Disentangling direct and indirect genetic effects from partners and offspring on maternal depression using trio-GCTA

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This paper has been published in *Nature Mental Health* with the DOI: 10.1038/s44220-024-00207-3. It is available at the following URL: https://doi.org/10.1038/s44220-024-00207-3

Word count (excl. Abstract, Tables, Figures, References): 3670.

Keywords: depressive symptoms, maternal depression, trio-GCTA, indirect genetic effects

Abstract

Maternal depressive symptoms are highly prevalent and can negatively impact affected individuals and family members. Understanding aetiological influences on maternal depression, such as genetic liability, is key to inform treatment and prevention efforts. In the present study, we quantified direct and indirect genetic effects (i.e., when genetic variants in other individuals influence risk of maternal depression through the environment) from partners and offspring on maternal depressive symptoms at multiple timepoints using genome-wide complex trait analysis with parent-offspring trios. We used data from the Norwegian Mother, Father and Child cohort study, including up to 21,000 genotyped parent-offspring trios. Models with indirect genetic effects had best fit at three of five timepoints (3, 5, and 8 years after birth). The variance in maternal depressive symptoms explained by direct genetic effects ranged from 5-14%, while indirect genetic effects explained 0-14% of variance across timepoints. Heritable traits in family members contribute to maternal depressive symptoms through the environment at several timepoints after birth.

Introduction

Many women experience the onset of depressive symptoms during the postpartum period[1–3]. Depression and depressive symptoms experienced by mothers, which we refer to here using the term ‘maternal depression’, may persist for several years[4,5], and can have negative impacts for affected individuals, children, partners, and the broader family system. It has been associated with adverse child outcomes such as concurrent child psychopathology symptoms[6,7], disturbances in mother-offspring interactions[8], and detrimental effects on parental and family functioning[9,10]. Negative effects of maternal depression both for affected women and the broader family highlight the need for effective treatment and preventive interventions. Understanding aetiological influences, including both individual and family-level factors, is key to inform such efforts.

Several individual characteristics increase risk of maternal depression, such as a history of psychiatric illness[11] and adverse life events[4]. Depression in women is moderately influenced by genetic factors, with heritability estimates (i.e., the proportion of phenotypic variance explained by genetic variance) at around 40%[12,13]. Although few studies have examined the heritability of maternal depression specifically, similar and slightly lower heritability estimates for postpartum depression and depressive symptoms have been reported[14–16]. Recent genome-wide association studies (GWAS), which seek to identify single nucleotide polymorphisms (SNPs) associated with outcomes, have identified a number of independent genetic variants associated with adult depression and depressive symptoms[17–19]. Thus, recent GWAS studies have yielded novel insights into the genetic architecture of adult depression.

Maternal depression may also be influenced by characteristics of the partner and the quality of the partner relationship. For instance, it has been found that higher relationship satisfaction and partner involvement reduces risk of depressive symptoms[4,20]. Other relationship-related factors associated with risk of depressive symptoms include higher levels of conflict, worse communication, lack of emotional support, and lack of instrumental support[20]. As a result, several preventative interventions for maternal depression aim to improve skills in communication and conflict resolution[21].

Characteristics of children in the family may also increase risk of maternal depression. Difficult infant temperament has been associated with increased risk of depressive symptoms in multiple studies[22–25]. Studies have also found that psychopathology symptoms and sleep problems in children can influence parental depressive symptoms using both genetically informative[26,27] and longitudinal[28,29] designs.

Given that maternal depression is related to partially heritable partner and child characteristics, it is possible that genetic effects on maternal depressive symptoms may act indirectly, as well as directly. While direct genetic effects occur when genetic variants in one individual influence depression risk for that same individual, indirect genetic effects are dependent on the genes of other individuals[30–32]. For instance, genetic variants can exert a direct effect on depression risk in an individual (e.g., a child) as they are inherited, and those variants could also indirectly influence another person's risk (e.g., their mother) through their behaviour (i.e., indirect genetic effects from child to mother via the environment). Studies have identified both evocative genotype-environment correlation, whereby genetically influenced phenotypes in children evoke reactions in other people[27,33,34], and genetic effects mediated by parental behaviour[30,35,36]. Most GWAS studies seek to identify direct genetic effects yet may inadvertently tag indirect genetic effects. Some studies use family designs, such as estimating within-sibship effects by incorporating data from siblings, to account for parent to offspring indirect genetic effects[37].

