ASSOCIATIONS BETWEEN MATERNAL DEPRESSIVE SYMPTOMS AND RISK FOR OFFSPRING EARLY-LIFE PSYCHOPATHOLOGY: THE ROLE OF GENETIC AND NON-GENETIC MECHANISMS

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ABSTRACT

Background: Although maternal depressive symptoms are robustly associated with offspring early-life psychopathology symptoms, it is not clear which potential mechanisms are at play. We aimed to estimate the relative importance of genetic transmission and direct environmental exposure in these associations at three occasions in early childhood.

Methods: Biometric modeling of maternal sisters and their offspring from the Norwegian Mother and Child Cohort Study. The analyzed sample comprised 22,316 mothers and 35,589 offspring. Mothers reported their own depressive symptoms using the Symptom checklist, and offspring's concurrent symptoms of psychopathology using the Child Behavior Checklist at 1.5, 3, and 5 years postpartum.

Results: Associations between maternal symptoms of depression and offspring emotional problems were predominantly explained by passive genetic transmission at 1.5 and 3 years postpartum. At age 5, associations were more due to direct environmental exposure. For offspring behavioral problems, there was no net increase in the importance of direct environmental exposure across occasions.

Conclusions: Associations between maternal depressive symptoms and offspring psychopathology symptoms remained after accounting for shared genes, consistent with a small, causal effect. For offspring emotional problems, this effect appeared to increase in importance over time. Our findings imply that treatment of maternal depressive symptoms could also benefit the offspring, and that genetic confounding should be considered in future studies of such mother-offspring associations.

INTRODUCTION

Children of mothers with depressive symptoms appear to have more emotional and behavioral problems, with meta-study correlation estimates of 0.23 and 0.21, respectively (Goodman *et al.*, 2011, Netsi *et al.*, 2018). Such associations are often interpreted to be causal, in that the child is assumed to be exposed to the mother's symptoms via social mechanisms, such as withdrawn or harsh parenting (Lovejoy *et al.*, 2000), modeling processes (Cummings and Davies, 1994) or disrupted attachment (Cummings and Davies, 1994). Exposure to maternal symptoms can also happen during pregnancy. The fetal programming hypothesis, which has found support from both human (e.g. Davis *et al.*, 2007) and animal research (e.g. Golub *et al.*, 2016), posits that physiological consequences of maternal prenatal depressive symptoms can directly impact the development of the fetus, manifesting later as emotional or behavioral problems. However, adult depression (Sullivan *et al.*, 2000) and child emotional (Rice *et al.*, 2002) and behavioral problems (Young *et al.*, 2000) are heritable, and parents and children share both their environment and half of their genetic material. If there is an overlap in genes influencing risk for maternal depressive symptoms and child mental health problems, then at least part of the mother-child association can be attributed to genetic confounding.

Traditional observational designs cannot account for genetic confounding in mother-offspring associations, but genetically informative designs such as the sibling, adoption, and Children-of-Twins (CoT) design can isolate the potential, remaining environmental effect. Overall, there is evidence for a remaining environmental effect of maternal depressive symptoms on child emotional and behavioral problems (Gjerde *et al.*, 2017, Kendler *et al.*, 2018, Natsuaki *et al.*, 2014), but when exposure happens during pregnancy, the association appears to be confounded by genes shared between mother and child (Gjerde *et al.*, 2017, Hannigan *et al.*,

2018), leaving the fetal programming hypothesis less likely to explain mother-child associations.

Early childhood is a sensitive period in life, characterized by rapid changes and numerous developmental milestones. A previous sibling comparison study conducted by our group indicated that the environmental effect might become more important as the children grow older (Gjerde *et al.*, 2017). For the purpose of understanding the nature of parent-offspring associations, the CoT design may be the most optimal, as this method can quantify the importance of passive genetic transmission versus environmental exposure by modeling separate genetic and environmental routes that account for intergenerational covariation (McAdams *et al.*, 2018). The genetic route is due to *passive genetic transmission* – i.e. that mothers have passed on risk genes which explain variance both in the maternal and offspring phenotype. The environmental route of transmission is interpreted to be due to exposure to symptoms through various types of behavior, and can be referred to as *direct environmental exposure (Silberg et al., 2010).* To date, no CoT studies have investigated early childhood. We therefore lack knowledge on the nature of intergenerational associations between maternal depressive symptoms and offspring's emotional and behavioral problems during this developmentally important period.

The first aim of the current investigation was to estimate the relative importance of passive genetic and/or direct environmental exposure for the association between maternal depressive symptoms and offspring concurrent emotional and behavioral problems at three developmental periods (age 1.5, 3, and 5 years). Second, we aimed to clarify whether direct environmental exposure becomes more important for the mother-offspring association across these developmental periods.

