Family Disruption and Child Neurobehavioral Development

An Epidemiological Perspective

Yllza Xerxa
Family Disruption and Child Neurobehavioral Development

*An Epidemiological Perspective*

Ontwrichting van het gezin en de gedrags- en hersenontwikkeling van het kind

*Een epidemiologisch perspectief*

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GENERAL INTRODUCTION

Nearly half of my friends grew up in divorced families, some did well and some did very poorly. And I have always wondered, why?

For young children, family disruption is considered the primary agent in shaping their ontogenetic development. As such, children experience family disruption including parental conflict or separation, experience parental hostility or any other form of psychopathology, or were bullied by a sibling. It is actually uncommon to not experience any of these family risk factors to some degree. However, it is unclear in which periods children are vulnerable and in what sequence family events impact them most, and who is most likely to be affected. In this thesis we used different indicators of chronic family disruption such as parental conflict, parental separation, parental hostility, and parental psychopathology with child developmental outcomes. Our focus lies on the chronicity of these processes because continued exposure (in certain periods) can lead to poor developmental outcomes.¹

Therefore, we explored family disruption occurring in the prenatal vs. postnatal period or occurring in both periods and how different exposures interact in relation to developmental outcomes. Importantly, vulnerability is shaped by the occurrence of different risk factors that interact, mediate or simply confound each other. In this thesis we also explore how family disruption becomes behaviorally or biologically embedded.

Imagine two children similar to my friends, Eneda and Estri both 10 years old, sitting in math class waiting for the bell to ring. It is the time when the teacher places your test on your desk, face down. Eneda is engaged and keeps staying focused to complete the test. While Estri tries to stay focused but keeps getting distracted by not feeling motivated, then by the whispering of a classmate, then by the sunny day outside, and then starts constantly moving the chair.

Eneda experienced conflict and family separation. Estri’s parents were dealing with anxiety and depression and her mother was hostile. Eneda is doing well and does not have adjustment problems, while Estri not. What happened in their development? In this thesis I take a closer look what underpins the different behavior in these two children. Is it the absence of a parent? The chronicity of conflict or hostility that shapes child behavior? Or is it both long-standing conflict and separation? Why are Eneda and Estri affected by family disruption in different ways? How will their behavior change during development?
In both epidemiologic and animal models, disturbances in child development (both neurological and cognitive) and behavior have been linked to prenatal family risk factors that persist through childhood. Characterization of specific adverse exposures provided evidence supporting the important role that family disruption has in modifying offspring developmental processes.\(^2\)\(^-\)\(^5\) Furthermore, prenatal and postnatal environmental factors can both have different effects during distinct stages of child development. Think first of Estri’s behavior. What exactly is it about parental conflict and separation that accounts for Estri’s emotional and behavioral problems? Is it her age of exposure to parents’ conflict itself, or separation that has impact on her behavior? Or is it rather the level of parental conflict?

It is well known that family disruption including poor family functioning or conflict, parental separation, parental anxiety/depression, and different forms of parenting are associated with long-term child emotional and behavioral problems,\(^3\) and with lower cognitive abilities and poorer school performance.\(^6\),\(^7\) There is also evidence that simply considering the number of events without considering the nature of disruption,\(^8\) or ignoring the influence of one disruption on other disruptions,\(^9\) or not accounting for the timing of the disruption\(^10\) will lead to insufficient understanding of child behavioral problems.

It is also well known that certain brain structures are affected by different types of adversities occurring during child development.\(^11\) Both animal and human studies suggest that early-life exposure to stressors may have the most potent impact during specific periods of neurodevelopment in childhood.\(^12\) For example, Romanian high risk children exposed to neglect, and low socioeconomic status during key neurodevelopmental sensitive periods (e.g., over the first five years of life) presented with structural changes in the children’s brain.\(^13\)

What brain regions underlie the different behaviors of Eneda and Estri? Their apparently different behaviors are not the result of one brain structure, rather they are the result of a connected brain structures known as total white and gray matter. Preclinical studies suggest that the hippocampus is highly susceptible to stressful experiences during pregnancy and infancy.\(^14\),\(^15\) Circulating glucocorticoids receptors in the hippocampus make this particular structure vulnerable to chronic stressors.\(^12\) As a result children exposed to pre- and postnatal adversities show reductions of hippocampal volumes.\(^13\) The other brain regions implicated in the response to chronic stress and adversity include limbic and frontotemporal structures of children.\(^16\)

While it is clear that research has demonstrated the importance of unidirectional associations between parent and child psychopathology across development for several decades,
relatively few studies investigated bidirectional associations between parent and child, namely the child’s impact on changes in parents’ psychopathology. Indeed, various studies investigating bi-directionality of dysfunctional parenting and child psychopathology suggest some bidirectional associations, but yet again, the associations of the within and between individuals variation by which parental psychopathology lead to changes in child psychopathology and vice versa remain unclear. Now think of Estri’s vulnerability. Is her ability not to stay focused during math test likely to be the result of coping patterns transmitted from her anxious and hostile mother alone, or from both parents’ psychopathology? Or is it rather a result of the test pressure, under pressure Estri tends to show more behavior problems than normally? Are Estri’s behavioral problems likely to influence her parents’ psychopathology?

Thus, any truly transactional model must encompass that not only the parental psychopathology but also the child as it actively participates in its own growth. This understanding requires explanations to the transactional model as equal emphasis must be placed on the bidirectional associations between the child and family environment. In this thesis, we disentangle transactional processes within and between individuals of parent and child psychopathology. Together, persistent effects in development are not some set of psychopathology symptoms but rather the processes by which these symptoms are maintained in the transaction between child and environment.

I hope that this thesis will ultimately provide a few answers, and most importantly a clearer picture of the questions lying before us. In chapter 2 we discuss various ways family disruption becomes a risk factor for child behavioral outcomes, and how potential interacting and mediating factors (e.g., family conflict and separation) play an important role in determining the outcomes. The first study of this chapter focuses on the association of family conflict and parental separation from pregnancy onward with child emotional and behavioral problems. It is well known that family conflict could underlie both marital instability and poor parenting and its consequences for children. There is also a substantial body of evidence to support the notion that parental separation affects child emotional and behavioral problems. However, whether parental separation has a negative effects on child problem behavior independent of conflict remains unknown. We therefore introduce a mediation approach that more fully encompasses mediation and interaction of two exposures simultaneously.

The developmental period between childhood and adolescence is a time of substantial cognitive change, and may be especially sensitive to family disruption. In study 2 we further explore to what extent family disruption is associated with school achievement. Specifically, we evaluate whether the associations of prenatal poor family functioning and parental separation with child school achievement are independent and whether the
associations are mediated by childhood non-verbal IQ. This study also assesses whether attention problems explain the associations of poor family functioning and parental separation from pregnancy onward with child school achievement.

The last paper of this chapter focuses on the contribution of parenting practices in early and mid-childhood in the association between parental education and child school achievement. Highly educated parents are more likely to employ more positive parenting practices and thus contribute to higher child school achievement. Moreover, child IQ is one of the most important contributors to school achievement. Thus, we evaluated the extent to which parenting practices and child non-verbal IQ in early childhood mediate the association between parental education and school achievement.

Chapter 3 presents an approach to examine bidirectional associations between parent and offspring psychopathology. It has long be acknowledged by proponents of the trans-actional model that any development in the individual is influenced by the interplay of processes in the individual’s context over time. This study included children from the general population over time to test the stability and change of bidirectional associations within and between individuals. We therefore employed an autoregressive latent trajectories approach to understand the variability at the individual level of development.

In the chapter 4, we aimed to investigate the effects of childhood loneliness on long-term mental health disruption in a follow-up study that extends into adulthood. A considerable number of studies has investigated the effects of loneliness in adults with social anxiety disorder and depression. However, less is known about the impact of childhood loneliness in light of persistent effects in mental health outcomes. In this prospective-longitudinal, community-representative study, we estimate the effect childhood loneliness and long-term disruption on adult psychiatric disorders (including anxiety, depression, and substance use disorders) while carefully controlling for indicators of other common childhood adversities.

Chapter 5 consists of two studies evaluating the effects of family functioning from pregnancy onward with child brain morphology and well-being. Childhood stress is known to have longstanding consequences. In the first study we obtained parents’ assessments of family functioning during pregnancy, and subsequently, ratings of childhood problem behavior and neuroimaging data in preadolescence. Our goal was to investigate to what extent the long-term disruption of poor family functioning associates with preadolescent problem behavior and subcortical brain development.

Microstructural properties related to more efficient neural processing are generally associated with fewer behavior problems, while microstructural properties related to less
efficient neural processing are associated with more problem behavior during development. A healthy family environment may lead healthy brain development and low levels of problem behavior. In the last study of this chapter we investigate whether more positive early-life family functioning (reverse-scoring) is associated with more global white matter microstructure.

The final chapter, No. 6, presents a parallel approach to neuroimaging data to further understand determinants of parents’ and children’s brain morphology. Higher levels of parental hostility are associated with child problem behavior and in particular aggressive behavior. Exposure to parental hostility can have both immediate and lasting effects on physical and psychological health. Moreover, in ‘at risk families’ parents are likely to show the neuroendocrine, immunological, and cardiovascular correlates of persistent stressors. Many of these physiological and psychological differences potentially explain changes in the brain, such as decreased hippocampus and amygdala volumes. We therefore investigate to what extent parental hostility is associated with differences in maternal, paternal and child brain structure if analyzed together, i.e. as triads that in turn underlie child aggressive behavior.

**Thesis objectives**

The main goal of this thesis is to explore family disruption factors that we consider of importance to child development psychopathology. We employ various methodological methods to study the associations of specific family disruption from pregnancy onward and child neurobehavioral development. We will also zoom in on bidirectional associations between parent and child psychopathology. In order to do so, the work presented in this thesis is embedded in population-cased cohort studies, namely the Generation R Study, which I will introduce in more detail.

The importance of the study setting is best illustrated by including children that have been followed from fetal life onward. The Generation R Study comprised 9,778 pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006. Generation R Study is representative of the general population with regard to family risk factors (e.g., 23% parents separated up to 10 years follow-up). More important, the follow-up data collection of the Generation R Study is one of the main advantages for family risk factor research, and in particular the imaging data of children and parents are a strength of this thesis. The follow-up from pregnancy onward render the Generation R Study a valuable tool to map how the various ways of adversity becomes neurobehavioral embedded, and how the timing of such adversity plays an important role in determining behavioral and cognitive outcomes. Of note, the study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants.
and from both the parents of minors. Participants gave written informed consent for each phase of the study (fetal, preschool, childhood and adolescence period). From the age of 12 years onwards, children must sign their own consent form, in accordance with Dutch Law. Children received oral information about the study.

The study of childhood loneliness and adult psychiatric disorders was embedded in a prospective-longitudinal, community-representative Great Smoky Mountains Study of 1,420 participants (49% female). Childhood predictors of adult outcomes included the following constructs: (1) DSM-based traumatic events, psychiatric and substance disorders, and (3) adversities and hardships. All constructs were assessed using the structured Child and Adolescent Psychiatric Assessment (CAPA).

These are the guiding challenges for this thesis:

• To identify periods of specific vulnerability of family disruption to child neurobehavioral outcomes.
• How timing of family exposures interacts with neurobehavioral development during childhood.
• How the vulnerability is shaped by the occurrence of different family factors that interact or mediate with each other in relation to child neurobehavioral outcomes.
• How different family factors becomes behaviorally and biologically embedded.

I do hope that this thesis will take science a few small steps forward. My goal was to understand a bit better how prenatal and childhood family disruption result in shaping the neurodevelopmental vulnerability to emotional, behavioral, and cognitive problems.
REFERENCES


Chapter 2

The complex role of parental separation in the association between family conflict and child problem behavior

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ABSTRACT

Background: Parental separation is a major adverse childhood experience. Parental separation is generally preceded by conflict, which is itself a risk factor for child problem behavior. Whether parental separation independent of conflict has negative effects on child problem behavior is unclear.

Method: This study was embedded in Generation R, a population-based cohort followed from fetal life until age 9 years. Information on family conflict was obtained from 5808 mothers and fathers. The four-way decomposition method was used to apportion the effects of prenatal family conflict and parental separation on child problem behavior into four non-overlapping components. Structural equation modeling was used to test bidirectional effects of child problem behavior and family conflict over time.

Results: Family conflict from pregnancy onwards and parental separation each strongly predicted child problem behavior up to pre-adolescence according to maternal and paternal ratings. Using the four-way decomposition method, we found evidence for a strong direct effect of prenatal family conflict on child problem behavior, for reference interaction, and for mediated interaction. The evidence for interaction implies that prenatal family conflict increased the children's vulnerability to the harmful effect of parental separation. There was no evidence of a pure indirect effect of parental separation on child problem behavior.

Conclusions: Overall, results indicated that if parental separation occurs in families with low levels of conflict, parental separation does not predict more child problem behavior. Moreover, the bi-directional pattern suggested that child problem behavior influences the persistence of family conflict.
INTRODUCTION

Parental separation affects approximately a third of all marriages in many societies. Parental separation has been related to diverse negative outcomes of the child, including mental and physical health problems. Many children from separated families show difficulties in functioning, including frequent emotional and behavioral problems. However, family conflict often long precedes the actual physical separation, thus making it difficult to determine whether the negative effects on children are caused by the parental separation or by the family conflict, which increases the risk of separation as well as causing child maladjustment. Furthermore, child maladjustment can often trigger or exacerbate family conflict. In some families, family conflict may start before the child is born and escalate over time. However, in other families, family conflict begins sometime after the child is born and increases over time, particularly if the child has physical, developmental, regulatory, emotional, or behavioral problems. Given this complex set of factors, it is important to consider the effects of prenatal family conflict on later family conflict, on separation, and on child maladjustment. Additionally, it is important to test mediation and interaction effects linking prenatal conflict and separation with child maladjustment. Finally, bi-directional effects between child maladjustment and family conflict are important to test. Before detailing our specific hypotheses, we summarize previous research relevant to associations between family conflict, separation, and child maladjustment.

Family Conflict

Many studies show that family conflict plays a central role in child maladjustment. Parents in high-conflict marriages are less warm towards their children, more rejecting, harsher in their discipline, and more withdrawn and depressed than parents in low-conflict marriages. When family conflict increases parental harshness, rejection, and inconsistency, it may lead to child maladjustment, such as internalizing and externalizing problems. Additionally, the effects of family conflict may vary depending on the age of the child, with toddlers showing developmental, self-regulatory, and attachment issues but preschoolers showing self-blame, fear, confusion, guilt and sadness. As children age, they develop a more sophisticated understanding of interactions between people, but they are still troubled by loyalty conflicts when their divorced parents remain locked in conflict.

Few studies have examined the stability of family conflict over time and even fewer have tested this stability starting prenatally. However, Kluwer and Johnson reported that a high level of conflict during pregnancy predicted worse marital relationships after the child was born. This may be because the stresses of parenting are added onto an already conflictual relationship.
Separation/Divorce

Separation and divorce represent a cascade of potentially stressful changes in the social and physical environment of families. Separation is often associated with increased parental distress, reduced attention paid to the child by one or both parents, disruption of the home environment, conflict over money and custody/visitation, and reduced economic circumstances, all of which are stressors for children.\(^3,25,26\) Parental preoccupation with issues pertaining to separation/divorce and adjustment to the new domestic arrangements can also interfere with effective parenting, which can lead to problems in their children.\(^19,20\)

Most prospective studies have found that both family conflict and parental separation stress children and can lead to maladjustment.\(^27\) Furthermore, the level of conflict preceding the separation influences child emotional and behavioral problems.\(^17,28\) Some research indicates that family conflict is a more important predictor child maladjustment than parental separation.\(^29\) Interaction effects between conflict and separation are likely, though they have not been widely studied. For example, separation may have fewer negative effects on children when conflict is low and parents can collaborate for their children's welfare before, during, and after the separation process.\(^30\) On the other hand, when conflict is high before, during, and after the separation, then the compound effects of conflict and separation may result in many negative consequences for the children. However, a few longitudinal studies have found that children in high-conflict families showed improved wellbeing after parental separation.\(^16,17\) This outcome may be contingent on the discrepancy between pre- and post-separation level of contact and conflict.

Gaps in Previous Research

Few studies thus far have explored the extent to which the association between parental separation and child maladjustment depends on family conflict and even fewer have tested this in young children. Most previous research has considered the effects of family conflict and divorce individually, but the two are likely to interact. The few studies\(^18,31\) that have considered both family conflict and parental separation did so by adjusting the regression analyses of separation predicting child behavior for family conflict. However, these studies have generally not tested the interaction effect between family conflict and parental separation. Moreover, family conflict has typically been assessed after the child was born. Because child behavior can influence family conflict and separation, reverse causality can create a bidirectional feedback loop, but this has been largely unexplored in previous studies.\(^32\) Measuring family conflict prenatally controls for such bidirectional effects. Furthermore, measuring both family conflict and child maladjustment at successive time points in a longitudinal design permits analysis of the bidirectional associations between parental and child behavior over time.\(^33,34\) Additionally, many studies of
Family conflict, parental separation, and child problem behavior

divorce/separation do not obtain ratings of child emotional and behavioral problems from both parents, although discrepancies between maternal and paternal ratings are a well-documented finding.35,36

Goals of our Research

To address these limitations in the literature, we examined effects of family conflict and parental separation on child maladjustment using a large, multi-ethnic population-based prospective cohort from the Generation R study.37 Both parents provided reports of family conflict prenatally and at age 9, and mothers reported on family conflict at age 5. Information about marital status (i.e., married/living together vs. separated/divorced) was obtained prenatally and at ages 3, 5, and 9. The parents each reported child behavioral and emotional problems at age 3 and 9 and mothers also provided reports at age 5. We used these data to test the following hypotheses: (a) prenatal family conflict is associated with later family conflict, separation, and child maladjustment; (b) parental separation is associated with child maladjustment; (c) parental separation might not affect child maladjustment independent of prenatal family conflict; and (d) bidirectional associations would be found between child maladjustment and family conflict.

METHOD

Participants

Our research was embedded in the Generation R Study, a multi-ethnic population-based cohort from fetal life onwards. The Generation R Study has been described in detail previously.37 Briefly, all pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants. Of the 8879 pregnant women enrolled during pregnancy, we excluded 1266 mothers with no partner and 490 with missing family conflict data, leaving 7123 mothers and 4561 fathers. Of the 7123 mothers who completed questionnaires on family conflict before the child was born, 1315 (18%) mothers were lost to follow-up, leaving 5,808 mothers with child report data. Not all of these 5,808 mothers were seen at every time point (i.e., ages 3, 5, and 9). We tabulated the number of mothers who reported being separated from their partners at each time point and calculated this as a percent of the mothers seen at that time point, as follows: (a) by age 3 (342/4174 = 8.2%); (b) from ages 3 to 5 (430/5163 = 8.9%); and (c) from ages 5 to 9 (298/4543 = 7.9%). Overall by the time the child was 9-years-old, 1,070 (23.6%) mothers were separated/divorced from their partner. At age 9 years, 4062 mothers reported data on child problem behavior (4223 and 5063 had reported child problem behavior at age
3 and 5 years, respectively (see supplementary Figure 1). At age 9 years, 3080 fathers reported data on child problem behavior (3556 had reported child problem behavior at age 3 years, respectively).

### Measures

#### Family Assessment Device

Family functioning was assessed with the General Functioning (GF) subscale of the Family Assessment Device - FAD,\textsuperscript{38,39} at 20 weeks pregnancy, as well as when the child was 5 and 9 years old. Both mothers and fathers completed this measure prenatally and at age 9, but only maternal report was available at age 5. The General Functioning scale is a validated self-report measure of family health and pathology consisting of 12 items. Half of the items describe healthy functioning, e.g., ‘In times of crisis, we can turn to each other for support’. The other half describe unhealthy functioning, e.g., ‘There are a lot of unpleasant and painful feelings in our family’. Parents were asked to rate how well each item described their family by selecting from four different responses ranging from 1 to 4: strongly agree, agree, disagree or strongly disagree. So that a higher total FAD score could indicate less well-functioning families, the six positively worded healthy items were reverse-coded. Then, all 12 items were summed and divided by 12, yielding a total score from 1 to 4. FAD score will therefore be referred to henceforth as family conflict. In the current study, internal consistencies (Cronbach’s alpha) ranged from 0.82 to 0.87.

#### Child Behavior Checklist

The Child Behavior Checklist for Ages 1½-5 (CBCL/1½-5;\textsuperscript{40}), and the Child Behavior Checklist for Ages 6-18 (CBCL/6-18;\textsuperscript{41}), were used to obtain standardized parent reports of children’s emotional and behavioral problems. The CBCL/1½-5 contains 99 problems items, which are scored on seven empirically based syndromes and three broadband scales (Internalizing, Externalizing, and Total Problems). Each item used a three point rating scale 0 = ’not true’, 1 = ‘somewhat or sometimes true’, and 2= ‘very true or often true’, based on the preceding two months. The CBCL/6-18 has 118 problem items, also yielding syndrome scales and the same three broadband scales, with ratings based on the preceding 6 months. Good reliability and validity have been reported,\textsuperscript{40} and the scales were found to be generalizable across 23 societies, including The Netherlands.\textsuperscript{42} We used the continuous Total Problems score (the sum of ratings on all problem items) as our outcome measure because it reflects all the behavioral and emotional problems tapped by the CBCL and is thus the best overall index of maladjustment. Cronbach’s alpha at the different time points ranged from 0.77 to 0.80.
Parental Separation/Divorce
Marital status questions from the Generation R Study parental questionnaires were used to measure the occurrence of parental separation at four different data collection rounds: during pregnancy and when the child was 3, 5, and 9 years old. At each time point, marital status was scored dichotomously: “married/living together” and “separated/divorced”. If parents reported “not living together anymore” or “divorced” the child was coded as having experienced separation. In the Netherlands, many unmarried couples have a registered partnership. Marriage and registered partnership are similar in many ways. They are both relationships formalized by law. When registered partners who live together with their children decide to separate, the procedure must be conducted as if it were divorce. For our study, once a family was classified as separated/divorced, that classification remained for all subsequent time points. With our data, we were not able to differentiate children who were exposed to multiple separation/divorces from those exposed to a single such event.

Covariates
Descriptive statistics for the parent and child characteristics used as possible confounders are presented in Table 1. Parental age, ethnicity, education, and parental psychopathology are well-established predictors of children’s problems in existing separation/divorce studies, as well as in many studies from the Generation R group. Maternal religion (e.g., Muslim vs. non-Muslim) has been an important variable in previous Generation R studies. Gestational age at birth was included as a confounder because perinatal problems are known risk factors for psychopathology. The divorce literature generally considers child gender as an important variable, given that separation/divorce often has differential effects on boys versus girls. For example, boys often become more oppositional and aggressive, whereas girls often show more dependency, anxiety, and depression.

Maternal and paternal age were assessed at intake. Parental ethnicity was categorized into Dutch, non-Western and other Western national origin. Parental education was classified in three levels: ‘low’ (maximum of three years general secondary school), ‘medium’ (>3 years general secondary school; intermediate vocational training), and ‘high’ (higher vocational training, Bachelor’s degree, higher academic education). Information on maternal religion was obtained with questionnaires filled in by the mothers during pregnancy. Based on their responses to two questions about religion, mothers were classified into four categories: not religious, Christian, Islamic and other religion. Date of birth and gender of the infant were obtained from community midwife and hospital registries at birth. Information on gestational age was established by fetal ultrasound examinations within the Generation R Study. Parental psychopathological symptoms were assessed at 20 weeks of pregnancy and when the child was 3 years old using the
Brief Symptom Inventory (BSI), a validated self-report questionnaire with 53 items to be answered on a five-point scale, ranging from ‘0 = not at all’ to ‘4 = extremely’. High validity and reliability have been reported for the Dutch translation. Cronbach’s alpha was $\alpha = 0.86$. In summary, it is important to control for factors such young maternal age, low education, minority status, child gender, religion, gestational age and

| Table 1. Baseline Characteristics for Participants with Information on Family Conflict (FAD) |
|-----------------------------------------------|---------------|
|                                              | Mother (n=5,808) | Father (n=4,561) |
| Age, M (SD)                                  | 30.9 (4.8)      | 33.3 (5.3)       |
| Ethnicity                                    |
| Dutch, (%)                                   | 62.6           | 67.9             |
| Other Western, (%)                           | 9.3            | 6.9              |
| Non Western, (%)                             | 28.1           | 25.2             |
| Education level                              |
| High, (%)                                    | 52.4           | 54.8             |
| Middle, (%)                                  | 28.9           | 25.7             |
| Low, (%)                                     | 18.7           | 19.5             |
| Religion                                     |
| Yes, (%)                                     | 57.7           |                  |
| No, (%)                                      | 42.3           |                  |
| Parental psychopathology score, M (SD)       | 0.26 (0.34)    | 0.13(0.21)       |
| Gestational age at birth, weeks, M(SD)       | 39.81 (1.83)   |                  |
| Gender, (% boy)                              | 49.5           |                  |
| Family functioning (FAD-score) prenatal, M (SD) | 1.54 (0.46) | 1.51 (0.39)     |
| Family functioning (FAD-score) at age 5, M (SD) | 1.50 (0.41) |                  |
| Family functioning (FAD-score) at age 9, M (SD) | 1.52 (0.44) | 1.49(0.41)      |
| Parental separation by age 3 years           |
| Yes, (%)                                     | 8.2            |                  |
| Parental separation between age 3-5 years    |
| Yes, (%)                                     | 8.9            |                  |
| Parental separation between age 5-9 years    |
| Yes, (%)                                     | 7.9            |                  |
| Parental separation by age 9 years           |
| Yes, (%)                                     | 23.6           |                  |
| Child problem behavior (CBCL-score) at age 1.5, M (SD) | 22.47 (14.7) |                  |
| Child problem behavior (CBCL-score) at age 3, M (SD) | 20.33 (14.6) | 22.34 (15.6)    |
| Child problem behavior (CBCL- score) at age 5, M (SD) | 19.16 (16.1) |                  |
| Child problem behavior (CBCL- score) at age 9, M (SD) | 17.18 (15.0) | 17.30 (14.9)    |

Note: Numbers denotes children included in one or more analyses. Values are frequencies for categorical and means and standard deviations (M ±SD) for continuous measures.
parental psychopathology, as they are often associated with family conflict, parental separation, and/or child maladjustment.\textsuperscript{3,12}

**Statistical Analyses**

Prior to our data analyses, missing values of the covariates were imputed using multiple imputations. With the Markov Chain Monte Carlo multiple imputation technique, 10 complete data sets were created.\textsuperscript{50} Multivariate analyses were performed on each imputed data set, and effect estimates were pooled. The data were analyzed using SAS 9.4 software.

To address our first hypothesis, we computed concurrent and predictive correlations among family conflict scores over time and CBCL Total Problems scores over time. Then, we used logistic regressions to analyze prenatal family conflict as a predictor of separation at ages 3, 5, and 9. We then analyzed with separate linear regressions the prospective associations of prenatal family conflict and parental separation with CBCL Total Problems scores over time. In a sensitivity analysis, we used generalized estimating equations (GEE; Litman et al., 2007), to test the interaction with age in the associations between family conflict and maladjustment. This analysis tested if the association of family conflict (as reported by both mothers and fathers) with child problem behavior depends on the age of the child by comparing the single estimate of the repeatedly assessed family conflict.

Our main analysis involved the use of the four-way decomposition method,\textsuperscript{51} to test if the association of prenatal family conflict with child problem behavior is due to mediation by, or interaction with, parental separation. To this aim, the association of prenatal family conflict with child problem behavior mediated by parental separation (referred as the total effect - TE) was decomposed into four non-overlapping components: (i) the controlled direct effect (CDE) of prenatal family conflict on child problem behavior with parental separation absent; (ii) the reference interaction (INT\textsubscript{ref}), which is the additive interaction of prenatal family conflict and parental separation on child’s problem behavior; this only operates if the effects of prenatal family conflict and parental separation on child problem behavior differ from the sum of the effect of being exposed to only family conflict and the effect of only separation; (iii) the mediated interaction (INT\textsubscript{med}), which operates when parental separation is causally dependent on prenatal family conflict, and the interaction of the two has an effect on child problem behavior (i.e., parental separation occurs due to family conflict, and separation has an effect on child problem behavior only at certain levels of family conflict); and (iv) the pure indirect effect (PIE), which operates when parental separation is associated with child problem behavior independent of prenatal family conflict (i.e. pure mediated effect). This regression-based approach was used to estimate these direct and indirect effects and
involved combining parameter estimates according to the analytic expressions in the literature. Confidence intervals were obtained from standard errors for these effects using the delta method.

We first ran the four-way decomposition model adjusting for all previously mentioned confounders. We then adjusted the model for child problem behavior at 1.5 years as an additional confounder. These primary analyses assumed no additional unmeasured confounding. However, because it is possible that potential unmeasured confounders could have affected our results, we posited and evaluated an unmeasured confounder in a sensitivity analysis. That is, an unobserved covariate that correlates with parental separation and child problem behavior to such an extent that it would substantially reduce or eliminate the natural direct and indirect effects (details can be found in Supplementary, Table 1).

The four-way decomposition model extends the formula from Baron, Kenny to take account of exposure-mediator interactions in mediation analysis. Several previous studies in the social science field have reported mediated effects in the presence of interaction, but in the past it was difficult to decompose the total effect into direct and indirect effects in these studies. Such a decomposition is important because, in many studies, the exposure and mediator do interact to affect the outcome.

