable clinical implications further down the line, as it implies that any translational insights from genome-wide studies of depression (conducted 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 other psychiatric traits³⁰, depressive symptoms in fathers is moderately correlated with maternal depressive symptoms around the perinatal period³¹ 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, as maternal reports were used for both prenatal depressive symptoms and offspring outcomes. Although this might have led to an inflation of the association between the variables, it is unlikely to have done so in a way that favors either genetic or phenotypic transmission (i.e., factors influencing mothers' general reporting behavior may be both genetic and environmental). Furthermore, maternal ratings are generally considered a good indicator of early-life behavior 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, such that mothers who provided data on offspring psychopathology scored significantly lower on prenatal depressive symptoms than those who did not [$t(8202) = -10.19, p < 0.001$]. This may 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 of the etiologies of the extremes of distributions of psychological traits have found them to be highly similar to those underpinning 'normal' variation^{32,33}, so there is no specific reason to expect this to be the case. Nonetheless, the possibility remains and could potentially be explored further in clinical samples. Finally, the absence of a specific measure of *post-natal* depression (i.e., earlier than 1.5 years after birth) could be considered a limitation, as it may 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, this 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 may play an important role in underpinning associations between maternal prenatal depressive symptoms and subsequent internalizing and externalizing problems in offspring early in childhood. In the case of internalizing problems, behavioral exposure to later maternal depressive symptoms may also be influential. The results of this study emphasize the importance of rigorous control for genetic confounding when investigating potential effects of prenatal exposures.

Acknowledgements

LJH is supported by a 1 + 3 multidisciplinary Ph.D. studentship from the UK Economic and Social Research Council. EME, LG, and EY is supported by the Medicine, Health Sciences and Biology Programme at the Norwegian Research Council (Grant Numbers 231105 and 262177). The MoBa study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research (NIH/NIEHS, contract no N01-ES-75558; NIH/NINDA, grant no.1 U01 NS 047537-01 and grant no. 2 U01 NS 047537-06A1). We are grateful to all the participating families in Norway who take part in this on-going cohort study. TAM is supported by a Sir Henry Dale Fellowship, jointly funded by the Wellcome Trust and the Royal Society (107706/Z/15/Z). This study presents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Role of the funding sources

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

The authors declare no competing interests.

Author contributions

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

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Tables

Table 1. Study sample size as stratified by parental sibship type (N individuals)

Family type (parent level)	N mothers	N children				
		Total	MZ	DZ	FS	Singleton
MZ	178	229			108	121
DZ	104	135			64	71
FS	10524	12814	86	272	4250	8206
MHS	338	391			126	265
PHS	460	516			136	380
Singleton	10591	21206	636	2160	18410	
Total	22195	35299	722	2432	23094	9043

Note - MZ = monozygotic; DZ = dizygotic; FS = full sibling; MHS = maternal half sibling; PHS = paternal half sibling; Singleton = no sibship;

Half-siblings in the offspring generation were not included in the analyses;

Child generation twins retained only in groups large enough to support analysis (FS and Singleton families); singleton children of singleton parents were not included

Table 2. Model-derived phenotypic associations within different family structures

Phenotypic correlation		Parent sibship type (child sibship type when marked *)		
		MZ	FS/DZ	HS
Internalizing	Maternal within person	0.64	0.64	0.64
	Maternal 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
Externalizing	Maternal within person	0.65	0.65	0.65
	Maternal 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

Note – correlations derived by standardizing covariances from best-fitting MCoTS models indicated in **eTable 2** and **eTable 3**

