MATERNAL PERINATAL AND CONCURRENT ANXIETY AND MENTAL HEALTH PROBLEMS IN EARLY CHILDHOOD: A SIBLING-COMPARISON STUDY

Running head: Maternal anxiety and child mental health problems

ABSTRACT

Do associations between maternal anxiety symptoms and offspring mental health remain after comparing differentially exposed siblings? Participants were 17,724 offspring siblings and 11,553 mothers from the Norwegian Mother and Child Cohort study. Mothers reported anxiety and depressive symptoms at 30 weeks' gestation, and 0.5, 1.5, 3 and 5 years postpartum. Child internalizing and externalizing problems were assessed at ages 1.5, 3 and 5, and modelled using multilevel analyses with repeated measures nested within siblings, nested within mothers. Maternal pre- and postnatal anxiety were no longer associated with child internalizing or externalizing problems after adjusting for maternal depression and familial confounding. Maternal anxiety when the children were in preschool age, however, remained significantly associated with child internalizing, but not externalizing problems.

Anxiety disorders and symptoms of anxiety are common during and after pregnancy (Lee et al., 2007; Ross & McLean, 2006). In addition to exerting a negative impact on the mothers, maternal anxiety in both the prenatal and postpartum periods is associated with child mental health problems (Glasheen, Richardson, & Fabio, 2010; Graignic-Philippe, Dayan, Chokron, Jacquet, & Tordjman, 2014; Stein et al., 2014; Talge, Neal, Glover, & Early Stress Transnational Res, 2007). These associations are evident both in large studies where brief questionnaires and parent report are often used, and in smaller studies that have relied on more detailed measures of mother and child (e.g. Davis et al., 2004; Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002). Mental health problems in children are often divided into an internalizing and externalizing spectrum (Achenbach, 1966), and are associated with an increased risk for mental disorders in adulthood (Hofstra, van der Ende, & Verhulst, 2002). Findings are mixed on whether exposure to maternal anxiety is associated with child internalizing or externalizing problems or both (Barker, Jaffee, Uher, & Maughan, 2011; O'Connor, Heron, Glover, & Alspac Study Team, 2002; Van Batenburg-Eddes et al., 2013). For optimal prevention, it is crucial to establish a clearer picture on whether the association between maternal anxiety and child mental health problems is due to different types of confounding, and at what age the child is most vulnerable to this exposure. For these purposes, large, prospective studies have been recommended (Glasheen et al., 2010).

Different mechanisms are likely to explain negative child outcomes when the exposure to maternal anxiety is prenatal compared to postpartum. Several possible prenatal mechanisms have been reviewed, including the role of the HPA axis and cortisol, compromised placental functioning, maternal immune system and relevant health behaviors (Beijers, Buitelaar, & de Weerth, 2014; Glover, O'Connor, & O'Donnell, 2010; Graignic-Philippe et al., 2014). The evidence for the involvement of the HPA axis and cortisol in child behavioral outcomes is weak, particularly when maternal anxiety is self-reported (Beijers et al., 2014). Findings from

a large number of animal and human studies point to epigenetics, in which the expression of genes is altered, as a central piece of the puzzle of prenatal mechanisms. More specifically, epigenetic regulation of the genome (particularly DNA methylation of immune function and the placenta and brain) has been suggested to mediate associations between prenatal maternal stress and negative behavioral outcomes in children (Appleton et al., 2013; Babenko, Kovalchuk, & Metz, 2015; Cao-Lei, Laplante, & King, 2016; Mitchell, Schneper, & Notterman, 2015; Monk, Spicer, & Champagne, 2012). The importance of epigenetic factors has been affirmed in studies that include natural disasters, such as Project Ice Storm (King, Dancause, Turcotte-Tremblay, Veru, & Laplante, 2012). Natural disasters can be used as natural experiments, where one advantage is the possibility to disentangle mothers' subjective distress from an objective exposure.

After birth, maternal anxiety may affect the offspring negatively through environmental processes. Possible mechanisms are disruption of mother-child interactions and attachment (Glasheen et al., 2010) or quality of parenting (Stein et al., 2014). The importance of cumulative exposure has also been highlighted, as it is associated with increased risk for negative outcomes in the children (Stein et al., 2014). Epigenetic mechanisms may also be at play in postpartum interactions between mother and child (Monk et al., 2012).

Furthermore, both prenatal and postpartum associations may be due to residual confounding from factors shared between mother and child. Genes represent an important source of confounding, as mother and child share 50% of their genome, and adult anxiety and child internalizing and externalizing problems are heritable . It is likely that at least some of the maternal genetic predisposition to anxiety is overlapping with the child's genetic predisposition to internalizing or externalizing symptoms. This can create spurious associations that can be erroneously interpreted as a causal influence of the exposure to maternal anxiety. It is intuitive that there should be some degree of overlap in the genetic

variance for maternal internalizing disorders and child internalizing symptoms. However, empirical studies find evidence to the contrary, both when the maternal phenotypes are anxiety (Eley et al., 2015) and depression (Silberg, Maes, & Eaves, 2010; Singh et al., 2011). Less intuitive is the genetic link between maternal internalizing disorders and child externalizing disorders, but partial genetic overlap has been found when the maternal phenotype is depression (Silberg et al., 2010; Singh et al., 2011), indicating pleiotropy. The genetic overlap in anxiety and depressive disorders is high (Kendler, 1996). There is also evidence of a moderate genetic overlap in anxiety and conduct problems in children (Gregory, Eley, & Plomin, 2004). Hence, it is reasonable to assume that a genetic overlap is also possible between maternal anxiety and child externalizing symptoms.

Exposure to maternal anxiety both during pregnancy and after birth needs to be considered together in order to evaluate whether the child's vulnerability to the exposure is particularly high during different developmental periods. Several studies that report an influence of maternal perinatal anxiety and child mental health problems have not controlled for maternal anxiety during the child's infancy and childhood (e.g. Loomans et al., 2011). Studies that do control for maternal anxiety after birth, however, often find that the association between prenatal anxiety and child mental health problems is no longer significant (e.g. Van Batenburg-Eddes et al., 2013). Adjusting for depression is also important, as anxiety disorders and depression are highly comorbid conditions (Kessler et al., 1994). Because anxiety and depression can require different therapeutic approaches (e.g. exposure versus cognitive or psychodynamic therapy), knowledge on disorder-specific contributions is necessary for providing adequate treatment of the mother, which, in the longer run, may improve child mental health. Only a handful of studies have included large samples, a prospective, longitudinal design, both prenatal and postpartum anxiety as well as measures of depression (Barker et al., 2011; O'Connor et al., 2002; Van Batenburg-Eddes et al., 2013).

These studies all find associations between perinatal anxiety and various child mental health outcomes, but are limited by the lack of genetically informative data to adjust for unmeasured familial confounding, the lack of measures of later maternal anxiety, and the narrow age span (3-4 years or 7-8 years) of the children included. In addition, these studies are limited to two cohorts: the Avon Longitudinal Study of Parents and Children (Barker et al., 2011; O'Connor et al., 2002; Van Batenburg-Eddes et al., 2013) and Generation R (Van Batenburg-Eddes et al., 2013). It is therefore not given that results are generalizable to other populations.

It is impractical let alone unethical to conduct a randomized controlled trial on maternal anxiety and child outcomes. Comparison of differentially exposed siblings is a well-established quasi-experimental design for ruling out important sources of confounding (Keyes, Smith, & Susser, 2013; Lahey & D'Onofrio, 2010). The sibling comparison design has for example contributed substantially to our understanding of harmful consequences of maternal smoking during pregnancy on offspring health. The comparison of siblings of mothers who smoked during one pregnancy but not the other controls for many familial confounds, thus providing a far more stringent test of association than most other research designs. With this method it has been shown that smoking is systematically linked to lower birth weight in the offspring, but does not appear to influence the offspring's risk for mental health problems (Gustavson et al., 2017; Kuja-Halkola, D'Onofrio, Larsson, & Lichtenstein, 2014; Lahey & D'Onofrio, 2010).

In contrast to other genetically informative designs such as the classical twin study (Martin & Eaves, 1977), the sibling comparison design cannot quantify the contribution of genetic and environmental influences on the study variables. It can however, rule out confounding due to genes inherited from the mother that contributes to both the maternal and child behavior, even though mother and child share only 50% of their genes. This is because parental alleles are randomly distributed across siblings. For example, if a mother experienced

anxiety during one pregnancy but not the other, both offspring would be equally likely to receive maternal alleles associated with perinatal anxiety, even if only one of them was directly exposed (Lahey & D'Onofrio, 2010). The sibling comparison design also rules out unmeasured confounding in situations where associations between mother and child phenotypes are attributable to environmental influences shared by siblings (Lahey & D'Onofrio, 2010). Examples include socioeconomic status and neighborhood effects.

The design cannot rule out confounding due to child behavior influencing maternal behavior (which could also happen during pregnancy), and it does not rule out confounding due to environmental confounds that are not shared by siblings (Lahey & D'Onofrio, 2010). For instance, child temperament could influence maternal levels of stress, or the increased size of the household following the birth of a new sibling could influence stress levels in both mothers and children.