Finally, we examined the bidirectional relations between child problem behavior and postnatal family conflict. Structural equation modeling methods were used with the covariance matrices as input. The goodness-of-fit of the estimated SEM models with the data was considered acceptable if the following criteria were met: the root mean square error of approximation (RMSEA) had a value of 0.05 or less, and the comparative fit index (CFI) and Tucker-Lewis index (TLI) had a value of 0.90 or higher. A baseline model was identified in which all paths were free to vary across time and across maternal and paternal reports. Then, for each type of effect (child-effect on mother, child-effect on father, mother effect on child, and father-effect on child), a model was run in which these effects were constrained to be equal across time.

RESULTS

Predictions from Prenatal Family Conflict
The correlations in Table 2 show that mothers’ and fathers’ reports of family conflict were moderately associated both in the prenatal period and at age 9 ($r_s = .44$). Within-informant longitudinal stability in family conflict ratings ($r_s = .38 -.53$ for mothers and .40 for fathers) was higher than cross-informant longitudinal stability ($r_s = .25$).
Prenatal ratings of family conflict had modest correlations with CBCL Total Problems score at age 3 ($r_s = .13 -.25$), age 5 ($r_s = .13-.21$), and age 9 ($r_s = .11-.19$), consistent with our first hypothesis.

| Table 2. Correlation Coefficients Between Family Conflict and Child Problem Behavior |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1 Family conflict (FAD) prenatal-mother report | - | 2 Family conflict (FAD) prenatal-father report | .44** | - |
| 3 Family conflict (FAD) at age 5-mother report | .40** .28** | - |
| 4 Family conflict (FAD) at age 9-mother report | .38** .25** .53** | - |
| 5 Family conflict (FAD) at age 9-father report | .25** .40** .34** .44** | - |
| 6 CBCL Total Problems scores at age 3-mother report | .25** .13** .23** .24** .15** | - |
| 7 CBCL Total Problems scores at age 3-father report | .14** .14** .13** .14** .19** .55** | - |
| 8 CBCL Total Problems scores at age 5-mother report | .21** .13** .27** .24** .15** .60** .42** | - |
| 9 CBCL Total Problems scores at age 9-mother report | .19** .12** .20** .29** .20** .43** .31** .59** | - |
| 10 CBCL Total Problems scores at age 9-father report | .11** .12** .13** .17** .31** .29** .41** .41** .61** | - |

**Correlation is significant at the 0.01 level (2-tailed).**

Also consistent with our first hypothesis, the odds ratios (ORs) results derived from logistic regressions (see Table 3) indicate that prenatal family conflict was associated with parental separation across childhood, after adjusting for parent age, ethnicity, education, religion, and psychopathology as well as child sex and gestational age at birth. The largest ORs were for separation by age 3 (ORs = 2.8 for mothers’ ratings and 3.14 for fathers ratings). However, ORs predicting separation between ages 3 and 5 and by age 9 were all > 2.0. Thus, regardless of the informant, each unit increase in prenatal family conflict doubled the relative risk of later parental separation.

**Family Conflict and Child Problem Behavior**

Table 4 presents results from the regression analyses predicting CBCL Total Problems across childhood from family conflict as reported by both mothers and fathers at various time points. For mothers’ ratings of prenatal family conflict, prediction of CBCL Total Problems scores was as strong for age 9 as for age 3, with a slight dip at age 5. For fathers’ reports of prenatal family conflict, prediction to age 9 was slightly weaker than prediction to age 3. For later reports of family conflict, concurrent associations between family conflict and CBCL Total Problems scores were stronger than associations for both informants. Overall, a child exposed to family conflict was more likely to have higher levels of behavioral and emotional problems at both concurrent and later ages, consistent with our first hypothesis.
Chapter 2

Our GEE sensitivity analysis tested the interaction between levels of family conflict as assessed by each informant and age in predicting child problem behavior at age 9. The GEE estimates were very similar to the results in Table 5, only the CIs varied slightly because this method takes into account within-individual correlation across the time points. Tests for homogeneity of the varying family conflict effects at different ages showed a significant interaction between levels of family conflict across time in predicting child problem behavior at age 9 (GEE: F = 10.97, $p_{int} = .001$ for mothers’ report and GEE: F = 16.37, $p_{int} = <.001$ for fathers’ report). Specifically, the strongest association

<table>
<thead>
<tr>
<th>Table 3. Associations between Mother and Father Reported Prenatal Family Conflict and Parental Separation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental Separation</td>
</tr>
<tr>
<td>by age 3</td>
</tr>
<tr>
<td>OR (95% CI) $p$</td>
</tr>
<tr>
<td>(n = 4,174)</td>
</tr>
<tr>
<td>between age 3-5</td>
</tr>
<tr>
<td>OR (95% CI) $p$</td>
</tr>
<tr>
<td>(n = 4,821)</td>
</tr>
<tr>
<td>between age 5-9</td>
</tr>
<tr>
<td>OR (95% CI) $p$</td>
</tr>
<tr>
<td>(n = 3,771)</td>
</tr>
<tr>
<td>by age 9</td>
</tr>
<tr>
<td>OR (95% CI) $p$</td>
</tr>
<tr>
<td>(n = 4,543)</td>
</tr>
<tr>
<td>Mother Reported</td>
</tr>
<tr>
<td>Prenatal family conflict (FAD), per score</td>
</tr>
<tr>
<td>(2.80, 3.56) $&lt;.001$</td>
</tr>
<tr>
<td>(FAD), per score</td>
</tr>
<tr>
<td>(n = 4,174)</td>
</tr>
<tr>
<td>Age 5 Family conflict (FAD), per score</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>(n = 3,556)</td>
</tr>
<tr>
<td>Age 9 Family conflict (FAD), per score</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>(n = 3,556)</td>
</tr>
<tr>
<td>Note: Binary logistic regression analysis of FAD and separation outcome. Odds ratios (ORs) are averaged from 10 imputed datasets. The models are adjusted for age, ethnicity, education and religion, parental psychopathology, child sex and gestational age at birth reported by mother and father. Separated mothers by age 3, (8.2%); between age 3-5, (8.9%); between age 5-9, (7.9%); by age 9, (23.6%).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. The Association of Family Conflict and Child Problem Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child problem behavior (CBCL –total score, per point)</td>
</tr>
<tr>
<td>age 3</td>
</tr>
<tr>
<td>B (95% CI) $p$</td>
</tr>
<tr>
<td>(n=4,223)</td>
</tr>
<tr>
<td>age 5</td>
</tr>
<tr>
<td>B (95% CI) $p$</td>
</tr>
<tr>
<td>(n=5,063)</td>
</tr>
<tr>
<td>age 9</td>
</tr>
<tr>
<td>B (95% CI) $p$</td>
</tr>
<tr>
<td>(n=4,062)</td>
</tr>
<tr>
<td>Mother Reported Family Conflict</td>
</tr>
<tr>
<td>Prenatal Family conflict (FAD), per score</td>
</tr>
<tr>
<td>5.01 (4.01, 6.02) $&lt;.001$</td>
</tr>
<tr>
<td>(FAD), per score</td>
</tr>
<tr>
<td>(n=4,223)</td>
</tr>
<tr>
<td>Age 5 Family conflict (FAD), per score</td>
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<tr>
<td>-</td>
</tr>
<tr>
<td>(n=3,556)</td>
</tr>
<tr>
<td>Age 9 Family conflict (FAD), per score</td>
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<tr>
<td>-</td>
</tr>
<tr>
<td>(n=3,556)</td>
</tr>
<tr>
<td>Father Reported Family Conflict</td>
</tr>
<tr>
<td>Prenatal Family conflict (FAD), per score</td>
</tr>
<tr>
<td>3.87 (2.27, 5.47) $&lt;.001$</td>
</tr>
<tr>
<td>(FAD), per score</td>
</tr>
<tr>
<td>(n=3,556)</td>
</tr>
<tr>
<td>Age 9 Family conflict (FAD), per score</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>(n=3,556)</td>
</tr>
<tr>
<td>Note: Linear regression analysis of FAD and CBCL outcome. Betas are averaged from 10 imputed datasets. The models are adjusted for age, ethnicity, education and religion, parental psychopathology, gestational age at birth and child sex reported by mother and father.</td>
</tr>
</tbody>
</table>

Our GEE sensitivity analysis tested the interaction between levels of family conflict as assessed by each informant and age in predicting child problem behavior at age 9. The GEE estimates were very similar to the results in Table 5, only the CIs varied slightly because this method takes into account within-individual correlation across the time points. Tests for homogeneity of the varying family conflict effects at different ages showed a significant interaction between levels of family conflict across time in predicting child problem behavior at age 9 (GEE: F = 10.97, $p_{int} = .001$ for mothers’ report and GEE: F = 16.37, $p_{int} = <.001$ for fathers’ report). Specifically, the strongest association
Family conflict, parental separation, and child problem behavior

Table 5. The Association of Parental Separation and Child Problem Behavior

<table>
<thead>
<tr>
<th></th>
<th>Child problem behavior (CBCL - total score, per point)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>age 3</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>(n=4,223)</td>
<td>(n=5,063)</td>
</tr>
<tr>
<td>Separation by age 3, (yes)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.90 (0.28, 3.52)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.08 (-1.14, 3.30)</td>
</tr>
<tr>
<td>Separation between age 3 - 5, (yes)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-</td>
</tr>
<tr>
<td>Model 2</td>
<td>-</td>
</tr>
<tr>
<td>Separation between age 5 - 9, (yes)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-</td>
</tr>
<tr>
<td>Model 2</td>
<td>-</td>
</tr>
<tr>
<td>Separation by age 9, (yes)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-</td>
</tr>
<tr>
<td>Model 2</td>
<td>-</td>
</tr>
<tr>
<td>(n=3,556)</td>
<td></td>
</tr>
<tr>
<td>Father reported</td>
<td>(n=3,091)</td>
</tr>
<tr>
<td>Separation by age 3, (yes)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>3.29 (0.46, 6.13)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.09 (-2.31, 4.49)</td>
</tr>
<tr>
<td>Separation between age 5-9, (yes)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-</td>
</tr>
<tr>
<td>Model 2</td>
<td>-</td>
</tr>
<tr>
<td>Separation by age 9, (yes)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-</td>
</tr>
<tr>
<td>Model 2</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Linear regression analysis of parental separation and CBCL outcome. Betas are averaged from 10 imputed datasets. Model 1 is adjusted for age, ethnicity, education and religion, parental psychopathology, gestational age at birth and child sex reported by mother and father. Model 2: model 1 + prenatal family conflict reported by mother and father.

with child problem behavior at age 9 was found when family conflict at age 9 was the predictor.

Parental Separation and Child Problem Behavior
To address our second hypothesis, we conducted regression analyses predicting CBCL Total Problems scores at different ages from parental separation at different ages. As shown in Table 5, parental separation was consistently related to higher CBCL Total Problems scores as reported by both mothers and fathers. However, consistent with our third hypothesis, no associations of parental separation were observed after prenatal
parental family conflict was added to the model for all the regressions presented in Table 5 except for the “separation by age 9” results for mother-reported Total Problems score, which had a $B = 1.67$, 95% CI: 0.12, 3.22, $p = .034$.

**Four-Way Decomposition Analysis**

Our four-way decomposition analysis provided an integrated test of our first three hypotheses, namely that prenatal conflict and parental separation would both associated with child emotional and behavioral problems but that separation might not be a significant predictor independent of prenatal family conflict. In this analysis, we tested direct, mediation, and interaction effects of prenatal family conflict and parental separation on CBCL Total Problems scores at age 9. Because the four components sum to the total effect, each component’s proportional share of the total effect can be obtained by dividing the coefficient for each effect (which approximates a beta value) by the total effect.

As shown in Table 6, a strong ‘direct effect’ (CDE) of prenatal family conflict on child problem behavior was present, with a large effect size. That is, in families with high levels of prenatal conflict, children had higher CBCL Total Problems scores at age 9. Second, there was evidence for a ‘reference interaction effect’ (INT ref) of prenatal family conflict and parental separation on child problem behavior, with a small effect size. The direction of this effect suggests that when prenatal family conflict was high, the children were more vulnerable to the harmful effects of parental separation. Third, if parental separation was preceded by prenatal family conflict, the interaction of the two ‘mediated’ the effect on child problem behavior with a small effect size (INT med). The direction of this effect suggests that parental separation had a negative effect on child problem behavior at high levels of family conflict, allowing for prenatal family

<table>
<thead>
<tr>
<th>Mediator: Parental separation</th>
<th>Child problem behavior (CBCL-total score, per point), (n=3,787)</th>
<th>Mother reported</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled direct effect</td>
<td>Reference interaction</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>$p$</td>
</tr>
<tr>
<td>Family conflict (FAD)</td>
<td>2.90 (1.69, &lt;.001)</td>
<td>19 (0.03, .013)</td>
</tr>
<tr>
<td>prenatal, per score</td>
<td>4.10</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Note: The models are adjusted for maternal age, ethnicity, education, religion, maternal psychopathology, gestational age at birth, child sex and prior child problem behavior when child was 1.5 years reported by mother. CI obtained from delta method standard errors. Parental separation mediated through prenatal family conflict were estimated as follows: $TE= (CDE + INTref + INTmed + PIE)$, where INTref and INTmed refer to the corresponding betas for controlled direct effect and pure indirect effect mediated through parental separation respectively. Overall proportions are not presented because the natural direct effect and indirect effect are in the opposite directions.
Figure 1. Bidirectional Associations of Child Problem Behavior and Family Conflict.

Note: Structural equation modeling of child problem behavior and family conflict. Numeric values are standardized path regression coefficients averaged from 10 imputed datasets. The models are adjusted for parental age, ethnicity, education and religion, gestational age at birth, child sex and age, prenatal parental psychopathology and prenatal family conflict reported by mother and father, (RMSEA =0.08; CFI=0.99; TLI=0.89). *p<0.01. **p<0.001.
conflict and separation to interact. As noted above, traditional methods of mediation do not allow for interaction between the effects of exposure (family conflict) and the effects of the mediator (parental separation). The ‘pure indirect effect’ (PIE) of parental separation on child problem behavior in the absence of prenatal family conflict was not significant and the confidence interval spanned zero, as shown in Table 6. Although the direction of this effect could suggest that parental separation might have some inverse (i.e., beneficial) effect on child behavior, this cannot be inferred from our data given the broad confidence interval and non-significant \( p \) value. In summary, we found that parental separation partially mediated the association between prenatal family conflict and CBCL Total Problems scores.

It should be noted that the results in Table 6 and reported here represent adjustment for our potential confounders, namely maternal age, ethnicity, education, religion, maternal psychopathology, gestational age at birth, child sex. We additionally adjusted for child emotional and behavioral problems at age 1.5 years, yielding results that were essentially unchanged. Our sensitivity analysis\(^{52}\) indicated that is unlikely to be eliminated by the influence of an unobserved confounder (details in Supplementary, Table 1). This suggests that even under the scenario of substantial unmeasured confounding, the effect of prenatal family conflict on child problem behavior is not purely mediated by parental separation.

**Bi-Directional Analysis**

To address our last hypothesis, we examined bi-directional effects between child maladjustment and family conflict. Structural equation modeling showed good fit to the data (RMSEA = 0.08, CFI = 0.99, TLI = 0.89), (Figure 1.). For cross-lagged standardized paths, coefficients are shown. The long-term bidirectional effects between child problem behavior and family conflict were positive for both directions based on maternal and paternal report. Thus, the structural equation model showed that both parent-to-child effects and child-to-parent effects operated, such that child maladjustment led to increased family conflict and vice versa.

**DISCUSSION**

We tested the longitudinal effects of family conflict and parental separation on child maladjustment using a large, multi-ethnic population-based prospective cohort from the Generation R Study. Innovative aspects of our study include that we measured family conflict prenatally as well as periodically up to age 9 and that we obtained ratings of family conflict and child problems from mothers and fathers both prenatally and at age 9. Also, we used an association pathway mediation analysis to better understand the
interaction of prenatal family conflict with postnatal parental separation as they relate
to child problem behavior. Findings generally supported our four major hypotheses, as
summarized below.

As hypothesized, prenatal family conflict predicted later family conflict, with longitudi-
dinal stability in family conflict ratings that were moderate to high for both maternal
and paternal reports of conflict up to age 9. Also, as we hypothesized, prenatal family
conflict, whether reported by mother or father, strongly predicted later parental separa-
tion across childhood, with the strongest association for separation by age 3. These
findings replicated previous studies \(^{16,18,27}\), showing that family conflict is associated
with separation.

Also consistent with our first hypothesis, prenatal ratings of family conflict modestly
predicted child maladjustment up to age 9. This replicates findings from previous stud-
ies showing that family conflict is consistently related to maladjustment in childhood.
This study extends previous findings by using paternal reports. Thus our findings from
family conflict and parental separation analyzed and measured separately confirm
previous research showing that both family conflict and parental separation predict
child behavioral and emotional problems, \(^{3,57}\) consistent with our first two hypotheses.
However, we advanced that research by showing that parental separation was no longer
predictive of maladjustment once prenatal parental family conflict was added to the
regression model, except for the “separation by age 9” results for mother-reported Total
Problems score, consistent with our third hypothesis.

To further test our hypothesis that parental separation might not affect child maladjust-
ment independent of prenatal family conflict, we used the 4-way decomposition model.
Results indicated that prenatal family conflict was strongly related to maladjustment.
Furthermore, the interaction of prenatal family conflict with separation predicted child
maladjustment. High levels of prenatal family conflict increased the vulnerability to
the effects of separation on child problem behavior. The observed mediated interaction
effect suggests that family conflict to some extent leads to separation and also interacts
with the effects of separation on child problem behavior. This result support the notion
that prenatal family conflict to some extent affects child problem behavior through a
pathway of parental separation.

An important benefit of the 4-way decomposition model used in this study is the ability
to estimate interaction and mediation effects of prenatal family conflict and parental
separation on child problem behavior. Although these effects were small in size, both
were observed and significant. Whether parental separation has a direct and independent
effect on child problems as opposed to family conflict leading to parental separation,
which then increases child problems, has to our knowledge not been previously studied. When prenatal family conflict was not included in the model (by setting it to 0), we found no substantive “pure indirect effect” (PIE). In other words, parental separation was not related to child problem behavior in the absence of family conflict.

Thus, our two interaction results support the hypothesis that parental separation did not increase child problem behavior if the level of prenatal family conflict was low. Our sensitivity analyses modelling unobserved confounders underscores these conclusions; the direct effect of prenatal family conflict on child problem behavior increased, whereas the indirect effect decreased. Traditional methods of mediation could not have shown that family conflict both causes separation and also interacts with the effect of separation. Furthermore, many studies have noted considerable difficulties of drawing conclusions about separation, leading to uncertainty regarding whether family conflict plays a more important role for child problem behavior than parental separation. Our results indicate that parental separation did not have a negative effect on child problem behavior at low levels of prenatal family conflict. Indeed, low family conflict has previously been identified as one of the major protective factors for children’s of separated parents.

Generally, parental psychopathology and family conflict are closely interwoven and predispose each other. Yet, in the current study, when we adjusted for parental psychopathology we found no change in results. Thus, our findings for the associations between family conflict, separation and child held regardless of other maternal, paternal, child and family factors. Our findings also did not depend on the gender of the parent reporting on the family conflict, which we could test because we obtained both mother and father reports prenatally and at age 9.

The associations of family conflict on the child have often been explained by the effects of parenting stress, and consequent negative parenting. Parental separation also may cause many stressful life changes for children, such as transition to a new home and/or school, changed relations with peers, financial insecurities, and visitation issues. To enable comparison with these studies we also analyzed family conflict and separation independently. While we replicated many findings reported in the literature, parental separation was not associated with child problem behavior after adjustment for family conflict. This is in contrast with some studies, which found that parental separation independently predicts child problems. These longitudinal studies found that children of high conflict families that separated experienced improvement in well-being. We did not find this in our study perhaps because we used different analytical approaches and ours was not a high risk sample exposed to extremely high levels of conflict.
Finally, our hypothesis about bidirectional associations between child maladjustment and family conflict was also confirmed. Parent-reported family conflict was associated with increases in child maladjustment across childhood and child maladjustment, which in turn, was associated with later family conflict levels. These findings underscore the importance of measuring problem behavior early in childhood, which can help further clarify the directionality of the associations between family conflict and child problem behavior.

Some possible limitations of this study should be discussed. First, we measured parental separation repeatedly only by mother reports. That is, we obtained reports of both mothers and fathers for family conflict as well as child problem behavior, but parental separation was reported only by mothers. However, this can be considered factual information. An important limitation is that information about post-separation family conflict was not available. It is likely that the degree of post-separation family conflict could moderate the effects of separation on children’s mental health. Additionally, we should be careful generalizing our findings to clinical populations, as this study was performed in a general population sample. Family conflict and parental separation cannot be easily studied as a cause of child problem behavior. In particular, separation is a predictor or indicator of a process, “a series of dominos cascading in several directions”. At the individual level, once a given family separates one cannot know what the outcome of the children in that family might have been if the separation had not occurred. However, future research might statistically stratify families for the level of family conflict and then compare post-separation family conflict and child outcomes in families in which separation then occurred or did not. Lastly, another limitation of this study is the absence of information for children who were exposed to more than one separation and/or divorce as a distinct group.

On the other hand, the study has several strengths. It is a population-based study with a large sample size, which made it possible to take into consideration numerous confounders. We used validated questionnaires with good reliability and validity. We also had repeated measurements of family conflict, parental separation, and child emotional and behavioral problems. Mothers and fathers participated in this study, and information about family conflict and child problem behavior as reported by both parents was available. Thus, our study used multiple informants, which increases the reliability of our findings and reduces the risk of reporter bias. Although we replicated that child problem behavior can increase the risk of family conflict, our primary conflict measure was prenatal, thus obviating this reverse causality issue in part. Also, we ensured temporal ordering by adjusting for pre-existing child emotional and behavioral problems.
Clinical Implications

Our study has several important clinical implications for prevention and treatment of emotional and behavioral disorders in children. Our findings that both family conflict and parental separation predict child maladjustment and that prenatal family conflict predicted child emotional and behavioral problems up to age 9 underscore that conflict and separation are significant risk factors for children. Practitioners should be aware that if parental separation occurs in families with high levels of conflict, some proactive intervention may be needed to help the children adjust. These children remain at risk for behavioral and emotional problems even after separation. Family counselors and practitioners should address conflict arising around new domestic arrangements, financial problems, parental care or guardianship even after separation. Furthermore, school-based or health-care based screening for emotional and behavioral problems in children experiencing family conflict and/or separation would be helpful as a prevention measure.67

In cases of severe family conflict, separation is seen by many parents and family counselors as a potential solution. Also, we did not find a positive effect of separation on child behavioral and emotional problems; the association was tentative at best, given the lack of statistical significance and broad confidence intervals. However, because clinicians sometimes do find beneficial effects of separation on children, examination of possible beneficial effects of separation merits further research. The interaction of family conflict and parental separation could be explored in adolescence and incorporated into studies addressing the impact of family conflict on emotional and behavioral problems.

Conclusions

Using the large and diverse Generation R sample, we found that family conflict from pregnancy onwards and parental separation each strongly predicted child problem behavior up to pre-adolescence according to maternal and paternal ratings. Our use of the four-way decomposition method yielded evidence prenatal family conflict increased the children's vulnerability to the harmful effect of parental separation but no evidence of a beneficial effect of parental separation on child problem behavior. Overall, our findings indicated that if parental separation occurs in families with low levels of conflict, parental separation does not predict more child problem behavior. Moreover, our bi-directional findings suggested that child problem behavior influences the persistence of family conflict.
REFERENCES


63. Lansford JE, Malone PS, Castellino DR, Dodge KA, Pettit GS, Bates JE. Trajectories of internalizing, externalizing, and grades for children who have and have not experienced their parents’ divorce or separation. *J Fam Psychol.* 2006;20(2):292-301.


SUPPLEMENTARY MATERIAL

Figure 1. Inclusion of the Study Sample

Parents who initially enrolled in Gen R study N=8,879

Exclusion:
- Information on mothers with no partner; N=1,266
- Missing N=490

Information on FAD eligible: N=7,123 mother; N=4,561 father;

Not assessed at age 3, 5, and 9 years; N=1,315*

Information on FAD available; N=5,808 mother

Separated mothers by age 3: N=342 (8.2%)
- Mothers with partner N=3,832 (91.8%)
- Total N=4,174

Mothers reported on child problem behavior data at age 3; N=4,223

Separated mothers between age 3-5: N=430 (8.9%)
- Total separated mothers by age 5; N=772 (15%)
- Mothers with partner N=4,391 (85%)
- Total N=5,163

Mothers reported on child problem behavior data at age 5; N=5,063

Separated mothers between age 5-9: N=298 (7.9%)
- Total separated mothers by age 9; N=1,070 (23.6%)
- Mothers with partner N=3,473 (76.4%)
- Total N=4,543

Mothers reported on child problem behavior data at age 9; N=4,062
Sensitivity analysis approach

Given a hypothetical unmeasured confounder under simplifying assumptions, we assessed how robust our mediation analysis is to violations of unmeasured confounding. The sensitivity parameters of the correlation $\rho$ between parental separation and child problem behavior regressions were tested. If unobserved variables exist that confound the associations between parental separation and child problem behavior, even after conditioning on the observed prenatal family conflict, we expect that the unmeasured confounding assumption is violated and $\rho$ is no longer zero. The sensitivity analysis was conducted by varying the value of $\rho$ and examining how the estimated Total Natural Indirect Effect (TNIE) changes. The results of the average mediation effect is -0.30, 95%CI: -0.005, 0.40 for a correlation that would reduce the effect of parental separation to zero. That is, the unobserved confounder would have to explain 30% of the variance in the child problem behavior for the estimate of TNIE (natural direct effect - NDE + natural indirect effect - NIE) to be zero (Supplementary, Table 1).

Table 1. Sensitivity Analysis for Unmeasured Confounding (N=3,787)

<table>
<thead>
<tr>
<th>Average of NDE and NIE</th>
<th>Estimate</th>
<th>(95% CI)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural indirect effect - (NIE)</td>
<td>-0.30</td>
<td>(-0.007, 0.43)</td>
<td>.014</td>
</tr>
<tr>
<td>Natural direct effect - (NDE)</td>
<td>3.42</td>
<td>(2.08, 4.23)</td>
<td>.001</td>
</tr>
<tr>
<td>Total natural indirect effect</td>
<td>3.12</td>
<td>(1.70, 4.18)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: Average mediation effect corresponding to unobserved confounder. Estimates represents the variance explained by the unobserved confounder for the mediator (parental separation) and the outcome (child problem behavior) respectively. The models are adjusted for maternal age, ethnicity, education, religion, maternal psychopathology, gestational age at birth, child sex and prior child problem behavior when child was 1.5 years reported by mother. Natural direct effect estimated as follows: NDE = (CDE+INT ref). Natural indirect effect estimated as follows: NIE = (PIE+INT med).
Chapter 3

From parent to child to parent: associations between parent and offspring psychopathology

Yllza Xerxa, Leslie A. Rescorla, Jan van der Ende, Manon H. J. Hillegers, Frank C. Verhulst, Henning Tiemeier

ABSTRACT

Parental psychopathology can affect child functioning, and vice versa. We examined bidirectional associations between parent and offspring psychopathology in 5,536 children and their parents. We asked three questions: (a) are parent-to-child associations stronger than child-to-parent associations? (b) are mother-to-child associations stronger than father-to-child associations? and (c) do within- and between-person effects contribute to bidirectional associations between parent and offspring psychopathology? Our findings suggest that only within-rater bidirectional associations of parent and offspring psychopathology can be consistently detected, with no difference between mothers and fathers. Child psychopathology was hardly associated with parental psychopathology. No evidence for cross-rater child-to-parent associations was found suggesting that the within-rater child-to-parent associations reflect shared method variance. Moreover, within-person change accounted for a part of the variance observed.
INTRODUCTION

Parental psychopathology has been found to increase risk for a wide range of negative mental health outcomes, including child internalizing and externalizing problems.\(^1\) The recognition of the importance of bidirectional associations in the transactions between parents and children is often attributed to Sameroff and Chandler.\(^2\) Further advocacy of the significance of the bidirectional associations in child development was also provided by Sameroff,\(^3\) who argued for a transactional model of development whereby the relationships between children and their caregivers “change, maintain, and then change again the characteristics of participants” (Sameroff, 1975, p. 3). Not only do behaviors of parents impact behaviors of their children, but children's behaviors also impact behaviors of their parents.\(^4\) In other words, children's adjustment problems reflects the continuous interplay between individual characteristics that children bring to their social interactions and the quality of social support and resources.\(^5\)\(^-\)\(^7\) Despite the fact that the bidirectional, theory of child development is now at least 50 years old, much research still regards children as the passive recipients of their parents’ socialization.\(^8\)\(^,\)\(^9\) To help address this limitation of much prior research, our study adopted a bidirectional approach. Using a large and diverse population sample, we analyzed data from a 10-year longitudinal study to test bidirectional associations between self-reported parental psychopathology and parent-rated child psychopathology at multiple time points. The study of bidirectional transactional associations between parents and children is consistent with a developmental psychopathology perspective of bidirectional influences on development.\(^10\)\(^,\)\(^11\)

Previous Studies of Bidirectional Associations in Parent and Child Psychopathology

Bidirectional associations have been studied with respect to child psychopathology and parenting practices such as dysfunctional parenting.\(^12\)\(^-\)\(^15\) Taken together, these studies found some evidence for a bidirectional association between parenting and child problems. Typically, maternal to child associations were stronger than paternal to child associations, although most studies relied on maternal reports only. Therefore, many studies that investigated the association between parental psychopathology and child psychopathology have primarily focused on the unidirectional relation from parent to child. These studies showed that parental psychopathology adversely affects child problem behavior, including depression, anxiety and aggression.\(^16\)\(^-\)\(^19\) The exposure to parent psychopathology may place children at risk for internalizing and externalizing problems through a number of processes. These processes include shared genetics, disruptions in parenting, exposure to parents’ maladaptive cognitions, affect, and behavior,\(^20\)\(^,\)\(^21\) as well as exposure to stressful life-events and lack of parental social support.\(^22\) However, children also play an active role in influencing their parents’ behavior and
well-being. Although less is known about the impact of child problem behavior on parental psychopathology, evidence suggests that children’s problem behavior, especially disruptive behavior, is likely to be associated with parental psychopathology. Much less is known about the bidirectional relationship between child problem behavior and parental psychopathology, such as depression and anxiety.