METHODS

Participants

The present study is part of the Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health (NIPH). MoBa is a prospective, ongoing, pregnancy cohort study (Magnus *et al.*, 2016). Participants were recruited from 1999 to 2008 at a routine ultrasound examination offered to all pregnant women in Norway at gestational week 17-18. The total sample includes >114,500 children, >95,000 mothers and >75,000 fathers. In total, 41% of eligible women participated. The current study is based on the Intergeneration Transmission of Risk (ITOR) subproject, in which kinship between participants in the parent and child generation has been identified through linkage with the Norwegian Twin Registry (NTR) (Nilsen *et al.*, 2013) and population data from Statistics Norway. Twin zygosity was determined using questionnaire items and logistic regression (see eAppendix1). The current sample comprised maternal twins/sisters and their offspring. One study unit consists of up to 6 individuals: a mother and her twin/sister, as well as up to two children per mother. In the mother generation, the sample consisted of 22,316 individuals: 89 monozygotic (MZ) and 52 dizygotic (DZ) twin pairs, 5,262 full sibling pairs (FS), 169 maternal half sibling pairs (MHS), 230 paternal half sibling pairs (PHS), and 16,514 were singletons. In the child generation, the sample comprised 35,589 individuals: 370 MZ and 1,229 DZ twin pairs, 11,546 FS and 128 MHS pairs, and 22,316 singletons.

Version 9 of the quality-assured MoBa data files were used, released in 2015. Written informed consent was obtained from all participants upon recruitment. The establishment and data collection in MoBa was previously based on a license from the Norwegian Data protection agency and approval from The Regional Committee for Medical Research Ethics,

and it is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committee for Medical Research Ethics. In the current study we use information obtained at 1.5, 3, and 5 years after birth.

Measures

Symptoms of maternal depression were assessed by self-report at 1.5, 3, and 5 years after birth, using the eight item version (Tambs and Røysamb, 2014) of the short form of the Symptom Checklist (SCL; Hesbacher *et al.*, 1980), originally designed to measure symptoms of depression and anxiety. The mothers answered to what extent the eight statements, covering the last two weeks, were true on a 1 ("not bothered") to 4 ("very bothered") scale. We created composite scores of the scale items for each of the three time points (ordinal Cronbach's alphas (Gadermann *et al.*, 2012) = 0.92, 0.94, and 0.93, respectively). The SCL-8 correlate highly with the SCL depression dimension (Tambs and Røysamb, 2014), and a five item version of this scale has been found to have a genetic correlation close to unity with mood disorders measured by the Composite International Diagnostic Interview (Gjerde *et al.*, 2011). The SCL-8 is therefore suitable for capturing genetic risk for depression.

Emotional and behavioral problems were measured using items from the Child Behavior Checklist (CBCL) for preschool children (Achenbach, 1992). In the questionnaires covering age 1.5, 3, and 5 years after birth, there are in total 13 items covering emotional problems, and 11 covering behavioral problems. For each item, mothers reported agreement on a 3-point Likert scale: 1 = "not true", 2 = "somewhat true", 3 = "very true or often true". We created composite scores for emotional and behavioral problems separately at all three occasions. Ordinal Cronbach's alphas (Gadermann *et al.*, 2012) were 0.65, 0.69, and 0.74 for emotional problems, and 0.70, 0.77, and 0.81 for behavioral problems, respectively. Correlations

between the short scales at 1.5, 3, and 5 years and the full CBCL scale for emotional problems measured when the children were 6 years old have been found to be 0.71, 0.79, and 0.87, respectively (Helland *et al.*, 2017).

Statistical analyses

The Multiple-Children-of-Twins-and-Siblings (MCoTS) is an extension of the CoT design (McAdams *et al.*, 2014), where multiple children per mother is included. In addition to twin sisters in the mother generation, sisters and half-sisters are also included. Both the CoT and MCoTS designs are extensions of the classical twin design (Jinks and Fulker, 1970), in which structural equation modeling is used to divide individual differences in a trait into genetic and environmental sources. Typically, three sources of variance are specified. Additive genetic variance (A) reflect the average influence of each allele on a trait, and would tend to make MZ twin pairs correlate twice as high as DZ twin pairs, and full siblings twice as much as half siblings. Shared environmental variance (C) reflect all environmental influences that make pairs of relatives more similar to each other (such as socioeconomic status). Unique environmental variance (E) reflect environmental influences that make relatives more different from each other. This component also includes potential measurement error. The importance of each of these sources of variance is usually expressed as a percentage of the total variance in a trait, and is determined by comparing correlations between different types of relatives. For instance, if monozygotic twin sisters (who share all their genetic material, and also all of their family environment) are on average more similar to each other than dizygotic twin sisters (who share on average 50% of their segregating genes, and also all family environment) then this greater similarity can only be explained by the monozygotic sisters sharing more of their genes. The CoT and MCoTS designs (described elsewhere

(McAdams *et al.*, 2018)), extend this logic to decompose variance in traits in both the mother and offspring generation.

The models can be used to divide variance in the parental exposure into additive genetic (A1), shared environmental (C1), and unique environmental (E1) components (Figure 1 and Figure 2a). As each mother can have up to two offspring in these models, any differences between those pregnancies are captured by the E1 parameter. Included in the model is also a freely estimated within-parent correlation parameter; rE_{wp}. This parameter will be estimated >0 if the phenotype correlates more strongly within the parent than between the parent and her twin or sibling.

Variance in the child outcomes can be separated into A2, C2 and E2 components (Figure 1 and 2a), that are not shared with the mother. To investigate mechanisms of transmission of risk, the covariance between the maternal and child phenotype is decomposed into a direct environmental exposure path (p) indexing direct environmental exposure, and a genetic path (A1'), indexing genetic transmission (Figure 1). The importance of the intergenerational parameters can be determined by looking at avuncular correlations, namely the correlations between aunts and their nephews or nieces. Offspring of MZ twins will share as much genetic material with their aunt as with their mother, whereas offspring of DZ twins will share 25% of their genetic material with their aunt. Further, it is assumed that offspring and their aunts share none of the family environment (C). Hence, if offspring resembles their mothers more than their aunts, this has to be due to environmental influences, and hence the p path must be >0. Likewise, if the offspring is correlated >0 with their aunt, genetic influences must play a role in this covariation and A1' >0. The genetic route of transmission is calculated by dividing the joint influence from all the genetic paths (a1 * 0.5 * a1') on the phenotypic correlation

between the mother and child phenotypes. The remaining part is accounted for by behavioral exposure (p).