Of the few studies utilizing genetically informative designs, most have reported that associations between maternal anxiety and offspring mental health problems remain after accounting for the genetic relatedness of mother and child. This has been found with regards to maternal anxiety and adolescent offspring anxiety in a children-of-twins study (Eley et al., 2015), postpartum maternal anxiety and toddler negative affect in an adoptive sample (Brooker et al., 2015), and maternal prenatal stress and mid-childhood antisocial behavior and anxiety in an in vitro sample (Rice et al., 2010). However, a notable exception was recently found in a Norwegian prospective study, also using MoBa data (described below). The authors concluded that exposure to maternal prenatal anxiety was not associated with child internalizing symptoms in 6 and 36 months old children after sibling comparison (Bekkhus et al., 2017). The study did however not include measures of externalizing symptoms in the children, nor adjust for maternal depressive symptoms or concurrently measured maternal anxiety symptoms. We are aware of only two other genetically informed studies that have

152 investigated perinatal maternal anxiety or stress (Brooker et al., 2015; Rice et al., 2010), and
153 only one of these included both prenatal and later measures of the maternal predictor (Rice et
154 al., 2010). Adjusting for later maternal stress, the association between prenatal stress and child
155 anxiety disappeared, whereas the association with child antisocial behavior remained (Rice et
156 al., 2010). Additional limitations of these studies include the use of a cross-sectional design
157 (Eley et al., 2015; Rice et al., 2010) and retrospective measures (Rice et al., 2010). None of
158 these studies investigated the development of problems in the important period spanning from
159 toddlerhood to school age. In sum, no previous studies have had a sufficient design for
160 establishing associations between mother's anxiety in the prenatal, postpartum and/or
161 preschool period and preschool children's internalizing or externalizing problems after
162 accounting for familial confounding.
163 In a recent study (Gjerde et al., 2017), associations between perinatal depression and
164 preschool offspring's internalizing and externalizing problems were found to be due to
165 unmeasured confounding in a genetically informative and prospective cohort sample. Using
166 the same cohort and design, we investigate i) associations between maternal anxiety
167 symptoms at several different periods during and after pregnancy and preschool offspring's
168 internalizing and externalizing problems, ii) whether these associations remain after two types
169 of control: measured covariates including depressive symptoms, and sibling comparison, and
170 iii) whether associations change with child age.
171
172 METHOD
173 **Sample**
174 The present study is part of a subproject of the Norwegian Mother and Child Cohort Study
175 (MoBa), conducted by the Norwegian Institute of Public Health (NIPH). MoBa is a
176 prospective, ongoing, pregnancy cohort study, and has been described in detail elsewhere

(Magnus et al., 2016). Participants were recruited from 1999 to 2009 at a routine ultrasound examination offered to all pregnant women in Norway at 17-18 weeks' gestation. The total sample now includes >114,500 children, >95,000 mothers and >75,000 fathers. In total, 41% of eligible women participated. The current study was restricted to families with more than one birth record in MoBa. Missing data were allowed on the time-variant variables, but not on the time-invariant variables resulting in 40,457 observations nested within 17,724 siblings from 11,553 mothers (of which 5,623, 5,691, 237 and two mothers had one, two, three, or four children, respectively).

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 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. In the current study we used information obtained at 30 weeks gestation, 0.5 years postpartum, and 1.5, 3 and 5 years postpartum. We will refer to these as the prenatal (gestation week 30), postpartum (0.5 years after birth) and concurrent (1.5, 3 and 5 years after birth) periods.

Measures

Maternal anxiety and depressive symptoms were each assessed using a short form of the Symptom Checklist (SCL; Derogatis, Lipman, Rickels, Uhlenluth, & Covi, 1974). The short form is the eight item SCL-8, that have been validated and thoroughly described elsewhere (Tambs & Røysamb, 2014). This is an abbreviated form of the short form SCL-25, that was constructed to measure symptoms of anxiety and depression (Hesbacher, Rickels, Morris, Newman, & Rosenfeld, 1980). A recommended cutoff for detecting caseness in SCL-25 is 1.75 (Sandanger et al., 1999), and 2.0 for SCL-5 (Strand, Dalgard, Tambs, & Rognerud, 2003). Within the MoBa questionnaires, the same SCL-8 measure was available in the

questionnaire issued from 30 weeks gestation and onwards. Participants rated to what extent a set of statements, covering the last two weeks of their life, are true on a 1 to 4 scale (1 = "not at all bothered", 4 = quite a bit bothered"). In order to assess anxiety and depressive symptoms separately, we divided the SCL-8 scale into the four items intended to measure anxiety ("Feeling fearful"; "Nervousness or shakiness inside"; "Suddenly scared for no reason"; "Feeling tense or keyed up") and the four items intended to measure depression ("Worrying too much about things"; "Feeling blue"; "Feeling helpless about the future"; "Feeling everything is an effort"), respectively (Tambs & Røysamb, 2014). We further created mean scores for each period separately, leaving us with three predictor variables reflecting mothers' anxiety symptom levels at each period: one for prenatal (gestation week 30), one for postpartum (0.5 years after birth) and one for concurrent anxiety (when the children were 1.5, 3 and 5 years old). The depression variables for each period were used as covariates. Internal consistency estimated by Cronbach's alpha for the anxiety items in our sample were 0.70 for the prenatal measure, 0.71 for the postpartum measure, and 0.72, 0.76 and 0.73 for the concurrent measures. The sum of the four anxiety items in SCL-8 have been found to correlate 0.90 with the anxiety score in SCL-25 (Tambs & Røysamb, 2014). Maternal concurrent anxiety can vary across child age, whereas the values for the prenatal and postpartum predictors, measured before the children were 1.5 years old, are repeated within a child across the last three time-points and are thus time-invariant (see Table 1 for specifications of variable levels).

The outcomes were child internalizing and externalizing problems at child ages 1.5, 3 and 5, measured with items from the Child Behavior Checklist preschool version (CBCL; Achenbach, 1992). Mothers reported agreement on a three-point Likert scale for each item. There were a total of 13 internalizing and 11 externalizing items. The items were selected by a team of psychologists based on clinical expertise, theory and factor loadings on internalizing

and externalizing behavior. The internalizing short scale has been found to correlate .71, .79 and .87 with the full CBCL internalizing scale at ages 1.5, 3 and 5 years, respectively (Helland, Røysamb, Wang, & Gustavson, 2017). As for time-varying concurrent maternal anxiety, internalizing and externalizing problems from the measures at age 1.5 to 5 were each represented by one time-variant variable. To capture more information and thereby reduce the influence of measurement error, we estimated factor scores based on an item response theory (IRT) analysis with a nominal response model instead of using sum scores. Unlike in classical test theory (CTT), where it is assumed that all categories in an item indexes performance equally well, IRT focuses on the performance of each item in a scale (Reise & Revicki, 2014). The reliability of an IRT score can therefore vary across each latent score of the measured construct. We calculated the average reliability of the IRT scores using the following formula: 1-mean($S.E._{measurement}$)^2. The average reliability of the two IRT scores was 0.48 and 0.71 for the internalizing and externalizing measure, respectively. As can be seen in Figure 1a and Figure 1b, the reliability was highest in the clinical range of the outcome variables. The resulting internalizing and externalizing factor scores were transformed to have a mean of 50, and a standard deviation of 10, and are thus interpreted as T-scores.

Covariates were child age and sex, and maternal depressive symptoms, parity, and education. Child age (i.e. the time variable of the growth curves) was centered to 5 years, and added in order to model change in child symptom levels as a function of child age. Child sex, coded as 0 = “boy” and 1 = “girl”, was included as associations may vary for boys and girls. Maternal parity and education were included as these have previously been shown to be associated with similar outcomes in children with anxious mothers (Petzoldt, Wittchen, Einsle, & Martini, 2016). Parity was coded as 0 = ”first birth” through 4 = ”four or more previous births”. Education, coded as 1 = ”9-year secondary school” through 6 = ”University,

technical college, >4 years", was defined for the parent with the highest achieved level of education at 17 weeks gestation.

Figure 1a and 1b here

Statistical analyses

The included data had a three-level structure, where responses at age 1.5, 3 and 5 years (level 1) were nested in siblings (level 2) nested in mothers (Table 1). We used linear multilevel models to account for dependency across siblings within mothers (level 3) and across tests within children (level 2) by estimating between-mother and between-sibling differences through the inclusion of random effects (Rabe-Hesketh & Skrondal, 2012). Maximum likelihood, assuming data were missing at random, was used as estimator in Stata 14 (StataCorp, 2015). Analyses included a random intercept that estimates between-variance at the sibling and mother level, and a random slope for age at the mother level that estimates variation in associations between the predictors and outcome as a function of child age across mothers. Age was added as a random slope instead of time, as we had exact measures of age on the children. Figure 2 provides an illustration of the basic model used.