We were interested in the reciprocal associations between parental psychopathology and problem behavior in children prior to adolescence. In the first decade of life, influences on child behavior usually are confined to the family context and to the school, with less influence from the wider environment, especially peers, than is the case with adolescents.

To our knowledge, there are only a few studies on bidirectional associations between parental psychopathology and problem behavior in preschool or school-aged children. These studies give a mixed picture. For example, Gross et al. and Gross et al. provided some support for bidirectional associations between parental depression and adolescent disruptive behaviors. However, Gross et al. did not provide support for reciprocal associations between child and parental psychopathology in preschoolers. They found that maternal and paternal depressive symptoms at child age 2 predicted child internalizing problems at age 4, but no reverse association in early childhood.

Nicholson et al. reported bidirectional associations of maternal depressive symptoms and child internalizing and externalizing problems based on mother reports only. The authors indicated that mother-to-child influences were greater than child-to-mother influences. Choe et al. provided no support for bidirectional associations between maternal depression and child externalizing behavior using mother-reported depressive symptoms and teacher-reported child externalizing problems. However, when allowing for the moderating effects of gender and the level of children’s effortful control (EC), Choe et al. found that child externalizing problems at age 3 were associated with fewer depressive symptoms in mothers of children with high EC at child age 10 years. In another study Antunez et al. found some support for bidirectional longitudinal associations between paternal but not maternal anxiety-depression and ODD problems in boys at age 3 but not in girls. Finally, in a study of adopted children and their adoptive parents Brooker et al. showed reciprocal longitudinal associations between parental anxiety and infant negative affect, assessed by mothers’ and fathers’ reports as well as by observations of interactions with the child. Genetic liabilities from birth parents did not explain the observed associations.

The few existing studies on bidirectional associations between parental psychopathology and child problem behavior at preschool and school age thus provide some support for the presence of reciprocal associations between parental psychopathology and child
problem behavior over time, but these studies have a number of limitations. First, most studies used small or selected samples across rather limited time periods, usually spanning infancy or early childhood. Few studies involved unselected samples of children from the general population over wide enough time intervals to cover major developmental periods and test the stability of bidirectional effects of parental and child psychopathology over time. Second, results are inconclusive with regard to the level of symmetry in the bidirectional associations between parent and child,\textsuperscript{28,29} with only some indicating that parent to child influences were greater than child to parent influences.\textsuperscript{25} Third, a particularly notable limitation of literature is that the extant research has primarily focused on group-level differences (i.e., between-person associations), thus overlooking stability and change at the individual level (i.e., within-person associations). Understanding the variability at the individual level is likely the most relevant for developmental theory and intervention science.\textsuperscript{32} Fourth, studies are inconsistent regarding whether these bidirectional associations are similar for maternal and paternal report of child problem behavior.

A frequently encountered problem in the study of child psychopathology is that of shared-rater variance. When the same reporter provides ratings on the predictor and the outcome, part of the explained variance may be due to the informant who is reporting rather than to the constructs the measures are assumed to represent. For example, if mothers report on their own problems as well as on their child’s problems, there is the likelihood of halo effects in ratings, reflecting shared informant variance and therefore resulting in inflated parent to child associations. Ringoot et al.\textsuperscript{31} showed that more than 30% of an effect can in some instances be attributed to this shared rater variance. Results provided support that shared rater variance affected the associations when parents reported on both their own depression and on child problem behavior, suggesting inflated associations between parental depression and child problem behavior. To avoid shared-rater variance, information on predictor and outcome variables must be obtained from multiple sources or informants (e.g., mothers’, fathers’, teachers’ reports, children’s self-reports). The present study in the general population extended the literature on bidirectional associations between parent and offspring psychopathology by examining the reciprocal associations of repeatedly measured parent and offspring psychopathology up to the child’s age of 10 years. Both parents provided reports of parental psychopathology in three periods namely, the prenatal period, when the child was approximately 3 years old and approximately 10 years old. The parents each reported child internalizing and externalizing problems at ages 3 and 10. With separate measures of maternal and paternal psychopathology as well as with separate ratings of child problem behavior by mothers and fathers, we were able to examine the differences between associations of child prob-
lem behavior and parental psychopathology as assessed by the same rater versus different raters. The current study had three main aims. First, we aimed to examine bidirectional associations between parent and child psychopathology over time, and whether parent to child associations are stronger than child to parent associations. Second, we aimed to examine whether mother to child associations are stronger than father to child associations. The third aim was to disaggregate within- and between-person effects in the bi-directional associations between parent and offspring psychopathology over time.

**METHOD**

**Participants**

Our study was embedded in the Generation R Study, a multi-ethnic population-based cohort from fetal life onwards. The Generation R Study has been described in detail previously. Briefly, all pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants. Of the 8,879 women enrolled during pregnancy, we excluded 1,266 mothers with no partner and 890 with missing parental psychopathology data, leaving 6,723 mothers and 5,025 fathers. For the current study, families were included if the child had behavior problem data collected at a minimum of one data point (i.e., ratings by mother at age 1.5, 3, or 10 years or by father at age 3 or 10). This resulted in 5,536 children and their parents. Self-reported psychopathology data were missing for 21% of mothers and 33% of fathers at child age 3 and 30% of mothers and 43% of fathers at child age 10. Maternal reports of child problems were missing for 20% of the children at age 3 and 30% at age 10, whereas paternal reports of child problems were missing for 33% of children at age 3 and 45% at age 10.

**Measures**

**Parental Psychopathology**

Mothers and fathers completed the Brief Symptom Inventory (BSI) to report on their psychiatric symptoms at 20 weeks pregnancy (prenatal time period, 18-25 weeks gestational age) and when their child was approximately 3 and 10 years old. The BSI is a validated self-report questionnaire with 53 items to be answered on a five-point scale, ranging from 0 = ‘not at all’ to 4 = ‘extremely’. At 20 weeks of pregnancy the complete 53 item questionnaire was employed, while at 3 and 10 years a short form was used including four of nine subscales. For each measurement we computed the Global Severity Index (GSI; ), which is the mean score of all items. The Brief Symp-
tom Inventory (BSI) is widely used instrument to measure self-reported psychological symptoms in samples of psychiatric patients and community non-patients. This instrument encompass three global indices and nine symptom dimensions covering clinically relevant psychiatric and psychosomatic symptoms. High validity and reliability have been reported for the Dutch translation. In the current study, internal consistencies (Cronbach’s alpha) ranged from 0.66 to 0.73.

**Child Problem Behavior**

The Child Behavior Checklist for toddlers (CBCL/1½-5) and for older children (CBCL/6-18) was used to obtain standardized parent reports of children’s problem behaviors. The CBCL/1½-5 contains 99 problems items, which are scored on three broadband scales (Internalizing, Externalizing, and Total Problems). The Internalizing scale comprises the Emotionally Reactive, Anxious/Depressed, Withdrawn/Depressed, and the Somatic Complaints scales, whereas the Externalizing scale comprises the Attention Problems and the Aggressive Behavior scales. Each item is scored on a three point rating scale 0 = ‘not true’, 1 = ‘somewhat or sometimes true’, and 2 = ‘very true or often true’, based on the preceding two months. The CBCL/6-18 has 118 problem items, also yielding syndrome scales and the two broadband scales Internalizing and Externalizing with ratings based on the preceding 6 months. The Internalizing scale comprises the Anxious/Depressed, Withdrawn/Depressed, and the Somatic Complaints scales, whereas the Externalizing scale comprises the Rule-Breaking Behavior and the Aggressive Behavior scales. Good reliability and validity have been reported for the CBCL/1½-5 and CBCL/6-18. The scales were found to be generalizable across 23 societies, including The Netherlands.

We used the continuous Internalizing and Externalizing Problems scores separately rather than Total Problems score (the sum of ratings on all problem items) as our outcome measures. These broadband scales tap a wide variety of children’s emotional (Internalizing) and behavioral (Externalizing) problems. Multiple studies have documented the validity of the CBCL’s Internalizing and Externalizing scales as broadband measures of child psychopathology, starting with Achenbach. Since that time, many other instruments assessing child psychopathology have adopted these broadband groups of problems. Cronbach’s alpha for the Externalizing scale ranged from 0.76 to 0.78, and for the Internalizing scale from 0.65 to 0.70.

**Covariates**

Maternal and paternal age were assessed at intake. Parental ethnicity was categorized into Dutch, non-Western and other Western national origin. Parental education was classified in three levels: ‘low’ (maximum of three years general secondary school), ‘medium’ (>3 years general secondary school; intermediate vocational training), and ‘high’
(Bachelor’s degree or higher academic education). Information about smoking (three categories: no smoking during pregnancy, smoked until pregnancy recognized, and continued smoking during pregnancy), alcohol intake during pregnancy (four categories: no alcohol consumption during pregnancy; alcohol consumption until pregnancy recognized; continued occasionally during pregnancy (<1 glass/week); and continued frequently during pregnancy (1+ glass/week)), was prenatally assessed by questionnaires. Date of birth and gender of the infant were obtained from community midwife and hospital registries at birth. We controlled for potential effect of confounders, including socioeconomic factors and maternal or paternal psychopathology at baseline as they are related to parental psychopathology and/or child problem behavior.44-46

The mean age of the children was 10 years. Half (49.5%) of the children were boys. Mothers were on average 31 years at the birth of the child, fathers 33 years. In total, 28% of mothers and 25% of fathers had a non-Western national origin. Whereas, 19% of mothers and 20% of fathers had low educational level. Of mothers included in the analyses, 10.4% had actively smoked during pregnancy, while 7.6% of mothers continued to use alcohol during pregnancy.

Statistical Analyses
First, we computed descriptive statistics and the correlations between parental psychopathology and CBCL Internalizing and Externalizing scores at different time points. Then, we used structural equation modeling (SEM) to test the bidirectional associations between measures of parent psychopathology (measured prenatally and at child ages 3 and 10) and child Externalizing or Internalizing problems (measured at ages 3 and 10). Prenatal maternal- and paternal-reported psychopathology were included in the model because these reports are not affected by the child’s problems and could therefore be used to test associations without a possible bidirectional association. The models were adjusted for baseline potential confounders, including parental age, ethnicity, education, child sex and age, smoking, alcohol consumption and prenatal parental psychopathology reported by mother and father.

Separately for Externalizing (Figure 1) and Internalizing (Figure 2), standardized linear regression coefficients were used in the cross-lagged panel SEM analyses at different ages of assessment and different informants. The model included paths from prenatal maternal and paternal BSI to child Externalizing and Internalizing scores at subsequent time points (e.g., ages 3, and 10), as well as from child Externalizing and Internalizing scores at earlier time points to maternal and paternal BSI scores at subsequent time points (e.g., ages 3 and 10). We also estimated the coefficients representing stability paths from one parental BSI score to the subsequent parental BSI scores and from one child Externalizing score to the next. Each SEM model also included cross-sectional correla-
tions between parental BSI and child Externalizing scores; and all paths and covariances were freely estimated. Furthermore, we evaluated in stratified analyses whether there are differences in the bidirectional associations between parent and offspring psychopathology determined by child gender.

To test whether the within-rater parent to child psychopathology are statistically different from the cross-rater associations, Wilson estimates of 84% confidence intervals of the estimates were compared. In contrast to 95% confidence intervals, 84% confidence lead to a probability of overlap of approximately 5%, and therefore, if confidence intervals of two estimates do not overlap, they differ significantly.

Including both maternal and paternal reports in the same SEM model addresses (dis)agreement between informants and thus was our model of choice. However, we also present an extended version of this classical SEM, namely an auto-regressive latent trajectory model with structured residuals (ALT-SR) to better disaggregate the within- and between-person associations of parental and offspring psychopathology differences. This model addresses both stability and change of psychopathology over time. The ALT-SR model incorporates latent growth curve modeling and correlates the latent intercepts (the estimated population mean level and residual between-person variance) and slopes (the between-person variance associated with the rate of the change) across parental BSI scores and child outcomes. We estimated the between-person associations by the latent growth measures and (co) variances. The covariance between our latent growth factors extracts the disaggregated between-person parameters (represented by $\Psi$ standardized below), thus pushing the remaining within-person variance into the residual auto-regressive and cross-lagged portion of the model. The cross-lagged and auto-regressive components of this model represent within-person deviations from one’s own typical trajectory.

In ALT-SR models, we first tested the within-person auto-regressive associations among parental BSI scores and child outcomes as well as the between-person intercepts and slopes. It is important to understand differences between the within- and between-person associations and how estimates can be biased when the variance in not disaggregated. We specified random intercepts and a linear slope with grow rates free to vary across individuals for both BSI scores and child outcomes (Internalizing and Externalizing problems). Next we tested reciprocal associations between parental BSI scores and child outcomes. All ALT-SR models were constraint to be equal over time. Covariance between the two intercepts (parental BSI scores and child outcomes), and the two slopes (parental BSI scores and child outcomes) were estimated. In each model we adjusted for all previously mentioned confounders at baseline, and for all models the intercepts and slopes were regressed on each of the confounders.
Figure 1. Structural equation modeling of parental psychopathology and child externalizing problems. Numeric values are standardized path regression coefficients. The models are adjusted for parental age, ethnicity, education, child sex and age, smoking, alcohol consumption and prenatal parental psychopathology reported by mother and father. (RMSEA=0.01; CFI=0.99; TLI=0.90). The dotted line represents the non-significant associations. The bold line represents significant associations that test our hypothesis. *p<0.01. **p<0.001.
Figure 2. Structural equation modeling of parental psychopathology and child internalizing problems. Numeric values are standardized path regression coefficients. The models are adjusted for parental age, ethnicity, education, child sex and age, smoking, alcohol consumption and prenatal parental psychopathology reported by mother and father. (RMSEA=0.02; CFI=0.99; TLI=0.92). The dotted line represents the non-significant associations. The bold line represents significant associations that test our hypothesis. *p<0.01. **p<0.001.
The SEM and ALT-SR models are conducted to enable causal inference, but they cannot demonstrate causality in the way that a randomized controlled trial (RCT) can do. Hence, we avoid causal language in the Results and Discussion sections and infer causality very cautiously, as suggested by Hernán.52

Since parental and offspring psychopathology were measured by both mothers and fathers and repeatedly over time, invariance was tested using $\Delta \chi^2$-chi square difference tests 53 to determine whether bidirectional estimates of the associations were statistically different between mothers and fathers. Three separate sets of constraints were imposed. The models were first fit with the bidirectional associations between parental and offspring psychopathology estimated freely, that is not constrained. Then two sets of models were constrained to be equal for mothers and fathers. One set constrained the associations from parental BSI to child Externalizing scores to be equal over time, and the other set constrained the associations from child Externalizing to parental BSI scores be equal over time. For example, the stability between parental BSI scores prenatal and age 3 was constrained to be equal to the stability of parental BSI scores between ages 3 and 10. Comparison of the free versus constrained path models indicates whether the associations for mothers and fathers are different. As $\Delta \chi^2$- is sensitive to sample size, we also examined the difference in comparative fit index ($\Delta$CFI) and root mean square error of approximation ($\Delta$RMSEA).54

To address missing data, we used full information maximum likelihood (FIML) to account for the missing data. FIML avoids uncertainties from estimating data and provides unbiased estimates of missing parameters in large sample size while retaining natural variability in missing data.55 Thus, each participant contributes to the data they have available at each time point to the likelihood function and no participants are removed from analyses through listwise deletion. In addition, we compared our findings with and without FIML procedures (i.e., listwise deletion was employed) and found no evidence that our estimates were biased by the missing data. The data were analyzed using SAS 9.4 for descriptive statistics and structural equation modeling - SEM, and Mplus. 856 for auto-regressive latent trajectory with structured residuals - ALT-SR.

Root mean square error of approximation (RMSEA) ≤ 0.05, and the comparative fit index (CFI) and Tucker-Lewis index (TLI) ≥ 0.90 were taken to indicate good fit in the SEM models. When comparing the estimated SEM models, goodness-of-fit was also evaluated using $\chi^2$.57
RESULTS

Parental and child characteristics are presented in Table 1. Mothers were on average 31 years at the birth of the child, fathers 33 years. In total, 28% of mothers and 25% of fathers had a non-Western national origin. Supplementary Tables 1 and 2 show the correlations, means and standard deviations between parental BSI measures and child Externalizing and Internalizing scores, respectively. Longitudinal correlations for child Externalizing and Internalizing problems were consistently higher for the same informant ratings (e.g. mothers’ ratings at different time points) versus cross-informant ratings (e.g. mothers’ ratings at one time point and fathers’ ratings at another time point). Also, correlations between parental psychopathology and child Externalizing or Internalizing problems were consistently larger if scores were based on the same informant (e.g., mothers’ self-reports of her psychopathology and mother-reported child behavior problem) versus different informants (e.g. mothers’ self-reports of her psychopathology and father-reported child behavior problem).

| Table 1. Baseline Characteristics of Study Sample (N=5,536) |
|---------------------------------|-------------|-------------|
| Age, M (SD)                     | Mother      | Father      |
| Ethnicity                       |             |             |
| Dutch, (%)                     | 62.6        | 67.9        |
| Other Western, (%)              | 9.3         | 6.9         |
| Non Western, (%)                | 28.1        | 25.2        |
| Educational level               |             |             |
| High, (%)                       | 52.4        | 54.8        |
| Middle, (%)                     | 28.9        | 25.7        |
| Low, (%)                        | 18.7        | 19.5        |
| Alcohol use during pregnancy    |             |             |
| No consumption during pregnancy, (%) | 37.4      |             |
| Until pregnancy recognized, (%) | 13.8        |             |
| Continued occasionally, (%)     | 38.4        |             |
| Continued frequently, (%)       | 10.4        |             |
| Smoking during pregnancy        |             |             |
| No smoking during pregnancy, (%) | 79.8        |             |
| Until pregnancy recognized, (%) | 12.5        |             |
| Continued during pregnancy, (%) | 7.6         |             |
| Gender, (% boy)                 |             |             |
| Age, years, M (SD)              |             |             |

Note: Numbers denotes children included in one or more analyses. Values are frequencies for categorical and means and standard deviations (M ±SD) for continuous measures.
Figure 1 shows the SEM of the bidirectional associations between parental BSI and child Externalizing scores reported by mothers and fathers. Results indicated good fit to the data (RMSEA = 0.01, CFI = 0.99, and TLI = 0.90). The standardized coefficients obtained in the SEM analyses are presented in the figure, with straight lines representing significant associations and dotted lines non-significant associations. The autoregressive coefficients showed that parental BSI scores were moderately stable and yet sufficiently variable over time to model change. Similar association patterns over time were observed between the repeatedly measured Externalizing and also the Internalizing scores (Figure 2). Both maternal and paternal BSI scores were associated with child Externalizing scores at ages 3, and 10, with children exposed to higher parental BSI scores having higher Externalizing scores. The association of maternal and paternal psychopathology with child outcome was consistently stronger if rated by the same rater than by the other parent, i.e. cross-informant. The reverse associations, those from child to parent are also shown in Figure 1. When reported within-rater, the associations between child Externalizing scores on parental psychopathology were similar to those for parent to child associations. No paths testing the associations between child Externalizing scores during childhood were associated with parental psychopathology across-rater.

Comparing the within- and across-rater associations by calculating 84% confidence intervals showed that, for example, the association of mother-reported child Externalizing scores at age 3 with mother-reported BSI scores at age 10 (84% CI: .04, .05) differed from the association of mother-reported child Externalizing scores with father-reported BSI scores at age 10 (84% CI: -.06, -.05), as the CIs do not overlap. Similarly, the associations of mother-reported child Internalizing scores at age 3 with mother-reported BSI scores at age 10 (84% CI: .03, .04) differed from the association of mother-reported child Internalizing scores with father-reported BSI scores at age 10 (84% CI: -.02, -.04). Based on these comparisons (not shown), there is evidence for a difference between the effect estimates of the within-rater parent to child psychopathology and the cross-rater associations.

Next, we tested the bidirectional association of parental psychopathology and child Internalizing scores with a similar model. Again, RMSEA = 0.02, CFI = 0.99, and TLI = 0.92, showed a good fit to the data (see Figure 2). The estimates for Internalizing were very similar to the results for child Externalizing scores. Prenatal maternal and paternal BSI scores were consistently related to higher child Internalizing scores at ages 3 and 10 as reported by mothers and fathers. For child Internalizing scores, results remained consistent over time, with higher Internalizing scores associated with parental psychopathology over time, but only within-rater. In summary, both mothers’ and fathers’ child Externalizing and Internalizing reports were associated with their level of psychopathology symptoms over time.
Figure 3. Autoregressive latent trajectory model with structured residuals (ALT-SR), disaggregating the within- and between-person associations of parental and offspring psychopathology. Numeric values are standardized path coefficients. The dotted lines represent the non-significant associations. The control variables (parental age, ethnicity, education, child sex and age, smoking, alcohol consumption and prenatal parental psychopathology reported by mother and father) are not shown in the figure for the ease of interpretation. ε (epsilon) = residual variance; BSI = parental psychopathology; EXT = child externalizing problems. MR = mother report; FR = father report. Full parameter estimates can be found in Supplementary Table 4.*p<0.01. **p<0.001.
Figure 4. Autoregressive latent trajectory model with structured residuals (ALT-SR), disaggregating the within- and between-person associations of parental and offspring psychopathology. Numeric values are standardized path coefficients. The dotted lines represent the non-significant associations. The control variables (parental age, ethnicity, education, child sex and age, smoking, alcohol consumption and prenatal parental psychopathology reported by mother and father) are not shown in the figure for the ease of interpretation. & = residual variance; BSI = parental psychopathology; INT = child internalizing problems. MR = mother report; FR = father report. Full parameter estimates can be found in Supplementary Table 4. *p<0.01. **p<0.001.
Figure 3 shows the results of the ALT-SR models for parental BSI and Externalizing scores reported by mothers and fathers. Intercept and slope factors represented by latent growth models indicated moderate to strong associations for between-person maternal and paternal BSI and child Externalizing scores. Specifically, we observed that higher initial levels of maternal BSI scores were associated with higher initial levels of Externalizing scores ($\Psi_{\text{standardized}} = 2.94$, $p < .001$), as well as higher initial levels of paternal BSI scores were associated with higher initial levels of Externalizing scores ($\Psi_{\text{standardized}} = 2.83$, $p < .001$). In the final within-person cross-lagged model, we observed bidirectional associations between maternal and paternal BSI and child Externalizing scores, whereby higher levels of maternal and paternal BSI scores than typical (i.e., higher than the individual mean) were associated with higher levels of child Externalizing scores at the next time point, and vice versa. Our final model resulted in good fit to the data (CFI = .97, RMSEA = .003).

Next, the covariance between random intercepts for maternal BSI and child Internalizing scores ($\Psi_{\text{standardized}} = 2.63$, $p < .001$), and paternal BSI and child Internalizing scores ($\Psi_{\text{standardized}} = 2.55$, $p < .001$) were modeled. When evaluating the within-person reciprocal effects, we found that higher levels of both maternal and paternal BSI scores were associated with higher levels of child Internalizing problems than their typical levels at the next time point, and vice versa. Our final model resulted in good fit to the data (CFI = .96 , RMSEA = .009) (Figure 4).

In addition, we tested whether bidirectional paths coefficients significantly differed across mothers and fathers using $\Delta \chi^2$- chi square difference tests. Invariant bidirectional paths estimated freely for both mothers and fathers provided a good fit to the data. When bidirectional path models were constrained to be equal across mothers and fathers, neither the paths from parental BSI to Externalizing scores, nor the paths from Externalizing to parental BSI scores differed between mothers and fathers. Next, the invariant bidirectional paths estimated freely for parental BSI and child Internalizing scores provided a good fit to the data. As before, when equality constraints were set, neither the patterns for BSI to child Internalizing scores, nor the paths from child Internalizing to BSI scores, differed significantly between mothers and fathers (Supplementary, Table 3). However, father and mother reports independently predicted child behavioral problems; that is, each parent contributed unique information.

Stratified analyses showed that our findings regarding the bidirectional associations between parent and offspring psychopathology did not differ by gender of the child. Likewise, the parent to child psychopathology associations did not vary by gender of the child (results not shown).
DISCUSSION

This large population-based study examined the bidirectional associations between parent and offspring psychopathology reported by mothers and fathers up to age 10. Specifically, we examined the associations between parent and offspring psychopathology by leveraging recent advances in modeling longitudinal associations that disaggregate within- and between-person associations. Ratings provided by both mothers and fathers enabled us to also examine differences between gender of the parents in the bidirectional associations of parent and offspring psychopathology. We highlight three main findings. First, parental psychopathology and child externalizing or internalizing problems were consistently associated within-raters but not across-raters. The magnitude of parent to child associations were stronger than the reverse associations. Second, maternal and paternal reports of psychopathology did not differ between within- and between-rater in the bidirectional associations with the child outcomes. Third, bidirectional associations between parent and offspring psychopathology were found at both the within- and between-person levels. Overall, finding bidirectional associations only within-rater of parent and offspring psychopathology but not across-rater, suggests that the observed within-rater child-to-parent associations probably reflect shared-rater variance.

Bidirectional Associations

The present findings provide consistent evidence of a bidirectional association of parent and offspring psychopathology within-raters, but not across-raters. That is, the associations of both maternal and paternal reports with child psychopathology over time appear to have been significantly affected by shared-rater variance. We did not find support for the notion that the bidirectional associations differed significantly between mothers and fathers. The use of different informants to test bi-directionality in one model enabled us to study the associations between parental psychopathology and child externalizing and internalizing problems within- and across-raters, both of which are important for informing research and clinical practice.

Within- and Between-Person Findings

The current study extends the prior work indicating the observed bidirectional associations between parental and offspring psychopathology by showing that these associations were evident at both within- and between-person levels. The between-person level showed that both mothers and fathers who reported higher levels of psychopathology also reported higher levels of child Externalizing or Internalizing problems, and vice versa. The within-person associations showed that, for a given person, changes in one’s typical level of psychopathology over time were associated to the subsequent child Externalizing or Internalizing problems, and vice versa. That is, in our study the observed associations are prominently expressed both as within- and as between-person
associations. This suggests that parental psychopathology and changes in child problem behavior occur due to individual differences in trajectory (i.e., between-person associations), as well as due to changes arising at the within-person level. Although the associations of both maternal and paternal reports of child externalizing or internalizing problems with parental psychopathology were observed within-raters but not across-raters over time, the model yielded significant between-person associations among all variables (i.e., significant covariances between intercepts). This suggests that mothers or fathers who reported higher levels of psychopathology also reported higher levels of child problem behavior. Furthermore, although prior research has shown that parent psychopathology may undermine to children’s healthy development, these earlier studies used a between-person approach that does not partition variance at multiple levels of analysis. Our model is an improvement on prior work as it takes into account within- and between-person effects, and specifically examines how deviations from one's typical level of psychopathology can affect changes in child problems at subsequent time points, and, further, how child problems can affect changes in psychopathology.

Parent to Child Associations

Our results indicated that parental psychopathology was associated with offspring psychopathology. This was true for both externalizing and internalizing problems in the child. The parent to child associations were stronger for within-rater associations than for cross-rater associations, but both sets of associations were significant. That is, coefficients were smaller when self-rated psychopathology of one parent was used to associate child psychopathology as rated by the other parent than when child psychopathology was rated by the same parent.

Theoretical models (e.g., Dodge, 1990) suggest four mechanisms could explain the observed associations between parental psychopathology and child outcome, including (a) genetic transmission; (b) pregnancy specific effects, which imply that, for example, maternal psychopathology may lead to direct physiological changes impacting fetal development; (c) exposure to parents’ maladaptive affect, behavior, cognitions, which can lead to dysfunctional modeling; and (d) contextual stressors, such as family disruption, that are related to the development of child problem behavior. For example, disadvantaged parents may have less time to facilitate children’s social activities. Although we cannot conclude which of these mechanisms contributed most to these associations, results of our study help guide the mechanistic understanding. In particular, we argue that the mechanism “b” is less likely compatible with our results, as we did not observe meaningful difference between maternal- and paternal-reported psychopathology in the bidirectional associations with child outcomes. Moreover, we carefully controlled for contextual stressors.
Further, our results are only partly consistently with the theoretical model that has emphasized the transactional processes of change in the development of child problems. Sameroff’s (1975) theory emphasized the development of the child as a product of the continuous dynamic interactions of the child and the experience provided by his or her social settings. Children and their parents mutually affect one another when children elicit particular types of responses from their parents and when parents’ behavior induces children to behave in particular ways in the future. We confirmed the parent to child associations, but child to parent associations were only observed within-rater. Moreover, the within-person change accounted for a substantial part of the variance observed. Because early childhood is a time of tremendous learning and growth, younger children may be more susceptible to parental influence than older children. Conversely, as children develop, their capacity to impact characteristics of their environments increases. For example, given that parents (and their behaviors) represent a central component of this environment, children’s ability to engage in meaningful interactions with parents will be greater than of infants, or might be bidirectional. It is also possible that both parent and child effects will weaken over time, because children become less depended on parents over time and more influenced by peers and other social factors, but they are still influenced by child- and parent-driven processes that combine to shape the home environment.