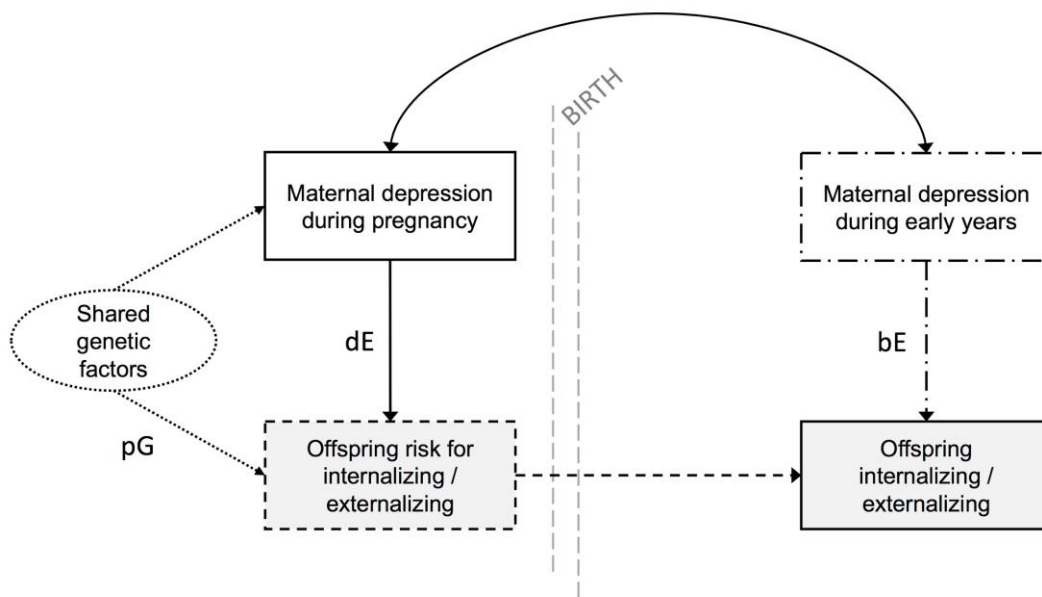


Figure 1. Schematic diagram of possible mechanisms for the transmission of risk for early-life internalizing and externalizing problems from maternal prenatal depression