Model fitting involves constructing one or several models that attempts to describe the data as closely but also as parsimonious as possible. A model can be simplified by dropping one or more parameters. The simpler model is often preferred if it does not fit the data significantly worse than the model where the parameter was retained.

We ran six MCoTS models on maternal depressive symptoms and concurrent child emotional and behavioral outcomes (two outcomes, each at three occasions). In addition, each of the six models included two nested submodels in which 1) the genetic transmission (A1'), or 2) direct environmental exposure (p) was dropped.The fit of these models were compared to the full model. We did not estimate the influence of shared environment (C) in the parent or child generation as separating genetic influences (A) from shared environmental influences (C) reliably in these models requires very large sample sizes. Also, the focus of this study was the intergenerational mode of transmission, rather than how much of the variance in the parent and child traits were explained by genetic versus environmental influences. We have included supplementary sensitivity analyses (Table S1 and Figure S1) where C was included to investigate whether the exclusion of C could have affected the estimates of A1' and p (the conclusions drawn from these models remained unchanged whether or not C was estimated). All models were fitted using full information maximum likelihood applied to raw data and compared using the chi-square distribution of the -2 log likelihood model fit statistic and Akaikes Information Criterion (AIC; Akaike, 1987). Child sex and maternal age where included as covariates.

To investigate whether the importance of direct environmental exposure changed over time, we fixed the p parameter post hoc to be identical to the estimate in the previous model, and checked for significant deterioration in fit. The full model at the same age period (with a freely estimated p parameter) was the reference for comparison. The modeling procedures were conducted in R, using the open source package OpenMx v2.3.1 (Neale *et al.*, 2016).

Results

Correlations were 0.17, 0.20, and 0.22 between maternal depressive symptoms and concurrent child emotional problems when children were 1.5, 3, and 5 years old, and 0.18, 0.17, and 0.21 for behavioral problems, respectively. The parameters for the two child outcomes are presented in a path diagram for a single mother-child dyad in Figure 2a, along with the parameter estimates from the best fitting models in Figure 2b.

For both outcomes at all three occasions, we found that neither the genetic nor the direct environmental route of transmission could be dropped without significant deterioration in model fit (Table 1). The best fitting model was therefore always the full model. For emotional problems, passive genetic transmission dominated when the children were 1.5 and 3 years old, explaining 69% and 62% of the correlations between the mother and child phenotypes, respectively. In terms of effect sizes, this means that of the total variance in child emotional problems, passive genetic transmission explained 21.1% at age 1.5 and 28.5% at age 3, whereas exposure to maternal symptoms through the direct transmission path (p) explained only 0.3% at age 1.5 and 0.6% at age 3. At age 5, however, the pattern appeared to change in favor of direct environmental exposure, accounting for 67% of the correlation (but only 2.2% of the variation in child emotional problems). For the second outcome, child behavioral problems, the association between mother and child was equally attributable to genetic

transmission (51%) and direct environmental exposure (49%) at age 1.5 years (effect sizes on child phenotype were 14.2% and 0.8%, respectively). At age 3, the genetic transmission accounted for 63% of the total correlation, and direct environmental exposure explained 37% (29.3% and 0.4% of the variation in the child phenotype, respectively). At age 5, the genetic transmission explained 46% of the total correlation, and the direct exposure path 54% (19.7% and 1.3% of the child phenotype, respectively). The effect sizes, or the extent to which genetic and environmental influences included in the best fitting models could explain variance in the child outcomes is summarized in Table S2, whereas the relative importance of genetic transmission versus direct environmental exposure for explaining the total correlation between mother and offspring is indexed in Figure 3.

To clarify whether direct environmental exposure becomes more important as the children grow older, we fixed the p path to be the same value as it was estimated to be at a previous developmental period. The reference models were the full models at age 3 and 5, of which fit statistics are presented in Table 1. For emotional problems, the direct transmission (i.e. p path) was not significantly different at child age 1.5 (0.06, 95% CI: 0.04, 0.08) and 3 years (0.08 [0.05, 0.10]; $\Delta\chi^2 = 2.25$, $\Delta df = 1$, $\Delta AIC = 0.25$). However, there was a significant deterioration in fit when fixing the p at age 5 (0.15 [0.11, 0.19]) to the same value as at age 1.5 ($\Delta\chi^2 = 27.3$, $\Delta df = 1$, $\Delta AIC = 25.3$) and at age 3 ($\Delta\chi^2 = 16.99$, $\Delta df = 1$, $\Delta AIC = 14.99$). The direct transmission of risk was therefore stronger at age 5 compared to age 1.5 and 3. Likewise, for behavioral problems, fixing the p path at age 3 (0.06 [0.04, 0.09]) to the same value as at age 1.5 (0.09 [0.07, 0.11]) did not result in a significantly worse fit ($\Delta\chi^2 = 3.5$, $\Delta df = 1$, $\Delta AIC = 1.47$). Nor did fixing the p path at age 5 (0.11 [0.08, 0.15]) to the same estimate as at age 1.5 ($\Delta\chi^2 = 2.64$, $\Delta df = 1$, $\Delta AIC = 0.64$). There was, however, a difference in the importance of the p path from age 3 to age 5 ($\Delta\chi^2 = 9.19$, $\Delta df = 1$, $\Delta AIC = 7.19$). Overall, the

evidence for developmental change was therefore less compelling for behavioral than for emotional problems.