**Child to Parent Associations**

Findings for child psychopathology in association with subsequent parent psychopathology were generally weaker than those in the parent to child direction. That is, when parents rated their child’s problems and then later rated their own psychopathology, the associations were significant but generally smaller than those for the parent to child associations across the same time periods. These child to parent associations were not affected by type of problem (externalizing vs. internalizing). However, these associations were significantly affected by shared-rater variance. This can be seen in the fact that cross-rater child to parent associations were generally very weak and not significant. Consequently, parents, who are often involved in their children’s presenting problems, are not necessarily neutral reporters. Specifically, parental psychopathology, may narrow the parent’s tolerance for child problem behavior, such that minor behavioral problems are misperceived as major issues. The narrowed band of tolerance found among parents with psychopathology symptoms would result in a lowered threshold for child problems, which in essence is based on a distorted perception of child problem behavior. Alternatively, parents’ negative perception of their children not supported by other informants must not directly follow from parental misperceptions of child problem behavior. Rather, high parental rates of reported child problems could stem from problematic interactions in family, rather than from parental negative perceptions.
Shared-Variance Issues
That the longitudinal associations between child and parent psychopathology were largely observed only within and not cross-rater, could in principle reflect three factors, namely cross-rater disagreement, information bias, and importantly, shared-rater variance, which is a particular form of information bias. First, the differences in the associations from child to parent psychopathology could depend on the rater, but associations across raters were absent or weak independent of the parental perspective on child behaviors. It is likely that mothers and fathers have different kinds of relationships with children that evoke different behaviors. For example, fathering practices in terms of coaching and team sport typically differ from maternal parenting, which more occurs at home. However, we found no differences between the associations of child psychopathology with mothers’ and fathers’ problem rating. Consequently, the pattern of the within- and across-rater associations was similar in mothers and fathers. Second, the informants’ reports about his/her own psychopathology or the psychopathology their child can be distorted. For example, parent’s reports on their child’s problems could be biased by their own emotional problems, or by poor understanding of the questions. If this distortion is related (indirectly, for example due to unmeasured background factors) to the outcome assessment of the child, this could introduce a spurious relation and constitute information bias. Third, these discrepancies in the bidirectional associations between one rater and across raters can reflect shared method variance bias. This type of information bias occurs if an external factor influences both the ratings obtained for the parent and the child. It is very likely that social desirability, negative affectivity, and acquiescence (tendency to agree) affect ratings to some degree. These factors suggest that if a parent rates both his/her own psychopathology and child problem behavior, inflated shared variance is likely to occur. Characteristics of the instrument, for example the related paper and pencil setting of the CBCL and BSI measures or similar item wording, can also allow bias. Thus the shared method variance can result from the construct (e.g. the psychopathological trait), the method and importantly the informant. However, in most studies the likelihood of shared-rater variance is considerable since they used the same informant both on measures of parental psychopathology and on measures of child problem behaviors. The findings of the current study extend the literature by showing associations and possible bias by shared method variance for both parents and different types of psychopathology.

Gender Findings
We found no evidence for parental gender differences between the bidirectional associations of parent and offspring psychopathology. Previous studies showed that mothers more frequently serve as primary caretaker in the family, and spend more time with children relative to fathers. However, we observed no differences in the associations of maternal and paternal psychopathology with child problems. This may indicate that
the effect of psychopathology is independent of the time spent with the child or that genetic factors largely determine intergenerational transmission of psychopathology.

Similarly, investigating child gender, we found that the inclusion of a bidirectional association for parent and offspring psychopathology did not differ by gender of the child. This is in line with results of the two meta analyses that focused specifically on interparental agreement in ratings of their child’s problems indicating that gender of the child did not moderate discrepancies in mother and father ratings of their child’s problems. However, discrepant reports with some evidence of moderation by child gender have also been published. For example, Choe, Olson, Sameroff found that boys with suboptimal self-regulation exposed to high levels of maternal depressive symptoms showed a higher risk of school-age behavior problems.

**Externalizing versus Internalizing problems**

A final important finding of our study is that we found similar patterns of associations for the SEM models for externalizing versus internalizing problems, suggesting that both mothers and fathers respond to their children’s externalizing and internalizing problems similarly. Externalizing and internalizing problems represent two different types of children’s problems, but have considerable shared variance due to a general psychopathology factor contributing to both. This may be why we did not detect differences regarding how parental psychopathology could differentially be associated by their child’s externalizing and internalizing problems.

**Strengths and Limitations**

Several limitations of our study should be noted. First, only parents reported on their own problems and child problem behavior. We do not know what the results would be if other informants on problem behavior were obtained, such as father ratings on maternal psychopathology, mother ratings on paternal psychopathology, clinician’s ratings on parental psychopathology and teacher-, clinician- or (if the child were old enough) self-reports on child problem behavior. Second, it is also likely parental psychopathology could reflect biological vulnerability to offspring problem behaviors. Biological vulnerability can be based on shared genetically characteristics, which may increase offspring susceptibility to develop emotional and behavioral problems. The strengths of the study lie in its large population-based sample and the SEM approach to longitudinal measurement testing of a bidirectional association among two parents’ and child psychopathology. Further, we included both maternal and paternal reports on child problem behavior and therefore could examine both separate maternal to child and paternal to child models, as well as combined parent to child associations. This indicates that psychopathology in fathers and mothers are equally associated with offspring psychopathology. Our analyses also suggest that the contributions of the parents are independent of each
other, thus not due to spousal resemblance. This underlines the importance of involving fathers in research. Another strength of this study underlies the use of ALT-SR model to simultaneously consider between-person associations among parental and offspring psychopathology (e.g., mean levels growth rates), with simultaneously modeling bidirectional associations between these variables as they manifest within-person over time.

Our findings have important implications for future research and clinical practice. First, they suggest that targeting parental psychopathology among high risk parents may be effective in reducing both child externalizing and internalizing problems during childhood. As the associations of child to parent psychopathology are small, interventions aimed at parental psychopathology that include a child component would likely be only marginally more effective. Yet in the long term such interventions could certainly enhance the parental and other family member’s well-being even if not measurable in terms of parental psychopathology. Overall, our findings show that psychopathology of parents is a crucial target of prevention and intervention efforts for children with developmental problems. However, whether interventions for children with psychopathology should largely focus on parents with psychiatric problems, only on children, or on both depends on the child age, the developmental status, and cognitive capacities. Moreover, any intervention to interrupt the negative transactional processes between parental psychopathology and child emotional and behavioral problems would need to be aware of other social influence and complexities determining when and in whom to intervene.

To conclude, our findings suggest that bidirectional associations of parent and offspring psychopathology can be consistently detected only within-rater but not across-rater. Moreover, the within-person levels of psychopathology explained substantial variance of child problems, and vice versa. Child Externalizing and Internalizing problems were both predicted by earlier parental psychopathology. In contrast, child psychopathology is only weakly associated with later parental psychopathology, and with cross-rater associations generally not significant. Child gender do not affect these associations. The findings highlight the importance of shared-rater variance, suggesting that using the same rater inflates the associations between parental psychopathology and child outcomes in both directions.
REFERENCES


### Supplementary Material

#### Supplementary Table 1. Correlation Coefficients, Means and Standard Deviations between Parental Psychopathology and Child Externalizing Behavior

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**Correlation is significant at the 0.01 level (2-tailed).**

#### Supplementary Table 2. Correlation Coefficients, Means and Standard Deviations between Parental Psychopathology and Child Internalizing Behavior

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**Correlation is significant at the 0.01 level (2-tailed).**
**Supplementary Table 3.** Differential Effects of Bidirectional Associations between Parental and Offspring Psychopathology: A Comparison between Mothers and Fathers (N=5,536).

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<td>.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2: Parental psychopathology à child externalizing problems</td>
<td>Model 1</td>
<td>128.9</td>
<td>44.5</td>
<td>.003</td>
<td>.02</td>
<td>.42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3: Child externalizing problems à parental psychopathology</td>
<td>Model 1</td>
<td>122.4</td>
<td>44.5</td>
<td>.006</td>
<td>.01</td>
<td>.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Internalizing problems, mother and father reports</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1: Parent reported psychopathology and child internalizing problems</td>
<td>284.7</td>
<td>89</td>
<td>.006</td>
<td>.99</td>
<td>.38</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2: Parental psychopathology à child internalizing problems</td>
<td>Model 1</td>
<td>132.1</td>
<td>44.5</td>
<td>.001</td>
<td>.03</td>
<td>.24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3: Child internalizing problems à parental psychopathology</td>
<td>Model 1</td>
<td>118.9</td>
<td>44.5</td>
<td>.004</td>
<td>.02</td>
<td>.37</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Model 1: In the first model all bidirectional associations of parent and child (internalizing or externalizing) problems were estimated freely. Model 2: In the second model all associations from parental BSI scores to child (externalizing or internalizing) problems were constrained equal. Model 3: In the third model all associations from child (externalizing or internalizing problems) problems to parental BSI scores were constrained equal. The models are adjusted for parental age, ethnicity, education, child sex and age, smoking, alcohol consumption and prenatal parental psychopathology reported by mother and father. The following indexes are reported: \( \chi^2 \) = chi-square difference test; RMSEA = Root mean square error of approximation; CFI = Comparative fit index; \( \Delta \) = change in statistical values.
**Supplementary Table 4.** ALT-SR Model: Bidirectional Associations between Parent and Offspring Psychopathology (N=5,536).

<table>
<thead>
<tr>
<th>ALT-SR effects</th>
<th>Parameter estimate (SE)</th>
<th>Parameter estimate (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within-person cross-lags</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI_{t} on CBCL_{t} - MR</td>
<td>0.40 (0.09)**</td>
<td>0.43 (0.08)**</td>
</tr>
<tr>
<td>BSI_{t} on CBCL_{t} - FR</td>
<td>0.36 (0.07)**</td>
<td>0.33 (0.07)**</td>
</tr>
<tr>
<td>Auto-regressive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI_{t} on BSI_{t} - MR</td>
<td>0.79 (0.10)**</td>
<td>0.81 (0.11)**</td>
</tr>
<tr>
<td>CBCL_{t} on CBCL_{t} - MR</td>
<td>0.37 (0.07)**</td>
<td>0.37 (0.06)**</td>
</tr>
<tr>
<td>BSI_{t} on BSI_{t} - FR</td>
<td>0.57 (0.09)**</td>
<td>0.59 (0.08)**</td>
</tr>
<tr>
<td>CBCL_{t} on CBCL_{t} - FR</td>
<td>0.39 (0.06)**</td>
<td>0.32 (0.06)**</td>
</tr>
<tr>
<td>(Co)variances (between-person)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI_{int} with CBCL_{int} - MR</td>
<td>2.94 (0.15)**</td>
<td>2.63 (0.14)**</td>
</tr>
<tr>
<td>BSI_{int} with CBCL_{slope} - MR</td>
<td>1.95 (0.13)**</td>
<td>1.72 (0.11)**</td>
</tr>
<tr>
<td>CBCL_{int} with BSI_{slope} - MR</td>
<td>2.25 (0.15)**</td>
<td>2.27 (0.13)**</td>
</tr>
<tr>
<td>BSI_{slope} with CBCL_{slope} - MR</td>
<td>1.13 (0.09)**</td>
<td>1.19 (0.09)**</td>
</tr>
<tr>
<td>BSI_{int} with CBCL_{int} - FR</td>
<td>2.83 (0.14)**</td>
<td>2.55 (0.14)**</td>
</tr>
<tr>
<td>BSI_{int} with CBCL_{slope} - FR</td>
<td>1.87 (0.11)**</td>
<td>1.54 (0.12)**</td>
</tr>
<tr>
<td>CBCL_{int} with BSI_{slope} - FR</td>
<td>1.99 (0.12)**</td>
<td>2.15 (0.14)**</td>
</tr>
<tr>
<td>BSI_{slope} with CBCL_{slope} - FR</td>
<td>1.10 (0.10)**</td>
<td>1.13 (0.11)**</td>
</tr>
<tr>
<td>Residual (co)variances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI ( \varepsilon_{it1} - \varepsilon_{it3} ) - MR</td>
<td>4.21 (0.45)**</td>
<td>4.07 (0.44)**</td>
</tr>
<tr>
<td>CBCL ( \varepsilon_{it1} - \varepsilon_{it2} ) - MR</td>
<td>3.89 (0.37)**</td>
<td>3.83 (0.38)**</td>
</tr>
<tr>
<td>BSI ( \varepsilon_{it1} - \varepsilon_{it3} ) - FR</td>
<td>4.15 (0.43)**</td>
<td>3.87 (0.39)**</td>
</tr>
<tr>
<td>CBCL ( \varepsilon_{it1} - \varepsilon_{it2} ) - FR</td>
<td>3.26 (0.33)**</td>
<td>3.12 (0.32)**</td>
</tr>
<tr>
<td>Fit statistics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \chi^2 )</td>
<td>438.53</td>
<td>429.77</td>
</tr>
<tr>
<td>( df )</td>
<td>144</td>
<td>144</td>
</tr>
<tr>
<td>RMSEA</td>
<td>.003</td>
<td>.009</td>
</tr>
<tr>
<td>SRMR</td>
<td>.009</td>
<td>.010</td>
</tr>
<tr>
<td>CFI</td>
<td>.97</td>
<td>.96</td>
</tr>
</tbody>
</table>

Note: ALT-SR = autoregressive latent trajectory with structured residuals. All models presented here are final models with all within correlation auto-regressive paths and cross-lagged associations being estimated. Variables on the left side of an ‘on’ statement are the dependent variable at \( t + 1 \). Those on the left side represent the independent variables. BSI = Parental psychopathology; CBCL = child Internalizing or Externalizing problems; In the table subscripts identify time of measurement. For example, a single ‘t’ indicates paths were constrained to be equal over time; ‘t +1’ represents an outcome for a specific unidirectional path at the next time point. Subscript ‘int’ indicates latent intercept (mean level) to obtain between-person parameter estimates. Subscripts with an epsilon \( (\varepsilon_{it}) \) indicate residual variance from Time 1 to Time \( n \). \( ^a \) includes estimates of mother- or father-reports psychopathology and child externalizing problems. \( ^b \) includes estimates of mother- or father-reports psychopathology and child internalizing problems. RMSEA = root mean square error of approximation; SRMR = standardized root mean square error of approximation; CFI = comparative fit index. MR = mother report; FR = father report.

\( *p<0.01. \quad **p<0.001. \)
Chapter 4

Childhood loneliness as a specific risk factor for adult psychiatric disorders

Yllza Xerxa, Leslie A. Rescorla, Lilly Shanahan, Henning Tiemeier, William E. Copeland

Psychological Medicine (in press)
ABSTRACT

**Background:** Loneliness is a major risk factor for both psychological disturbance and poor health outcomes in adults. This study aimed to assess whether *childhood* loneliness is associated with long-term disruption in mental health that extends into adulthood.

**Methods:** This study is based on the longitudinal, community-representative Great Smoky Mountains Study of 1,420 participants. Participants were assessed with the structured Child and Adolescent Psychiatric Assessment interview up to eight times in childhood (ages 9 to 16; 6,674 observations; 1993 to 2000) for childhood loneliness, associated psychiatric comorbidities and childhood adversities. Participants were followed up four times in adulthood (ages 19, 21, 25, and 30; 4,556 observations of 1,334 participants; 1999 to 2015) with the structured Young Adult Psychiatric Assessment Interview for psychiatric anxiety, depression, and substance use outcomes.

**Results:** Both self and parent-reported childhood loneliness were associated with adult self-reported anxiety and depressive outcomes. The associations remained significant when childhood adversities and psychiatric comorbidities were accounted for. There was no evidence for an association of childhood loneliness with adult substance use disorders. More associations were found between childhood loneliness and adult psychiatric symptoms than with adult diagnostic status.

**Conclusion:** Childhood loneliness is associated with anxiety and depressive disorders in young adults, suggesting that loneliness - even in childhood - might have long-term costs in terms of mental health. This study underscores the importance of intervening early to prevent loneliness and its sequelae over time.
INTRODUCTION

Loneliness is a distressing emotional state that arises from the discrepancy between one’s perceived and desired levels of social connection. As such, perceived loneliness can exist for individuals who are not socially isolated. Loneliness is a major risk factor for psychological disturbance and poor health outcomes in adulthood. In population-based studies, loneliness in adolescents has been prospectively associated with social anxiety and depression.

Loneliness is relatively common among both children and adults. For example, between 11% - 27% of children (aged 10 to 15 years) reported feeling lonely in the UK, while more than 40% of Americans of all ages reported feeling lonely. Perceived loneliness is also associated with a substantial increase in the risk of premature mortality, independent of income, education, sex, and ethnicity. A longitudinal analysis of four nationally representative US samples showed the influence of social isolation on several biomarkers of cardiovascular heart disease including hypertension, body mass index, waist circumference and inflammation (hs-CRP) across the lifespan. The magnitude of this effect is comparable to that of smoking and obesity or physical inactivity.

Much less is known about the long-term effects of childhood loneliness. A recent meta-analysis of 102 cross-sectional studies of childhood loneliness found associations with social anxiety (Mage below 21 years). The same meta-analysis looked at 10 longitudinal studies and reported small but positive associations between loneliness and social anxiety symptoms both within and across time, and across childhood and adolescence. To our knowledge, there is one longitudinal study on the association between childhood loneliness and depression in pre-school and school-aged children. No studies to date have addressed the key question of whether childhood loneliness is associated with long-term disruption in mental health that extends into adulthood.

Parents and children often disagree about the presence and severity of child symptoms and psychopathology. Thus, parental and child ratings may capture overlapping but largely distinct information about a child’s experience of loneliness and associated risk for psychiatric disorder outcomes. Loneliness is, by definition, a subjective, internal state of mind. Yet, it is reasonable to expect that raters who know the child well (e.g., parents, or friends) may have access to information about the individual’s loneliness and therefore provide accurate judgments of internal traits.

To address these gaps, we conducted a large population-based study of the association between childhood loneliness and psychiatric disorders in adulthood. We focused on loneliness measures assessed 8 times from children and a parent from ages 9 to 16 years.
Participants were then followed up 4 times in adulthood between ages 19 to 30 years, and assessed for anxiety, depression, and substance use symptoms and disorders. The present study had three main aims. First, we aimed to examine whether repeated measures of loneliness in childhood are associated with a broad range of psychiatric problems that include anxiety, depression, and substance use disorders in adults. We also examined the associations between groups of childhood loneliness trajectories and these psychiatric outcomes. Second, we aimed to examine whether the associations between childhood loneliness and adult psychiatric disorders persist after accounting for other co-occurring adverse childhood experiences. Finally, we examined whether parent-reported loneliness predicts adult outcomes similarly to child reported loneliness.

**METHOD**

**Participants**

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. Data were drawn from the Great Smoky Mountains Study (GSMS), a longitudinal, community-representative cohort in which participants were followed up from age 9 years into adulthood. The GSMS, which enrolled children in 11 predominantly rural North Carolina counties, was originally designed to estimate the prevalence of mental illness and service. Initially, three cohorts of children, aged 9, 11, and 13 years, were recruited from a pool of approximately 12,000 children using a 2-stage sampling design, resulting in 1,420 participants (630 girls [weighted percentage, 49.0%]). Sampling weights were applied to adjust for differential probability of selection. An ascertainment figure appears in Figure 1 in the Supplement, and the original study articles provide additional detail on sampling and derivation of sample weights.

Annual assessments were completed until participants were 16 years old and then they were assessed again at ages 19, 21, 25, and 30 years, for a total of 11,230 total assessments from January 1993 to December 2015. Across all assessments, 83.0% of possible interviews (11,230 of 13,530) were completed. Race/ethnicity was determined based on parent report. Before all interviews, parents and children signed institutional review board–approved informed consent and assent forms. All procedures and protocols for the present study were approved by the Duke University Institutional Review Board.
Measures

Childhood loneliness

Questions about perceived loneliness were collected as part of self or parental-report interviews using the Child and Adolescent Psychiatric Assessment (CAPA) from ages 9 to 16. The CAPA defines loneliness as “a feeling of being alone and/or friendless, regardless of the justification for the feeling; total daily duration of at least 1 hour.” The CAPA focuses on the 3 months immediately preceding the interview as its primary period. To assess this item, participants and their parents were asked first “Do you think s/he feels lonely?” and then “Sometimes children feel that they have no one who would help them. Does s/he ever feel like that?”. These two questions are followed by a series of secondary prompts, if necessary, to clarify whether the child met the operational definition of lonely. Secondary prompts comprised items such as: ‘How often is that?’, ‘When was the last time?’, ‘Does s/he feel cared for by friends?’, ‘Does s/he feel lonely even though s/he has some friends?’. More details how loneliness is defined and assessed through primary and follow-up prompts can be found in the Supplementary Figure 2.

These items index both a perceived quantitative lack of contacts in one’s social network and a perceived qualitative deficit in existing relations. As such, this construct is best considered perceived social isolation (feeling lonely) as opposed to objective social isolation (being lonely). Different dimensions of social functioning (e.g. subjective loneliness, network quality, and network size) have been found to have different associations with health. Subjective loneliness has been linked to psychological consequences
Loneliness is scored on a three-point rating scale 0 = ‘not at all’, 1 = ‘the interviewee definitely feels lonely in a way that interferes with at least two activities and is uncontrol-
lable’, and 2 = ‘the interviewee feels lonely most of the time’. For the current study, loneliness was scored dichotomously (‘0’ vs. ‘1’ and ‘2’) and we aggregated the loneliness measure between ages 9 to 16 into a single measure of childhood loneliness.

**Adult psychiatric disorders and functioning**

All outcomes except where noted were assessed using the Young Adult Psychiatric Assessment (YAPA), an upward extension of the CAPA interview administered to the participants. The assessment of adult psychiatric disorders resembled that of childhood disorders, but with only self- (and not parent-) reports. A three-month “primary period” was selected because longer recall periods are associated with forgetting and recall bias. Disorders included any DSM generalized anxiety disorder, social phobia, post-traumatic stress disorder PTSD, panic disorder, agoraphobia, depressive disorder, and substance use disorder (including, nicotine, alcohol, cannabis, and other illicit drugs). For the current study we examined anxiety, depressive, as well was substance use disorders. Each psychiatric disorder measure between ages 19 to 30 is aggregated into a single measure of adult psychiatric status. The participant was positive for diagnosis if criteria were met at any adult observation. In addition, we examined symptoms scores of the total anxiety, depressive, and substance use symptoms.

**Covariates**

Parent and child characteristics examined as potential confounders are depicted in the Appendix in the Supplement. These included the following: sex of the child, rural vs. urban area, family hardships (including low socio-economic status, single parent, change in parent structure, maltreatment, and depression of the mother), and childhood psychiatric comorbidities (including anxiety, depression and disruptive behavior). For psychiatric symptoms, the CAPA focuses on the 3 months immediately preceding the interview to minimize recall bias. Scoring programs written in SAS statistical software (SAS Institute Inc) combine information about the date of onset, duration, and intensity of each symptom to create DSM diagnoses. Test-retest reliability and validity of the CAPA diagnoses are similar to other psychiatric interviews. Psychiatric disorders assessed included anxiety disorders, depression disorder, and substance use disorders. The categories of family hardships or childhood adversities were assessed at each observation. A full description of these variables is available in a previous publication. In our study we aggregated childhood covariates between ages 9 to 16 into a single measure of each covariate.
Statistical Analysis
First, we computed descriptive statistics for self- and parent-reported loneliness at different time points. Then, we tested prospective associations of childhood loneliness (between ages 9 and 16 years) reported by parent and child with adult anxiety, depression, and substance use diagnostic status (between ages 19 and 30 years) with separate weighted logistic regressions. Then, we tested prospective associations of childhood loneliness with adult anxiety, depressive, and substance use symptom scores with separate linear regressions. All analyses applied sampling weights; therefore, results provide estimates of the original representative population from which the sample was drawn.

As a follow-up to primary analyses, a latent class growth analysis was used to test for the association of childhood loneliness trajectories with adult psychiatric disorders. Trajectories of loneliness were modeled in children from whom data were available for two or more time points (N = 1,334). Models with two to five trajectories were assessed and compared. We used full information maximum likelihood ratio to account for missing data. To assess model fit, we evaluated the bootstrap likelihood ratio test, the Bayesian information criterion, and the Akaike information criterion.27 Subsequently, linear regression analyses were assessed for childhood loneliness trajectory in relation to adult outcomes.

Across all assessments, 83% of possible interviews were completed (Table S1, available online). All 1,420 participants were interviewed at least once in childhood (ages 9 to 16); 1,260 participants (88.7%) had 3+ childhood observations. Of the total sample, 1,334 (94.0%) were followed up at least once in adulthood at ages 19, 21, 25, or 30. All analyses were performed using SAS 9.4 software. All missing values of the potential confounding factors were imputed using multiple imputations. With the Markov Chain Monte Carlo multiple imputation technique, 10 complete data sets were created. Multivariate analyses were performed on each imputed data set, and effect estimates were pooled.28

RESULTS
Prevalence of loneliness and the associations with sociodemographic factors
Descriptive information is provided in Table 1. The prevalence of childhood/adolescent loneliness was 13.4 %, meaning that > 1 in ten children reported feeling lonely at some point by age 16. Overall, prevalence of loneliness differed by sex of the child (more common in girls than boys), but not by race/ethnicity and rural vs. urban area. In our study, the within-individual correlation of loneliness measure over time was r = 0.42.
Table 1. Prevalence of childhood loneliness between ages 9 to 16 and association with childhood adversities

<table>
<thead>
<tr>
<th>Overall childhood loneliness</th>
<th>Never lonely N (%)</th>
<th>Ever lonely N (%)</th>
<th>p value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, girl</td>
<td>529 (43)</td>
<td>101 (53.2)</td>
<td>0.042</td>
</tr>
<tr>
<td>Rural areas</td>
<td>739 (60.1)</td>
<td>100 (52.6)</td>
<td>0.863</td>
</tr>
<tr>
<td>Psychosocial risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>489 (39.8)</td>
<td>84 (44.2)</td>
<td>0.131</td>
</tr>
<tr>
<td>Single parent</td>
<td>491 (39.9)</td>
<td>105 (44.7)</td>
<td>0.256</td>
</tr>
<tr>
<td>Change in parent structure</td>
<td>386 (31.4)</td>
<td>76 (40)</td>
<td>0.305</td>
</tr>
<tr>
<td>Maltreatment</td>
<td>262 (21.3)</td>
<td>74 (38.9)</td>
<td>0.136</td>
</tr>
<tr>
<td>Depression mother</td>
<td>193 (15.7)</td>
<td>64 (33.7)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Numbers denotes children included in one or more analyses. Numbers are unweighted, and percentages are weighted. * p value from binary logistic regression of childhood loneliness and childhood adversities outcome. The models (Odds ratio [ORs]) are adjusted for child sex.

Table 2. Prevalence of childhood loneliness between ages 9 to 16 and association with childhood psychiatric disorders

<table>
<thead>
<tr>
<th>Overall childhood loneliness</th>
<th>Child-report loneliness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never lonely N (%)</td>
</tr>
<tr>
<td>Psychiatry disorders</td>
<td></td>
</tr>
<tr>
<td>Any anxiety diagnosis</td>
<td>86 (6.4)</td>
</tr>
<tr>
<td>Any depression diagnosis</td>
<td>28 (2.1)</td>
</tr>
<tr>
<td>Disruptive behavior disorder</td>
<td>122 (9.1)</td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Any anxiety symptoms</td>
<td>1.7 (2.2)</td>
</tr>
<tr>
<td>Any depression symptoms</td>
<td>0.2 (0.1)</td>
</tr>
<tr>
<td>Disruptive behavior</td>
<td>0.1 (0.3)</td>
</tr>
</tbody>
</table>

| Parent-report loneliness     |                         |                      |
| Psychiatry disorders         | 1294 (91.1)             | 126 (8.9)            |           |
| Any anxiety diagnosis        | 82 (6.1)                | 10 (12.8)            | <0.001    |
| Any depression diagnosis     | 59 (4.4)                | 11 (14.1)            | <0.001    |
| Disruptive behavior disorder | 229 (1.1)               | 22 (28.2)            | <0.001    |
| Psychiatric symptoms         | M (SD)                  | M (SD)               |           |
| Any anxiety symptoms         | 1.7 (2.3)               | 5.4 (4.6)            | <0.001    |
| Any depression symptoms      | 1.4 (1.3)               | 3.3 (2.0)            | <0.001    |
| Disruptive behavior          | 2.7 (2.9)               | 5.3 (4.2)            | <0.001    |

Numbers denotes children included in one or more analyses. Values are frequencies for categorical (numbers are unweighted, and percentages are weighted). Means and standard deviations (M ± SD) for continuous measures. * p value from binary logistic regression of childhood loneliness and childhood psychiatric disorder outcomes. The models (Odds ratio [ORs]) are adjusted for child sex and adversities.
Concurrent analyses showed that childhood loneliness was associated with change in parent structure, as well as maternal depression, after adjustment for sex of the child. We observed no associations between childhood loneliness and low socio-economic status, single parent family status, and child maltreatment.