To examine direct and indirect genetic effects on maternal depression, trio genome-wide complex trait analysis (trio-GCTA[38]) can be used. Trio-GCTA is an extension of

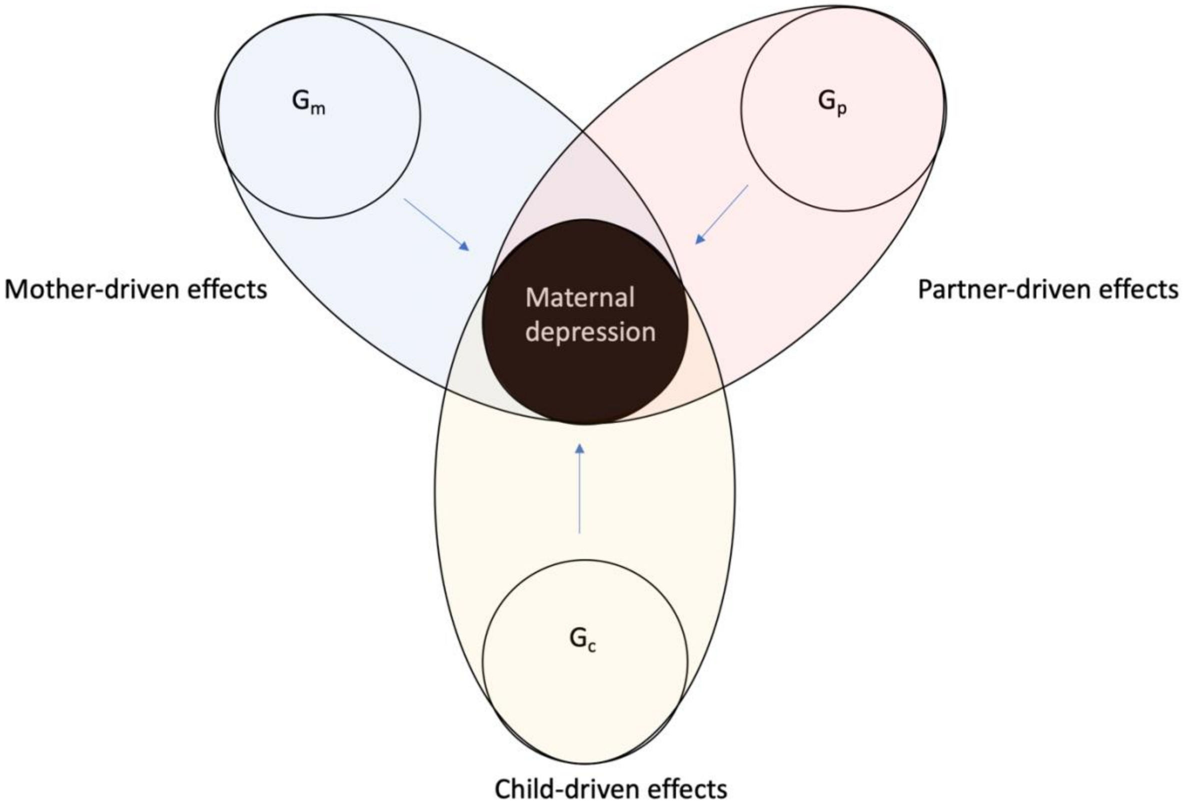
GCTA, a statistical method in which heritability is estimated based on SNPs across a chromosome or the full genome[39–41]. Trio-GCTA utilises genotyped data from mothers, partners, and children, and can disentangle direct and indirect genetic effects of mothers, partners, and children on maternal depression, as illustrated in Figure 1.

The trio-GCTA approach has several strengths, above and beyond allowing for the quantification of direct and indirect genetic effects on a phenotype. Firstly, it eliminates risk of reverse confounding, i.e., if the observed association between a risk factor and an outcome at least in part reflects the influence of the outcome on the risk factor. This is a limitation of most observational studies of risk factors for depression. In the trio-GCTA framework, partner- and child-driven effects are based on genomic data and cannot be explained by reverse confounding, as depressive symptoms in the mother cannot change DNA sequences in other individuals (i.e., partner and child). Secondly, trait-based models which examine indirect genetic effects (e.g., polygenic scores calculated using untransmitted alleles) are limited by the scope of included phenotypic measures, wherever less than all relevant partner and offspring traits are assessed. Variance-component approaches such as trio-GCTA allow for estimating the *total* contribution of indirect genetic effects without the need to measure partner and offspring traits.

In the present study, we aim to estimate genetic effects on maternal depressive symptoms using trio-GCTA with parent-offspring data from the Norwegian Mother, Father and Child Cohort Study (MoBa[42]). The sample comprises mothers with five measurement points from six months after birth until eight years after birth. We aim to quantify the influence of direct and indirect genetic effects on maternal depressive symptoms at each timepoint, separating mother-driven, partner-driven, and child-driven effects.

Figure 1.

Conceptual Model of Mother-, Partner- and Child-Driven Effects on Maternal Depression.