Note – pG = passive genetic; dE = direct exposure; bE = behavioral exposure

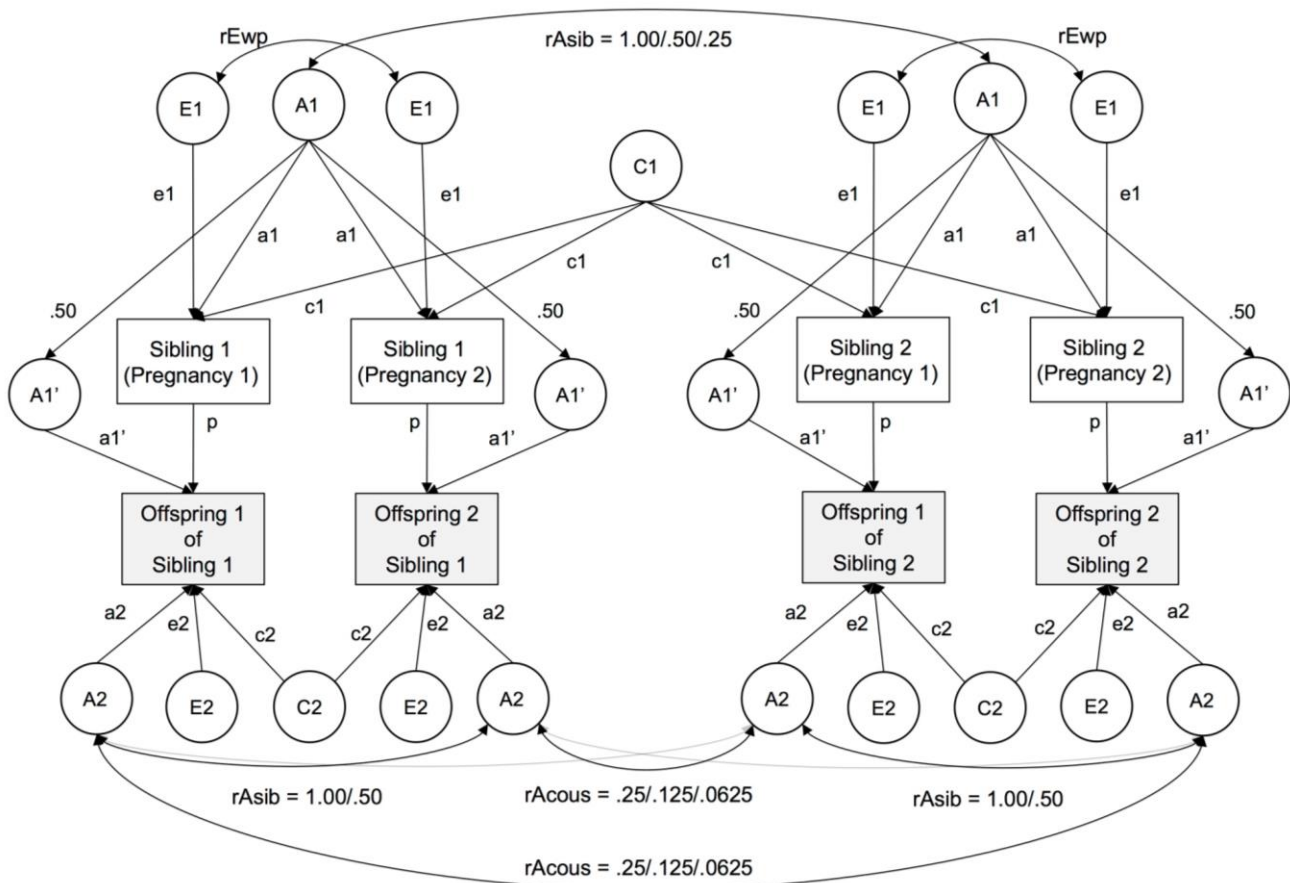


Figure 2. Structural equation model path diagram from the multiple children of twins and siblings (MCOTs) model

Note – Correlation values (i.e., for r_{Asib} and r_{Acous}) are given for MZ/Full sibling & DZ/Half-sibling dyads respectively. These values refer to the genetic relationship at the parent level in all cases apart from r_{Asib} between A2 variance components, which refers to the genetic relationship between siblings within a nuclear family; A1/a1 = maternal genetic factors (variance component/path); C1/c1 = maternal common environmental factors; E1/e1 = maternal unique environmental factors; r_{Ewp} = within-person correlation between maternal unique environmental factors; A1'/a1' = child genetic factors associated with A1; A2/a2 = child generation specific genetic factors; C2/c2 = child common environmental factors; E2/e2 = child unique environmental factors; p = phenotypic transmission path; r_{Ewp} is fixed to 1 when children are twins of either zygosity; MZ twin children share a single A1p parameter;