Next, we tested the associations of child- and parent-reported loneliness with anxiety, depression, and substance use disorder within childhood. Child- and parent-reported of loneliness were concurrently associated with childhood anxiety, depression, and substance use disorder (table 2). The association of loneliness with psychiatric disorders outcomes was consistently stronger if loneliness was rated by the child than by the parent.

Further, we tested whether childhood loneliness was associated with number of arguments with peers and teased or bullied during childhood (Table 1 in the Supplement). Concurrent associations showed that childhood loneliness was associated with number of arguments with peers and teased or bullied in childhood. In contrast, we observed no associations of childhood loneliness and frequency of contact with peers, confidante with family and peers, as well as shyness with peers. These associations and nonassociations suggest that our measure best approximates subjective loneliness.

**Childhood loneliness and adult psychiatric disorders**

We then examined the associations of child- and parent-reports loneliness and psychiatric disorders in adulthood adjusted for demographic variables and childhood adversities. As shown in Table 3, self-reported loneliness was associated with anxiety disorder (OR = 3.53, 95% CI 1.55 - 8.04, \( p = 0.002 \)) but not with depressive and substance use disorders. Next, to test whether childhood loneliness was associated with adult psychiatric symptoms. Self-reported loneliness was associated with anxiety (B = 1.20, 95% CI 0.43 - 1.97, \( p = 0.002 \)), and depressive symptoms scores (B = 0.76, 95% CI 0.27 - 1.25, \( p = 0.002 \)), but not with substance use symptoms (B = 0.20, 95% CI, -0.14 - 0.54, \( p = 0.246 \)). Effect estimates were modestly attenuated when we accounted for childhood psychiatric status (model 2).

In fully adjusted models (model 2), we observed no associations between parent-reported loneliness and any measure of adult diagnostic status. Parent-reported loneliness was, however, associated with adult anxiety (B = 1.12, 95% CI 0.49 - 1.75, \( p = 0.001 \)) and depressive (B = 1.12, 95% CI 0.49 - 1.75, \( p = 0.001 \)) psychiatric symptoms.

**Childhood loneliness trajectories and adult psychiatric disorders**

We tested associations of childhood loneliness trajectories with adult psychiatric disorders and symptoms. Figure 1 illustrates the mean scores for the total sample of the
### Table 3. The association between childhood loneliness between ages 9 to 16 with adult psychiatric and substance use disorders

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Overall</th>
<th>Any anxiety diagnosis</th>
<th>Any depression diagnosis</th>
<th>Substance use disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td><strong>Child-report loneliness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never lonely n (%)</td>
<td>1260 (94.4)</td>
<td>184 (14.6)</td>
<td>137 (10.9)</td>
<td>398 (31.6)</td>
</tr>
<tr>
<td>Ever lonely n (%)</td>
<td>74 (5.6)</td>
<td>33 (44.6)</td>
<td>20 (27.0)</td>
<td>34 (45.9)</td>
</tr>
<tr>
<td>Model 1</td>
<td>5.95 (2.77 to 12.7)</td>
<td>&lt;0.0001</td>
<td>2.72 (1.08 to 6.83)</td>
<td>0.033</td>
</tr>
<tr>
<td>Model 2</td>
<td>3.53 (1.55 to 8.04)</td>
<td>0.002</td>
<td>1.86 (0.73 to 4.71)</td>
<td>0.190</td>
</tr>
<tr>
<td><strong>Parent-report loneliness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never lonely n (%)</td>
<td>1215 (91.1)</td>
<td>177 (14.6)</td>
<td>136 (11.2)</td>
<td>392 (32.3)</td>
</tr>
<tr>
<td>Ever lonely n (%)</td>
<td>119 (8.9)</td>
<td>40 (33.6)</td>
<td>21 (17.6)</td>
<td>40 (33.6)</td>
</tr>
<tr>
<td>Model 1</td>
<td>2.95 (1.51 to 5.75)</td>
<td>0.001</td>
<td>1.61 (0.61 to 4.23)</td>
<td>0.331</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.43 (0.67 to 3.04)</td>
<td>0.354</td>
<td>0.91 (0.32 to 2.57)</td>
<td>0.861</td>
</tr>
</tbody>
</table>

### Psychiatric symptoms

<table>
<thead>
<tr>
<th>Psychiatric symptoms</th>
<th>Any anxiety symptoms</th>
<th>Any depression symptoms</th>
<th>Substance use symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p value</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td><strong>Child-report loneliness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never lonely, M (SD)</td>
<td>2.5 (3.2)</td>
<td>2.1 (2.0)</td>
<td>1.1 (1.4)</td>
</tr>
<tr>
<td>Ever lonely, M (SD)</td>
<td>4.5 (4.2)</td>
<td>3.4 (2.6)</td>
<td>1.5 (1.7)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.91 (1.16 to 2.66)</td>
<td>&lt;0.0001</td>
<td>1.25 (0.76 to 1.72)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.20 (0.43 to 1.97)</td>
<td>0.002</td>
<td>0.76 (0.27 to 1.25)</td>
</tr>
<tr>
<td><strong>Parent-report loneliness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never lonely, M (SD)</td>
<td>2.4 (3.2)</td>
<td>2.1 (2.0)</td>
<td>1.1 (1.4)</td>
</tr>
<tr>
<td>Ever lonely, M (SD)</td>
<td>4.4 (4.1)</td>
<td>3.2 (2.4)</td>
<td>1.3 (1.5)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.78 (1.17 to 2.40)</td>
<td>&lt;0.0001</td>
<td>0.93 (0.54 to 1.32)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.12 (0.49 to 1.75)</td>
<td>0.001</td>
<td>0.48 (0.08 to 0.88)</td>
</tr>
</tbody>
</table>

Regression analysis of childhood loneliness and adult psychiatric outcomes. Values are frequencies for categorical (numbers are unweighted, and percentages are weighted) and means and standard deviations (M ± SD) for continuous measures. Model 1 is adjusted for child sex and childhood adversities. Childhood adversities include low family socioeconomic status, change in parent structure, mother depression. Model 2 is additionally adjusted for childhood psychiatric disorders. Child psychiatric disorders include anxiety, depression, and disruptive disorders. Odds ratio (OR) indicate binary logistic regression coefficients for psychiatric disorders. B statistics indicate linear regression coefficients for psychiatric symptoms.

a Model 2 is additionally adjusted for childhood psychiatric symptoms.
Childhood loneliness and adult psychiatric disorders

three trajectory groups. The first class (N = 1260, 94.4%), termed “low”, consisted of children who reported no or very few feelings of loneliness over time. The second class (N = 65, 5.1%), labelled “moderate” included children with a moderate increasing levels of loneliness. Finally, there was a small group of children (N = 9, 0.5%), with slightly higher levels of lonely feelings than the moderate group. The three-class model was found to be the optimal model, with the lowest Bayesian information criterion scores and p values = 0.05 for the bootstrap likelihood ratio test (Table S2 in the Supplement). Because of the sample size for the high group, it will be combined with the moderate group for all analyses.

As shown in Table 4, children in the moderate/high groups had higher levels of anxiety disorders than the children who were in the low group. There were no differences in depression and substance use disorder between groups. Children in the moderate/high groups had higher levels of anxiety and depressive symptoms than those in the low loneliness group. No differences in substance use symptoms between groups were found.

Table 4. Childhood loneliness trajectories with adult psychiatric and substance use disorders

<table>
<thead>
<tr>
<th>Child-report loneliness</th>
<th>Psychiatric disorders</th>
<th>Substance use disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any anxiety diagnosis</td>
<td>Any depression diagnosis</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lonely</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Moderate/ high group</td>
<td>6.34 (2.78 to 9.94)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lonely</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Moderate/ high group</td>
<td>3.82 (1.45 to 7.24)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Regression analysis of childhood loneliness trajectories and adult psychiatric outcomes. Model 1 is adjusted for child sex and childhood adversities. Childhood adversities include low family socioeconomic status, change in parent structure, mother depression. Model 2 is additionally adjusted for childhood psychiatric disorders. Child psychiatric disorders include anxiety, depression, and disruptive disorders. Odds ratio (OR) indicate binary logistic regression coefficients for psychiatric disorders. B statistics indicate linear regression coefficients for psychiatric symptoms. a Model 2 is additionally adjusted for childhood psychiatric symptoms.
DISCUSSION

This prospective population-based study examined the associations of childhood loneliness and adult psychiatric disorders while carefully controlling other common childhood adversities and childhood psychiatric functioning. We highlight three key findings. First, childhood loneliness was prospectively associated with adult self-reported anxiety and depression but not substance use outcomes. Moreover, children exposed to persistently moderate and high levels of loneliness trajectories showed more symptoms of anxiety and depression. Second, these associations remained when we account for childhood-assessed adversities and psychiatric comorbidities (e.g., anxiety, depression, and conduct disorder). Third, the associations were stronger for self- than for parent-reported childhood loneliness, although there was evidence of cross-informant associations for psychiatric symptoms. Overall, our findings suggest that children’s experience of loneliness is associated with increased risk for psychiatric disorders, and has the potential to have lifelong effects on one’s social and emotional functioning.

Prior studies examining developmental trajectories of loneliness from childhood to early adulthood have indicated that between 3% and 22% of people experience persistent loneliness. With our data spanning 20+ years and multiple informants, we were able to extend previous findings across developmental periods indicating that loneliness experienced in childhood had particularly robust associations with adult self-reported anxiety and depression. Importantly, our results suggest that the associations of childhood loneliness with adult psychiatric outcomes were independent of childhood sociodemographic factors, adversities, and psychiatric functioning, indicating a unique contribution of loneliness to mental health outcomes later in life. No such associations were observed for adult substance disorders or symptoms.

The trajectory analysis largely confirmed the primary analysis with evidence of that moderate to high loneliness is likely to affect anxiety and depression outcomes. Within these groups, loneliness tended to peak between ages 14 and 16 during early adolescence when peer groups and influences are taking on increasing importance. At the same time, it is notable that the rank order of the trajectories stayed the same from childhood through adolescence suggesting the potential for early identification of children at risk. These results suggest that childhood loneliness may be a potential risk factor to emerging mental health problems and that age appropriate interventions for loneliness may alleviate later suffering.

The finding that early childhood loneliness precedes mental health outcomes suggests that loneliness may be attributed to myriad processes including neural, neuroendocrine, genetic mechanisms, as well as physiological stress state. The evolutionary theory
of loneliness posits that loneliness increases the motivation to attend to and approach social stimuli for potential relief from the aversive state (e.g., like hunger, thirst, and pain promotes behavior change to increase the likelihood of the survival of one’s genes). The evolutionary theory of loneliness suggests that such experiences may contribute to (a) increased vigilance for social threats along with increased anxiety, hostility, and social withdrawal to avoid predation, (b) increased sleep fragmentation, (c) elevated vascular activity, increase extended periods of hypothalamo-pituitary adrenal activations, and decreased gene expression and immunity to deal with potential assaults that may arise, (d) decreased impulse control (e.g., prepotent responding), and (e) increased depressive symptomatology. Tests of these mechanisms is beyond the scope of this work but may explain the long-term associations observed here.

Our study extended prior findings by using a multi-informant approach to address the potential for a bias when relying only on self-report data. Because loneliness is a subjective experience, and an internal state of mind, it is often examined using self-reports. However, as close others (e.g., parents, teacher, or friends) can observe behavioral changes resulting from loneliness, they could provide additional information on children’s loneliness. In our study, both self- and parent loneliness ratings were associated with adult self-reported anxiety and depression outcomes, though higher associations were observed by self-reported loneliness. Self-ratings may be the best indicators of internal traits such as loneliness, but parental reports also pick up on problems that suggest long-term distress. Discrepancies between informants might arise from substantial changes in individuals’ social experiences and expectations across adolescent development. These differences between self- and parent-reports loneliness could also be explained attentional processes in adults, either directly or indirectly (e.g., mothers or fathers).

The current study has several limitations. First, this study was representative of a rural area in the Southeast US but not the US population. Second, loneliness was measured using a series of primary and secondary prompts but only coded into a single item. Insofar as the measure is limited, it may underestimate the effect of loneliness on adult outcomes. Next, this study did not include potential influence of genetic variation on the young adult’s mental health. Genetic and environmental determinants of loneliness (e.g., predispositional vulnerability and exposures to specific life experiences), could contribute to differences across individuals in which pathways operate. For example, McGuire et al. showed significant heritability and non-shared environmental influences for children’s loneliness using adoption and twin studies. Strengths of the present study are a large samples, repeated assessments of loneliness across childhood and adolescence, multiple informants, and assessment of a broad spectrum of measured childhood covariates.
Our findings may have implications for future research and clinical practice. First, increased opportunities for social contact and social support, and improved social skills may reduce the risk of future psychiatric disorders in lonely children. However, such work needs to be targeted at the subjective experience of loneliness rather than merely at increasing objective social contacts. Overall, early interventions targeting children’s maladaptive social cognitions may be an efficient way to alleviate such subjective feelings of loneliness. Such interventions would have to be implemented in developmentally-appropriate way given the social, cognitive and emotional changes from childhood to adolescence.

In summary, our findings show that loneliness is relatively common and is observed by parents and children early in life. The question is whether this is a transient dysphoric state that affects current health only or it has the potential to compromise emotional health long-term. The current study suggests that loneliness is not transient and the effects are long-term. It is also important to remember that even if childhood loneliness is a risk factor for adult distress, most children with childhood loneliness do not experience adult distress. Future research should identify who is at risk for such long-term effects of loneliness and how this risk is propagated across significant developmental transitions.
REFERENCES

10. Miller G. Why loneliness is hazardous to your health. American Association for the Advancement of Science; 2011.
Supplementary Figure 1. Ascertainment of the original Great Smoky Mountains study sample

- Approximately 12,000 non-American Indian children aged 9, 11, and 13 in 11 counties
- Random sample of 4,067 selected using a household equal probability design
- 3,896 (95.8%) completed telephone screen
- Top 25% on screen
- Lower 75%
- 2,887 children
- Random subset
- 337 children
- 1,071 (79.6%) agreed to participate.
- 1,420 children total participated in at least one assessment
- 450 American Indian children aged 9, 11, and 13 in 11 counties
- 431 (95%) completed telephone screen
- All recruited
- 349 (81%) agreed to participate.

Supplementary Figure 2.

**LONELINESS**

A feeling of being alone and/or friendless, regardless of the justification for the feeling; total daily duration of at least 1 hour.

**NOTE RELEVANT INFORMATION FROM PEER RELATIONSHIPS.**

**Do you think s/he feels lonely?**

How often is that?
When was the last time?
How did s/he feel then?

**Sometimes children feel that they have no one who would help them. Does s/he ever feel like that?**

Does s/he feel cared for by friends?
Does s/he feel lonely even though s/he has some friends?
Does s/he feel left out by others?
Does s/he get left out of other children’s activities?
How does s/he feel about that?
Does s/he think that’s likely to change?
Can you stop him/her feeling lonely?
What happens if you try?

**LONELINESS**

0 = Absent
2 = The subject definitely feels intrusively and uncontrollably lonely in at least 2 activities
3 = He feels lonely almost all the time.

**PDS9001**

Intensity

Onset
### Supplementary Table 1. Prevalence of childhood loneliness between ages 9 to 16 and association with childhood peer relationship

<table>
<thead>
<tr>
<th>Child- and parent-report loneliness</th>
<th>Never lonely n (%)</th>
<th>Ever lonely n (%)</th>
<th>p value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall childhood loneliness</td>
<td>1230 (86.6)</td>
<td>190 (13.8%)</td>
<td></td>
</tr>
<tr>
<td>Peer relationship</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of contact with peers</td>
<td>494 (40.2)</td>
<td>106 (55.8)</td>
<td>0.081</td>
</tr>
<tr>
<td>No Confidant(e) among peers</td>
<td>712 (57.9)</td>
<td>116 (61.1)</td>
<td>0.843</td>
</tr>
<tr>
<td>No confidant(e) in family</td>
<td>685 (57.9)</td>
<td>116 (61.1)</td>
<td>0.322</td>
</tr>
<tr>
<td>Number of arguments with peers</td>
<td>104 (8.5)</td>
<td>48 (25.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Shyness with peers</td>
<td>369 (30)</td>
<td>93 (48.9)</td>
<td>0.056</td>
</tr>
<tr>
<td>Teased or bullied</td>
<td>372 (30.2)</td>
<td>115 (60.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Numbers denotes children included in one or more analyses. Numbers are unweighted, and percentages are weighted. "p value from binary logistic regression of childhood loneliness and childhood peer relationship outcomes. The models (Odds ratio [ORs]) are adjusted for child sex.

### Supplementary Table 2. Comparison of latent class growth analysis of loneliness trajectories model fit indices

<table>
<thead>
<tr>
<th>Fit indices</th>
<th>Entropy a</th>
<th>AIC b</th>
<th>BIC c</th>
<th>BLRT p value d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of class</td>
<td>2</td>
<td>0.91</td>
<td>175.86</td>
<td>180.21</td>
</tr>
</tbody>
</table>

a AIC = Akaike’s Information Criterion; b BIC = Bayesian Information Criterion; c BLRT = Bootstrap Likelihood Ratio Test.
Chapter 5

Association of poor family functioning from pregnancy onward with preadolescent behavior and subcortical brain development

Yllza Xerxa, Scott W. Delaney, Leslie A. Rescorla, Manon H. J. Hillegers, Tonya White, Frank C. Verhulst, Ryan L. Muetzel, Henning Tiemeier

*Jama Psychiatry, 78(1), 29-37.*
ABSTRACT

Importance: The association of poor family functioning, a potent stressor, with child behavior is potentially long term and relevant for a person’s well-being later in life. Whether changes in brain development underlie the associations with preadolescent behavior and help identify periods of vulnerability is unclear.

Objective: To assess the associations of poor family functioning from pregnancy onward with cortical, white matter, and subcortical volumes, and to examine the extent to which, in particular, hippocampal volume mediates the association of prenatal parental environmental exposures with child problem behavior in preadolescence.

Design, Settings, and Participants: This population-based cohort study, conducted from April 2002 to January 2006, was embedded in Generation R, a multiethnic population-based cohort from fetal life onward. All pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. Of the 8879 pregnant women enrolled during pregnancy, 1266 mothers with no partner data and 490 with missing family functioning data were excluded, as well as 1 sibling of 32 twin pairs. After excluding an additional 657 children with poor imaging data quality or incidental findings, the final sample consisted of 2583 mother-child pairs. Data analysis was performed from March 1, 2019, to June 28, 2019.

Exposures: Mother- and father-rated poor family functioning was repeatedly measured by the General Functioning subscale of the Family Assessment Device.

Main Outcomes and Measures: Our primary hypothesis, formulated after data collection but before analysis, was that poor prenatal family functioning would be associated with smaller hippocampal and amygdala volumes in late childhood. High-resolution structural neuroimaging data of children aged 10 years were collected with a single 3-T magnetic resonance imaging system. Child emotional and behavioral problems were assessed with the Child Behavior Checklist.

Results: Data were available for 2583 children (mean [SD] age, 10.1 [0.6] years; 1315 girls [50.9%]). Data for parents included 2583 mothers (mean [SD] age, 31.1 [4.7] years; 1617 Dutch race/ethnicity [62.6%]) and 1788 fathers (mean [SD] age, 33.5 [5.3] years; 1239 Dutch race/ethnicity [69.3%]). Children exposed to prenatal maternal-reported poor family functioning had smaller hippocampal (B = −0.08; 95% CI, −0.13 to −0.02) and occipital lobe (B = −0.70; 95% CI, −1.19 to −0.21) volumes in preadolescence. There was no evidence for an association of exposure to poor family functioning at mid- or late childhood with brain morphology. Hippocampal volumes
partially mediated the association of prenatal maternal-reported poor family functioning with preadolescent problem behavior ($B = 0.08; 95\% \text{ CI}, 0.03-0.13$), even after adjusting for prior child problems at age 1.5 years. Analyses of combined maternal and paternal family functioning ratings showed similar results, but associations were largely driven by maternal family functioning reports.

**Conclusions and Relevance:** In this population-based cohort study, prenatal maternal-reported poor family functioning was associated with a smaller hippocampus in preadolescents. This difference in brain structure may underlie behavioral problems and is a possible neurodevelopmental manifestation of the long-term consequences of poor family functioning for the child.

**Key points**

**Question:** To what extent is the persistent association of poor prenatal family functioning with preadolescent problem behavior mediated by subcortical brain development?

**Findings:** In this population-based cohort study of 2583 children with neuroimaging data, smaller hippocampal volumes were found in preadolescents exposed to prenatal maternal-reported poor family functioning. Smaller hippocampal volumes partially mediated the association of prenatal maternal-reported poor family functioning with preadolescent problem behavior.

**Meaning:** Subcortical brain characteristics found after more than 10 years of follow-up may help clinicians understand why poor family functioning is associated with child neurodevelopment and well-being.
INTRODUCTION

Poor family functioning can compromise child development; several studies in the literature refer to a range of negative exposures during childhood that are associated with mental health outcomes. Poor family functioning often includes, but is not limited to, high levels of conflict and lack of cohesion, disorganization, and poor quality of communication. Prior research on child brain development has highlighted the importance and long-term developmental consequences of adverse childhood experiences, often due to poor parenting and parental stress in samples of high-risk children. Despite this evidence, it remains unclear (1) why these negative effects persist throughout childhood, (2) at what age children are most vulnerable to poor family functioning, and (3) whether this is generalizable to poor family functioning in the general population. As a potent stressor, poor family functioning interferes with children’s ability to regulate stress physiology and may be associated with disruption in typical brain development.

Prenatal stressful life events and maternal anxiety and depression during pregnancy increase children’s risk for socioemotional and cognitive problems. Research has investigated the biologic correlates and mediators of these findings. These animal and human preclinical studies suggest that the hypothalamic-pituitary-adrenal axis plays a role in mediating the effects of maternal stress on the fetal brain. Furthermore, brain imaging research suggests that maternal stress is associated with changes in the limbic and frontotemporal structures of children. There is also a large amount of literature showing that stress in adults and similarly in children induces the production of stress hormones leading to a modulation of brain function. Animal studies suggest that this may be accomplished, in part, by changing the structure of neurons, especially in the hippocampus, amygdala, and prefrontal cortex. Overall, preclinical studies during pregnancy and childhood indicate that the hippocampus is highly susceptible to early stressful experiences, because of its high density of glucocorticoid receptors and persistent postnatal neurogenesis.

In a clinical study of monozygotic twins discordant for trauma exposure, Gilbertson et al. showed that combat veterans with persistent posttraumatic stress disorder (PTSD) had a smaller hippocampus volume than combat veterans without PTSD. However, the non–trauma-exposed identical twins of the combat veterans with PTSD also had a smaller hippocampus. Thus, a smaller hippocampus may also indicate a preexisting familial vulnerability factor that predisposes to pathological stress reactions in the event of a traumatic exposure.

Several gaps in our understanding remain. First, the period of exposure assessment in prior studies varies, and exposures are rarely assessed repeatedly. Large follow-up studies
with repeated measures of family functioning are needed to identify whether periods of specific vulnerability exist. Second, few prospective studies in the general population have been able to demonstrate whether structural brain changes mediate the association between childhood adversities and adjustment problems.\textsuperscript{21,22} Finally, most studies focus on maternal reports of family functioning only, whereas adding paternal reports of family functioning may capture a different aspect of family functioning or affect children differently.\textsuperscript{23,24}

We conducted a neuroimaging follow-up study of the relationship between poor family functioning from pregnancy onward and preadolescent brain development. Our primary hypothesis was that poor prenatal family functioning would be associated with smaller hippocampal and amygdala volumes in late childhood. We also postulated that these subcortical volumes would mediate the association of prenatal parental environmental exposures with measures of preadolescent problem behaviors at age 10 years. In the primary analyses, we examined global brain outcome measures, ie, total brain volume, total gray and cerebral white matter volumes, and hippocampal and amygdala volumes. This represents the first step of a hierarchical approach that is followed by secondary analyses only if any associations found in the first step are further tested in substructures.

**METHODS**

**Participants**

Our research was embedded in the Generation R Study, a multi-ethnic population-based cohort from fetal life onwards.\textsuperscript{25} Briefly, all pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants and from both parents of minors. Participants gave written informed consent for each phase of the study (fetal, preschool, childhood, and adolescence period). In accordance with Dutch law, children must sign their own consent form starting from the age of 12 years onward. Children received oral information about the study. Of the 8879 pregnant women enrolled during pregnancy, we excluded 1266 mothers with no partner data and 490 with missing family functioning data, leaving 7123 eligible mother-child pairs with 4561 actively participating fathers. We randomly excluded 1 sibling of 32 twin pairs. Data from the late-childhood assessment wave (ie, mean child age 10 years) included a research center visit, questionnaires, and a magnetic resonance imaging (MRI) assessment.\textsuperscript{26} After excluding an additional 657 children with poor imaging data quality or incidental findings, our final sample consisted of 2583 mother-
child pairs (eFigure 1 in the Supplement). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

**Measures**

**Family Assessment Device**

Family functioning was assessed using the General Functioning subscale of the Family Assessment Device (FAD), a validated self-report measure of family health and pathology consisting of 12 items (resulting scores range from 1 = not at all to 4 = poor family functioning), with higher scores indicating poor family functioning. Both mothers and fathers completed this measure at 20 weeks of pregnancy (18-25 weeks’ gestational age) and when their child was aged 10 years (late childhood). In addition, mothers completed the questionnaire when their child was aged 6 years (midchildhood). The FAD uses the Dutch term gezin, which refers only to the nuclear family (ie, siblings and parents). However, even if a pregnant woman already has a child, the wording of the FAD items makes it likely that parents would primarily have their partner in mind (eMethods in the Supplement).

**Child Problem Behavior**

The Child Behavior Checklist for Ages 1.5 to 5 and the Child Behavior Checklist for Ages 6 to 18 were used to obtain standardized parent reports of children’s emotional and behavioral problems. We used the continuous Total Problems score (the sum of ratings on all problem items; scores range from 0 [not true] to 1 [somewhat or sometimes true] or 2 [very true or often true], with higher scores indicating more emotional and behavior problems) for children aged 10 years as our outcome measure (eMethods in the Supplement).

**Image Acquistion**

All images were acquired using the same sequence on the same 3-T 750w Discovery scanner (GE Healthcare) when children were aged 10 years. High-resolution, T1-weighted structural MRI data were acquired using a coronal inversion recovery fast spoiled gradient recalled sequence. Structural MRI data were processed through the FreeSurfer analysis suite, version 6.0 (Athinoula A. Martinos Center for Biomedical Imaging) (eMethods in the Supplement).

**Covariates**

Child age at MRI (based on date of birth) and sex were obtained from birth records. Maternal and paternal age were assessed at intake. Parental race/ethnicity, education, smoking, alcohol consumption, parity, marital status, and parental psychopathology (using the total score of the Brief Symptom Inventory were assessed prenatally using
self-report questionnaires. Harsh parenting was assessed when the child was aged 3 years using the Parent-Child Conflict Tactics Scale,34 a self-report questionnaire completed by the mother and father (eMethods in the Supplement).

**Statistical Analysis**

Statistical analyses of the data were performed from March 1, 2019, to June 28, 2019. First, we computed descriptive statistics and the correlations between mother- and father-reported poor family functioning scores at different time points (eTable 10 in the Supplement). Then, the prospective associations between maternal and paternal family functioning as assessed at each time point and child brain morphology were determined with separate linear regressions. We ran all models adjusting for all baseline previously mentioned confounders including maternal and paternal psychopathology. The interaction between child sex and poor family functioning was entered into the model in a separate step. In addition, we used structural equation modeling to test prenatal parental family functioning with a latent construct in relation to preadolescent brain morphology. Similarly, a latent construct based on child problem behavior reported by mothers and fathers was constructed (eMethods in the Supplement).

We used a stepwise hierarchical approach to limit the number of comparisons. Total brain volume, cerebral white and gray matter volumes, and amygdala and hippocampus volumes were examined in relation to poor family functioning. If we observed an association with any of these brain measures, subsequent analyses of substructures were conducted to facilitate interpretation of results obtained with the primary outcome measures (eMethods in the Supplement). A visualization of primary and secondary brain measures is presented in eFigure 3 in the Supplement. False discovery rate was applied to adjust for multiple comparisons.35 We adjusted for multiple hypothesis testing of 5 outcomes—ie, total brain volume, total gray and cerebral white matter volumes, hippocampal and amygdala volumes—and the 2 relevant exposure periods (prenatal and early childhood) in the multiple testing correction (10 comparisons). Furthermore, we tested for potential periods of heightened susceptibility to adversity using repeated measures of poor family functioning measures in relation to brain outcomes36,37 (eMethods in the Supplement).