Notes. Figure 1 illustrates hypothetical effects on risk of maternal depression risk which can be estimated using trio-GCTA. *Mother-driven effects* represent direct genetic effects on maternal depressive symptoms. *Partner-driven* and *child-driven* effects reflect indirect genetic effects from partners and offspring, respectively.

Results

We evaluated intrafamilial influences on maternal depressive symptoms at 6 months, 1.5 years, 3 years, 5 years, and 8 years after birth using SNP data from parent-offspring trios. Models including indirect genetic effects had best fit at 3, 5, and 8 years after birth, however differences in AIC values between the competing models were small. Therefore, we focus on characterising the total contribution of indirect genetic effects, instead of comparing the absolute contributions of partner and offspring effects. Likelihood ratio tests (at 5% level) generally suggested a similar pattern of model fit as AIC values. We report the parameter estimates and model fit statistics for each model per timepoint in Table 1. Figure 2 shows the variance decomposition at the different timepoints with parameter estimates from the best-fitting models.

In general, the proportion of explained variance in depressive symptoms by genetic effects (comprising both direct and indirect effects) was larger at later timepoints after birth (i.e., from 3 years after birth and onwards). The variance in maternal depressive symptoms explained by direct genetic effects in the models with the lowest AIC values was 8% at 6 months after birth, 7% at 1.5 years, 14% at 3 years, 5% at 5 years, and 13% at 8 years after birth (see Table 1). The proportion of variance explained by both offspring and partner indirect genetic effects was 14% at 3 years after birth. Offspring indirect genetic effects explained 10.5% of variance at 5 years after birth, which was more than the variance explained by direct genetic effects. Partner indirect genetic effects explained 6% of variance at 8 years after birth.

At 3 years after birth, the covariance between direct maternal and indirect offspring genetic effects was negative and the correlation was -0.63, indicative of a negative gene-environment correlation. Covariances between direct and indirect genetic effects at 5 and 8 years were close to zero.

Table 1.

Parameter Estimates and Fit Statistics for Each Model Specification.