Discussion

The main goal of our study was to investigate mechanisms underlying the association between maternal depressive symptoms and early life offspring psychopathology. We found that children of mothers with more depressive symptoms are at increased risk for emotional and behavioral symptoms both through a shared genetic liability with their mothers, and through direct environmental exposure. However, the relative importance of each was not the same across the two outcomes, nor were they always the same at different ages.

Many studies have found associations between maternal depression and psychopathology in offspring (Goodman *et al.*, 2011, Netsi *et al.*, 2018), but few have utilized designs that can parcel out and quantify the importance of familial confounding from these associations (Kendler *et al.*, 2018, McAdams *et al.*, 2015, Silberg *et al.*, 2010, Singh *et al.*, 2011). Using an extended version of the CoT design (McAdams *et al.*, 2018), applied to data at three age periods, our study is the first to quantify the contribution from two different routes of transmission of risk from maternal depressive symptoms to offspring concurrent early life psychopathology.

For emotional problems, the association with maternal depressive symptoms was primarily explained by genetic transmission at age 1.5 and 3, but by age 5, direct environmental exposure explained two thirds of the association. That the mother-child association was environmental, and not merely a consequence of familial confounding stemming from shared genes is in line with the finding from a previous paper by our group that utilized a sibling

comparison approach (Gjerde *et al.*, 2017), and also with previous CoT studies (McAdams *et al.*, 2015, Silberg *et al.*, 2010, Singh *et al.*, 2011). Although our study cannot conclude why direct environmental exposure appears to become more important over time, we can think of several possible explanations. As children grow older and their ability to think about other people's thoughts and feelings (theory of mind) becomes more sophisticated (Wellman *et al.*, 2001), they may become more affected by their mother's depressive symptoms. Five year olds may also demand a different type of attention, which could be disturbed by depressive symptoms. Further, five year olds have been exposed to their mother's depressive symptoms longer. Research on cumulative exposure suggest that the persistency of maternal depressive symptoms is associated with increased risk for psychopathology (Netsi *et al.*, 2018). Although we have modeled the hypothesis that the effect goes from the mother to the offspring, we cannot exclude the possibility that the association is child driven; i.e. that an emotional child could elicit depressive symptoms in a mother.

For behavioral problems, there was no net increase in the importance of direct environmental exposure across occasions, and the importance of each source of intergenerational association was more similar than for emotional problems. Previous CoT studies of externalizing outcomes on teenage children of depressed mothers also present a mixed picture. One study finds evidence for both routes of transmission, a second finds evidence for intergenerationally shared genetic factors (Singh *et al.*, 2011) and a third for direct environmental exposure (McAdams *et al.*, 2015). Overall, ours and previous findings indicate the importance of both family environment and genetic transmission in understanding the links between maternal depression and offspring behavior problems.

The U.S. Preventive Task Force have recommended screening for depression in all pregnant women (Siu and USPST, 2016). However, as indicated by the present study and others (Gjerde *et al.*, 2017, Netsi *et al.*, 2018), depression in mothers when children are in preschool age can negatively affect children's mental health. It is therefore reasonable to discuss whether this recommendation should be extended to also include screening of mothers in the first few years after pregnancy, as suggested in a recent editorial in JAMA Psychiatry (Weissman, 2018).

Some limitations need mentioning. First, shared method variance (mothers reporting on both their own and their children's symptoms) may have artificially increased associations between symptoms in mothers and their children. A meta-analysis found that A meta-analysis found that the discrepancy between the mother-offspring correlations when teachers were the raters of the child outcomes versus when the mothers were the raters was 0.1 for internalizing problems and 0.09 for externalizing problems, or 40% for both outcomes (Goodman *et al.*, 2011). To date, true effects cannot be disentangled from the effect of shared method variance in MoBa, but efforts are being made to collect data to do so in the future. We can therefore only speculate on what consequences the findings from this meta-analysis may have for the estimates presented in the present study. Four possible scenarios stand out: 1) If the difference in correlations between maternal symptoms and child symptoms between teachers and mothers is entirely due to depressed mothers overrating their children's symptoms because of the depression, we would expect that the bias will go into the estimate of direct environmental transmission (p). Our estimate of p would under this scenario be artificially high. 2) It is also possible that the discrepancy between the teacher rating and mother rating is due to a rating bias tendency that is inherent in mothers' personality. If this tendency is not heritable, the bias would also upwardly bias the estimate of the p parameter. 3) However, if this rating bias