Table 1 here

Figure 2 here

Is maternal anxiety at different developmental stages associated with child internalizing and externalizing problems?

To investigate whether maternal anxiety was associated with child internalizing and externalizing problems we first ran a set of models where only one predictor was included for each outcome separately, adjusted for covariates (referred to as Model 0). Predictors without interpretable zero points were centered on their means to obtain meaningful intercepts (Hox, 2010). As we included separate predictors for the prenatal (gestational week week 30), postpartum (0.5 years) and concurrent (1.5, 3 and 5 years) period, a total of three models were each run for child internalizing and externalizing problems separately. Interactions between each anxiety predictor and child age were also included in the models, in order to allow for differential associations of anxiety with child symptom levels as a linear function of child development. A positive interaction would imply that the association between the predictor and outcome becomes stronger over child age, whereas a negative interaction would imply that the association becomes weaker.

Adjusting for measured confounding

For the second set of analyses (Model 1) we included all anxiety predictors simultaneously, so that each anxiety exposure period is adjusted for the others, along with the covariates and interactions between each anxiety predictor and child age. In the next set of models (Model 2), we also adjusted for maternal depression at all periods, to investigate whether anxiety had a unique association with child internalizing and externalizing problems over and above the association with maternal depression. In addition, interactions between each depression predictor and child age were included. Based on previous recommended cutoffs for short forms of the SCL, the regression coefficients in Model 1 and 2 can be interpreted as the expected average T score change in internalizing or externalizing symptoms in children when we compare mothers without anxiety symptoms with mothers with a clinically relevant level of anxiety symptoms.

Adjusting for unmeasured confounding

Finally, in Model 3 we conducted sibling comparisons to adjust for unmeasured, familial confounding. This was done by mean-centering each of the anxiety predictors and depression covariates within mothers. A deviation score was thus created for each sibling within a mother. If the siblings were equally exposed they would get identical scores and not contribute to the estimated association. Because the centered predictors are orthogonal to all between-family varying variables, this procedure adjusts for potentially confounding genetic and environmental influences that are shared among siblings. The results can therefore be interpreted as the change in child T scores when the same mother moves from zero symptoms of anxiety to a clinically significant level, all else being constant. In this sibling comparison model, we adjusted for the same variables as in Model 2, with the exception of parental education (as this was not unique to each child). All models were run separately for internalizing and externalizing problems.

RESULTS

We ran preliminary tests to check for multicollinearity by extracting variance inflation factors (VIFs) from the predictors included in Model 1-3 (see Supplementary). None approached the value 10. Pearson's correlation coefficients between the exposures and outcomes are shown in Table 2. The correlations ranged from r = .11 to .66. The lowest correlations were between maternal anxiety in gestation week 30 and child externalizing symptoms, and between postpartum anxiety and externalizing symptoms. The highest correlation was between concurrent maternal anxiety and depressive symptoms. As a measure of how similar children within mothers were on the exposures, we used intraclass correlations. The correlations were r = .50, .45 and .48 for prenatal, postpartum and concurrent anxiety exposure, respectively.

Table 2 here

Internalizing problems

The results for the analyses on the predictors separately (aim 1) are illustrated under Model 0 in Figure 3, but not reported in tables, as these analyses were run to investigate whether there were grounds for carrying out analyses with stricter control and for comparison with previous studies. For all anxiety predictors, the associations were statistically significant and positively associated with internalizing problems. The unstandardized estimates varied between 4.96 (95% CI = 4.33-5.58) for maternal anxiety at 6 months postpartum, and 5.75 (95% CI = 5.20-6.30) for concurrent maternal anxiety. The interpretation of these estimates is that for each unit increase in maternal anxiety, internalizing problems increase with a T-score of 4.96-5.75.

Associations after adjusting for measured confounding

In Model 1 (Figure 3 and Table 3), maternal anxiety symptoms at gestation week 30 and up to 5 years after birth were significantly associated with child internalizing problems. The largest association was found for concurrent maternal anxiety symptoms (b = 4.63, 95% CI = 4.04-5.23). In Model 2 (Figure 3 and Table 3), all associations between the maternal anxiety predictors and internalizing problems were attenuated. Anxiety symptoms at 0.5 years postpartum were no longer significantly associated with internalizing problems.

Associations after adjusting for unmeasured confounding (sibling comparison)

Adjusting for familial confounding in addition to depressive symptoms and other covariates (Model 3; Figure 3 and Table 3), only concurrent maternal anxiety symptoms (b = 1.75, 95% CI = 0.27-3.23) remained statistically significantly associated with child internalizing

problems. Estimates for all predictors, with the exception of maternal anxiety 0.5 years postpartum were further attenuated, and not statistically different from zero. The concurrent depression symptoms covariates were still significantly associated with internalizing problems (b = 2.14, 95% CI = 1.07, 3.20). All main effects are shown in Figure 3. The pattern of successive attenuation was evident for all predictors.

Interaction effects

In Model 1, both maternal postpartum and concurrent anxiety were found to interact with child age (b = 0.33 and 0.80, 95% CIs = 0.09, 0.58 and 0.57, 1.03, respectively), indicating that the association between maternal anxiety and child internalizing problems increased as the children grew older. The latter remained after adjusting for depression (Model 2), but was attenuated (b = 0.39, 95% CI = 0.10, 0.67). After sibling comparison however (Model 3, Table 3), there were no significant interactions between the anxiety predictors and child age.

Table 3 here

Externalizing child problems

When the predictors were investigated one at a time (Model 0, all anxiety predictors were statistically significantly and positively associated with externalizing problems. The estimates varied between 3.11 (95% CI = 2.51-3.70) for maternal anxiety at 30 weeks' gestation, and 4.12 (95% CI = 3.60-4.64) for concurrent maternal anxiety.

Associations after adjusting for measured confounding

Results for externalizing problems are shown in Table 4 and Figure 3. Adjusted only for covariates and each other, maternal anxiety symptoms at all periods were positively and

statistically significantly associated with externalizing problems (Model 1). The strongest association was found for maternal concurrent anxiety symptoms (b = 3.60, 95% CI = 3.04, 4.16). The pattern of findings changed dramatically in Model 2, adjusted for depression predictors and interactions, as none of the anxiety predictors remained significantly associated with the outcome. Hence, for externalizing problems, maternal anxiety had no unique contributions, beyond the contributions from maternal depressive symptoms. In this model, maternal depression at week 30 during pregnancy, 0.5 years postpartum and concurrently were all statistically significantly associated with externalizing problems.

Associations after adjusting for unmeasured confounding (sibling comparison)

Adjusting for familial confounding (Model 3) did not change the pattern of results. None of the anxiety predictors were statistically significantly associated with the outcome.

Table 4 and Figure 3 here

Interaction effects

In Model 1 (Table 4), concurrent anxiety interacted with child age (b = 0.56, 95% CI = 0.34, 0.77). The interaction was positive, indicating that the association between maternal anxiety and externalizing problems increased across time. After adjusting for depressive symptoms and their interaction with child age, none of the interactions were significantly different from zero (Model 2), a pattern that remained in Model 3.

DISCUSSION

In this large prospective cohort study, we investigated to what extent exposure to maternal symptoms of anxiety during the perinatal and preschool period were associated with

preschool child internalizing and externalizing problems above and beyond the associations with maternal perinatal and concurrent depressive symptoms. The sibling design further allowed us to account for familial confounding stemming from unmeasured genetic and shared environmental influences on the associations.

Our first aim was to investigate whether any associations could be found between maternal anxiety at different stages of development and child internalizing or externalizing problems. Both perinatal maternal anxiety and concurrent maternal anxiety were significantly and positively associated with internalizing and externalizing problems in preschool children. These patterns of result are comparable with findings from several cross-sectional studies (e.g. Glasheen et al., 2010; O'Connor et al., 2002). However, there are also examples of previous cross-sectional studies that do not find associations between maternal anxiety and child mental health outcomes (Glasheen et al., 2010). This variation in findings is not surprising given the large diversity in anxiety measures, periods of exposure and sample sizes. Regardless, our findings indicated that all periods of anxiety exposure were associated with child internalizing and externalizing problems.

Our second aim was to assess whether these associations remained after controlling for measured confounding (the children's age and sex, and parity and educational level in the mother). For both internalizing and externalizing problems, most associations remained significant in these models.

When we also adjusted for concurrently measured depressive symptoms, most of the associations with internalizing problems remained, but associations with externalizing problems did not. A similar pattern of results was found in a previous study utilizing the ALSPAC cohort (Barker et al., 2011), where it was found that maternal prenatal and postpartum anxiety was associated only with internalizing and not with externalizing problems in 7-8 year old children after adjusting for concurrent maternal depressive

symptoms. Also in a more recent study of 3-4 year old children from both ALSPAC and the Generation R samples, associations between maternal anxiety and child externalizing problems disappeared when maternal depression was adjusted for (Van Batenburg-Eddes et al., 2013).