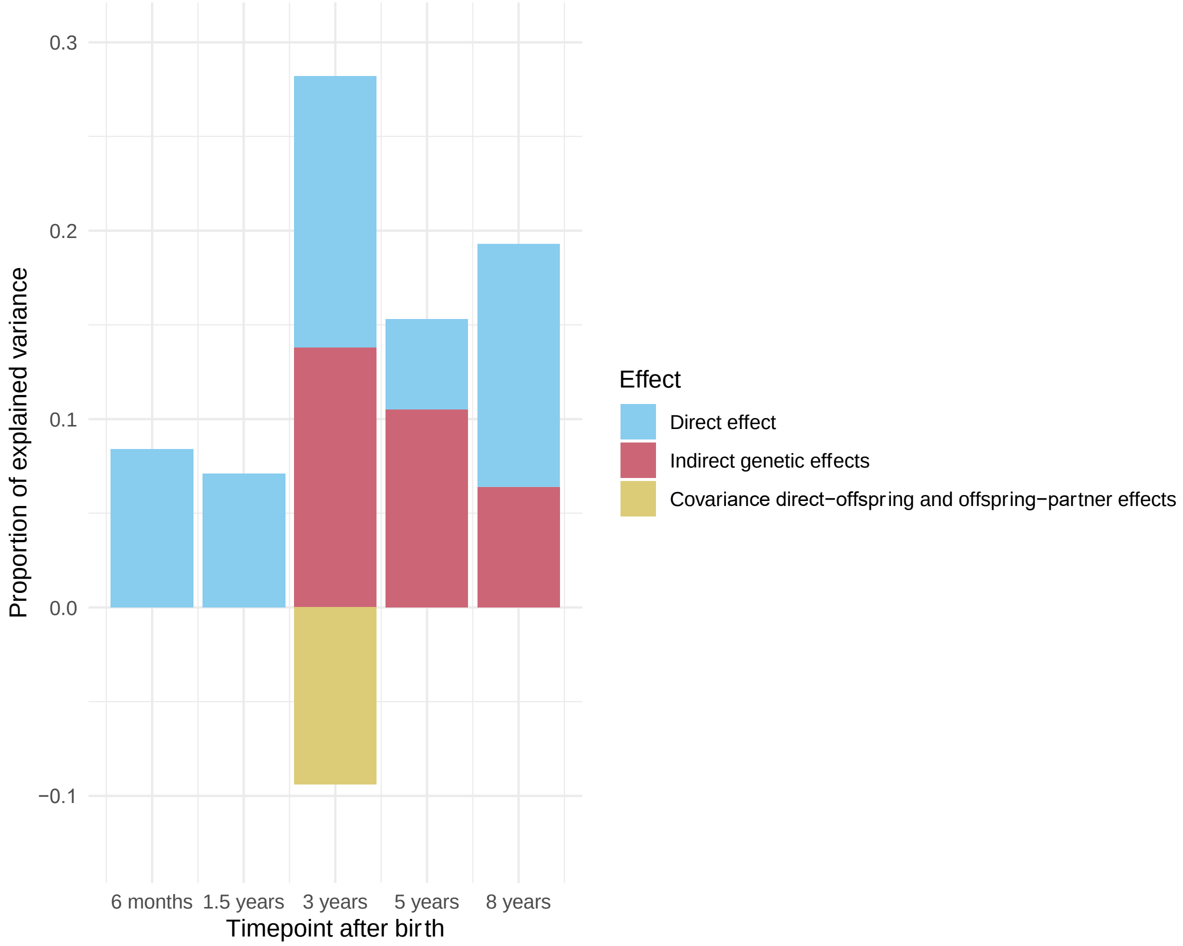
				Parameters							
Timepoint after birth	$\boldsymbol{\sigma^2_m}$ **(SE)**	$\boldsymbol{\sigma^2_p}$ **(SE)**	$\boldsymbol{\sigma^2_o}$ **(SE)**	$\boldsymbol{\sigma_{mp}}$ **(SE)**	$\boldsymbol{\sigma_{om}}$ **(SE)**	$\boldsymbol{\sigma_{op}}$ **(SE)**	$\boldsymbol{\sigma^2_e}$ **(SE)**	**-2ll**	**AIC**	**df**	**p-value**
6 months											
Full model	.099 (.023)	.003 (.007)	.016 (.023)	.010 (.015)	-.019 (.020)	.003 (.009)	.898 (.022)	58924.21	59042.21	59	—
No covariances	.081 (.016)	.005 (.016)	.009 (.017)	—	—	—	.906 (.023)	58925.87	59037.87	56	.64
Direct and offspring indirect effect	.092 (.020)	—	.021 (.021)	—	-.014 (.017)	—	.901 (.022)	58925.27	59037.27	56	.79
Direct and partner indirect effect	.083 (.015)	.006 (.015)	—	.007 (.011)	—	—	.910 (.021)	58925.72	59037.72	56	.68
Direct genetic	**.084 (.015)**	—	—	—	—	—	**.916 (.015)**	**58926.34**	**59034.34**	**54**	**.83**
1.5 years											
Full model	.070 (.027)	.003 (.025)	.041 (.036)	.008 (.020)	-.011 (.026)	-.002 (.024)	.898 (.031)	52273.83	52391.83	59	—
No covariances	.061 (.018)	.003 (.019)	.035 (.020)	—	—	—	.901 (.027)	52274.12	52386.12	56	.96
Direct and offspring indirect effect	.065 (.024)	—	.041 (.026)	—	-.005 (.020)	—	.900 (.026)	52274.08	52386.08	56	.97
Direct and partner indirect effect	.069 (.018)	.011 (.018)	—	.012 (.012)	—	—	.920 (.025)	52276.15	52388.15	56	.51
Direct genetic	**.071 (.017)**	—	—	—	—	—	**.929 (.017)**	**52277.62**	**52385.62**	**54**	**.58**
3 years											
Full model	**.144 (.035)**	**.039 (.034)**	**.099 (.048)**	**.062 (.026)**	**-.075 (.034)**	**-.019 (.034)**	**.813 (.040)**	**41000.48**	**41118.48**	59	—
No covariances	.082 (.024)	.032 (.023)	.055 (.026)	—	—	—	.832 (.034)	41009.14	41121.14	56	.03
Direct and offspring indirect effect	.107 (.031)	—	.095 (.033)	—	-.035 (.025)	—	.833 (.033)	41009.10	41121.10	56	.03
Direct and partner indirect effect	.094 (.023)	.043 (.022)	—	.040 (.016)	—	—	.863 (.032)	41007.53	41119.53	56	.07
Direct genetic	.097 (.023)	—	—	—	—	—	.903 (.023)	41018.51	41126.51	54	.00
5 years											
Full model	.053 (.046)	.002 (.012)	.123 (.061)	.007 (.029)	-.009 (.043)	-.013 (.035)	.845 (.043)	28660.66	28778.66	59	—