tendency is heritable, as almost all human behavioral traits are (Polderman *et al.*, 2015), this will upwardly bias the estimate of the passive genetic transmission (a1'). 4) The bias could also come from the child's behavior. Having a depressed mother could make the child act differently at home, but not at school. A scenario like this would also imply that our p estimate is too high. On the positive side, an alternative explanation to these scenarios is that the discrepancy in ratings could simply be due to the fact that mothers see their children in more settings, making their assessments of their children more valid than that of the teachers. Second, we have made the assumption that the environmental mode of transmission moves from mothers to their children. However, it is not implausible that the transmission moves both ways, or that it is offspring behavior that influences maternal symptoms. For instance, it is easy to imagine that fussy or difficult children could induce feelings of hopelessness or other depressive symptoms in their parents. Third, due to limited statistical power, we could not investigate potential sex differences in mechanisms of transmission of risk. However, such differences are not unlikely, as there are evidence that boys and girls differ in their susceptibility to negative consequences of maternal depressive symptoms, both when the exposure happen prenatally (Sandman *et al.*, 2013) and postnatally (McGinnis *et al.*, 2015, Quarini *et al.*, 2016). Fourth, it is possible that the associations between maternal depressive symptoms and child emotional and behavioral problems could be partly explained by various prenatal influences, such as maternal prenatal depressive symptoms (Barker *et al.*, 2011, Kerr *et al.*, 2013) or obstetric complications (Kerr *et al.*, 2013). However, associations between prenatal maternal depressive symptoms and child emotional and behavioral problems are found to be genetically confounded (Gjerde *et al.*, 2018, Hannigan *et al.*, 2018), and the genetics of depressive symptoms is rather stable (Nes *et al.*, 2007). We can therefore assume that most of the potential prenatal influence is controlled for by the postnatal depressive symptoms included in the present study. However, future studies should strive to include

prenatal factors such as obstetric complications as potential confounders. Fifth, the significant attrition in MoBa could have yielded a sample in which severely depressed mothers are under-represented. The possibility therefore remains that mechanisms of transmission are qualitatively different in severely depressed mothers, and this should be tested in clinical samples.

Conclusion

Children of mothers with depressive symptoms have more early life psychopathology symptoms than can be expected from passive genetic transmission alone. Although our results suggest that treating depressive symptoms in mothers could decrease their children's risk for developing symptoms of psychopathology, the non-negligible genetic transmission implies that children of mothers with depressive symptoms would also be at risk even if they had grown up in an environment free of depressive symptoms.

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Declaration of interests

The authors declare no conflicts of interests.

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Table 1

Model fit statistics for each age within the two outcomes

Model	-2LL	ep	AIC	df	ΔLL	p
1. Emotional problems 1.5 years						
1.1 Full model	**134066.65**	**21**	**36590.65**	**48738**	**-**	**-**
1.2 Direct transmission only	134158.42	20	36680.42	48739	91.77	<0.001
1.3 Genetic transmission only	134093.32	20	36615.32	48739	26.67	<0.001
2. Emotional problems 3 years						
2.1 Full model	**110113.29**	**21**	**30121.29**	**39996**	**-**	**-**
2.2 Direct transmission only	110219.19	20	30225.19	39997	105.90	<0.001
2.3 Genetic transmission only	110150.93	20	30156.93	39997	37.65	<0.001
3. Emotional problems 5 years						
3.1 Full model	**79187.48**	**21**	**21847.48**	**28670**	**-**	**-**
3.2 Direct transmission only	79199.86	20	21857.86	28671	12.38	<0.001
3.3 Genetic transmission only	79262.05	20	21920.05	28671	74.57	<0.001
4. Behavioral problems 1.5 years						
4.1 Full model	**136072.93**	**21**	**36676.93**	**49698**	**-**	**-**
4.2 Direct transmission only	136133.16	20	36735.16	49699	60.23	<0.001
4.3 Genetic transmission only	136141.52	20	36743.52	49699	68.59	<0.001
5. Behavioral problems 3 years						
5.1 Full model	**110078.15**	**21**	**30084.15**	**39997**	**-**	**-**
5.2 Direct transmission only	110162.25	20	30166.25	39998	84.10	<0.001
5.3 Genetic transmission only	110104.37	20	30108.37	39998	26.22	<0.001
6. Behavioral problems 5 years						
6.1 Full model	**79032.73**	**21**	**21692.73**	**28670**	**-**	**-**
6.2 Direct transmission only	79062.77	20	21720.77	28671	30.04	<0.001
6.3 Genetic transmission only	79079.75	20	21737.75	28671	47.02	<0.001

578 Model comparisons for the two outcomes (emotional and behavioral problems), each at three separate age periods. For each model, the fit of the reduced version of the model,
579 where either the genetic intergenerational path, or the environmental intergenerational path is dropped, is compared to the full model where all these parameters are retained.
580 Best fitting models are shown in bold. -2LL = two times the negative log likelihood – an estimate of how well the model fits the data ; ep = number of estimated parameters
581 included in the model; AIC = Akaike's Information Criterion – an indicator of how well the model fits the data that also penalizes complex models; df = degrees of freedom;
582 ΔLL = the difference in log likelihood compared to the full model; p = probability value for rejecting the null hypothesis