Associations between maternal anxiety symptoms and child mental health problems may be the result of several possible mechanisms. The association may be causal, such that there is a direct effect of exposure to the mother's anxiety symptoms on child's risk for mental health problems. Alternatively, the same genes might be influencing both the parent and child phenotype, or aspects of the shared family environment may contribute both to a higher risk for anxiety in the mother and mental health problems in the child. Our control for such unmeasured genetic and shared environmental confounding through the sibling comparison analyses indicated that associations between perinatal measures of maternal anxiety symptoms and internalizing problems are confounded by genetic and environmental influences shared between mothers and children, in line with previous studies (e.g. Bekkhus et al., 2017). Only maternal concurrent anxiety symptoms remained significantly associated with preschool offspring's internalizing problems. We can only speculate on which mechanisms might be at play, but it is possible that anxious mothers use parenting techniques that are harmful to the child (Creswell, Apetroaia, Murray, & Cooper, 2013), or that the child learns anxious behavior from the mother (Askew & Field, 2008). The associations may also be bidirectional, as indicated in a previous study on maternal depression and child mental health problems (McAdams et al., 2015), or be mediated through other phenomena, such as sleep problems (Ystrom et al., 2017). These findings may also be accounted for by shared method bias, which we discuss in the limitations section.

Externalizing problems, on the other hand, were not associated with maternal anxiety when concurrent depressive symptoms where included in the analyses. Compared to a

previous study where maternal concurrent depressive symptoms where unadjusted for concurrent anxiety symptoms (Gjerde et al., 2017), the associations in the present study with maternal depressive symptoms are only slightly attenuated after adjusting for maternal anxiety symptoms. The finding fits well with two other genetically informative studies employing distinct designs, where evidence of direct environmental transmission was found between parental and offspring anxiety (Brooker et al., 2015; Eley et al., 2015). The implication of our finding is that maternal anxiety symptoms may have a more specific influence on the risk for child mental health problems than depressive symptoms.

For our third and final aim, we investigated whether the associations between maternal anxiety and their children's internalizing and externalizing problems were equally strong across preschool years. The impact of anxiety symptoms did not change in the late compared to the early preschool years.

Our findings may appear to contrast with the literature on epigenetic changes following exposure to maternal stress during pregnancy (Babenko et al., 2015; Monk et al., 2012). We can only speculate on what the explanation for this discrepancy might be, but three possibilities stand out. First, behavioral phenotypes are multifactorial and polygenic (Rutter, 2006). Thus, even if epigenetic alterations occur in the exposed children, these may not be sufficient in explaining more than a fraction of the variance in the phenotype that they code for, and therefore not be sufficient for causing behavioral change. Second, it has recently been found that even methylation processes are to a great extent under genetic control (Polderman et al., 2015). It is therefore possible that familial confounding could help explain epigenetic findings, as for instance has been indicated for the association between methylation at the SOCS3 gene and BMI (Li, Wong, Southey, & Hopper, 2017). Third, despite the convincing literature on the role of epigenetic regulations for associations between maternal anxiety and negative child outcomes up to several decades after exposure, we are nowhere near

understanding the specific mechanisms in which DNA alterations contribute to gene expression and ultimately to phenotypic expression (Babenko et al., 2015; Cao-Lei et al., 2016). Hopefully, future studies on genetic biomarkers or sibling studies including measures of genomic methylation can help bridge the gap between findings from genetically informative epidemiological studies and studies such as Project Ice Storm (King et al., 2012).

Strengths and limitations

Strengths in the present study include a large, longitudinal population-based sample, genetically informative data, and measures of both anxiety and depressive symptoms. However, the following limitations need to be acknowledged. Anxious and depressed mothers might be more inclined to worry about their children, which could cause a bias towards reporting more emotional and behavior problems. Mothers' ratings of their children were obtained at the same time they rated their own symptoms. This may have caused confounding due to shared method variance (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). Many studies have investigated whether anxious and/or depressed mothers exaggerate their children's mental health problems, but firm conclusions have not yet been reached (De Los Reyes et al., 2015). Unfortunately, the potential effect of a shared informant bias from the potential effect of maternal anxiety and depression symptoms on their children's mental health problems cannot be separated in the MoBa. The design in the present study adjusts for time-invariant rating bias, and bias associated with depression. The time-variant rater bias that would remain could not be adjusted for. If anxious mothers did indeed rate their children more negatively, we would expect to see the same pattern for internalizing as for externalizing problems. This was not the case in the present study. It is possible that the lack of a significant association between maternal concurrent anxiety and child externalizing symptoms could be explained by previous observations of anxious/depressed mothers' rating bias being higher

when rating internalizing than externalizing symptoms in their children (Kroes, Veerman, & De Bruyn, 2003; Salbach-Andrae, Lenz, & Lehmkuhl, 2009). More distortion when reporting internalizing symptoms could be due to mothers remembering better symptoms in their children that resemble their own symptoms. Alternatively, as internalizing symptoms are often less visible than externalizing symptoms, more distortion may be expected for the more ambiguous internalizing symptoms, in accordance with the social attribution theory (Kroes et al., 2003). Distortion does however not appear to be greater for anxious than depressed mothers, either for ratings of internalizing (Kroes et al., 2003), or externalizing symptoms (Chilcoat & Breslau, 1997). Therefore, should our results be explained solely by rater bias, we would expect to find approximately the same association between concurrent depression and externalizing symptoms as for concurrent anxiety and externalizing symptoms. Instead, concurrent maternal depressive symptoms had a much larger association with externalizing symptoms. It is therefore reasonable to assume that the remaining associations found in this study cannot be explained by shared method bias alone.

We used a pregnancy cohort sample of Norwegian mothers and their children. The recruitment rate was low, and attrition occurred during follow-up (Magnus et al., 2006). We handled attrition by including all cases with data at one or more of the preschool measures of child internalizing and externalizing problems, and estimated the models assuming responses were missing at random. We were reluctant to use multiple imputation on these clustered data, as this is still considered experimental in the statistical literature. When studying possible self-selection bias in MoBa, it has been found that women in MoBa differ from other childbearing women in Norway on several exposures and outcomes (Nilsen et al., 2009). Mental health variables were not studied with regard to selection bias, but it is possible that the most anxious and depressed mothers may have dropped out early or never participated in the study. While the detected differences in exposure and outcomes in MoBa compared to the general

population in Norway did affect prevalence estimates, they did not bias association measures (Nilsen et al., 2009). It is therefore likely that the associations found in the present study should generalize to similar populations. However, it is possible that the results may not be valid in other settings, such as in developing countries, or particularly poor neighborhoods, where more stressors and heterogeneity could be expected.

CONCLUSION

In the present sample, associations between pre- and postnatal maternal anxiety and child internalizing problems appeared to be confounded by genetic or environmental factors shared between mother and child. The association between pre- and postnatal maternal anxiety and child externalizing symptoms appeared to be confounded by maternal depressive symptoms as well as by shared genetic or environmental factors. Maternal anxiety during the preschool years however, remained associated with concurrent child internalizing, but not externalizing problems, after sibling comparison. Anxiety symptoms may therefore have more specific influences on child mental health problems, compared to maternal depression, which has been found to impact on both child internalizing and externalizing problems. Our results underscore the importance of concurrent maternal anxiety as a risk factor in the development of child mental health problems, which has often been overshadowed by the focus on maternal depression in the previous literature.

550 REFERENCES

551 Achenbach, T. M. (1966). The classification of children's psychiatric symptoms: a factor-
552 analytic study. *Psychological monographs, 80*, 1-37.

553 Achenbach, T. M. (1992). *Manual for the Child Behavior Checklist/2-3 and 1992 Profile*.
554 Burlington , VT: Department of Psychiatry, University of Vermont.

555 Appleton, A. A., Armstrong, D. A., Lesseur, C., Lee, J., Padbury, J. F., Lester, B. M., &
556 Marsit, C. J. (2013). Patterning in placental 11-B hydroxysteroid dehydrogenase
557 methylation according to prenatal socioeconomic adversity. *Plos One, 8*, 7.
558 doi:10.1371/journal.pone.0074691

559 Askew, C., & Field, A. P. (2008). The vicarious learning pathway to fear 40 years on. *Clinical*
560 *Psychology Review, 28*, 1249-1265. doi:10.1016/j.cpr.2008.05.003

561 Babenko, O., Kovalchuk, I., & Metz, G. A. S. (2015). Stress-induced perinatal and
562 transgenerational epigenetic programming of brain development and mental health.
563 *Neuroscience and Biobehavioral Reviews, 48*, 70-91.
564 doi:10.1016/j.neubiorev.2014.11.013

565 Barker, E. D., Jaffee, S. R., Uher, R., & Maughan, B. (2011). The contribution of prenatal and
566 postnatal maternal anxiety and depression to child maladjustment. *Depression and*
567 *Anxiety, 28*, 696-702.