Next, we tested whether any subcortical brain structures mediated the association between prenatal maternal-reported poor family functioning and preadolescent problem behavior factor at age 10 years. To this aim, we used a mediation analysis framework providing estimates of the natural direct effect size, the natural indirect effect size, and the total effect size.38 All models were adjusted for baseline confounders and child problem behavior when the child was aged 1.5 years.
Inverse probability weights\textsuperscript{39} were tested to correct for any participants lost to follow-up (eMethods in the Supplement). In sensitivity analyses, all microstructural left and right hemispheres were used for their respective volumes (eTables 8 and 9 in the Supplement).

The unstandardized $\beta$ coefficients (B) and 95\% CIs were calculated. All missing values (maximum percentage, maternal psychopathology = 10.8\%) of the potential confounding factors were imputed using multiple imputations.\textsuperscript{40} Statistical significance was set at a 2-sided P value of less than .05. All analyses were performed using SAS software, version 9.4 (SAS Institute).

**RESULTS**

The descriptive sample characteristics regarding parental socioeconomic factors, parental psychopathology, and child age at the time of MRI scanning are shown in Table 1. Data were available for 2583 children (mean [SD] age, 10.1 [0.6] years; 1315 [50.9\%] girls). Data for parents included 2583 mothers (mean [SD] age, 31.1 [4.7] years; 1617 [62.6\%] Dutch race/ethnicity) and 1788 fathers (mean [SD] age, 33.5 [5.3] years; 1239 [69.3\%] Dutch race/ethnicity).

As shown in Table 2, prenatal maternal-reported poor family functioning was associated with a decreased total brain volume, cerebral white matter volume, and total gray volume in late childhood (model 1, $B = -26.8$ [95\% CI, $-34.6$ to $-18.9$]; $B = -9.76$ [95\% CI, $-13.3$ to $-6.20$]; $B = -16.7$ [95\% CI, $-21.3$ to $-12.2$], respectively; $P < .001$), but these associations did not survive correction for multiple testing. Poor prenatal family functioning was associated with a smaller hippocampal volume after adjusting for intracranial volume, an association that remained after correction for multiple testing ($B = -0.08$; 95\% CI, $-0.13$ to $-0.02$). Adjusting for harsh parenting also did not meaningfully change this association. We observed no association between poor family functioning and amygdala volume (model 1, $B = -0.01$ [95\% CI, $-0.03$ to $0.02$]; $P = .59$).

We observed no associations between mid- or late-childhood poor family functioning scores and any measure of brain morphology in fully adjusted models. Concurrent associations between late-childhood family functioning and brain outcomes are depicted in eTable 1 in the Supplement. Windows of susceptibility results showed the associations of repeated maternal-reported family functioning with hippocampal volume (poor family functioning $\times$ exposure period interaction $P = .01$), but no other brain outcomes varied by the timing of family functioning measurement (eResults in the Supplement).
Exposure to prenatal maternal-reported poor family functioning was associated with smaller occipital lobe volume (B = −0.70; 95% CI, −1.19 to −0.21). We further explored the nominally significant anatomical findings and present the results of the relation between poor family functioning and the occipital lobe stratified by regions (eTable 3 in the Supplement). These post hoc analyses suggest that children prenatally exposed to poor family adjustment have a smaller lateral occipital lobe (B = −0.47 [95% CI, −0.61 to −0.09]; P = .01). In contrast, we observed no associations between any family

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
<th>Mother (n=2,583)</th>
<th>Father (n=1,788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M (SD)</td>
<td>31.1 (4.7)</td>
<td>33.5 (5.3)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch, (%)</td>
<td>62.6</td>
<td>69.3</td>
</tr>
<tr>
<td>Other Western, (%)</td>
<td>9.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Non Western, (%)</td>
<td>28.1</td>
<td>24.9</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High, (%)</td>
<td>52.4</td>
<td>56.4</td>
</tr>
<tr>
<td>Middle, (%)</td>
<td>28.9</td>
<td>27.4</td>
</tr>
<tr>
<td>Low, (%)</td>
<td>18.7</td>
<td>16.2</td>
</tr>
<tr>
<td>Alcohol use during pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No consumption during pregnancy,</td>
<td>37.4</td>
<td></td>
</tr>
<tr>
<td>Until pregnancy recognized, (%)</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>Continued occasionally, (%)</td>
<td>38.4</td>
<td></td>
</tr>
<tr>
<td>Continued frequently, (%)</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No smoking during pregnancy, (%)</td>
<td>79.8</td>
<td></td>
</tr>
<tr>
<td>Until pregnancy recognized, (%)</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Continued during pregnancy, (%)</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Parental psychopathology score, M (SD)</td>
<td>0.26 (0.3)</td>
<td>0.13 (0.2)</td>
</tr>
<tr>
<td>Marital status, prenatal, Yes (%)</td>
<td>90.6</td>
<td></td>
</tr>
<tr>
<td>Child age at the MRI scan, years, M (SD)</td>
<td>10.1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Gender, (% boy)</td>
<td>49.1</td>
<td></td>
</tr>
<tr>
<td>Harsh parenting score, M (SD)</td>
<td>1.73 (1.57)</td>
<td>1.74 (1.57)</td>
</tr>
<tr>
<td>Poor family functioning - FAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor family functioning (FAD-score) prenatal, M (SD)</td>
<td>1.48 (0.4)</td>
<td>1.49 (0.4)</td>
</tr>
<tr>
<td>Poor family functioning (FAD-score) at age 5, M (SD)</td>
<td>1.50 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Poor family functioning (FAD-score) at age 9, M (SD)</td>
<td>1.51 (0.4)</td>
<td>1.48 (0.4)</td>
</tr>
<tr>
<td>Child problem behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBCL total problems score at age 10, M (SD)</td>
<td>17.2 (15.0)</td>
<td>17.3 (14.9)</td>
</tr>
</tbody>
</table>

Note: Numbers denotes children included in one or more analyses. Values are frequencies for categorical and means and standard deviations (M ±SD) for continuous measures.
Table 2. Associations of poor family functioning with brain morphology.

<table>
<thead>
<tr>
<th>Mother reported poor family functioning</th>
<th>Total brain volume (cm³)</th>
<th>Cerebral white matter, (cm³)</th>
<th>Total gray volume, (cm³)</th>
<th>Amygdala volume, (cm³)</th>
<th>Hippocampus volume, (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global brain measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>B: -26.8</td>
<td>p: &lt;.001</td>
<td>p: .002</td>
<td>B: -16.7</td>
<td>p: &lt;.001</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-34.6 to -18.9)</td>
<td></td>
<td></td>
<td>(-21.3 to -12.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-17.9 to -1.19)</td>
<td></td>
<td></td>
<td>(-10.1 to -0.41)</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>B: -9.13</td>
<td>p: .033</td>
<td>p: .105</td>
<td>B: -5.05</td>
<td>p: .105</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-17.4 to -0.74)</td>
<td></td>
<td></td>
<td>(-9.93 to -0.19)</td>
<td></td>
</tr>
<tr>
<td><strong>Specific brain volumetric measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>B: -15.6</td>
<td>p: .001</td>
<td>p: .002</td>
<td>B: -10.4</td>
<td>p: &lt;.001</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-24.9 to -6.36)</td>
<td></td>
<td></td>
<td>(-15.8 to -4.97)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-14.7 to 3.81)</td>
<td></td>
<td></td>
<td>(-8.90 to 1.86)</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>B: -4.18</td>
<td>p: .311</td>
<td>p: .444</td>
<td>B: -2.91</td>
<td>p: .444</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-14.1 to 4.50)</td>
<td></td>
<td></td>
<td>(-8.31 to 2.49)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Linear regression analysis of FAD and brain morphology outcome. Betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume). Model 2 is additionally adjusted for maternal age, ethnicity, education, marital status, parity, maternal psychopathology, smoking and alcohol consumption. Model 3 is additionally adjusted for harsh parenting assessed when child was 3 years old. Global brain measures are not adjusted for total ICV. \( p_{FDR} \) = false discovery rate correction for multiple testing. Number of tests = 5 outcomes and the 2 relevant exposure periods (prenatal and early childhood). Critical value for FDR = 0.05. \( p \text{ Homogeneity for age of FAD assessment} \) = Multiple-partial test used to test whether exposure from different time points of poor family functioning relates in the same manner to brain morphology outcome.
functioning score and temporal, frontal, and parietal lobar volumes (eTable 2 in the Supplement). Similarly, no associations were found between family functioning and thalamus, accumbens, caudate, and putamen volumes (eTable 4 in the Supplement).

After adjusting for socioeconomic factors and paternal psychopathology, we observed no associations between paternal-reported family functioning at either time point and brain morphology (eTables 5 and 6 in the Supplement). We found no interaction by child sex in the association between family functioning and any brain measure. The results using the prenatal parental family functioning factor reflect the common variance in the associations of maternal and paternal family functioning with preadolescent brain outcomes. These results were very similar to those of the unique prenatal maternal-reported associations (eFigure 2 in the Supplement).

As the Figure illustrates, hippocampal volume partially mediated the association of prenatal maternal-reported poor family functioning with preadolescent problem behavior.

Figure 1. Hippocampal volume as mediator of the association between prenatal maternal-reported poor family functioning and preadolescent problem behavior.

Mediation analysis of hippocampal volumes at age 10 years in association with maternal-reported poor family functioning per FAD score during pregnancy with preadolescent problem behavior factor at age 10. B statistics are averaged from 10 imputed data sets. Model is adjusted for child age at brain MRI scan, child sex, total ICV, maternal age, race/ethnicity, education, parity, marital status, maternal psychopathology, smoking and alcohol consumption, and prior child problem behavior when child was aged 1.5 years and harsh parenting when child was aged 3 years. FAD indicates Family Assessment Device; ICV, intracranial volume; MRI, magnetic resonance imaging.

Path A
B = -0.05, p = <.001
(95% CI: -0.07, -0.03)

Path B
B = -0.86, p = .001
(95% CI: -1.12, -0.57)

Path C
B = 2.37, p = <.001
(95% CI: 1.76, 2.91)

Path AB
B = 0.08, p = .001
(95% CI: 0.03, 0.13)

Path C'
B = 2.29, p = <.001
(95% CI: 1.84, 2.73)

Path C
B = 2.37, p = <.001
(95% CI: 1.76, 2.91)

Path B
B = -0.86, p = .001
(95% CI: -1.12, -0.57)

Path A
B = -0.05, p = <.001
(95% CI: -0.07, -0.03)

*aPreadolescent problem behavior factor
Path A is the association of prenatal maternal-reported poor family functioning with hippocampal volume at age 10, and path B is for the association of hippocampal volume with preadolescent problem behavior factor. Path C (in black) is the total association between poor prenatal family functioning and preadolescent problem behavior with hippocampal volume not in the model. Path C’ (in red) is the direct association between prenatal maternal-reported poor family functioning and preadolescent problem behavior factor with hippocampal volume in the model.

The latent construct of maternal- and paternal-reported child problems. Preadolescent problem behavior factor captures covariation across raters, or the extent to which a given dimension is reflected across parents (ie, a between-rater dimension factor).
factor at age 10 years (B = 0.08; 95% CI, 0.03-0.13). The observed indirect association suggests that lower hippocampal volumes account for a portion of the observed preadolescent problem behavior in late childhood. When we adjusted for preexisting child problem behavior at age 1.5 years, we found no meaningful change in mediation results.

Last, in order to ascertain whether selection bias substantially altered any associations, we weighted complete cases by the inverse of their probability of being a complete case to address a possible source of bias due to selection. Results were essentially unchanged (eTable 7 in the Supplement).

**DISCUSSION**

This cohort study of children from fetal life onward suggests that poor maternal-reported prenatal family functioning is associated with brain development in late childhood. In particular, we observed smaller hippocampal volumes in children exposed to poor family functioning occurring prenatally but not in mid- or late childhood. The association remained when we accounted for parental psychopathology and harsh parenting, indicating a unique association of poor prenatal family functioning with differences in preadolescent brain development. The contribution of prenatal maternal-reported poor family functioning to preadolescent problem behavior was partially mediated by hippocampal volumes. Interestingly, prenatal maternal-reported poor family functioning was associated with smaller occipital lobe volumes. Associations between poor family functioning and brain outcomes did not differ by child sex.

The vulnerability of the hippocampus to prenatal family functioning is consistent with previous studies reporting that the hippocampus matures rapidly and is functional very early in childhood. That the association between poor family functioning and hippocampal volumes was observed only from prenatal maternal-reported family functioning and not from mid- or late-childhood family functioning may reflect a sensitive period, which occurs early in life. Other research supports this inference. For example, higher levels of early-life maternal support have been linked to increased volume of the hippocampus. Our key finding, namely the interaction of poor family functioning with child age, suggests that pregnancy is a vulnerable period when development in response to parental care disruptions is maximally dynamic.

In contrast to our hypothesis, we were not able to demonstrate an association between poor family functioning and amygdala volumes. The lack of a discernible sensitive period to family functioning for amygdala development is consistent with previous studies
of children exposed to adversity, which have found no difference in amygdala volume in adults. 47

The present findings provide evidence for a smaller occipital lobe in children exposed to prenatal maternal-reported poor family functioning. This observation, which was not expected a priori, should be interpreted with caution until it is replicated. However, the face-processing systems relating to occipital regions, in particular the lateral occipital lobe, were found to be particularly vulnerable to early-life adversities. 48-50

Furthermore, we found that the association between prenatal maternal-reported poor family functioning and preadolescent problem behavior was partially mediated by hippocampal volumes. This may suggest that brain morphologic changes precede or may even contribute to behavioral changes. Our results are consistent with the extant literature, showing that smaller hippocampal volumes partially mediated the contribution of early-life stress to higher levels of behavioral problems. 21 However, it is likely that the associations in the mediation model are more complex, and they may well be bidirectional. A sample with multiple repeated measures of imaging data starting early in childhood would be necessary to test the directionality between behavior and brain development. Indeed, a twin study in veterans with PTSD showed that a smaller hippocampus may reflect a preexisting vulnerability to stress and thus reverse causality. 20 Alternatively, the difference in hippocampal volume could be explained by genetic variation. Recently, a genome-wide association meta-analysis identified a few genetic loci associated with hippocampal volume, 51 which could be (indirectly) associated with poor family functioning.

In addition, associations between paternal-reported family functioning and brain structural measures did not remain after adjustment for sociodemographic factors and paternal psychopathology. Although prenatal parental family functioning factors reflect a common variance across mother- and father-reported family functioning, their association with brain structural measures was largely driven by the maternal report. Thus, the clear association found using maternal-reported functioning during pregnancy suggests that direct maternal physiological changes may underlie the findings. This is consistent with the developmental origins hypothesis that the prenatal or early postnatal environment can be associated with negative health outcomes later in life. Maternal psychological distress may lead to a suboptimal intrauterine environment with long-term consequences for the growth and health of the child. 52-54 Intrauterine stress exposure may affect child development via dysregulation of the hypothalamic-pituitary-adrenal axis, but it may also affect brain development through inflammatory responses and changes in the balance of the autonomic nervous system. 55 Another potential mechanism is dietary behavior and poor nutrition by which a variation in maternal
nutrition (either a surplus or paucity of maternal nutrition) plays multiple roles in the health outcomes of children. However, postnatal experiences cannot be ruled out as a mechanism underlying our findings, because the prenatal period could be a marker of exposures in the early postnatal period, such as poor parenting. Thus, children of parents with poor family functioning may be more likely to experience a less optimal environment, which underlies the relation with brain developmental differences.

Parental psychopathology remains another important mechanism potentially underlying our observations. However, when we adjusted for parental psychopathology, we found that the association between poor prenatal family functioning and hippocampal volumes was, if anything, stronger. Thus, our results suggest that poor family functioning and parental psychopathology are closely associated and may predispose each other, but higher levels of parental psychopathology did not account for the association of poor family functioning with hippocampal volume.

The current study has several limitations. First, this study has a population-based design, but the relative homogeneity of the population limits its generalizability. Second, we found an association between poor prenatal family functioning and preadolescent brain morphology among children aged 10 years. Although we assessed prenatal family functioning, we cannot establish whether these associations result from strictly prenatal exposures or whether our measure indexes childhood exposure during the period up to age 6 years when parents were reassessed. Third, because poor family functioning was associated with brain findings in children aged 10 years, it is possible that the associations of family functioning reported prenatally had their effects in utero. However, because no scans were obtained before age 10, this cannot be determined. Furthermore, we were unable to examine whether the parental hippocampus is a marker of vulnerability that increases the likelihood of poor family adjustment and whether this propensity is transmitted genetically to the children. Strengths of the present study are the large number of participants and broad spectrum of measured covariates, which enabled us to adjust for multiple confounders. Because of our longitudinal design, we were able to look at possible sensitive periods by leveraging baseline and repeated assessments of poor family functioning reported by both mothers and fathers.

In summary, the findings of this cohort study suggest that prenatal maternal-reported poor family functioning is associated with smaller hippocampal and occipital lobe volumes in preadolescents. Importantly, no such association was found for poor family functioning reported later in childhood, ie, at ages 6 and 10 years, suggesting that there is a sensitive period for the associations of poor family functioning during pregnancy with hippocampal and occipital lobe development. The association of maternal-reported poor family functioning during pregnancy with preadolescent problem behavior was
partially mediated by hippocampal volume. That the associations between poor prenatal family functioning and hippocampal volumes were found after more than 10 years of follow-up may help clarify why poor family functioning is associated with child neurodevelopment and well-being. This study increases our understanding of how poor family functioning shapes brain and behavioral development and underscores the need to search for effective family interventions.
REFERENCES:


SUPPLEMENTARY ONLINE CONTENT

eMethods. Description of the measures; Covariates; Statistical analyses; Latent factors analysis; Generalized estimating equation analysis; Complementary sensitivity analyses.
eResults. Complementary sensitivity analyses.
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eTable 2. The associations of poor family functioning and lobar measures
eTable 3. The associations of poor family functioning and occipital lobe stratified by regions
eTable 4. The associations of poor family functioning and subcortical brain morphology
eTable 5. The associations of paternal-reported poor family functioning and brain morphology
eTable 6. The associations of paternal-reported poor family functioning and lobar measures
eTable 7. Inverse probability weighting approach for the associations of poor family functioning and brain morphology
eTable 8. The associations of poor family functioning and microstructural measures of brain morphology stratified by hemispheres
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eTable 10. Correlation coefficients between maternal and paternal report of poor family functioning
eFigure 1. The inclusion of the study sample
eFigure 2. Path model of prenatal parental family functioning factor and brain morphology
eFigure 3. The list of primary and secondary brain morphology
eReferences
eMETHODS. DESCRIPTION OF THE MEASURES

Family Assessment Device
The General Functioning scale is a validated self-report measure of family health and pathology consisting of 12 Items. The items were selected to correlate highly with six scale scores (one from Problem Solving, four from Communication, two from Roles, one from Affective Responses, three from Affective Involvement and one from Behavior Control). Half of the items describe healthy functioning, e.g., ‘In times of crisis, we can turn to each other for support’. The other half describe unhealthy functioning, e.g., ‘There are a lot of unpleasant and painful feelings in our family’. Parents were asked to rate how well each item described their family by selecting from four different responses ranging from 1 to 4. We reverse-coded the six positively-worded healthy-functioning items so that a higher total FAD score indicated less well-functioning families. All 12 items were summed and divided by 12, yielding a score range from 1 to 4. The instruction read: “think about your (nuclear) family now”. In Dutch, the nuclear family (gezin) and extended family or family of origin are different words (familie) and concepts. Because questions do not reference specific family members or roles, mothers and fathers can respond regardless of their family’s structure. The FAD score will be referred to henceforth as the poor family functioning score. In the current study, internal consistencies (Cronbach’s alpha) ranged from 0.82 to 0.87 across time periods and reporters.

Child Problem Behaviors
The Child Behavior Checklist (CBCL) covers a broad range of emotional and behavioral problems of the child. The CBCL/1½–5 contains 99 problems items, which are scored on seven empirically based syndromes and three broadband scales (Internalizing, Externalizing, and Total Problems). Each item used a 3-point rating scale of 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true), based on the preceding 2 months. The CBCL/6–18 has 118 problem items, also yielding syndrome scales and the same three broadband scales, with ratings based on the preceding 6 months. Good reliability and validity have been reported, and the scales have been found to be generalizable across 23 societies, including The Netherlands. We used the continuous Total Problems score (the sum of ratings on all problem items) as our mediator measure because it reflects all the behavioral and emotional problems tapped by the CBCL and is thus the best overall index of maladjustment.

Image Acquisition
Following a three-plane localizer scan, a high-resolution T1-weighted inversion recovery fast spoiled gradient recalled sequence was acquired with the parameters: $T_R = 8.77$ ms, $T_E=3.4$ ms, $T_I = 600$ ms, flip angle = 10°, field of view (FOV) = 220 mm×220 mm, Acquisition Matrix = 220×220, slice thickness=1mm, number of slices=230.
Morphological Image Processing

Structural MRI data were processed through the FreeSurfer analysis suite, version 6.0. Briefly, nonbrain tissue was removed, voxel intensities were normalized for B1 inhomogeneity, whole-brain tissue segmentation was performed, and a surface-based model of the cortex was reconstructed. In our group, we have developed a metric of image quality which automatically characterizes the amount of motion/artifact based on signal intensities outside of the brain. In the image processing we additionally controlling for a metric for that described motion artifact and quality. Global metrics of volume were extracted (e.g., total brain volume and subcortical volume), and a number of subcortical and cortical structures (amygdala, orbitofrontal cortex, etc.) were automatically labeled. The averaged left and right hemispheres for all measures were used in primary analyses. In sensitivity analyses, all microstructural left and right hemispheres were used for their respective volumes. Surface reconstructions were visually inspected for accuracy and data not suitable for statistical analysis were excluded (eFigure 1 in the Supplement).

Covariates

Parental ethnicity was categorized into three groups: Dutch, non-Western, and other Western national origin. Parental education was classified in three levels: ‘low’ (maximum of three years general secondary school); ‘medium’ (>3 years general secondary school; intermediate vocational training); and ‘high’ (bachelor’s degree or higher academic education). Information about smoking (three categories: no smoking during pregnancy; smoked until pregnancy recognized; and continued smoking during pregnancy), alcohol intake during pregnancy (four categories: no alcohol consumption during pregnancy; alcohol consumption until pregnancy recognized; and continued occasionally during pregnancy (<1 glass/week); and continued frequently during pregnancy (>=1 glass/week)) was assessed prenatally using self-report questionnaires. During pregnancy, marital status was scored dichotomously: “married/living together” and “separated/divorced.” Parity was scored dichotomously: previous pregnancies: 0 vs. ≥1. Parental psychopathological symptoms were assessed at 20 weeks of pregnancy using the Brief Symptom Inventory (BSI), a validated self-report questionnaire with 53 items pertaining the presence and severity of specific symptom dimensions. Each item is answered on a five-point scale, ranging from ‘0 = not at all’ to ‘4 = extremely’. High validity and reliability have been reported for the Dutch translation. Harsh parenting was assessed when the child was 3 years old using the Parent-Child Conflict Tactics Scale, a validated self-report questionnaire completed by mother and father. In our research group, a harsh discipline scale was confirmed using factor analysis. This resulted in a scale consisting of six items, representing constructs of psychological aggression and (mild) physical assault. Each item is answered on a thirteen-point scale, ranging from ‘0 = not at all’ to ‘12 = higher severity of harsh discipline’.
In our study, we included unmarried partnered couples, but not unpartnered women. That is, not all couples were married but all women included in the study had a partner at baseline. In the Netherlands, many unmarried couples have a registered partnership.

**Statistical analyses**

Separate models estimated each brain measure as a depended variable. Maternal and paternal family functioning repeatedly measured each separately were included in the models as independent variables. We ran all models adjusting for all baseline previously mentioned confounders. The co-occurrence of childhood adversities could mediate or confound the associations of poor family functioning on childhood brain outcomes. Therefore, models additionally adjusted for harsh parenting, which was assessed at child age 3 to examine effect estimate change. The interaction between child sex and poor family functioning were entered into the model in a separate step. Adjustment for multiple comparisons was made using the Benjamini-Hochberg method \(^{14}\) to obtain a False Discovery Rate (FDR) of 0.05. In the primary analyses we examined global brain outcomes, i.e. total brain volume, total gray matter volume, total cerebral white matter volume, as well as the hippocampal and the amygdala volumes. This represents the first step of a hierarchical approach which is followed by models representing secondary analyses; the latter examined lobar volumes to further explore any finding in the first step. Against, the background of more than 100+ brain measures available in Freesurfer, a hierarchical approach is important as variable selection is mandatory even with a sample size of \(n = 2583\).

The hippocampus and amygdala volumes are tested as the structural brain measure of interest in virtually any research on child stress and abuse. Hence, we account for all five brain structures and the two relevant exposure periods (prenatal and early childhood) in the multiple testing correction.

In secondary analyses we thus tested the association of family adjustment with brain lobar volumes given the finding with total brain volume. We tested other subcortical structures to test the specificity of the finding with the hippocampus. Additionally, we further explored the anatomical findings and present the results of poor family functioning and occipital lobe stratified by regions such as lateral, lingual, cuneus, and pericalcarine in Supplementary eTable 3 because of the association of prenatal family functioning and occipital lobe volumes.

We have included the total intracranial volume as a covariate in our models for subcortical brain measures to compensate for head size variability.
As a second step, we examined potential periods of heightened susceptibility to poor family functioning using maternal or paternal functioning measures at different time points (e.g., prenatal, mid-childhood and late-childhood) to simultaneously estimate the associations between maternal or paternal functioning with brain outcomes (i.e., whether parental functioning measured during different time points was associated in the same manner to child outcomes).\textsuperscript{15,16}

In sensitivity analyses, we calculated inverse probability weights to correct for lost to follow-up, i.e., to account for potential selection bias when including only participants with available data as compared with the full cohort recruited during pregnancy.\textsuperscript{17}

**Latent factors analysis**

Maternal- and paternal-reported family functioning were modeled as latent variable via common confirmatory factor analytic (CFA) methods (eFigure 2). The models were allowed to correlate, and were estimated with the robust maximum likelihood estimator using standardized latent variables. The association between the latent construct of family functioning and preadolescent brain morphology captures covariation across raters, or the extent to which a given dimension is reflected both across parents (i.e., a “between-rater” dimension factor). Similarly, a latent construct for maternal- and paternal-reported child problem behavior was estimated (Figure 1). The latent constructs showed good model fit as judged with the comparative fit index (CFI, acceptable fit ≥ .90).\textsuperscript{18} The association of parental family functioning factor and preadolescent brain morphology were performed using structural equation modeling. The goodness of fit of these models was compared with the Bayesian information criterion (BIC) and Akaike's information criterion (AIC). A lower value for AIC and BIC indicates a better fit.\textsuperscript{19} The latent child problem behavior factor was used in mediation model to test whether the associations between prenatal maternal-reported family functioning and child problem behavior factor was mediated by hippocampal volumes (Figure 1).

**Generalized estimating equation analysis**

Using multivariable linear regression with generalized estimating equations (GEE),\textsuperscript{15,16} we simultaneously estimated the associations between maternal or paternal functioning measured prenatally, in mid-childhood and in late-childhood with brain outcomes (i.e., whether parental functioning measured during different time points was associated in the same manner to child outcomes). In addition, to test the unique period of susceptibility, we tested the interaction with the child’s age in the associations between poor family functioning and brain measures (poor family functioning x exposure period interaction \(p\)-value = .001). This analysis tested if the association of poor family functioning (as reported by both mothers and fathers) with child brain morphology depends on the age of the child by comparing the estimates of the repeatedly assessed
poor family functioning. Although this approach retains the interpretation of a set of separate multiple regressions (by providing a single estimate of effect for exposure at each time point), it also takes the variance into account between family functioning over time, while assessing the differences in associations between poor family functioning and brain morphology. All models were adjusted for potential effects of confounders, including socioeconomic factors and maternal or paternal psychopathology at baseline. The GEE retains the MCAR assumption for the missing data.
**eTable 1.** Concurrent associations of poor family functioning and brain morphology.

<table>
<thead>
<tr>
<th>Mother reported poor family functioning</th>
<th>Total volume (cm$^3$)</th>
<th>Cerebral white matter, (cm$^3$)</th>
<th>Total gray volume, (cm$^3$)</th>
<th>Amygdala volume, (cm$^3$)</th>
<th>Hippocampus volume, (cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global brain measures</td>
<td>Specific brain volumetric measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Age 9 poor family functioning (FAD), per score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-9.13 (-17.7 to -0.59)</td>
<td>.036 .081</td>
<td>-4.10 (-7.98 to -0.22)</td>
<td>.038 .081</td>
<td>-5.05 (-10.1 to -0.03)</td>
</tr>
<tr>
<td>Model 2</td>
<td>-1.13 (-9.61 to 7.34)</td>
<td>.793 .886</td>
<td>-1.60 (-5.51 to 2.31)</td>
<td>.423 .823</td>
<td>0.36 (-4.57 to 5.29)</td>
</tr>
<tr>
<td>Model 3</td>
<td>-0.50 (-3.17 to 4.07)</td>
<td>.789 .790</td>
<td>-1.27 (-5.20 to 2.66)</td>
<td>.527 .658</td>
<td>0.90 (-4.04 to 5.85)</td>
</tr>
</tbody>
</table>

Note: Linear regression analysis of FAD and brain morphology outcome. Betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume). Model 2 is additionally adjusted for maternal age, ethnicity, education, parity, marital status, maternal psychopathology, smoking and alcohol consumption. Model 3 is additionally adjusted for harsh parenting assessed when child was 3 years old. Global brain measures are not adjusted for total ICV. $p_{FDR}$ = false discovery rate correction for multiple testing. Number of tests = 5 outcomes and exposure period (late childhood). Critical value for FDR = 0.05.
**Table 2.** The associations of poor family functioning and lobar measures.