Figure legends

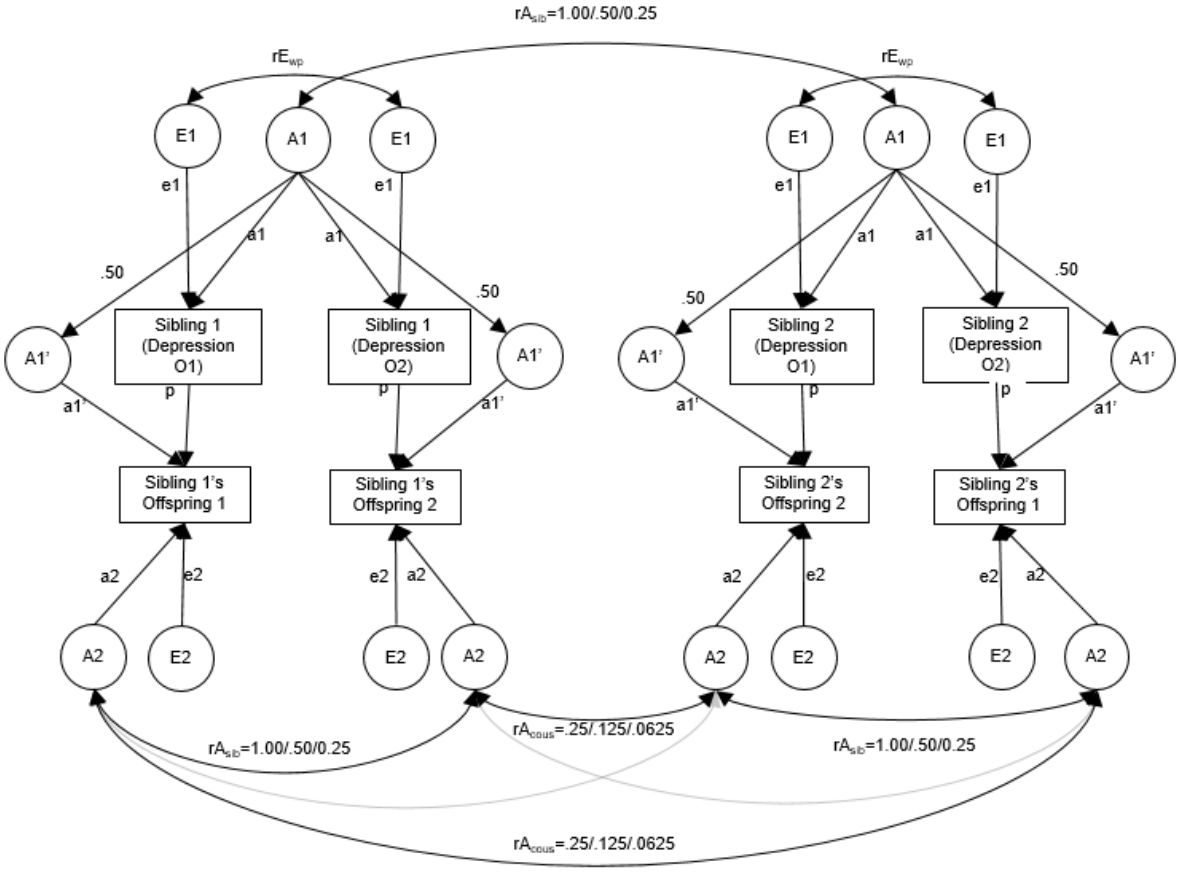
Figure 1: Path diagram of the full multiple children of twins and siblings structural equation model

Figure 2a: Parameters

Figure 2b) Estimated parameters from best fitting models

Figure 3: Correlations between mother and child explained by genetic vs direct environmental transmission

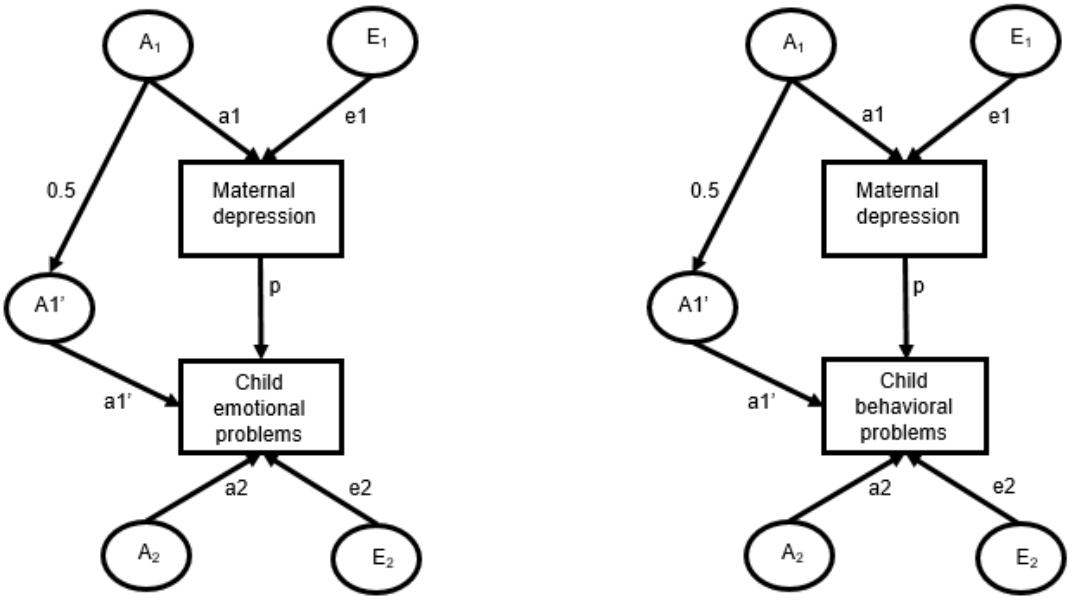
Figure 1. Path diagram of the full multiple children of twins and siblings structural equation model