568 Beijers, R., Buitelaar, J. K., & de Weerth, C. (2014). Mechanisms underlying the effects of
569 prenatal psychosocial stress on child outcomes: beyond the HPA axis. *European Child*
570 *& Adolescent Psychiatry, 23*, 943-956. doi:10.1007/s00787-014-0566-3

571 Bekkhus, M., Lee, Y., Nordhagen, R., Magnus, P., Samuelsen, S. O., & Borge, A. I. H.
572 (2017). Re-examining the link between prenatal maternal anxiety and child emotional
573 difficulties, using a sibling design. *International Journal of Epidemiology*, 156-165.
574 doi:10.1093/ije/dyx186

Brooker, R. J., Neiderhiser, J. M., Leve, L. D., Shaw, D. S., Scaramella, L. V., & Reiss, D. (2015). Associations between infant negative affect and parent anxiety symptoms are bidirectional: Evidence from mothers and fathers. *Frontiers in Psychology, 6*, 10. doi:10.3389/fpsyg.2015.01875

Cao-Lei, L., Laplante, D. P., & King, S. (2016). Prenatal maternal stress and epigenetics: Review of the human research. *Current Molecular Biology Reports, 2*, 16-25. doi:10.1007/s40610-016-0030-x

Chilcoat, H. D., & Breslau, N. (1997). Does psychiatric history bias mothers' reports? An application of a new analytic approach. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 971-979. doi:10.1097/00004583-199707000-00020

Creswell, C., Apetroaia, A., Murray, L., & Cooper, P. (2013). Cognitive, affective, and behavioral characteristics of mothers with anxiety disorders in the context of child anxiety disorder. *Journal of Abnormal Psychology, 122*, 26-38. doi:10.1037/a0029516

Davis, E. P., Snidman, N., Wadhwa, P. D., Glynn, L. M., Schetter, C. D., & Sandman, C. A. (2004). Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy, 6*, 319-331. doi:doi:10.1207/s15327078in0603_1

De Los Reyes, A., Augenstein, T. M., Wang, M., Thomas, S. A., Drabick, D. A. G., Burgers, D. E., & Rabinowitz, J. (2015). The validity of the multi-informant approach to assessing child and adolescent mental health. *Psychological Bulletin, 141*, 858-900. doi:10.1037/a0038498

Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenluth, E. H., & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behavioral Science, 19*, 1-15.

Eley, T. C., McAdams, T. A., Rijsdijk, F. V., Lichtenstein, P., Narusyte, J., Reiss, D., . . . Neiderhiser, J. M. (2015). The intergenerational transmission of anxiety: A Children-

of-Twins study. *American Journal of Psychiatry, 172*, 630-637. doi:10.1176/appi.ajp.2015.14070818

Gjerde, L. C., Eilertsen, E. M., Reichborn-Kjennerud, T., McAdams, T. A., Zachrisson, H. D., Zambrana, I. M., . . . Ystrøm, E. (2017). Maternal perinatal and concurrent depressive symptoms and child behavior problems: a sibling comparison study. *Journal of Child Psychology and Psychiatry*, 779-786. doi:10.1111/jcpp.12704

Glasheen, C., Richardson, G. A., & Fabio, A. (2010). A systematic review of the effects of postnatal maternal anxiety on children. *Archives of Womens Mental Health, 13*, 61-74. doi:10.1007/s00737-009-0109-y

Glover, V., O'Connor, T. G., & O'Donnell, K. (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehavioral Reviews, 35*, 17-22. doi:10.1016/j.neubiorev.2009.11.008

Graignic-Philippe, R., Dayan, J., Chokron, S., Jacquet, A. Y., & Tordjman, S. (2014). Effects of prenatal stress on fetal and child development: A critical literature review. *Neuroscience and Biobehavioral Reviews, 43*, 137-162. doi:10.1016/j.neubiorev.2014.03.022

Gregory, A. M., Eley, T. C., & Plomin, R. (2004). Exploring the association between anxiety and conduct problems in a large sample of twins aged 2–4. *Journal of Abnormal Child Psychology, 32*, 111-122. doi:10.1023/B:JACP.0000019765.29768.1c

Gustavson, K., Ystrom, E., Stoltenberg, C., Susser, E., Suren, P., Magnus, P., . . . Reichborn-Kjennerud, T. (2017). Smoking in pregnancy and child ADHD. *Pediatrics, 139*, 8. doi:10.1542/peds.2016-2509

Helland, S. S., Røysamb, E., Wang, M. V., & Gustavson, K. (2017). Language difficulties and internalizing problems: bidirectional associations from 18 months to 8 years among boys and girls. *Development and Psychopathology*. doi:10.1017/S0954579417001559

Hesbacher, P. T., Rickels, K., Morris, R. J., Newman, H., & Rosenfeld, H. (1980). Psychiatric illness in family practice. *Journal of Clinical Psychiatry, 41*, 6-10.

Hofstra, M. B., van der Ende, J., & Verhulst, F. C. (2002). Child and adolescent problems predict DSM-IV disorders in adulthood: A 14-year follow-up of a Dutch epidemiological sample. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*, 182-189. doi:10.1097/00004583-200202000-00012

Hox, J. J. (2010). *Multilevel analysis. Techniques and applications*. New York Routledge.

Huizink, A. C., de Medina, P. G., Mulder, E. J., Visser, G. H., & Buitelaar, J. K. (2002). Psychological measures of prenatal stress as predictors of infant temperament. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*, 1078-1085.

Kendler, K. S. (1996). Major depression and generalised anxiety disorder. Same genes, (partly)different environments--revisited. *British Journal of Psychiatry*, 68-75.

Kessler, R. C., McGonagle, K. A., Zhao, S. Y., Nelson, C. B., Hughes, M., Eshleman, S., . . . Kendler, K. S. (1994). Lifetime and 12 month prevalence of DSM-III-R psychiatric disorders in the United States - Results from the National Comorbidity Survey. *Archives of General Psychiatry, 51*, 8-19. Keyes, K. M., Smith, G. D., & Susser, E. (2013). On sibling designs. *Epidemiology, 24*, 473-474. doi:10.1097/EDE.0b013e31828c7381

King, S., Dancause, K., Turcotte-Tremblay, A. M., Veru, F., & Laplante, D. P. (2012). Using natural disasters to study the effects of prenatal maternal stress on child health and development. *Birth Defects Research Part C-Embryo Today-Reviews, 96*, 273-288. doi:10.1002/bdrc.21026

Kroes, G., Veerman, J. W., & De Bruyn, E. E. J. (2003). Bias in parental reports? Maternal psychopathology and the reporting of problem behavior in clinic-referred children.

European Journal of Psychological Assessment, 19, 195-203. doi:10.1027//1015-5759.19.3.195

Kuja-Halkola, R., D'Onofrio, B. M., Larsson, H., & Lichtenstein, P. (2014). Maternal smoking during pregnancy and adverse outcomes in offspring: Genetic and environmental sources of covariance. *Behavior Genetics, 44*, 456-467. doi:10.1007/s10519-014-9668-4

Lahey, B. B., & D'Onofrio, B. M. (2010). All in the family: Comparing siblings to test causal hypotheses regarding environmental influences on behavior. *Current Directions in Psychological Science, 19*, 319-323. doi:10.1177/0963721410383977

Lee, A. M., Lam, S. K., Mun Lau, S. M. S., Chong, C. S. Y., Chui, H. W., & Fong, D. Y. T. (2007). Prevalence, course, and risk factors for antenatal anxiety and depression. *Obstetrics and Gynecology, 110*, 1102-1112. doi:10.1097/01.aog.0000287065.59491.70

Li, S., Wong, E. M., Southey, M. C., & Hopper, J. L. (2017). Association between DNA methylation at SOCS3 gene and body mass index might be due to familial confounding. *International Journal of Obesity, 41*, 995-996. doi:10.1038/ijo.2017.56

Loomans, E. M., van der Stelt, O., van Eijsden, M., Gemke, R., Vrijkotte, T., & Van den Bergh, B. R. H. (2011). Antenatal maternal anxiety is associated with problem behaviour at age five. *Early Human Development, 87*, 565-570. doi:10.1016/j.earlhumdev.2011.04.014

Magnus, P., Birke, C., Vejrup, K., Haugan, A., Alsaker, E., Daltveit, A. K., . . . Stoltenberg, C. (2016). Cohort profile update: The Norwegian Mother and Child Cohort Study (MoBa). *International Journal of Epidemiology.* , 382-388. doi:10.1093/ije/dyw029