No covariances	**.048** **(.032)**	**.000** **(.000)**	**.105** **(.034)**	**—**	**—**	**—**	**.846** **(.039)**	**28660.84**	**28772.84**	**56**	**.98**
Direct and offspring indirect effect	**.048** **(.041)**	**—**	**.105** **(.042)**	**—**	**-.000** **(.033)**	**—**	**.846** **(.043)**	**28660.84**	**28772.84**	**56**	**.98**
Direct and partner indirect effect	.079 (.031)	.010 (.014)	—	.028 (.020)	—	—	.912 (.032)	28669.44	28781.44	56	.03
Direct genetic	.078 (.031)	—	—	—	—	—	.922 (.031)	28671.08	28779.08	54	.06
8 years											
Full model	.154 (.043)	.045 (.032)	.011 (.017)	-.014 (.026)	-.027 (.030)	.019 (.016)	.797 (.043)	31532.67	31650.67	59	—
No covariances	.128 (.031)	.063 (.031)	.000 (.000)	—	—	—	.809 (.043)	31534.82	31646.82	56	.54
Direct and offspring indirect effect	.164 (.042)	—	.025 (.041)	—	-.038 (.033)	—	.850 (.043)	31537.67	31649.67	56	.17
Direct and partner indirect effect	**.129** **(.031)**	**.064** **(.031)**	**—**	**-.014** **(.022)**	**—**	**—**	**.807** **(.043)**	**31534.40**	**31646.40**	**56**	**.63**
Direct genetic	.130 (.031)	—	—	—	—	—	.870 (.031)	31539.09	31647.09	54	.27

Notes. Bold values indicate the model specification with the lowest AIC estimate for each timepoint. σ_m^2 represents the variance explained by direct genetic effects; σ_p^2 and σ_o^2 the variance explained by Partner and offspring indirect genetic effects, respectively; σ_{om} the covariance between maternal direct genetic effects and offspring indirect genetic effects; σ_{op} the covariance between indirect partner and offspring genetic effects; and σ_e^2 the residual variance of the phenotype. P-values below .05 (the threshold value for statistical significance) indicate that a given model exhibited a worse fit than the full model in a likelihood ratio test. P-values above .05 indicate that a given model did not demonstrate a significantly worse fit compared with the full model.

Figure 2.

Estimates of Direct and Indirect Genetic Effects at Separate Timepoints.



Notes. Figure 2 shows the parameter estimates from best-fitting trio-GCTA models at each timepoint. The variance in maternal depressive symptoms explained by direct genetic effects ranged from 5-14%, while indirect genetic effects explained 0-14% of variance across timepoints. The variance components are standardised and sum to 1, so that the remaining variance not accounted for is explained by residual error (not shown in Figure 2). Sample sizes were 21,146 at 6 months, 17,789 at 1.5 years, 13,888 at 3 years, 10,360 at 5 years, and 10,582 at 8 years. The covariance between direct effects and partner indirect genetic effects is not expected to contribute to variance in maternal depressive symptoms and is therefore not shown in Figure 2.

Discussion

In a large-scale sample including up to 21,000 Norwegian parent-offspring trios, we found evidence of direct genetic effects at all timepoints and indirect genetic effects from partners and/or offspring on maternal depressive symptoms at 3, 5, and 8 years after birth. Although our data did not allow us to select specific models which distinguished effects from family members, models with indirect genetic effects had better fit for these timepoints. Thus, these findings highlight the importance of considering intrafamilial effects, such as partner and offspring indirect genetic effects, on maternal depressive symptoms across the early childbearing years.

The variance explained by direct genetic effects for maternal depressive symptoms from the best-fitting models ranged from 5% (5 years after birth) to 14% (3 years after birth). Thus, we found varying heritability estimates across timepoints after birth. It would be useful for future studies to investigate heterogeneity in estimates of direct genetic effects on maternal depressive symptoms to determine if varying estimates across timepoints are linked to timepoint-specific genetic and environmental influences or methodological aspects (e.g., related to trio-GCTA or statistical power). Given the limited ability to distinguish alternative models, we cannot separate sampling variability from true heterogeneity across time in the current analysis.

In this study, estimates of direct genetic effects on maternal depressive symptoms are not confounded by indirect effects, which may wrongly be attributed to direct genetic effects if not accounted for[43]. Comparisons of heritability estimates to previous findings are further complicated by heterogeneous operationalisations of depression across studies[44], sample differences, and analysis differences. Our estimates of direct genetic effects are lower than what has been reported in several previous studies, in which the SNP-based heritability of major depressive disorder has been estimated to 21%[45], 32%[46], and depressive symptoms to

21%[47]. Furthermore, our sample differs from these studies in that we quantified direct genetic effects in mothers only, which could contribute to observed differences. In addition, we assessed depressive symptoms in the last 14 days, which would be expected to have lower heritability than life-time diagnoses of depression. Previous twin studies have found that the heritability of lifetime risk of major depressive episode diagnoses is substantially higher than of depression risk in a given year[48]. Our estimates are closer to heritability estimates reported in previous GWAS studies of diverse depression phenotypes[17–19].

Interestingly, the variance explained by direct genetic effects on maternal depressive symptoms at 8 years after birth (13%) was similar to the variance explained by indirect genetic effects (of mothers and fathers) on child depressive symptoms at the same time-point, as estimated in a previous study in this cohort[35]. Cheesman et al.[35] also found that the indirect effects were partly mediated by a measure of maternal anxiety and depressive symptoms.