<table>
<thead>
<tr>
<th></th>
<th>Temporal lobe, (cm³)</th>
<th>Frontal lobe, (cm³)</th>
<th>Parietal lobe, (cm³)</th>
<th>Occipital lobe, (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>p_{FDR}</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td><strong>Mother reported poor family functioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor prenatal family functioning (FAD), per score</td>
<td>Model 1</td>
<td>-0.16 (-0.8 to 0.53)</td>
<td>.652</td>
<td>.869</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>0.05 (-0.71 to 0.80)</td>
<td>.903</td>
<td>.903</td>
</tr>
<tr>
<td>Age 5 poor family functioning (FAD), per score</td>
<td>Model 1</td>
<td>-0.04 (-0.85 to 0.77)</td>
<td>.928</td>
<td>.928</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>0.05 (-0.78 to 0.89)</td>
<td>.898</td>
<td>.903</td>
</tr>
</tbody>
</table>

*p Homogeneity for age of FAD assessment* = Multiple-partial test used to test whether exposure from different time points of poor family functioning relates in the same manner to brain morphology outcome.

Note: Linear regression analysis of FAD and lobar measures. Betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume). Model 2 is additionally adjusted for maternal age, ethnicity, education, parity, marital status, maternal psychopathology, smoking and alcohol consumption. Global brain measures are not adjusted for total ICV. *p_{FDR}*, false discovery rate correction for multiple testing. Number of tests = 4 outcomes and the 2 relevant exposure periods (prenatal and early childhood). Critical value for FDR = 0.05.
**Table 3.** The associations of poor family functioning and occipital lobe stratified by regions.

<table>
<thead>
<tr>
<th>Mother reported poor family functioning</th>
<th>Brain morphology (N = 2,583)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Occipital lobe anatomical region</td>
</tr>
<tr>
<td></td>
<td>Lateral occipital, (cm³)</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Poor prenatal family functioning (FAD), per score</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.54 (-0.79 to -0.29)</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.47 (-0.61 to -0.09)</td>
</tr>
<tr>
<td>Age 5 poor family functioning (FAD), per score</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.27 (-0.56 to 0.02)</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.15 (-0.45 to 0.14)</td>
</tr>
</tbody>
</table>

Note: Linear regression analysis of FAD and occipital anatomical region. Betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume). Model 2 is additionally adjusted for maternal age, ethnicity, education, parity, marital status, maternal psychopathology, smoking and alcohol consumption.
Table 4. The associations of poor family functioning and subcortical brain morphology.

<table>
<thead>
<tr>
<th>Mother reported poor family functioning</th>
<th>Global brain measures</th>
<th>Specific brain volumetric measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thalamus volume, (cm³)</td>
<td>Accumbens volume, (cm³)</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Poor prenatal family functioning (FAD), per score</td>
<td>0.02 (-13.3 to -6.20)</td>
<td>.623</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td>-0.01 (-0.02 to -0.01)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.03 (-0.05 to 0.11)</td>
<td>.433</td>
</tr>
<tr>
<td>Age 5 poor family functioning (FAD), per score</td>
<td>-0.04 (-0.13 to 0.05)</td>
<td>.356</td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.01 (-0.02 to 0.01)</td>
<td>.298</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.04 (-0.13 to 0.05)</td>
<td>.528</td>
</tr>
</tbody>
</table>

Note: Linear regression analysis of FAD and brain morphology outcome. Betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume). Model 2 is additionally adjusted for maternal age, ethnicity, education, parity, marital status, maternal psychopathology, smoking and alcohol consumption.
eTable 5. The associations of paternal-reported poor family functioning and brain morphology.

<table>
<thead>
<tr>
<th>Father reported poor family functioning</th>
<th>Total brain volume, (cm$^3$)</th>
<th>Cerebral white matter, (cm$^3$)</th>
<th>Total gray volume, (cm$^3$)</th>
<th>Amygdala volume, (cm$^3$)</th>
<th>Hippocampus volume, (cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>B</strong> (95% CI)</td>
<td><strong>p</strong></td>
<td><strong>p_{FDR}</strong></td>
<td><strong>B</strong> (95% CI)</td>
<td><strong>p</strong></td>
</tr>
<tr>
<td>Poor prenatal family functioning (FAD), per score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-23.1</td>
<td>&lt;.001</td>
<td>.005</td>
<td>-7.98</td>
<td>.002</td>
</tr>
<tr>
<td>(-34.3 to -12.1)</td>
<td></td>
<td></td>
<td></td>
<td>(-13.1 to -2.92)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>-7.34</td>
<td>.211</td>
<td>.422</td>
<td>-2.40</td>
<td>.375</td>
</tr>
<tr>
<td>(-18.9 to 4.16)</td>
<td></td>
<td></td>
<td></td>
<td>(-7.72 to 2.91)</td>
<td></td>
</tr>
<tr>
<td>Age 9 poor family functioning (FAD), per score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-13.2</td>
<td>.013</td>
<td>.026</td>
<td>-5.82</td>
<td>.002</td>
</tr>
<tr>
<td>(-23.7 to -2.73)</td>
<td></td>
<td></td>
<td></td>
<td>(-10.6 to -1.03)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>-8.95</td>
<td>.092</td>
<td>.387</td>
<td>-4.39</td>
<td>.074</td>
</tr>
<tr>
<td>(-19.3 to 1.45)</td>
<td></td>
<td></td>
<td></td>
<td>(-9.20 to 0.42)</td>
<td></td>
</tr>
<tr>
<td><em>p Homogeneity for age of FAD assessment</em></td>
<td>.069</td>
<td>.055</td>
<td>.132</td>
<td>.600</td>
<td>.162</td>
</tr>
</tbody>
</table>

Note: Linear regression analysis of FAD and brain morphology outcome. Betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume). Model 2 is additionally adjusted for paternal age, ethnicity, education, parity, marital status, paternal psychopathology, smoking and alcohol consumption. Global brain measures are not adjusted for total ICV. *p_{FDR} = false discovery rate correction for multiple testing. Number of tests = 5 outcomes and the 2 relevant exposure periods (prenatal and early childhood). Critical value for FDR = 0.05. *p Homogeneity for age of FAD assessment = Multiple-partial test used to test whether exposure from different time points of poor family functioning relates in the same manner to brain morphology outcome.
Table 6. The associations of paternal-reported poor family functioning and lobar measures.

<table>
<thead>
<tr>
<th>Father reported poor family functioning</th>
<th>Temporal lobe, (cm³)</th>
<th>Frontal lobe, (cm³)</th>
<th>Parietal lobe, (cm³)</th>
<th>Occipital lobe, (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor prenatal family functioning (FAD), per score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.87 (-1.85 to 0.11)</td>
<td>.083</td>
<td>.226</td>
<td>-1.10 (-2.52 to 0.32)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.51 (-1.56 to 0.53)</td>
<td>.334</td>
<td>.605</td>
<td>-0.75 (-2.26 to 0.75)</td>
</tr>
<tr>
<td>Age 9 poor family functioning (FAD), per score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.28 (-0.64 to 1.20)</td>
<td>.552</td>
<td>.791</td>
<td>0.17 (-1.12 to 1.47)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.38 (-0.55 to 1.31)</td>
<td>.426</td>
<td>.686</td>
<td>0.33 (-0.98 to 1.65)</td>
</tr>
</tbody>
</table>

Note: Linear regression analysis of FAD and lobar measures. Betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume). Model 2 is additionally adjusted for paternal age, ethnicity, education, parity, marital status, paternal psychopathology, smoking and alcohol consumption. Global brain measures are not adjusted for total ICV. $p_{FDR}$, false discovery rate correction for multiple testing. Number of tests = 4 outcomes and the 2 relevant exposure periods (prenatal and early childhood). Critical value for FDR = 0.05. $p$ Homogeneity for age of FAD assessment = Multiple-partial test used to test whether exposure from different time points of poor family functioning relates in the same manner to brain morphology outcome.
## eTable 7. Inverse probability weighting approach for the associations of poor prenatal family functioning and brain morphology.

<table>
<thead>
<tr>
<th>Mother reported poor family functioning</th>
<th>Brain morphology (N = 2,583)</th>
<th>Global brain measure</th>
<th>Specific brain volumetric measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total brain volume,</td>
<td>Cerebral white matter,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(cm³)</td>
<td>Total gray volume,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amygdala volume,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hippocampus volume, (cm³)</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Poor prenatal family functioning FAD, per score</td>
<td>-9.50 (-17.9 to -1.13)</td>
<td>.026</td>
<td>-4.19 (-8.07 to -0.32)</td>
</tr>
<tr>
<td></td>
<td>-5.16 (-10.1 to -0.31)</td>
<td>.037</td>
<td>-0.02 (-0.05 to 0.005)</td>
</tr>
<tr>
<td></td>
<td>-0.02 (-0.13 to -0.02)</td>
<td>.004</td>
<td>-0.08 (-0.07 to 0.04)</td>
</tr>
<tr>
<td>Age 5 poor family functioning (FAD), per score</td>
<td>-5.47 (-14.7 to 3.81)</td>
<td>.248</td>
<td>-1.86 (-6.19 to 2.40)</td>
</tr>
<tr>
<td></td>
<td>-3.59 (-8.98 to 1.78)</td>
<td>.190</td>
<td>-0.004 (-0.03 to 0.03)</td>
</tr>
<tr>
<td></td>
<td>-0.014 (-0.046 to 0.018)</td>
<td>.391</td>
<td>-0.02 (-0.07 to 0.04)</td>
</tr>
</tbody>
</table>

Note: Inverse probability weighting under missing data of poor prenatal family functioning and brain morphology outcome. Betas are averaged from 10 imputed datasets. Models are adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume), maternal age, ethnicity, education, parity, marital status, maternal psychopathology, smoking and alcohol consumption. Global brain measures are not adjusted for total ICV.

## eTable 8. The associations of poor family functioning and microstructural measures of brain morphology stratified by hemispheres.

<table>
<thead>
<tr>
<th>Mother reported poor family functioning</th>
<th>Brain morphology (N = 2,583)</th>
<th>Amygdala volume, (cm³)</th>
<th>Hippocampus volume, (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Left amygdala volume</td>
<td>Right amygdala volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left hippocampus</td>
<td>Right hippocampus</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Poor prenatal family functioning FAD, per score</td>
<td>-.012 (-.027 to .03)</td>
<td>.110</td>
<td>-.009 (-.025 to .006)</td>
</tr>
<tr>
<td></td>
<td>.243 (-.066 to -.012)</td>
<td>.005</td>
<td>-.037 (-.066 to -.009)</td>
</tr>
<tr>
<td>Age 5 poor family functioning (FAD), per score</td>
<td>-.006 (-.023 to .010)</td>
<td>.444</td>
<td>.003 (-.015 to .020)</td>
</tr>
<tr>
<td></td>
<td>.748 (-.035 to .025)</td>
<td>.828</td>
<td>-.014 (-.046 to .018)</td>
</tr>
</tbody>
</table>

Note: Linear regression analysis of FAD and brain morphology outcome stratified by hemispheres. Betas are averaged from 10 imputed datasets. Models are adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume). Model 2 is additionally adjusted for maternal age, ethnicity, education, parity, marital status, maternal psychopathology, smoking and alcohol consumption.
**eTable 9.** The associations of poor family functioning and lobar measures stratified by hemispheres.

<table>
<thead>
<tr>
<th>Mother reported poor family functioning</th>
<th>Temporal lobe, (cm³)</th>
<th>Frontal lobe, (cm³)</th>
<th>Parietal lobe, (cm³)</th>
<th>Occipital lobe, (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>p</td>
<td>B (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Poor prenatal family functioning (FAD), per score</td>
<td>-.120 (-.289 to .529)</td>
<td>.566</td>
<td>.478 (-.066 to 1.02)</td>
<td>.085</td>
</tr>
<tr>
<td></td>
<td>-.062 (-.473 to .349)</td>
<td>.768</td>
<td>.221 (-.370 to .812)</td>
<td>.464</td>
</tr>
<tr>
<td>Age 5 poor family functioning (FAD), per score</td>
<td>-.127 (-.582 to .328)</td>
<td>.584</td>
<td>-.201 (-.805 to .402)</td>
<td>.513</td>
</tr>
<tr>
<td></td>
<td>-.182 (-.273 to .637)</td>
<td>.434</td>
<td>-.602 (-.1.25 to .050)</td>
<td>.070</td>
</tr>
</tbody>
</table>

Note: Linear regression analysis of FAD and lobar measures stratified by hemispheres. Betas are averaged from 10 imputed datasets. Models are adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume), maternal age, ethnicity, education, parity, marital status, maternal psychopathology, smoking and alcohol consumption.
**Table 10.** Correlation coefficients between maternal and paternal report of poor family functioning.

<table>
<thead>
<tr>
<th>Poor family functioning</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Prenatal, mother report</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Prenatal, father report</td>
<td>.45**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Age 5, mother report</td>
<td>.38**</td>
<td>.26**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Age 9, mother report</td>
<td>.37**</td>
<td>.22**</td>
<td>.52**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Age 9, father report</td>
<td>.25**</td>
<td>.39**</td>
<td>.35**</td>
<td>.45**</td>
<td></td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (2-tailed).**
eFigure 1. Inclusion of the study sample

Parents who initially enrolled in Gen R study N=8,879

Information on FAD eligible:
N = 7,123 mother; N = 4,561 father;

Exclusion:
Information on mothers with no partner; N= 1,266

Information on FAD available and brain structural MRI at age 9; N = 3,272

Exclusion:
No brain imaging data; N = 3,851

Exclusion:
Children with poor imaging data; N = 638
Major incidental finding; N = 19

Exclusion:
One random twin from each pair; N = 32

Children with information on FAD available and brain structural MRI; N = 2,583
eFigure 2. Path model of prenatal parental family functioning factor and brain morphology.

Note: Structural equation modeling of parental family functioning factor and preadolescent brain morphology. Numeric values are standardized path regression coefficients of latent factor. Models are adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume), maternal age, ethnicity, education, parity, marital status, maternal psychopathology, smoking and alcohol consumption. The dotted line represents the non-significant associations.

eFigure 3. The list of primary and secondary brain morphology
EResults.

Complementary sensitivity analyses

Latent factor model
The latent variable models suggest that prenatal parental poor family functioning factor is associated with smaller offspring total brain volume, cortical gray, white matter, and hippocampal volumes in late childhood, but not with amygdala volume (eFigure 2). The association between the latent construct of prenatal maternal- and paternal-reported family functioning and preadolescent brain morphology captures covariation across raters, or the extent to which a given dimension is reflected across parents (i.e., a “between-rater” dimension factor). Maternal and paternal family functioning were positively correlated. This model indicated good fit to the data. Overall, results were very similar to those using prenatal maternal-reported family functioning.

Generalized estimating equation
Tests for homogeneity of the associations of poor family functioning with hippocampal volumes at different child ages showed evidence for an interaction indicating that results differed by child age. The GEE estimates of poor family functioning and brain outcomes were very similar to the results in Table 5, only the CIs varied slightly because this method takes into account within-individual correlation across the time points.

Inverse probability weighting approach
We calculated inverse probability weights to reduce a possible selection bias in this cohort study, thereby adding to the representatives of the study population with respect to the full cohort recruited during pregnancy. That is, we corrected for potential selection bias that can arise when only parent and children with available predictor and outcome data were included. Overall, we used information available for all participants at recruitment to predict probability of participation in the study and used the inverse of those probabilities as weights in the analyses so that result would be representative for the initial population of this cohort study (eSupplementary Table 7).
REFERENCES:


GENERAL DISCUSSION

The development of the child is neither a function of the child alone nor of experience alone, but a product of the combination of an individual and his or her experience. Epidemiology has the potential to identify the risk factors that can affect child development. It is particularly effective if conducted using longitudinal designs in child and general psychiatry as well as in other fields. The current thesis addresses the complexity of child development by investigating how family disruption occurring prenatally and early childhood explain child neurodevelopment and well-being. Most importantly, findings presented in this thesis reflect the availability of large data sets for analyses and the ability to examine change over time. In this final chapter, I will interpret the overall findings presented in this thesis in light of the larger body of published literature, address methodological considerations, and outline the clinical and public health implications, as well as provide directions for future research.

Family adversities and neurobehavioral development

Over the past decades, a vast body of evidence has accumulated that family environmental risk factors impact child developing psychopathology. There are multiple explanations for how exposure to family adversities, during pregnancy or early life, has an impact on the risk of developmental delays and mental health. Perhaps the most compelling example of family risk factors for childhood psychopathology comes from the now classic examples of Rutter and coworkers in 1977. These studies in British children revealed several factors within the family environment that are associated with childhood disturbances including marital conflict, low social class, and maternal psychopathology. More recently, studies suggest that the impact of family adversities on child neurodevelopment begins in the womb. However, changes that have their origin in the womb do not mean that they cannot be altered again later. Thus, environmental influences that affect the brain and behavior of the offspring begin prenatally and continue through adolescence and early adulthood. For example, we showed evidence that exposure to poor family functioning or conflict influence child development differently than parental separation does. Moreover, we demonstrated that such disruption extends over time rather than occurring at one time point. In the following paragraphs, I will discuss the evidence for the association between prenatal and early environmental factors and child behavioral outcomes, with a special focus on neurodevelopmental outcomes, and evidence that some component of these associations is due to specific mediators.

Types of adversities and offspring behavioral development

It is now widely recognized that children exposed to poor family functioning or conflict, poor parenting practices, and separation during childhood are at risk for a variety of behavioral, cognitive, and psychological consequences. Traditional understanding of
child behavioral development has focused on the influences of family functioning and separation without disentangling the differential effects of these specific exposures. More recently, the characterization of adverse exposures has provided evidence supporting the critical role that family environmental factors have in modifying developmental processes. As we present in chapter 2, children exposed to family disruption (including family conflict and separation) witness a breaking expectable environment. We present data showing that such exposures, if occurring during a critical period of development such as pregnancy or early childhood, have detrimental effects. These early family disruptions are likely to be long lasting risk factors for poor child behavioral outcomes. However, it is not difficult to think of possible ‘common’ causes of parental conflict or poor parenting and their consequences for children. The key issue is thus whether or to what extent child problems can be attributed to parental separation. For this reason, we modelled the complex mediation and interaction between family conflict and separation on child problems to best identify interventions that will improve child outcomes. Specifically, we test pathways through which parental conflict might influence child problems and whether these pathways are primarily a function of parental separation or reflect an interaction of family conflict and separation. It gives insight into the role of different pathways of parental conflict and separation.

We showed that at low levels of conflict not all children are affected by parental separation and those that are can be affected in different ways. The applied method to simultaneously examine the mediation and additive interaction illustrated that there was no evidence of a pure indirect effect of parental separation on child problem behavior. The direction of this effect did, however, suggest that parental separation might have some protective effect on child problems behavior in those children who were exposed to low levels of parental conflict. Examining possible beneficial effects merits further investigation. The interpretation of these findings must account for the influence of potential confounding by baseline family environmental factors. This includes exposure to unfavorable socio-demographic factors, prenatal smoking and alcohol consumption, and parental psychopathology. However, after adjusting for potential confounding influences we still found an additional direct effect of prenatal and childhood family disruption on child emotional and behavioral problems. In addition, we showed in a sensitivity analysis that it is unlikely that unmeasured confounding would have changed the conclusions.

Next, we studied the impact of family factors on cognitive development. Children exposed to poor pre- and postnatal family functioning or separation are at risk for cognitive delays, which is a likely contributor of lower school achievement. Until now, accumulating evidence has demonstrated that family disruption may influence child school achievement, but none had determined whether family disruption from pregnancy
onward is associated with later offspring school achievement. Attention problems in children are also a known contributor of low school attainment exposed to early family disruption. We aimed to unravel the association of parental education, parenting practices and offspring school achievement. Not surprisingly, in chapter 2.3 we first observed that higher parental education is associated with good parenting practices, which in turn are associated with higher school achievement. Jointly, the findings described in chapter 2.2 and 2.3 support a significant role of family disruption in child school achievement, whether characterized by poor family functioning, poor parenting practices, or parental separation.

Children influence their environment and environments influence children, it is thus clear that a bidirectional model must be employed in particular in the interrelation between parental and child psychopathology. In chapter 3, we used measures of maternal and paternal psychopathology as well as with maternal and paternal ratings of child problem behavior to examine whether within-rater and across bidirectional associations of parent and offspring psychopathology can be consistently detected. With-in rater associations assess the change of symptoms over time, across rater associations compare symptoms between individuals. Firstly, we found no difference between mothers and fathers in any of the observed associations between parent and child. Secondly and importantly, child psychopathology was hardly associated with parental psychopathology later in time. We found no evidence for cross-rater child-to-parent associations. This suggests that the within-rater child-to-parent associations, which we did find, reflected shared method variance. This describes the phenomenon that using the same rater for a subjective exposure and outcome might have inflated the observed associations. Thus, it is very likely that parent’s reports on their child’s problems could be biased by their own cognition, or by poor understanding of the questions, or by their temperament or how they tend to answer questions on emotions.

To further highlight the processes between experience and development, we carried out an autoregressive cross-lagged model. With this approach we disentangled the contribution of within- between-person variation in bidirectional associations of environmental exposures to offspring psychopathology. The two levels of this analysis (within- and between-individual associations) clearly carry different substantive interpretations. For example, within individual variability (intra-individual change) refers to the underlying question of how the child psychopathology changes or remains stable based on only their individual level of exposure. While the between individual observation refers to, on population mean level, children who are exposed to parental psychopathology tend to show more psychopathology symptoms than children who are exposed to a lower level of parental psychopathology. Nevertheless, the between-person observation (inter-individual differences) reflects the aggregate $n$ within-individual observations in
which exposure to higher levels of parental psychopathology led to higher levels of child psychopathology. We observed that within-person levels of psychopathology explained substantial variance of child psychopathology, and vice versa.

From a social information perspective, a child is an individual in the context of social exchanges that unfold over time, rather than, say, a system of temporally ordered-person distributions in which children's rank orders shift conditionally over time (i.e., between-person associations).\[11\]

Next, we turned to loneliness as a risk factor for long-term mental health. Studies showed that loneliness is associated with generalized anxiety disorder, major depression, and dementia among adults.\[12\] Available evidence is mostly based on studies within one developmental period, studies of long-term effects across developmental periods are scarce. Thus, the impact of childhood loneliness has not been studied in light of possible persistent effects in mental health outcomes. The results we describe in chapter 4 are the first longitudinal evidence of the association between childhood loneliness and adult psychiatric disorders. Using data from a population-based cohort with up to 25 years follow-up and data collection using multiple informants, we were able to extend previous findings across developmental periods. Our results indicate that loneliness experienced in childhood had particularly robust associations with adult self-reported anxiety and depression outcomes. Notably, adjustment for childhood adversities did not meaningfully change the observed associations. Such findings suggest that, long-term effects of loneliness across significant developmental transitions contribute to the occurrence of adulthood psychiatric disorders.

**Types of adversities and offspring neurodevelopment**

In the last years, epidemiological studies advanced the idea that early family disruptions compromise neural and psychological outcomes. Recent work in neuroscience has begun to shed light on how family disruption that occurs during a critical period of brain development, accounts for altered developmental outcomes. Such an impact of family environment on child neurodevelopment begins in the womb, can alter the development of the fetus, with a long lasting effect on the child.\[4\] Our findings from chapter 5 suggest that prenatal maternal-reported poor family functioning is associated with smaller hippocampal and occipital lobe volumes in preadolescents. Importantly, upon analyzing combined maternal and paternal functioning, we observed similar results; however, maternal-reported poor family functioning largely drove the associations. It is known that the intrauterine environment significantly influences growth and development via dysregulation of the hypothalamic pituitary-adrenal axis,\[13,14\] but it may also affect brain development through inflammatory responses and changes in the balance of the autonomic nervous system.\[15\] Specifically, no such association was found for poor
family functioning reported later in childhood, i.e., at ages 6 and 10. Thus, the timing of exposure is important in considering the effects of family disruption on brain development, which brings us to the role of sensitive or critical periods.

If physiological changes occur in the womb, this does not imply that they cannot be altered again later. For example, some of the neurodevelopmental effects of prenatal stress exposures or raised in the utero cortisol can be buffered by poor parenting between parent and the child postnatally. Notably, the results we describe in chapter 5 provide evidence that the association of maternal-reported poor family functioning during pregnancy with preadolescent problem behavior was partially mediated by hippocampal volumes. Thus, some of the brain changes that are observed in response to poor prenatal family functioning, may cause changes in problem behavior later in life.

In a further study of family disruption, we investigated the associations of family functioning from pregnancy onward and global white matter microstructure. Our findings suggest that higher levels of prenatal family functioning were associated with greater white matter microstructure in preadolescent children (chapter 5.1). A growing number of studies have indicated that both negative and positive experiences occurring prenatally, and in childhood alter white matter structural development. For example, maternal prenatal anxiety is associated with less white matter microstructure. In contrast, we did not find evidence suggesting an association between mid-childhood family functioning and white matter microstructure. The reported results demonstrate that the fetal and infant brain may be vulnerable to poor family functioning, such as conflict.

When a family member is assessed this measurement will reflect not only the respondent’s mind set but also reflect the influence of other family members, the respondent’s relationship to the other family members, and the whole family. Thus, by using triadic data analysis (mother-father-child) in chapter 6, we elucidate what is occurring in families. For instance, we found that the interrelations between parental hostility (dyad mother-father) within family contribute to the triadic mother-father-child brain function. This method assumes that dyad members are distinguishable, which enabled us to test whether there are empirically meaningful differences between the member of the family. Our findings suggest that maternal and paternal hostility is associated with smaller parental brain structures as well as with smaller preadolescent brain development. By conducting mediation analyses, we found that parent and child brain morphology contributed to child aggressive behavior in children exposed to parental hostility. Specifically, smaller maternal and child hippocampal volumes, but not paternal, contribute to more aggressive behavior in preadolescents exposed to prenatal parental hostility. This implies, that parental hostility is accompanied by structural differences in maternal and
paternal brain structures as well as with differences in preadolescent brain development, which in turn increases preadolescent aggressive behavior.

**Methodological considerations**

*Although we all have a strong desire for straightforward explanations of life, development is complicated and models for explaining it need to be complicated enough to usefully inform our understanding.*

*Arnold Sameroff, 1975*

**Stability and change**

An important question which continually confronts the researcher in the study of child development is how to best characterize the nature of developmental change. Simply put, we can ask whether development is best characterized by stability (e.g., does a child behavior or a trait, such as externalizing problems, remain stable in its expression over time?) or change (e.g., could an individual’s degree of externalizing problems fluctuate across the life span?). An important aspect of the debate on stability versus change has to do with the degree to which early experiences play a formative role in later development. A series of studies investigating the effects of early experience in children's social, physical, and cognitive development was conducted by the British psychiatrist Michael Rutter. Rutter and his colleagues were able to investigate whether the degree of children’s recovery from these early experiences was affected by how long they had been institutionalized in Romanian orphanages.20

To answer the questions mentioned above, we have traced an epidemiologic sample of children and their parents across childhood by using repeated assessments of the exposure and the outcome. Thinking of stability as consistency and instability as a change, the most important study design characteristics that we applied in this thesis are to develop well-defined research questions, to combine different analytical methods, and to aim to diminish of bias. Methodology for how studies of children exposed to family disruption across time could test the potential for change in behavior is described in each chapter of this thesis.

**Models of developmental changes in childhood** – After I identified the behavioral consequences of family disruption, I will discuss how this behavior changes and whether any change is stable. In addition to representing conceptually different temporal patterns of stability and change, we have employed multivariable linear regression with generalized estimating equations (GEE)21,22 approach to simultaneously examine repeated measures of family disruption in relation to neurobehavioral outcomes (i.e., whether family functioning measured during different time points was associated in the same manner to child neurobehavioral outcomes). To explore the possibility of unique periods of
susceptibility, we tested the interaction with the child’s age in the associations between family disruption and neurobehavioral outcomes (e.g., poor family functioning x exposure period interaction p-value = .001). Although this approach retains the interpretation of a set of separate multiple regressions (by providing a single estimate of effect for exposure at each time point), it takes the variance between family disruption over time into account, while assessing the differences in associations between poor family disruption and child neurobehavioral outcomes.

**Between-individual variation of change** - In spite of the results described in this thesis indicating relatively high stability coefficients over time, all types of behavioral and family adversities yielded variance in change of child development over time. Thus, the specific exposure adversities are associated with a change in symptoms from pregnancy onward. In addition to the fact that we were measuring exposures in a period of life that give rise to rapid changes in child neurodevelopment, changes in symptoms of all adversities were also detected. For instance, in chapter 5 we found that poor family functioning from pregnancy onward was associated with child neurodevelopment and well-being.