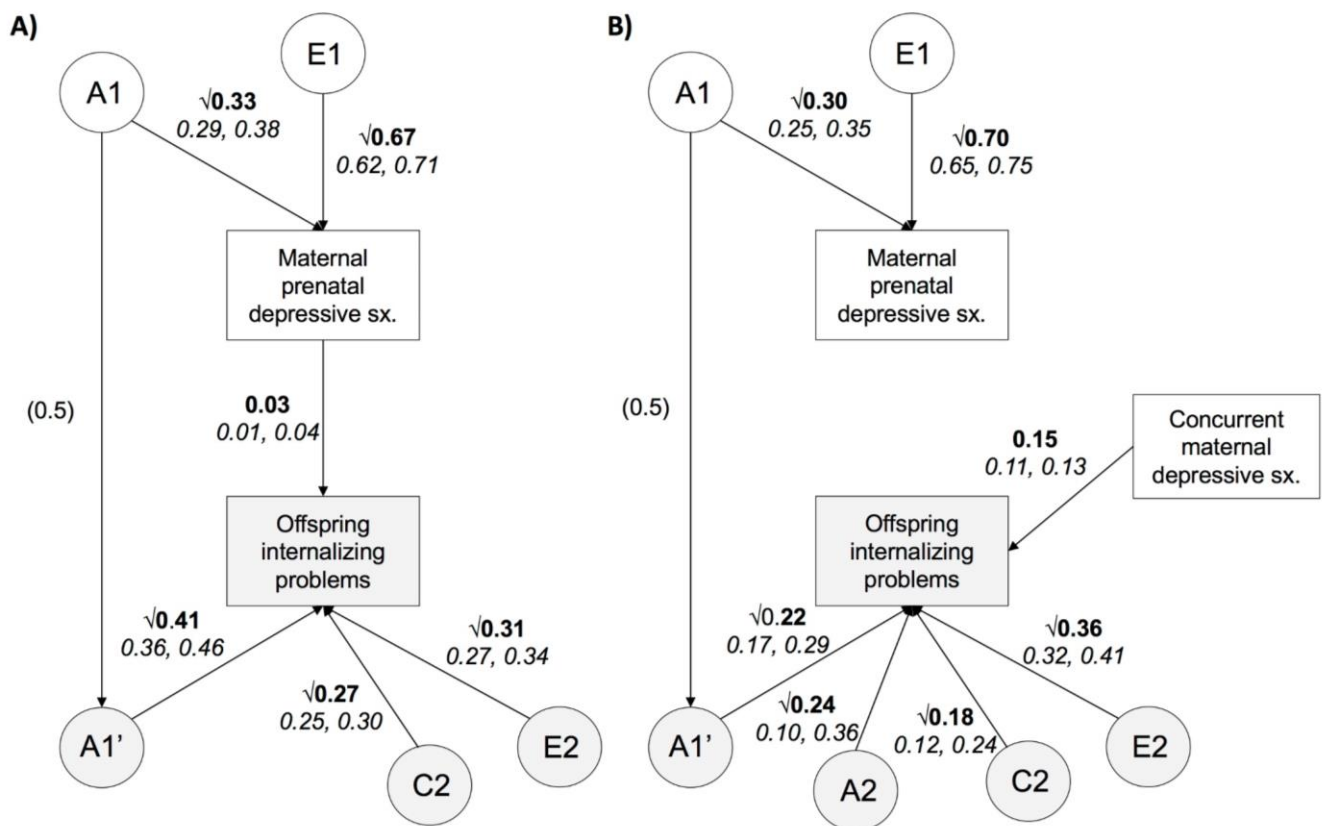


Figure 3. Parameter estimates from the best-fitting model of the association between maternal prenatal depressive symptoms and offspring early-childhood internalizing problems (A) and the same model including concurrent maternal depressive symptoms as a covariate (B)

Note – 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; p = phenotypic transmission path;

Significant parameter estimates in bold typeface; 95% confidence interval limits for each parameter are displayed immediately below in italic font

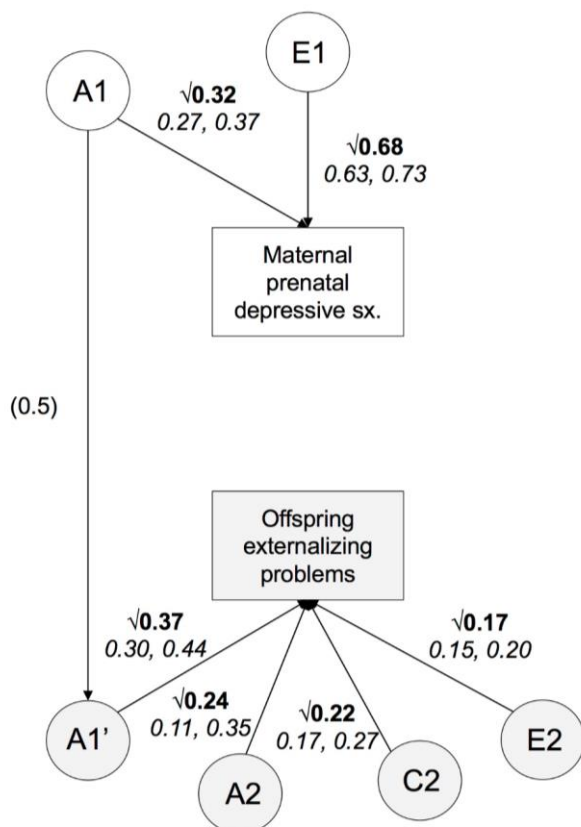


Figure 4. Parameter estimates from the best-fitting model of the association between maternal prenatal depressive symptoms and offspring early-childhood externalizing problems

Note – 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; p = phenotypic transmission path