Our findings are broadly in line with the conceptualisation of maternal depression as a family-wide mental illness[9,49], the risk of which is influenced both by individual factors (e.g., direct genetic effects), and family-level characteristics, as has been shown previously[50]. The results of the present study suggest that genetic effects from both partners and offspring, mediated through the environment, contribute to maternal depressive symptoms at multiple timepoints after birth. Thus, both partner and offspring indirect genetic effects may represent family-level factors influencing depressive symptoms. Nevertheless, given the limited ability to statistically distinguish alternative models, uncertainty regarding the magnitude of specific parameter estimates should be considered relatively large. A particular strength of the trio-GCTA approach is that all indirect genetic effects from partners and offspring at each timepoint are quantified without having to rely on a wide range of measures of such environmental effects. Furthermore, there is no risk of reverse confounding, which may otherwise limit observational studies of risk factors for maternal depression based on self-report data. Thus, indirect genetic effects index environmental influences while eliminating common methodological artifacts such as recall bias.

The prevalence of depressive symptoms in MoBa mothers was higher at 18 months and three years after birth compared with six months postpartum, while continuing to increase for mothers with multiple births[51]. Our results indicated that indirect genetic effects contributed to maternal depressive symptoms at child age 3 and beyond, influencing risk of maternal depressive symptoms at these timepoints. It is possible that indirect genetic effects on depressive symptoms arise when family resources are more limited, for instance as many parents will have returned to the workforce after parental leave when children are aged three and older. Offspring indirect genetic effects could also possibly reflect phenotypes subject to early development, for instance related to sleep, language, and temperament. Previous studies have suggested that genetic factors which influence adult depressive and anxiety symptoms are mostly the same across timepoints in adulthood[52,53]. Future studies could examine the stability of direct and indirect genetic effects on maternal depressive symptoms and if these influences involve the same or different SNPs across time in longitudinal analyses.

At 3 years after birth, results indicated that there was a negative gene-environment correlation for direct genetic and offspring indirect genetic effects. This suggests that the same genes in mothers and offspring work in opposite directions with regards to maternal depressive symptoms at this timepoint. We note that a negative correlation between direct and indirect genetic effects was also found in a recent study of ADHD using trio-GCTA with the child at 8 years as the focal individual[36]. Eilertsen et al.[36] highlight that negative correlations between genetic effects of children and parents could help sustain genetic variation in populations across time, which has been argued elsewhere on the basis of animal studies [54]. In the present study, the observed negative gene-environment correlation could for instance arise if children of parents with high genetic risk of depressive symptoms are inclined to exhibit behaviours which tend to reduce risk of depressive symptoms. This also implies that indirect genetic effects could suppress the heritability estimate for maternal depression in studies not including family members.

Trio-GCTA is a variance decomposition approach which benefits from not requiring the comprehensive measuring of all relevant partner and offspring traits to quantify indirect genetic effects. Therefore, we examined indirect genetic effects while remaining agnostic to specific phenotypes involved in these influences. Future studies of indirect genetic effects using trait-based models may investigate possible traits and mechanisms.

Our study has several limitations which should be kept in mind when interpreting the results. First, differences between the competing models with regards to model fit statistics (AIC and likelihood values) were generally small. Therefore, the statistical support in favour of any specific model deemed best-fitting should not be interpreted as strong. Second, we cannot exclude the possible influence of selection bias or bias due to attrition in MoBa[55,56]. Furthermore, our sample was restricted to women with children and their partners and a Norwegian context, and the study was based on European ancestry genotype data, limiting the generalizability of our findings beyond this group. Third, estimates of indirect genetic effects can be biased by assortative mating and population stratification, as demonstrated in polygenic score studies of educational outcomes[57,58]. Partner correlations for depression phenotypes are typically moderate in magnitude[59,60], which has been found in MoBa also [61,62]. When assortative mating occurs for a trait, it is generally expected to increase the heritability of the trait. However, two recent studies, both using polygenic scores, did not find evidence of widespread assortative mating for depression in MoBa[63,64]. We note that these studies may have yielded estimates which are biased downwards because of low predictive power of the depression polygenic score itself. Torvik et al.[62] identified a small genetic correlation among MoBa partners for depression using a structural equation modeling approach. How assortative mating would bias estimates and inferences derived from trio-GCTA is currently uncertain[38]. Future studies should examine the extent that estimates of indirect genetic effects on depression from trio-GCTA may also capture bias from factors such as assortative mating and population stratification[36,38].