672 Magnus, P., Irgens, L. M., Haug, K., Nystad, W., Skjaerven, R., & Stoltenberg, C. (2006).
673 Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). *International*
674 *Journal of Epidemiology, 35*, 1146-1150. doi:10.1093/ije/dyl170
675 Martin, N. G., & Eaves, L. J. (1977). The genetical analysis of covariance structure. *Heredity,*
676 *38*, 79-95.
677 McAdams, T. A., Rijsdijk, F. V., Neiderhiser, J. M., Narusyte, J., Shaw, D. S., Natsuaki, M.
678 N., . . . Eley, T. C. (2015). The relationship between parental depressive symptoms
679 and offspring psychopathology: evidence from a children-of-twins study and an
680 adoption study. *Psychological Medicine*. doi:10.1017/S0033291715000501.
681 Mitchell, C., Schneper, L. M., & Notterman, D. A. (2015). DNA methylation, early life
682 environment, and health outcomes. *Pediatric Research, 79*, 212.
683 doi:10.1038/pr.2015.193
684 Monk, C., Spicer, J., & Champagne, F. A. (2012). Linking prenatal maternal adversity to
685 developmental outcomes in infants: The role of epigenetic pathways. *Development*
686 *and Psychopathology, 24*, 1361-1376. doi:10.1017/s0954579412000764
687 Nilsen, R. M., Vollset, S. E., Gjessing, H. K., Skjaerven, R., Melve, K. K., Schreuder, P., . . .
688 Magnus, P. (2009). Self-selection and bias in a large prospective pregnancy cohort in
689 Norway. *Paediatric and Perinatal Epidemiology, 23*, 597-608. doi:10.1111/j.1365-
690 3016.2009.01062.x
691 O'Connor, T. G., Heron, J., Glover, V., & Alspac Study Team. (2002). Antenatal anxiety
692 predicts child behavioral/emotional problems independently of postnatal depression.
693 *Journal of the American Academy of Child and Adolescent Psychiatry, 41*, 1470-1477.
694 doi:10.1097/01.chi.0000024880.60748.38

Petzoldt, J., Wittchen, H. U., Einsle, F., & Martini, J. (2016). Maternal anxiety versus depressive disorders: specific relations to infants' crying, feeding and sleeping problems. *Child Care Health and Development, 42*, 231-245. doi:10.1111/cch.12292

Podsakoff, P. M., MacKenzie, S. B., Lee, J. Y., & Podsakoff, N. P. (2003). Common method biases in behavioral research: A critical review of the literature and recommended remedies. *Journal of Applied Psychology, 88*, 879-903. doi:10.1037/0021-9101.88.5.879

Polderman, T. J., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M., & Posthuma, D. (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics, 47*, 702-709. doi:10.1038/ng.3285

Rabe-Hesketh, S., & Skrondal, A. (2012). *Multilevel and longitudinal modeling using Stata* (3 ed. Vol. 1). Texas: Stata Press.

Reise, S. P., & Revicki, D. A. (2014). *Handbook of item response theory modeling: Applications to typical performance assessment.* New York: Routledge.

Rice, F., Harold, G. T., Boivin, J., van den Bree, M., Hay, D. F., & Thapar, A. (2010). The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. *Psychological Medicine, 40*, 335-345. doi:10.1017/s0033291709005911

Ross, L. E., & McLean, L. M. (2006). Anxiety disorders during pregnancy and the postpartum period: A systematic review. *Journal of Clinical Psychiatry, 67*, 1285-1298.

Rutter, M. (2006). *Genes and behavior: Nature-nurture interplay explained*. Oxford: Blackwell Publishing.

718 Salbach-Andrae, H., Lenz, K., & Lehmkuhl, U. (2009). Patterns of agreement among parent,
719 teacher and youth ratings in a referred sample. *European Psychiatry, 24*, 345-351.
720 doi:10.1016/j.eurpsy.2008.07.008
721 Sandanger, I., Moum, T., Ingebrigtsen, G., Sorensen, T., Dalgard, O. S., & Bruusgaard, D.
722 (1999). The meaning and significance of caseness: The Hopkins Symptom Checklist-
723 25 and the Composite International Diagnostic Interview II. *Social Psychiatry and*
724 *Psychiatric Epidemiology, 34*, 53-59. doi:10.1007/s001270050112
725 Silberg, J. L., Maes, H., & Eaves, L. J. (2010). Genetic and environmental influences on the
726 transmission of parental depression to children's depression and conduct disturbance:
727 an extended Children of Twins study. *Journal of Child Psychology and Psychiatry, 51*,
728 734-744. doi:10.1111/j.1469-7610.2010.02205.x
729 Singh, A. L., D'Onofrio, B. M., Slutske, W. S., Turkheimer, E., Emery, R. E., Harden, K. P., .
730 . . Martin, N. G. (2011). Parental depression and offspring psychopathology: a
731 Children of Twins study. *Psychological Medicine, 41*, 1385-1395.
732 doi:10.1017/s0033291710002059
733 StataCorp. (2015). *Stata multilevel mixed-effects reference manual. Release 14*. Texas:
734 StataCorp LP.
735 Stein, A., Pearson, R. M., Goodman, S. H., Rapa, E., Rahman, A., McCallum, M., . . .
736 Pariante, C. M. (2014). Effects of perinatal mental disorders on the fetus and child.
737 *Lancet, 384*, 1800-1819. Strand, B. H., Dalgard, O. S., Tambs, K., & Rognerud, M.
738 (2003). Measuring the mental health status of the Norwegian population: A
739 comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nordic*
740 *Journal of Psychiatry, 57*, 113-118. doi:10.1080/08039480310000932
741 Talge, N. M., Neal, C., Glover, V., & Early Stress Transnational Res, P. (2007). Antenatal
742 maternal stress and long-term effects on child neurodevelopment: how and why?

Journal of Child Psychology and Psychiatry, 48, 245-261. doi:10.1111/j.1469-7610.2007.01714.x

Tambs, K., & Røysamb, E. (2014). Selection of questions to short-form versions of original psychometric instruments in MoBa. *Norwegian Journal of Epidemiology*, 195-201.

Van Batenburg-Eddes, T., Brion, M. J., Henrichs, J., Jaddoe, V. W. V., Hofman, A., Verhulst, F. C., . . . Tiemeier, H. (2013). Parental depressive and anxiety symptoms during pregnancy and attention problems in children: a cross-cohort consistency study. *Journal of Child Psychology and Psychiatry, 54*, 591-600. doi:10.1111/jcpp.12023

Ystrom, E., Hysing, M., Torgersen, L., Ystrom, H., Reichborn-Kjennerud, T., & Sivertsen, B. (2017). Maternal symptoms of anxiety and depression and child nocturnal awakenings at 6 and 18 months. *Journal of Pediatric Psychology*. doi:10.1093/jpepsy/jsx066

Table 1

Variables used in the multilevel analyses

	Level	Mean	Std. Dev.	Min.	Max.
Dependent variables					
Internalizing	1	50	10	35.72	104.21
Externalizing	1	50	10	31.26	92.92
Predictors (Raw)					
Prenatal anxiety	2	1.16	0.29	1	4
Postpartum anxiety	2	1.14	0.29	1	4
Concurrent anxiety	2	1.16	0.31	1	4
Predictors (Grand-mean centered)					
Prenatal anxiety	2	0	0.29	-0.16	2.84
Postpartum anxiety	2	0	0.29	-0.14	2.86
Concurrent anxiety	1	0	0.31	-0.16	2.84
Predictors (Group-mean centered)					
Prenatal anxiety	2	0	0.12	-1.33	1.50
Postpartum anxiety	2	0	0.13	-1.88	2.25
Concurrent anxiety	1	0	0.12	-1.58	1.50
Covariates					
Child age (years)	1	-2.02	1.47	-3.72	1.67
Child sex	2	0.49	0.50	0	1
Parity	2	0.79	0.82	0	4
Parental education level	2	4.91	1.04	1	6
Prenatal depression	2	1.26	0.36	1	4
Postpartum depression	2	1.26	0.29	1	4
Concurrent depression	2	1.29	0.42	1	4
Gr.MC prenatal depression	2	0	0.36	-0.26	2.74
Gr.MC postpartum depression	2	0	0.38	-0.26	2.74
Gr.MC concurrent depression	1	0	0.42	-0.29	2.71
GMC prenatal depression	2	0	0.16	-1.67	1.69
GMC postpartum depression	2	0	0.17	-1.69	2.25

GMC concurrent depression	1	0	0.17	-1.50	1.50

N. of observations were 40,457 for all variables. N. of obs = number of observations across the level 1 measures (at 1.5, 3 and 5 years after birth); Level = nested data structure: 1 for occasions and 2 for sibling level. Prenatal = gestation week 30; Postpartum = 0.5 years after birth; Concurrent = 1.5, 3 and 5 years after birth. Predictors and covariates are grand-mean centered (Gr.MC) lest they have a meaningful zero point. Group-mean centering (GMC) of predictors enables sibling comparison.

Table 2

Pearson's correlation coefficients between the anxiety and depression scales

Measures	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Internalizing (1)	—							
Externalizing (2)	.35***	—						
Prenatal a*nx*. (3)	.15***	.11***	—					
Postpart. a*nx*.(4)	.14***	.11***	.44***	—				
Conc. anx. (5)	.17***	.15***	.39***	.45***	—			
Prenatal depr. (6)	.15***	.13***	.63***	.38***	.33***	—		
Postpart. d*epr*. (7)	.16***	.14***	.37***	.63***	.38***	.48***	—	
Conc. depr. (8)	.19***	.20***	.34***	.37***	.66***	.41***	.47***	—

N = 40,457. *** = p<0.001. Prenatal anx./depr. = anxiety/depressive symptoms at gestation week 30; Postpart. Anx/depr. = anxiety/depressive symptoms 0.5 years postpartum; Conc.anx./depr. = anxiety/depressive symptoms when the child is between age 1,5 – 5 years old.