Path diagram showing the structural equation model where the traits (depressive symptoms) of a mother and her sister/twin is included in the top half, and the traits (emotional or behavioral problems) of up to two offspring per mother is included in the bottom half. rEwp = within-person correlation between maternal unique environmental factors. This parameter will be estimated >0 if the phenotype correlates more strongly within the parent than between the parent and her twin or sibling; rAsib = genetic correlation between mother twins/sisters/half-sisters (A1 to A1) and offspring twins/siblings (A2 to A2); rAcous = genetic correlation between offspring cousins, which vary depending on offspring having mothers that are twins/sisters/half-sisters; A1/a1 = maternal genetic factors (A1 = variance component, a1 = path); E1/e1 = maternal unique environmental factors; A2/a2 = offspring specific genetic factors; A1'/a1' = offspring genetic factors shared with A1. This parameter will be estimated >0 if offspring correlate >0 with their aunt, and indicate that genes influencing the parental trait also influences the offspring trait. Hence, mothers transmit risk genes to their offspring during meiosis; E2/e2 = offspring unique environmental factors; p = behavioral exposure path. This parameter will be estimated >0 if offspring correlate higher with their mothers than with their aunts, and indicate that social mechanisms or other environmental influences contribute to risk for offspring behavioral or emotional problems.

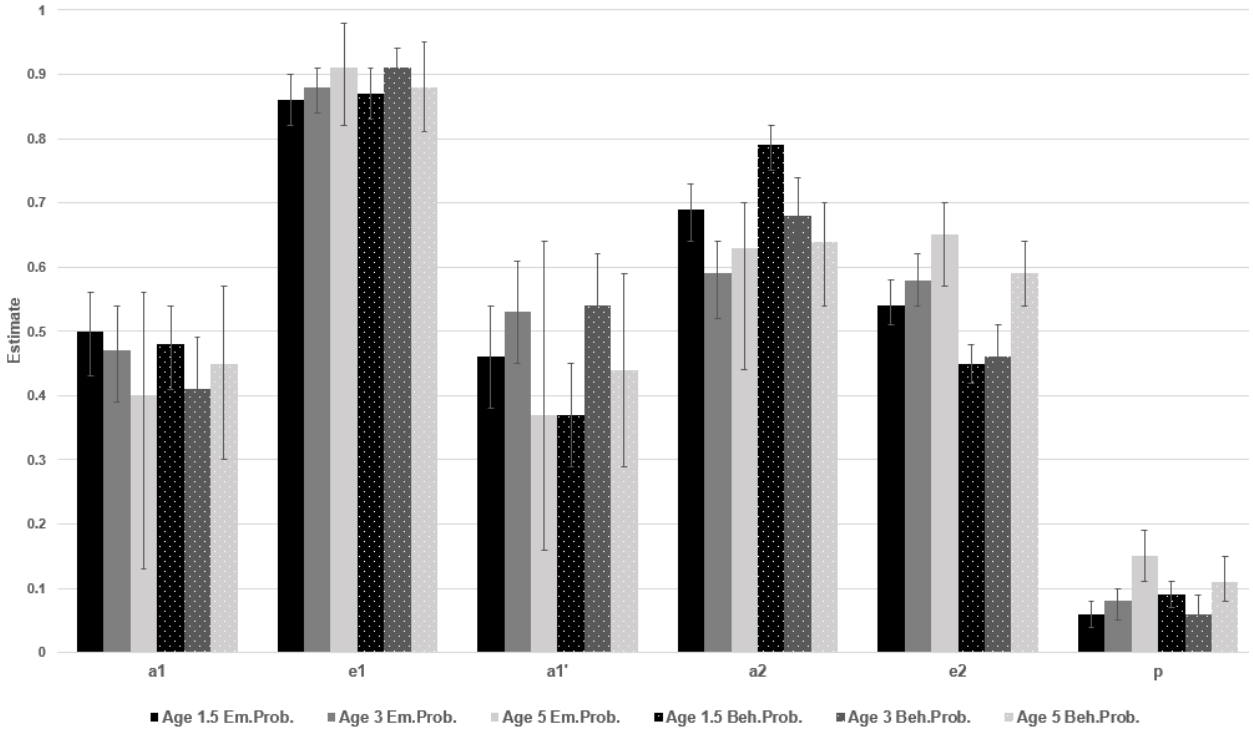
Figure 2. Parameters

a)