Conclusion

In the present study, we quantified direct and indirect genetic effects on maternal depressive symptoms in MoBa at 5 measurement time points after birth. We found support for offspring and partner indirect genetic effects on depressive symptoms in mothers at 3, 5, and 8 years after birth. Our results point to the importance of considering intrafamilial effects, such as indirect genetic effects from other family members, for understanding risk for maternal depressive symptoms. These indirect genetic effects operate through the environment and contribute to risk of maternal depressive symptoms at several timepoints after birth. Thus, our results illustrate the utility of genomic designs and the trio-GCTA method in investigating environmental influences on maternal depressive symptoms using genetic data. Most importantly, our study shows that heritable traits in close family members have a directional environmental effect on depressive symptoms in women during childbearing years.

Methods

Participants

Participants were recruited from MoBa[42], a population-based study conducted by the Norwegian Institute of Public Health, for which all pregnant Norwegian women were eligible to participate. Invitations to participate were sent to 277,702 women and the participation rate was 41%. In total, the cohort consists of 114,500 children, 95,200 mothers and 75,200 fathers. We used data from version 12 of the quality-assured MoBa data files. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The present study was approved by the Regional Committees for Medical and Health Research Ethics (project number: 2013/863). The genotype pipeline for the MoBa study is described in Corfield et al.[65], which involved retaining only participants with European ancestry genotype data. Details specific to the current analysis are further described in the Supplementary Materials. Informed consent was obtained from all study participants. The participants did not receive monetary compensation.

Selection of parent-offspring trios

The quality control of genotype data retained 25,332 complete mother-father-offspring trios. We used parent-offspring trios with data on maternal depressive symptoms collected at five timepoints after birth: 6 months, 1.5 years, 3 years, 5 years, and 8 years. Sample sizes decrease across the measurement time points mainly due to attrition, which has been described elsewhere[42]. We estimated a genomic relatedness matrix, which represents an empirical estimate of the genetic relatedness among all individuals in the sample [40]. We used a threshold of 0.10 for the largest genetic correlation allowed between any two individuals (ignoring pairs of parents and offspring), to limit confounding due to closely related individuals being included in analyses[41]. This threshold has been applied in previous trio-GCTA studies with the aim of excluding closely related individuals while maintaining a large number of parent-offspring trios[36,38]. We computed the GRM and selection of individuals using the ‘bottom up’ algorithm with functions from the OpenMendel project [66]. Final sample sizes at each timepoint after birth (number of trios) were 21,146 at 6 months, 17,789 at 1.5 years, 13,888 at 3 years, 10,360 at 5 years, and 10,582 at 8 years.

Measures

Maternal depressive symptoms in the last 14 days were assessed using an eight-item short form version of the Symptom Checklist (SCL)[67,68]. This measure has been previously validated[69,70]. Individual sum scores of the four depressive symptoms in the SCL were created for each timepoint. A single measure was used for mothers with more than two questionnaires at a single timepoint (i.e., if mothers had more than one child). We randomly chose one child for inclusion in the analyses (and used the associated symptom measure) for mothers of multiple children in MoBa. We applied a logarithmic transformation to the symptom sum scores to reduce skewness. The scores were then standardised using the mean score and standard deviation at the first timepoint (i.e., 6 months after birth), so that means and standard deviations at later timepoints can be interpreted relative to this.

Statistical analysis

The statistical approach in GCTA has been termed genomic relatedness matrix (GRM) restricted maximum likelihood (GREML) and uses a mixed linear model to estimate heritability with genomic data[39–41]. It is assumed that SNPs contribute to phenotypic variation and that these effects correlate between individuals with similar genotypes. The GREML approach quantifies the SNP-based heritability[41], i.e., the effects tagged by genotyped and imputed SNPs used in the analysis. This heritability estimate is therefore dependent on the set of SNPs which have been collected. GCTA has typically been used in samples of unrelated individuals, but was extended by Eaves et al.[71] to also include data from mothers and offspring, allowing for the estimation of maternal indirect genetic effects. Eilertsen et al.[38] extended this method to estimate indirect genetic effects from any individual in parent-offspring trios (trio-GCTA).

In the present study, the focal individuals were mothers and parameters are interpreted with reference to maternal depressive symptoms. The variance components which are estimated are:

$$Var(y_k) = \sigma_m^2 + \sigma_p^2 + \sigma_o^2 + \sigma_{om} + \sigma_{op} + \sigma_e^2$$

σ_m^2 represents the variance explained by direct genetic effects; σ_p^2 and σ_o^2 the variance explained by partner and offspring indirect genetic effects, respectively; σ_{om} the covariance between maternal direct genetic effects and offspring indirect genetic effects; σ_{op} the covariance between indirect partner and offspring genetic effects; and σ_e^2 the residual variance of the phenotype. The residual variance estimate may include genetic effects not captured by SNPs included in the analysis, unique environmental effects, and shared environmental effects not captured by SNPs. The covariance between direct maternal genetic effects and partner indirect genetic effects (σ_{mp}) is estimated, but not expected to contribute to variance in maternal depressive symptoms, as parents are not related. Several assumptions are made in trio-GCTA. Genetic and residual effects are assumed to follow a multivariate normal distribution. The different genetic effects can be dependent but individual SNP effects are assumed to be independent. Furthermore, it is assumed that random mating occurs in the population. It has recently been shown that assortative mating for depressive symptoms in MoBa does not seem to be substantial[63].