Table 3

Results from multilevel modeling of child internalizing problems

	Model 1		Model 2		Model 3 (sib. comparison)	
Fixed effects	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Intercept	*49.42***	*49.14, 49.69*	*49.59***	*49.31, 49.86*	*49.55***	*49.30, 49.81*
Prenatal anxiety	2.77***	2.10, 3.44	1.68***	0.90, 2.47	0.38	-0.94, 1.69
Postpartum anxiety	2.39***	1.71, 3.09	0.69	-0.12, 1.50	0.81	-0.54, 2.17
Concurrent anxiety	4.63***	4.04, 5.23	2.05***	1.31, 2.79	1.75*	0.27, 3.23
Prenatal anxiety x child age	0.19	-0.04, 0.42	0.21	-0.06, 0.48	0.36	-0.14, 0.86
Postpartum anxiety x child age	0.33**	0.09, 0.58	0.17	-0.11, 0.45	0.34	-0.18, 0.85
Concurrent anxiety x child age	0.80***	0.57, 1.03	0.39**	0.10, 0.67	0.20	0.38, 0.78
Random effects	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
$var\ (\varepsilon_{ijk})$	63.67	62.32, 65.05	63.48	62.13, 64.86	63.64	62.29, 65.02
$var\ (n_{jk})$	8.55	7.31, 9.99	8.62	7.38, 10.06	8.05	6.83, 9.48
$var\ (n_{0k})$	32.46	29.96, 35.16	30.55	28.12, 33.19	39.50	36.81, 42.40
$var\ (n_{1k})$	1.03	0.80, 1.32	1.02	0.79, 1.31	1.15	0.91, 1.44
	Est. (corr)	**95% CI**	**Est. (corr)**	**95% CI**	**Est. (corr)**	**95% CI**
$cov\ (n_{0k}, n_{1k})$	4.25 (0.73)	3.57, 4.93	4.07 (0.73)	3.40, 4.75	5.02 (0.74)	4.30, 5.73
AIC	295,117.0		294,770.1		296,049.6	

* = p<0.05, ** = p<0.01, *** = p<0.001. Model 1 adjusted for each anxiety period + interaction between anxiety symptoms at each period and child age + age, sex, parity and education. Model 2 = Model 1 + adjusted for depressive symptoms at each period and interaction between depressive symptoms at each period and child age. Model 3 = Model 2, not adjusted for education + sibling comparison. $var\ (\varepsilon_{ijk})$ = variance at the individual level; $var\ (n_{jk})$ = variance at the sibling level; $var\ (n_{0k})$ = variance in intercept at mother level; $var\ (n_{1k})$ = variance in slope at mother level; $cov\ (n_{0k}, n_{1k})$ = covariance intercept and slope at mother level. Prenatal anxiety = gestational week 30; Postpartum anxiety = 0.5 years postpartum;Concurrent anxiety = 1.5, 3 and 5 years postpartum (concurrent measure with child internalizing and externalizing problems).

Table 4

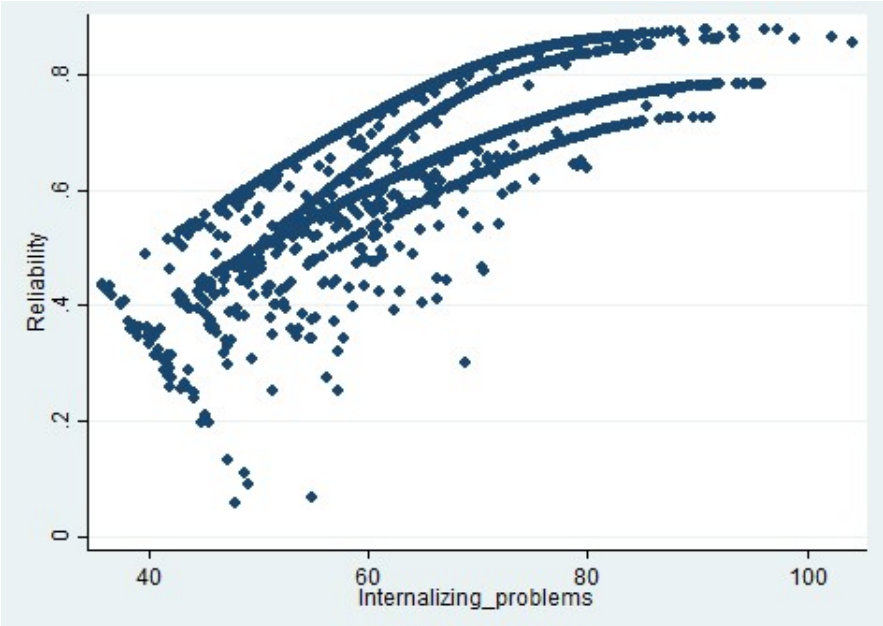
Results from multilevel modeling of child externalizing problems

	Model 1		Model 2		Model 3 (sib. comparison)	
Fixed effects	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Intercept	*47.83****	*47.55, 48.11*	*48.01****	*47.74, 48.29*	*48.03****	*47.78, 48.28*
Prenatal anxiety	1.56***	0.91, 2.21	0.41	-0.36, 1.17	0.05	-1.18, 1.28
Postpartum anxiety	1.57***	0.90, 2.24	0.36	-0.43, 1.14	0.72	-0.54, 1.98
Concurrent anxiety	3.60***	3.04, 4.16	0.48	-0.22, 1.17	0.81	-0.54, 2.17
Prenatal anxiety x child age	0.08	-0.13, 0.29	0.07	-0.18, 0.32	-0.07	-0.52, 0.38
Postpartum anxiety x child age	0.09	-0.14, 0.31	0.12	-0.14, 0.38	0.24	-0.22, 0.70
Concurrent anxiety x child age	0.56***	0.34, 0.77	-0.09	-0.35, 0.18	-0.13	-0.66, 0.39
Random effects	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
$var\ (\varepsilon_{ijk})$	49.93	48.86, 51.02	49.80	48.73, 50.89	49.97	48.89, 51.06
$var\ (n_{jk})$	12.57	11.40, 13.87	12.68	11.50, 13.98	12.29	11.12, 13.59
$var\ (n_{0k})$	41.58	38.99, 44.35	39.00	36.48, 41.69	45.97	43.25, 48.86
$var\ (n_{1k})$	1.32	1.11, 1.57	1.28	1.07, 1.52	1.35	1.14, 1.60
	Est. (corr)	**95% CI**	**Est. (corr)**	**95% CI**	**Est. (corr)**	**95% CI**
$cov\ (n_{0k}, n_{1k})$	5.30 (0.72)	4.66, 5.95	5.01 (0.71)	4.37, 5.64	5.66 (0.72)	5.00, 6.32
AIC	290,773.0		290,369.8		291,365.4	

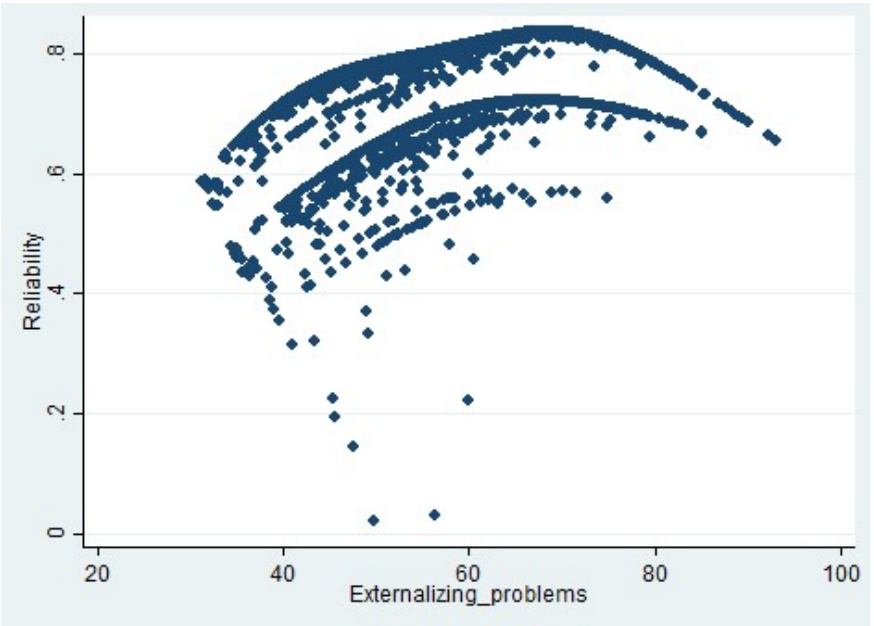
* = p<0.05, ** = p<0.01, *** = p<0.001. Model 1 adjusted for each anxiety period, and interaction between anxiety symptoms at each period and child age + age, sex, parity and education. Model 2 = Model 1 + adjusted for depressive symptoms at each period and interaction between depressive symptoms at each period and child age. Model 3 = Model 2, not adjusted for education + adjusted for familial confounding (sibling comparison). Please see Table 3 for explanations of abbreviations.