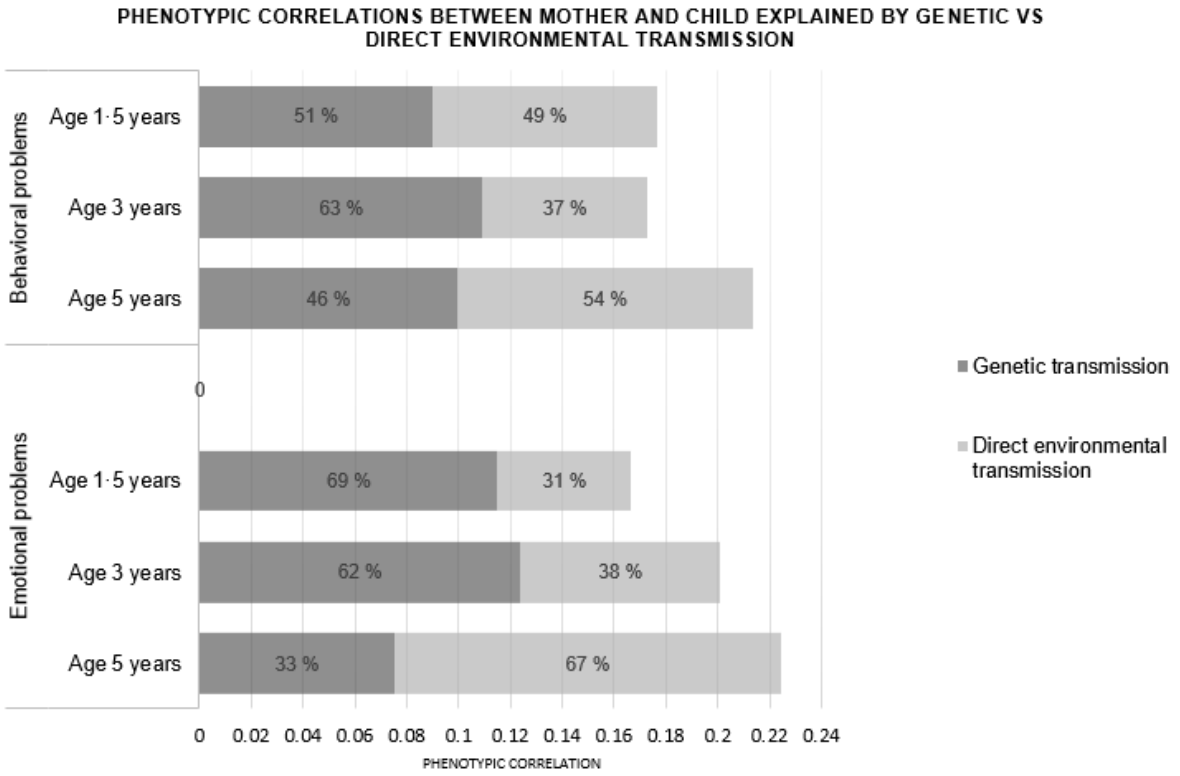
Simplified path diagram showing the main parameters to be estimated for each model. The parameters a1 and e1 inform on the causes of individual differences in maternal depressive symptoms, a2 and e2 on the causes of individual differences in child emotional and behavioral problems, and a1' and p on the mechanisms of intergenerational transmission of risk.

b) Estimated parameters from best fitting models



Bar chart showing the magnitude of the parameter estimates with 95% confidence intervals from the best fitting models across each time-point (1.5, 3, and 5 years after birth) and phenotypes (offspring emotional and behavioral problems).

Figure 3. Correlations between mother and child explained by genetic vs direct environmental transmission



Supplementary contents

eAppendix1: Description of how zygosity was determined for MoBa participants and their children

We determined genetic relatedness between participants from kinship information in Statistics Norway for mothers, and from kinship information in MoBa for offspring. Zygosity (whether twins are monozygotic or dizygotic) for the parent generation was determined using linkage with the Norwegian Twin Registry, as well as questionnaire items administered by phone or mail. These questionnaire items have been shown to classify correctly more than 97% of twin pairs (Magnus *et al.*, 1983). For the offspring generation, maternal reports on zygosity were obtained using questionnaire items administered by phone or mail, and a sub-group of the same-sex offspring twins was also genotyped. A logistic regression model, regressing genotype classifications on the questionnaire items was fit to the twin pairs having both measurements. The fitted model was then used to classify the twin pairs that had not been genotyped, based on the questionnaire responses. The discrepancy between classification by questionnaire and genotyping had an expected misclassification rate of <4% in our sample.

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Table S1

Path estimates for the best fitting models when C was included

	A1	**C1**	**E1**	**A2**	**A1'**	**C2**	**E2**	**p**
Emotional problems age 1.5	0.50	0	0.86	0.69	0.46	0	0.54	0.06
Emotional problems age 3	0.43	0	0.89	0	0.66	0.39	0.61	0.06
Emotional problems age 5	0.40	0	0.91	0.63	0.37	0	0.65	0.15
Behavioral problems age 1.5	0.48	0	0.87	0.79	0.37	0	0.45	0.09
Behavioral problems age 3	0.41	0	0.91	0.68	0.54	0	0.46	0.06
Behavioral problems age 5	0.45	0	0.88	0.64	0.44	0	0.59	0.15

Table S2

Proportions of the variance in the child phenotypes explained by the variance sources included in the best fitting models

	Genetic		Environmental		
	Shared with maternal phenotype ($a1'^2$)	**Unique to child phenotype (a^2)**	**Unique to child (e^2)**	**Direct transmission (p^2)**	**Passive rGE (maternally transmitted genes and environment)**
Child emotional problems at age 1.5 years	21.1%	47.7%	29.5%	0.3%	1.4%
Child emotional problems at age 3 years	28.5%	34.9%	34.1%	0.6%	1.9%
Child emotional problems at age 5 years	14.0%	39.4%	42.1%	2.2%	2.2%
Child behavioural problems at age 1.5 years	14.2%	63.0%	20.5%	0.8%	1.6%
Child behavioural problems at age 3 years	29.3%	47.2%	21.7%	0.4%	1.4%
Child behavioural problems at age 5 years	19.7%	41.3%	35.4%	1.3%	2.3%

Figure S1.

Phenotypic correlations between mother and child explained by genetic vs direct environmental transmission