We tested 5 models per timepoint, as reported in Table 2. The first model estimated all variance components (i.e., the full model). The subsequent models estimated fewer parameters, dropping either the covariance parameters for the direct and indirect genetic effects (Model 2), or one indirect genetic effect and covariance (Models 3 and 4). The final model estimated only direct genetic effects and the error component. Each model included the fixed effects of child sex, genotype batches, imputation batches, and principal components of mothers and fathers. Model fit was assessed using Akaike's Information Criteria (AIC)[72]. The model considered to have best fit at each timepoint was the model with the lowest AIC value. We also conducted likelihood ratio tests where we compared the goodness of fit of the full model with the nested models (i.e., Models 2-5). However, there are challenges regarding the interpretation of likelihood ratio tests with family data[73,74]. We are not aware of work examining interpretation of likelihood ratio tests in the context of GREML methods which involve direct and indirect genetic effects. We therefore relied on AIC for selecting models with best fit at each timepoint. The models were estimated using the Julia programming language[75], via the package VCModels.jl[76].

Table 2.

Models and Variance Components Estimated in Each Model.

Model	**Parameters estimated**
1. Full model (all effects)	$\sigma_m^2;\ \sigma_p^2;\ \sigma_o^2;\ \sigma_{om};\ \sigma_{op};\ \sigma_{mp};\ \sigma_e^2$
2. No covariances between direct and indirect effects	$\sigma_m^2;\ \sigma_p^2;\ \sigma_o^2;\ \sigma_e^2$
3. Direct and offspring indirect effect	$\sigma_m^2;\ \sigma_o^2; \sigma_{om}; \sigma_e^2$
4. Direct and partner indirect effect	$\sigma_m^2;\ \sigma_p^2;\ \sigma_{mp}; \sigma_e^2$
5. Direct genetic effects only	$\sigma_m^2;\ \sigma_e^2$

Notes. σ_m^2 represents the variance explained by direct genetic effects; σ_p^2 and σ_o^2 the variance explained by partner and offspring indirect genetic effects, respectively; σ_{om} the covariance between maternal direct genetic effects and offspring indirect genetic effects; σ_{op} the covariance between indirect partner and offspring genetic effects; and σ_e^2 the residual variance of the phenotype.

Data availability statement

MoBa data can be accessed by application to the Regional Committee for Medical and Health Research Ethics in Norway and MoBa (https://www.fhi.no/en/ch/studies/moba/for-forskere-artikler/research-and-data-access/). The consent given by the participants does not open for storage of data on an individual level in repositories or journals.

Code availability statement

The code used in this study is available upon request from the first author. Example code for fitting variance component models structured according to relationship matrices with VCModels.jl is provided at: https://github.com/espenmei/VCModels.jl

Acknowledgements

The Research Council of Norway supported R.C., R.B.N., E.R., and T.A.M. (grant no. 288083), HA (grant no. 274611), AH (grant no. 274611; 336085), L.D.B. (grant no. 314843), and EY (grant no. 288083, 262177, 336078, 331640). LJH was supported by the South-Eastern Norway Regional Health Authority (#2022083 and #2018058). LDB has received internationalization support from UiO:Life Science. J.R.B is supported by a Sir Henry Wellcome Postdoctoral Fellowship [215917/Z/19/Z]. The positions of T.A.M. and Y.I.A., were funded by a Wellcome Trust Senior Research Fellowship awarded to T.A.M. (grant number 220382/Z/20/Z)

EY is funded by the European Research Council under the Horizon 2020 (grant no. 818425) and the Horizon Europa program (Grant No. 101045526). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Executive Agency (REA). Neither the European Union nor the granting authority can be held responsible for them.

Author Contributions Statement

L.D.B., E.M.E. and E.Y. were responsible for the concept, design, and analysis of data. L.D.B., E.M.E., Z.A., R.C., Y.I.A., J.R.B., H.A., L.J.H., T.A.M., A.H., R.B.N., E.R. and E.Y. contributed to the interpretation of the results. Drafting of the manuscript was done by L.D.B, while E.M.E., Z.A., R.C., Y.I.A., J.R.B., H.A., L.J.H., T.A.M., A.H., R.B.N., E.R. and E.Y provided critical revision of the manuscript for important intellectual content.

Competing Interests Statement

The authors declare no competing interests.

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