Figure 1

a)

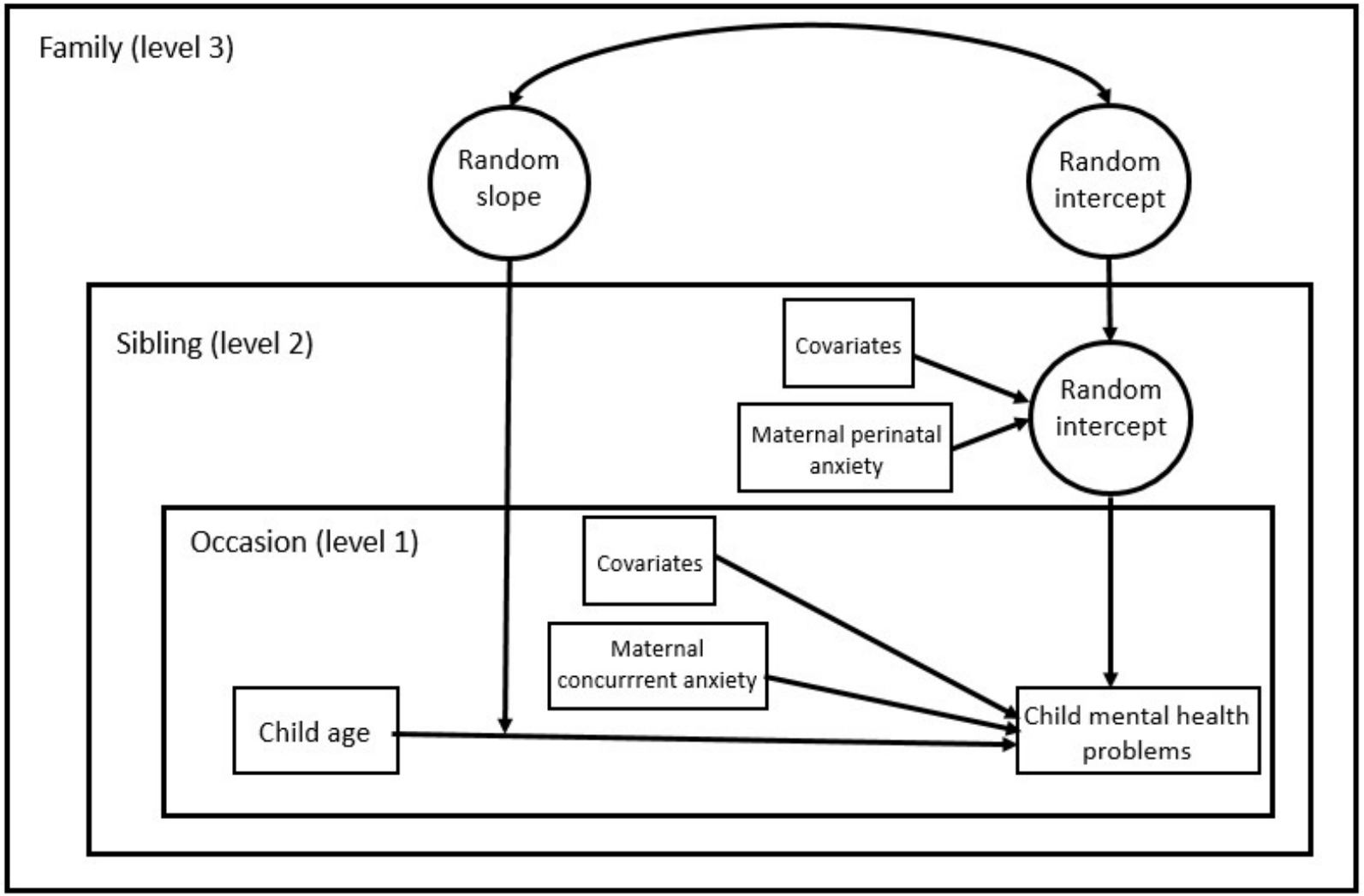


b)



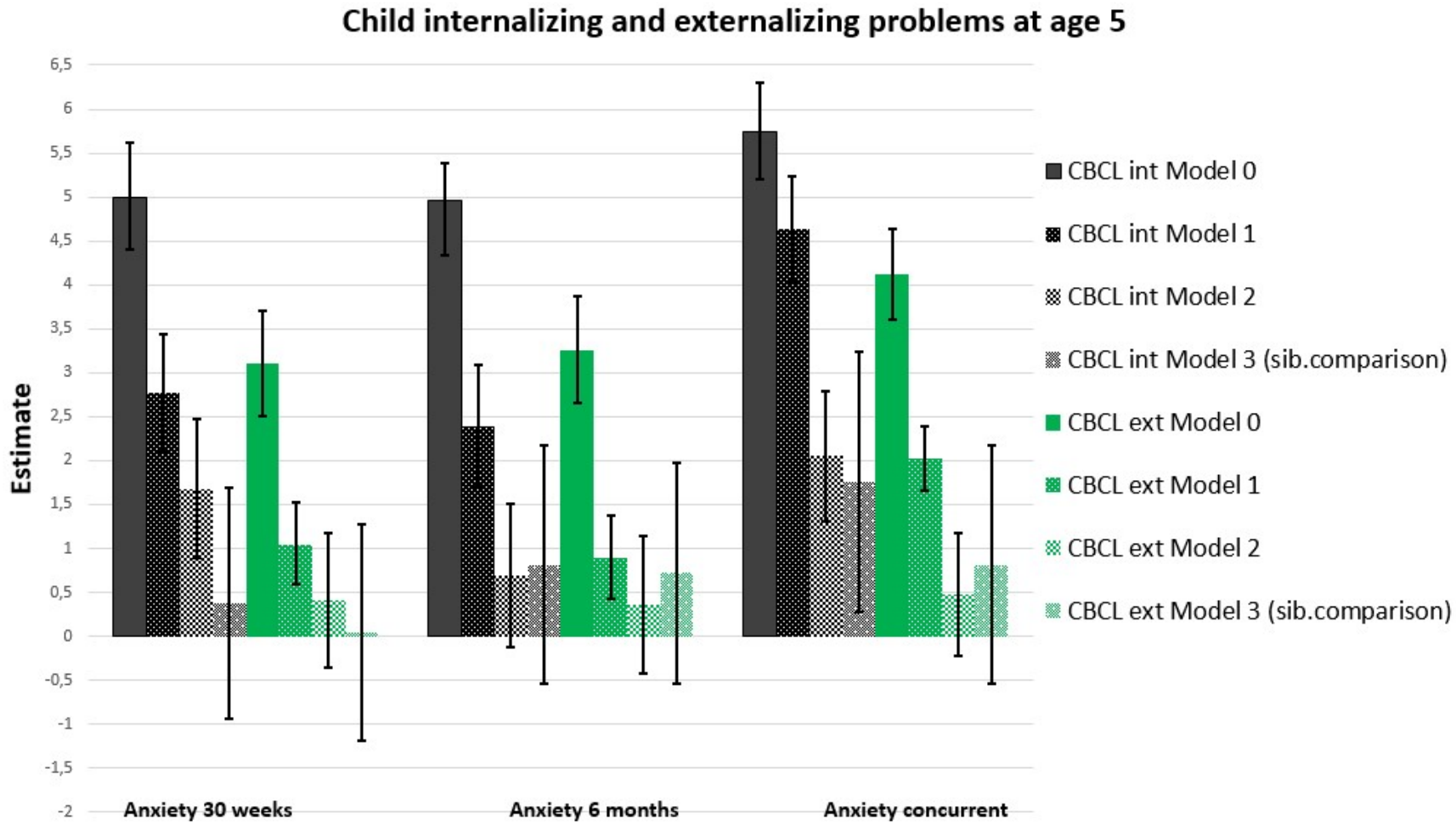
Reliability as a function of scores on the outcome variables

Figure 2



Basic model used in the analyses. The frames represent each nesting level in the data. Rectangles represent fixed (observed) variables, whereas the ellipses represent random (latent) variables.

Figure 3



Main unstandardized estimatess with 95% CI of anxiety on internalizing and externalizing problems at age 5. CBCL = Child Behavior Checklist, int = internalizing problems, ext = externalizing problems, Model 0 = adjusted for covariates, Model 1 = Model 0 + adjusted for each anxiety period, Model 2 = Model 1 + adjusted for each depression period, Model 3 (sib. control) = Model 2 + adjusted for familial confounding. 30 weeks = 30th gestation week; 6 months = 6 months postpartum; concurrent = 1.5, 3 and 5 years after birth. The bars should be read from left to right, as this corresponds to the key presented from top to bottom.