**Sensitive periods under developmental change** - The notion of a sensitive period implies that a certain experience at a certain time during development may give rise to a change in the future developmental outcome. Research shows, however, that events subsequent to the sensitive period may also modify or undo earlier effects constituting a further change at later point in development. Thus, another strength of this method is to the ability to detect developmental windows, which underlie critical and sensitive period phenomena, and must be differentiated from the effect of change of exposure over time. As illustrated in Chapter 2 and 5, we identified particularly important windows of time when environmental exposures such as poor prenatal family functioning impact child neurodevelopment. That is, a sensitive period describes the effects an experience has on the development during narrow windows of time. In contrast, critical periods result after sensitive period ends but negative experiences may continue to affect child brain function. For example, we found that postnatal family disruption such as harsh parenting might affect brain development in childhood. Thus, sensitive and critical period models rely on experience that facilitate biological encoding of expectable environment during developmental windows; these models have distinct implications for our understanding of the impact of adversity. We can hypothesize that family disruption during sensitive and critical periods of development is more likely to have persistent effects on neural and behavioral function later in time.

Indeed, even within a domain of sensory development or psychopathology such as anxiety and depression there will be different sensitive and critical periods. For example, there are multiple critical and sensitive periods for different forms of psychopathology.
However, few studies have shown interest in identifying whether family risk factors at any time point or during sensitive period are associated with child neurobehavioral development. Finally, given the complexity of the different types of adversity in child development, further research may want to consider the use of mixture models for combinations of adverse experiences to identify how different types of adversity interact and lead to effects of child neurodevelopment.

**Bi-directionality and developmental change over time** - We have repeatedly emphasized the importance of studying bidirectional associations in the transactions between parents and children. We have highlighted this as important for identifying developmental change and stability, but the contribution of within-between-person variation in bidirectional associations of environmental exposures to offspring psychopathology is relatively understudied. In other words, how a person varies from his or her own baseline level (in our study the baseline was psychopathology during pregnancy). The two levels of analysis - within and between individual variation - clearly carry different substantive interpretations.\(^{10,11}\) Our logic to analyzing between-person and within-person effects is to estimate how much of its variation is due to each source. We found evidence for between person-person variation (person-to-person differences in mean psychopathology levels) as well as within-person variation (i.e., variation around a person’s level with more or less psychopathology at a given time) in bidirectional associations of parent and offspring psychopathology. That is, even though psychopathology levels vary across time, to the extent that some individuals report more psychopathology at a certain time point, psychopathology will also vary across people and these latter variations may explain association ascribed to the first.

These different levels of inference also carry different strength and weaknesses. For instance, when bidirectional associations are fixed within individuals, each child serves as his or her own control group. That means we estimated the effect based only on within child variation (e.g., the child compared to him/herself). In contrast, between child estimates carry the advantage of accounting for aspects that differ systematically between children, such as temporally stable aspects of child psychopathology. However, in analyses of between-person associations, biases due to unobserved confounding cannot be ruled out. Moreover, it is difficult to refer a developmental theory underlying the between-person associations between parent and offspring psychopathology. Rather, developmental theory is largely a within-individual endeavor.

**Mediation and interaction models**

The methodology for examining mediation analysis has expanded dramatically over the past 10 years. It is common for the effect of one exposure on an outcome to operate in some way through the presence or absence of another exposure (a potential mediator).
One issue that has seen increasing interest is the interaction between two environmental exposures, but interaction that occurs between genetic and environmental exposures has received particular interest. Interaction between two (causally) related exposures is one manifestation of this complexity and thus traditional methods of mediation were extended to allow for exposure-mediator interaction or nonlinearities.²⁸,²⁹

For these reasons, we have used an approach that more fully encompasses mediation and interaction simultaneously. In Chapter 2 we show that the overall effect of prenatal parental conflict on child problem behavior, in the presence of parental separation as a mediator with which family conflict may interact, can be decomposed into four components: (i) how much of an effect is mediated, (ii) how much is due to interaction, (iii) how much is due to both mediation and interaction together, and (iv) how much is due to the direct effect of exposure.³⁰ The intuition behind this decomposition is that if the parental conflict affects child maladjustment, then at least one of these four conditions must be met. This four-way decomposition method showed that prenatal family conflict to some extent affects child problem behavior through the pathway of parental separation. Finally, and perhaps most importantly, parental separation was not associated with child problem behavior in absence of family conflict. That is, we did not find a risk increasing effect of separation on child emotional and behavioral problems; the association was tentative at best, given the lack of statistical significance and broad CIs. Furthermore, because no post-separation conflict data were obtained in our sample, we cannot establish the effect of parental post-separation conflict on children’s adjustment to separation.

The similar findings between traditional mediation and four-way method highlight the fact that controlled direct effects are of interest in policy evaluation because they consider what the effect of the exposure would remain if we were to intervene on the mediator across the population.²⁹,³¹,³² In our case the controlled direct effect represents the impact of parental conflict on child behavior problems if we were to successfully intervene and reduce the prevalence of parental separation.

**Modeling the difference between and within (over time) individuals**

As discussed in the section above on stability and change, the idea of dynamic, bi-directional association processes between experience and development is core of most developmental models. Developmental continuity and change of most complex traits are assumed to be driven by self-organizing transactions between individual and context over time.³³

One of the most well-known and often used models to test bi-directionality is structural equation modeling (SEM). We saw an example of this in Chapter 3. We studied bi-
directionality in the association between parent and child psychiatric symptoms with separate measures of maternal and paternal psychopathology as well as separate ratings of child internalizing and externalizing problems by both mothers and fathers. We were able to show that only within-rater (i.e., both the rating on parental psychopathology and child outcomes were obtained from the same parent) bidirectional associations of parent and offspring psychopathology could be consistently detected. Structural equation models are often criticized for not adequately addressing issues of confounding, and yield estimates that are difficult to interpret meaningfully. Moreover, the parameters are typically interpreted as between-person effect. However, if issues of confounding are adequately addressed by including all relevant confounders, then the SEM approach can be a useful tool for an estimated population average mean.

Importantly, building on the recent discussions on disaggregating the within- and between-person associations we have employed, in the same chapter, autoregressive latent trajectory with structured residuals (ALT-SR) to better understand developmental processes. Interestingly, the ALT-SR suggested that bidirectional associations were actually explained by both the within- and between-individuals of parents and child psychopathology. Thus, from a substantive view, the bidirectional associations were evident at the level of analysis that is arguably the most relevant to developmental theory, i.e., the within-person level. From a methodological view, this means that bidirectional associations remained after accounting for many potential confounders (certainly those that do not vary with time). However, parent and offspring psychopathology were consistently associated within-raters but not across-raters. A methodological strength of within subject analyses is ‘fixing’ of associations to reflect only within-child variation. This provides evidence that there is a causal relation between parents and offspring psychopathology captured by the within- and between-individual component of the model. However, we did not examine bidirectional associations between the within-person interactions with time or bidirectional interactions between within- and between-individual parent and offspring psychopathology, and that the bidirectional estimates do not vary randomly across children. In terms of multiple levels of inference, such as within- and between-individual variances, each association requires sufficient statistical power. Specifically, statistical power can also be affected by the number, timing, the reliability of variables and their distributions, model size, missing data, and so forth. Given this complexity, it is important that the Generation R Study has a robust sample size and a relatively high number of longitudinal behavioral observations.

**Multi-informant approach**

The question is, does the average self and other agreement in child or parent psychiatric symptom rating account for a psychometric challenge? Yes, indeed! The estimates that are averages between two judges found in both child and adult literature lead to a
psychometric challenge with a clear prescription: Use more judges. As we indicated in all chapters of this thesis, when assessing data from multiple informants such as child and parents it is now commonly accepted that each informant provide potentially valuable data. However, inconsistencies often arise among multiple informants referred to as ‘informant discrepancies’, even when informants complete parallel or identical measures.

Two methods, both implemented in this thesis, lead our discussion about principles underlying the use of multiple informants’ reports. First, the use of a single informant’s report involves testing whether each informant observes child behavior in a particular context. However, a frequently encountered problem in the study of child psychopathology is that shared-rater variance might inflate the associations when they are measured by the informants on the same survey. Thus, when the same reporter provides ratings on the predictor and the outcome, part of the explained variance may be due to the informant who is reporting rather than to the constructs the measures are assumed to represent. As described in Chapter 3, the fact that associations of parent to offspring psychopathology were largely observed only within and not cross-rater, could in principle reflect three factors, namely cross-rater disagreement, information bias, and importantly, shared-rater variance, which is a particular form of information bias. There are three factors/mechanisms that may lead to informant discrepancies and possible attribution bias: including informant attributions (different perceived causes of the problem behavior), informant perspectives (does the problem behavior warrant treatment), and goal of assessment process (differences in the perceived outcomes of the assessment). Moreover, to minimize shared-rater variance, information on predictor and outcome variables must be obtained from multiple sources or informants. For example, it would be advantageous if other informant ratings on problem behaviour were obtained, such as father ratings on maternal psychopathology, mother ratings on paternal psychopathology, clinician’s ratings on parental psychopathology and teacher-, clinician- or (if the child were old enough) self-reports on child problem behaviour.

Second, we used a statistical method to investigate, in combination, multiple measures of a single assessment to create a ‘latent’ variable representation of that assessment. This method focuses on the variance shared among multiple informants (e.g., maternal and paternal reports) of the same assessment and time point. By using combinational algorithms, structural equation models (e.g., Chapter 5 and 6), latent factor reflects the common variance across mother and father-reported family disruption. As a result, only a small percentage of variance was explained within these models, suggesting it would be helpful to consider additional variables to account for variance in various common and informant perspective factors. However, in their study examining how repeated measurements of self-, parent and teacher-reported problems in adolescence relate to
internalizing and externalizing DSM disorders in adulthood, Van der Ende et al., (2020) showed that the added value of an additional informant may not add much to a carefully selected informant beyond the precision of the estimate.48

**Implications and future perspectives**

From this thesis several lessons can be learned. First, the potential for prevention and treatment of family dissolution in light of persistent effects in mental health outcomes in childhood, deserves advocacy to both clinical settings and in public health. Preventive interventions with small effects at the individual level, and relatively minor decrease in family disruption could have a major impact on the burden of functioning at the population level.

The large number of adverse consequences associated with behavioral outcomes during childhood support the notion that this is a large public health concern, both for individuals and society. In order to prevent child maladjustment, it is important to identify family risk factors and indicators. As for interventions, we believe that there is enough evidence to pursue poor family functioning as a risk factor for child maladjustment. Continuous monitoring of child maladjustment occurrence is crucial to detecting changes relevant to the individual and to public health. At the same time, practitioners should be aware that if poor family functioning, parenting practices, and separation occurs in early childhood, some proactive intervention may be needed to help the children adjust and prevent low school achievement. Hence, school-based or health-care-based screening for maladjustment problems and low school achievement in children experiencing family disruption would be helpful as a prevention measure.49

Post-separation conflict and children's overall adjustment is a theme that merits further research. Clinicians know through their own experience that many children of parental separation do well. Well-designed longitudinal studies are needed to examine possible beneficial effects of parental separation. The last factor to consider is the number of disruptions the children will experience. This factor has not been directly studied by researchers because repeated disruptions are hard to specify and quantify.

We described in this thesis that children are neither condemned nor protected by their own characteristics or by their characteristics of parents alone. The complexity of parental psychopathology opens up the possibility for many paths of intervention to facilitate the development of children and their families. Thus, the psychopathology of parents is a crucial target of prevention and intervention efforts for children with developmental problems. Where relationships are problematic, intervention should be directed at one or more these three parts (e.g., mother, father, child). However, whether interventions for children with psychopathology should largely focus on parents with psychiatric problems, only on children, or on both depends on the child’s age, the developmental
status, and cognitive capacities. Moreover, any intervention to interrupt the negative transactional processes between parental and offspring psychopathology would need to be aware of other social influence and complexities determining when and in whom to intervene. Although we can learn from observational studies of the development of different groups of children or parents, we can never fully test causal hypotheses for most groups of interest because we cannot randomly assign infants to different emotional and behavioral problems or parents to competence or incompetence. However, the converging evidence for the existence of bidirectional associations between parents and children provides a strong basis for intervening more effectively to improve the lives of families facing challenges from either child or parent.

Finally, subcortical brain changes found after more than 10 years of follow-up suggest that the fetal and infant brain may be vulnerable to family disruption, such as poor functioning and parental hostility. This serves as a powerful reminder that clinicians need to address family factors and, where necessary, intervene or refer to specialists. Parallel research on parents and children interventions could help identify at-risk individuals for more efficient allocation interventions to optimize maternal-paternal-child neurodevelopment. Moreover, multiple repeated measures of imaging data starting early in childhood would be necessary to test the directionality between behavior and brain development. Research on the parental brain, particularly studies testing brain response to parent-child interactions, can uncover how the brain reacts to social stimuli. Assessing such patterns in relation to the child’s long-term development can offer new insights into the origins of psychopathology. Another unresolved issue in population neuroscience is the need to shift research from the functioning of a single brain to the coordination of several brains, to understand how brain-to-brain synchrony enables formation of social bonds and collaboration among families and groups.

**Concluding remarks**

Findings of this thesis illustrated how prenatal and childhood family disruption result in neurodevelopmental vulnerability to develop emotional, behavioral, and cognitive problems. Bidirectional associations between parental psychology and child externalizing and internalizing problems were consistently associated only within-raters but not across-raters. Thus, these observations are likely to reflect shared-rater variance. At the level of the brain, poor family functioning was associated with changes in brain development that in turn contributed to preadolescent problem behaviors. Finally, we found that the dyadic mother-father characterized by hostility is associated with the mother and father structural brain differences as well as with children’s brain development. Differences in brain structures of parents and children underlie the associations between parental hostility and preadolescent aggressive behavior.
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Chapter 8

Summary
SUMMARY

It is well known that family disruption including poor family functioning or conflict, parental separation, parental anxiety/depression, and different forms of parenting are associated with long-term child emotional and behavioral problems, and with lower cognitive abilities and poorer school performance. However, it is unclear in which periods children are vulnerable and in what sequence family events impact them most, and who is most likely to be affected. In the current thesis, we examined associations of family disruption from pregnancy onward with child neurodevelopment and well-being.

In Chapter 2, we examined associations of family conflict from pregnancy onward and child problem behavior up to preadolescence according to maternal and paternal ratings. This is illustrated furthermore by using a four-way decomposition approach yielded evidence prenatal family conflict increased the children’s vulnerability to the harmful effect of parental separation. The additive interaction between prenatal family conflict and separation lend support to the idea that consequences of parental conflict and separation on child maladjustment often occur only when multiple links in the chain fails simultaneously. Such findings also suggest that, if parental separation occurs in families with low levels of conflict, parental separation does not increase child problem behavior. Moreover, sensitivity analyses testing for unobserved confounding underscores these conclusions; the direct effect increased, whereas the indirect effect decreased. Finally, bidirectional findings suggest that child problem behavior influences persistence of family conflict.

Chapter 2.1. describes associations of maternal and paternal reported poor family functioning and parental separation with child school achievement at age 12 while carefully controlling for indicators of innate cognitive ability of mothers. These analyses showed that the associations of pre- and postnatal poor family adjustment and parental separation with child school achievement were independent and each explained by childhood non-verbal IQ at age 6 years. By carrying out mediation analysis, we illustrated that child attention problems independent of IQ mediated the associations of both poor family functioning and parental separation with lower school achievement. Collectively, our findings indicate that in children exposed to early family disruption, a less optimal cognitive ability impacts school achievement later in childhood.

Next to the insights into child school achievement, in Chapter 2.2. we found that the association of parental education (either early or mid-childhood) and school achievement at age 12 is explained by early non-verbal IQ at age 6. Further, parental education is also related to offspring school achievement through parenting practices, family
routines in early and mid-childhood mediated the relation between parental education and the child’s school achievement.

In **Chapter 3**, with separate measures of maternal and paternal psychopathology as well as with separate ratings of child problem behavior by mothers and fathers, we were able to show that only within-rater bidirectional associations of parent and offspring psychopathology can be consistently detected, with no difference between mothers and fathers. Importantly, child psychopathology was hardly associated with parental psychopathology. We found no evidence for cross-rater child-to-parent associations was found suggesting that the within-rater child-to-parent associations reflect shared method variance. To further highlight the processes between experience and development, we carried out autoregressive cross-lagged model. We observed repeated support for a between-person association, such that children who were exposed to parental psychopathology, on average, tended to show more internalizing and externalizing problems than were children who were exposed less problems. Further, within-person change accounted for a part of the variance observed.

In **Chapter 4**, results are based on the prospective-longitudinal, community-representative Great Smoky Mountains Study of 1,420 participants. We investigated the associations of childhood loneliness and long-term disruption in mental health that extends into adulthood. Our findings suggest that loneliness is a transient dysphoric state that affects current health and has the potential to compromise emotional health long-term. Childhood adversities did not meaningfully change the observed associations. In contrast, we found no evidence for an association of children experienced loneliness with substance use disorder.

In **Chapter 5**, we report our findings investigating a neuroimaging follow-up study of the relationship between poor family functioning from pregnancy onward with preadolescent brain development and whether this underlies emotional and behavioral problems. We were able to show that prenatal maternal-reported poor family functioning is associated with smaller hippocampal and occipital lobe volumes in preadolescents. In contrast, no such association was found for poor family functioning reported later in childhood, i.e., at ages 6 and 10. Importantly, after adjusting for prior child problem behavior at age 1.5 years, the association of maternal-reported poor family functioning during pregnancy with preadolescent problem behavior was partially mediated by hippocampal volumes. Upon analyzing combined maternal and paternal functioning, we observed similar results; however, maternal-reports poor family functioning largely drove the associations.
In the following Chapter 5.1, we reported results that investigated whether more positive early-life family functioning would be associated with more global white matter microstructure, after extensive adjustment for baseline confounders. We observed that higher levels of prenatal family functioning were associated with greater white matter microstructure in preadolescent children. Further, we found no evidence suggesting an association between mid-childhood healthy family functioning and brain morphology outcomes. We concluded that children exposed to parental healthy family functioning may impact neurodevelopmental advantages throughout childhood.

In Chapter 6, we examined associations of prenatal and early childhood parental hostility would be associated with difference in maternal, paternal and child brain structures if analyzed in together, i.e. as triads. We found that prenatal parental hostility is associated with smaller volumes of total gray matter, white matter, and the hippocampus in children, suggesting that parental psychopathology may have long-lasting neurodevelopmental correlates in children. Maternal and paternal hostility were each associated with differences in his or her own brain morphology as well as his or her partner’s total white and gray matter, hippocampus and amygdala volumes. The association of parental hostility during pregnancy and child aggressive behavior was partially mediated by the child’s as well as maternal hippocampal volumes. Our findings suggest that hostility of a parent negatively relates to different family subsystems.

Finally, Chapter 7 discusses overall findings presented in this thesis, methodological considerations, clinical and public health implications, as well as provide directions for future research. From this thesis, we conclude that prenatal and childhood family disruption result in neurodevelopmental vulnerability to develop emotional, behavioral, and cognitive problems.
SAMENVATTING

Het is algemeen bekend dat een ontwrichtte gezinssituatie, zoals slecht functioneren in het gezin, conflict, echtscheiding van ouders, angst en depressie van ouders en bepaalde vormen van ouderschap, geassocieerd zijn met langdurige problemen bij het kind, waaronder emotionele en gedragsproblemen, een slechter cognitief functioneren en slechtere schoolprestaties. Het is echter onduidelijk in welke ontwikkelingsfase kinderen kwetsbaar zijn hiervoor, in welke volgorde familiegebeurtenissen de meeste impact hebben, en wie de grootste kans heeft op zulke problemen. In dit proefschrift verkennen we de associaties tussen gezinsontwrichting vanaf de zwangerschap en de hersenontwikkeling van het welzijn van het kind.

In hoofdstuk 2 onderzochten we de associaties tussen familieconflict sinds de zwangerschap en door moeder en vader gerapporteerde probleemgedrag van kinderen tot aan adolescentie. Dit is verder geïllustreerd door het gebruik van een vierwegsdecompositie, welke suggereerde dat prenataal familieconflict leidt tot een toegenomen kwetsbaarheid van het kind voor de gevolgen van een echtscheiding van de ouders. De additieve interactie tussen prenataal familieconflict en echtscheiding suggereert dat het kind zich vaak alleen slechter aanpast aan ouderlijk conflict en echtscheiding als meerdere schakels in de keten tegelijkertijd falen. Zulke bevindingen suggereren dat ouderlijke echtscheiding niet het probleemgedrag van het kind verhogen als de echtscheiding plaatsvindt in een gezin met weinig conflict. Dit werd verder ondersteund door sensitiveitsanalyses waarbij de ongeobserveerde confounding werd getest; het directe effect nam toe, terwijl het indirecte effect afnam. Tot slot suggereerden bidirectionele bevindingen dat probleemgedrag van het kind invloed heeft op de persistentie van gezinsconflicten.

Hoofdstuk 2.1 beschrijft de associaties van de door moeder en vader gerapporteerde slechte familie functioneren en ouderlijke scheiding met de schoolprestaties van het kind op 12-jarige leeftijd, waarbij zorgvuldig gecorrigeerd werd voor de indicatoren van het intrinsieke cognitieve vermogen van de moeders. Deze analyses lieten zien dat de associaties van slechte pre- en postnataal familieaanpassingen en echtscheidingen met de schoolprestaties van het kind onafhankelijk van elkaar zijn, en dat ze worden verklaard door het non-verbale IQ bij 6 jaar oud. Via een mediatieanalyse illustreerden we dat aandachtsproblemen bij het kind onafhankelijk van IQ deze associaties mediëren. Samengevat suggereren onze bevindingen dat in kinderen uit gezinnen met vroege gezinsontwrichting een lager cognitief vermogen impact heeft op schoolprestaties later in de kindertijd.

In hoofdstuk 2.2 tonen we verder aan dat de associatie tussen het opleidingsniveau van de ouders en schoolprestaties van het kind bij 12 jaar wordt verklaard door non-verbaal
IQ op 6-jarige leeftijd. Deze associatie werd gemedieerd door opvoedpraktijken en gezinsroutines in de vroege en midden-kindertijd.

In hoofdstuk 3 gebruikten we aparte maten voor psychopathologie van de moeders en vaders, en voor moeder en vader gerapporteerd probleemgedrag van het kind om aan te tonen dat bidirectionele associaties tussen psychopathologie van ouder en kind consistent kunnen worden gedetecteerd als de data van dezelfde ouder kwam, zonder verschil tussen data van de vaders en moeders. Het niveau van psychopathologie van het kind was echter amper geassocieerd met psychopathologie in de ouders. Ook vonden we geen associaties tussen ouderlijke psychopathologie en psychopathologie van het kind als gerapporteerd door de andere ouder. Dit suggereert dat de metingen van de psychopathologie van het kind gekleurd worden door de psychopathologie van de ouder van wie de meting komt. Ook hebben we de analyses uitgevoerd met verdere herhalingen van alle metingen, waarbij we dezelfde patronen vonden.

Hoofdstuk 4 is uitgevoerd in 1420 deelnemers van de prospectieve, longitudinale, populatie-representatieve Great Smoky Mountains Study. We onderzochten de associatie tussen eenzaamheid tijdens de kindertijd en langdurige verstoring van de mentale gezondheid tot in de volwassenheid. Hier vonden we dat eenzaamheid een tijdelijke dysforische staat is die de huidige mentale gezondheid beïnvloedt en dus kan leiden tot emotionele problemen op de lange termijn. De aanwezigheid van tegenslagen tijdens de kindertijd had weinig invloed op deze associatie. Daarentegen vonden we geen associatie tussen eenzaamheid tijdens de kindertijd en stoornissen gerelateerd aan middelenmisbruik.

In hoofdstuk 5 rapporteren we onze bevindingen van een hersenscanstudie naar de associatie tussen slecht familiefunctioneren sinds de zwangerschap en hersenontwikkeling van het schoolgaande kind, en of deze associatie ten grondslag ligt aan emotionele en gedragsproblemen. We toonden aan dat slecht familiefunctioneren als gerapporteerd tijdens de zwangerschap geassocieerd is met kleinere volumes van de hippocampus en de occipitale kwab in de kinderen. We vonden dergelijke associaties niet voor slecht gezinsfunctioneren zoals gerapporteerd in latere fasen van de kindertijd, namelijk bij 6 en 10 jaar. Interessant genoeg vonden we ook, nadat gecorrigeerd was voor probleemgedrag van het kind bij 1,5 jaar, dat de associatie tussen slecht prenataal familiefunctioneren en later probleemgedrag van het kind gemedieerd werd door het hippocampale volume. We vonden vergelijkbare resultaten als het functioneren gerapporteerd door beide ouders werd gecombineerd, hoewel de moeder gerapporteerde maat het meeste invloed had.

In hoofdstuk 5.1 onderzochten we of familiefunctioneren tijdens de kindertijd samenhang met de witte stof in de hersenen. We vonden dat beter prenataal familiefunctione-
ren samenhing met betere indicatoren van de witte stof in schoolgaande kinderen. Dit vonden we niet voor familiefunctioneren tijdens latere fases van de kindertijd. Hieruit concluderen we dus dat ouderlijk familiefunctioneren impact heeft op de hersenontwikkeling tijdens de kindertijd.

In hoofdstuk 6 verkenden we de associaties tussen pre- en postnatale ouderlijke hostiliteit en de hersenstructuren van kind, moeder en vader. De analyses werden uitgevoerd op de triades, dus op het kind en de ouders in hetzelfde statistische model. We vonden dat prenatale ouderlijke hostiliteit samenhing met kleinere volumes van de totale grijze stof, de totale witte stof en de hippocampus van het kind, wat suggereert dat ouderlijke psychopathologie samenhangt met de hersenontwikkeling van het kind. Hostiliteit van de moeder en vader hingen samen met hun eigen hersenstructuur en met die van hun partner, gekeken naar grijze stof, witte stof, de hippocampus en de amygdala. Verder toonden we aan dat de associatie tussen prenatale ouderlijke hostiliteit en later agressief gedrag van het kind werd gemedieerd door de hippocampale volumes van het kind en van de moeder. Samengevat toont dit aan dat ouderlijke hostiliteit negatieve invloeden heeft op verschillende subsystemen van het gezin.

Ten slotte bespreekt hoofdstuk 7 de algemene bevindingen van dit proefschrift, de methodologische afwegingen, de implicaties voor klinische zorg en de volksgezondheid, en richtingen voor verder onderzoek. Uit al dit werk concluderen we dat verstoringen in het gezin – zowel prenataal als tijdens de kindertijd – leiden tot kwetsbaarheden in de hersenontwikkeling die kunnen leiden tot emotionele, cognitieve en gedragsproblemen.
Appendix

Acknowledgements
Author Affiliations
Publications Not Part of This Thesis
PhD portfolio
Words of Gratitude / Dankwoord
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**PhD period:** Aug 2015 - Jun 2020  
**Promotors:** Prof. Dr. H. Tiemeier, Prof. Dr. F.C. Verhulst

## 1. PhD training

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Appendix

Research Integrity, Erasmus MC 2018 0.3

International conferences
IACAPAP, Prague, Czech Republic (poster presentation) 2018 1.0
SRCD, Baltimore, USA (oral presentation) 2019 2.0
SER, Boston, USA (poster presentation) 2020 1.0
IACAPAP, Singapore (oral presentation) 2020 2.0

Symposia, meetings & workshops
Generation R Behavioral Group Meetings, Rotterdam, the Netherlands (oral presentation) 2016-2020 1.0
ACTION meeting, Amsterdam, the Netherlands 2017 0.3
Psychiatry Ground Rounds - The Robert Larner College of Medicine at the University of Vermont (oral presentation) 2020 1.0
ASEBA (Achenbach System of Empirically Based Assessment) Manual for Progress & Outcomes of Problems & Strengths, Burlington, USA 2020 1.0

2. Teaching activities

Courses
Biostatistical methods I, SPSS/R (research assistance) 2017 2.4

Supervision Master thesis
Johanneke Tceu-De Kwart, (Clinical Psychology, Erasmus University Rotterdam). Association of Maternal Childhood Trauma and Child Behavioral Problems” 2018-2019 3.0
Gelitza Croes (Clinical Psychology, Erasmus University Rotterdam). Association of Prenatal Organophosphate Pesticides Exposure with Neuromotor Development in Young Children 2018-2019 3.0

3. Other activities
Peer review (e.g., JAMA Psychiatry, JCPP, JCCAP, Developmental Psychology) 2018-present 2.0
Six months research visit at the University of Vermont, Burlington USA 2020

4. Grants and prices
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1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours
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Yllza Xerxa was born in Gjakova, Kosovo. Yllza obtained both psychological and pedagogical degree, and a master's degree in Clinical Psychology at the University of Prishtina, Kosovo. After her master program, she has worked for the foundation “Children for Tomorrow” under the supervision of team from the University Medical Center, Hamburg-Eppendorf. The services she has provided include assessment, short-term and long-term individual and family psychotherapy, and counseling. In Rotterdam, Yllza obtained a Master’s degree in Epidemiology at the Netherlands Institute of Health Sciences. During her master’s program Yllza’s interests in research developed, and in 2016 she started a PhD program supervised by Prof. dr. Henning Tiemeier, and Prof. dr. Frank Verhulst, at the Department of Child and Adolescent Psychiatry and the Generation R Study Group at the Erasmus MC in Rotterdam, resulting in the work presented in this thesis. In 2020 she was awarded a Grant of the Royal Netherlands Academy of Arts and Sciences (KNAW) Ter Meulen, which gave her the opportunity to work as a visiting researcher at the Vermont Center for Children, Youth and Families, Department of Psychiatry, University of Vermont, Burlington, United States.