Family Disruption and Child Neurobehavioral Development
An Epidemiological Perspective

Yllza Xerxa

ISBN: 978-94-6361-551-8

Family Disruption and Child Neurobehavioral Development
An Epidemiological Perspective

Ontwrichting van het gezin en de gedrags- en hersenontwikkeling van het kind
Een epidemiologisch perspectief

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof. dr. F.A. van der Duijn Schouten

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on

Wednesday 16 June 2021 at 15.30hrs

by

Yllza Xerxa
born in Gjakova, Kosovo

Erasmus University Rotterdam

Doctoral Committee:

Promotors:	Prof. dr. H.W. Tiemeier
	Prof. dr. F.C. Verhulst
Other members:	Prof. dr. M.A. Ikram
	Prof. dr. R. Keizer
	Prof. dr. C. Schuengel

Paranymphs:	Michiel Arjen van den Dries
	Adelina Nikoliqi

In the memory of Professor Leslie A. Rescorla

Manuscripts that form the basis of this thesis

Xerxa, Y., Rescorla, LA., Serdarevic, F., Van IJzendoorn, MH., Jaddoe, VW., Verhulst, FC., Luijk, MPCM., Tiemeier, H. (2020). The Complex Role of Parental Separation in the Association Between Family Conflict and Child Problem Behavior. *Journal of Clinical Child & Adolescent Psychology,* 49(1):79-93. (Chapter 2).

Xerxa, Y., Martinez, NT., Rescorla, LA., Jansen, PW., Tiemeier, H. Compounded Change: Poor Family Functioning, Parental Separation, and Offspring School Achievement. Manuscript submitted for publication. (Chapter 2.1).

Martinez, NT., **Xerxa, Y.,** Law, J., Jansen, PW., Tiemeier, H. The Double Advantage of High Parental Education for Offspring's Educational Achievement: The Role of Parenting Practices. Manuscript submitted for publication. (Chapter 2.2).

Xerxa, Y., Rescorla, LA., Van der Ende, J., Hillegers, MHJ., Verhulst, FC., Tiemeier, H. (2021). From Parent to Child to Parent: Associations Between Parent and Offspring Psychopathology. *Child Development,* 92(1):291-307. (Chapter 3).

Xerxa, Y., Rescorla, LA., Shanahan, L., Tiemeier, H., Copeland, WE. Childhood Loneliness as a Specific Risk Factor for Adult Psychiatric Disorders. *Psychological Medicine* (in press). (Chapter 4).

Xerxa, Y., Delaney, SW., Rescorla, LA., Hillegers, MHJ., White, T., Verhulst, FC, Muetzel, RL., Tiemeier, H. (2020). Association of Poor Family Functioning From Pregnancy Onward With Preadolescent Behavior and Subcortical Brain Development. *JAMA Psychiatry,* 78(1):29-37. (Chapter 5).

Delaney, SW., **Xerxa, Y.,** Muetzel, RL., White, T., Haneuse, S., Ressler, KJ., Tiemeier, H., Kubzansky, LD. Long-term Associations Between Early-life Family Functioning and Preadolescent White Matter Microstructure. Manuscript submitted for publication. (Chapter 5.1).

Xerxa, Y., Lamballais, S., Muetzel, RL., Ikram, MA., Tiemeier, H. The Interrelation of Maternal and Paternal Hostility with Both Child and Parent Brain Morphology in the Association with Child Aggressive Behavior. A Population Based Neuroimaging study. Manuscript to be submitted for publication. (Chapter 6).

TABLE OF CONTENTS

Chapter 1	General Introduction	11
Chapter 2	The Complex Role of Parental Separation in the Association Between Family Conflict and Child Problem Behavior	23
Chapter 2.1	Compounded Change: Poor Family Functioning, Parental Separation, and Offspring School Achievement	51
Chapter 2.2	The Double Advantage of High Parental Education for Offspring's Educational Achievement: The Role of Parenting Practices	77
Chapter 3	From Parent to Child to Parent: Associations between Parent and Offspring Psychopathology	97
Chapter 4	Childhood Loneliness as a Specific Risk Factor for Adult Psychiatric Disorders	129
Chapter 5	Association of Poor Family Functioning From Pregnancy Onward With Preadolescent Behavior and Subcortical Brain Development	149
Chapter 5.1	Long-term Associations Between Early-life Family Functioning and Preadolescent White Matter Microstructure	187
Chapter 6	The Interrelation of Maternal and Paternal Hostility with Both Child and Parent Brain Morphology in the Association with Child Aggressive Behavior. A population Based Neuroimaging Study	215
Chapter 7	General Discussion	243
Chapter 8	Summary / Samenvatting	263
Appendix	Acknowledgements	273
	Author Affiliations	277
	Publications Not Part of This Thesis	279
	PhD portfolio	281
	Words of Gratitude / Dankwoord	283
	About the Author	287

Chapter 1

General introduction

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,[17,18] 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.[19] 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.[1]

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.[3] There is also a substantial body of evidence to support the notion that parental separation affects child emotional and behavioral problems.[9] 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,[20] and may be especially sensitive to family disruption.[21] 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.[22] Moreover, child IQ is one of the most important contributors to school achievement.[23] 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 transactional model that any development in the individual is influenced by the interplay of processes in the individual's context over time.[19] 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[24,25] and depression.[26] 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.[27] 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.[28,29] Exposure to parental hostility can have both immediate and lasting effects on physical and psychological health.[30] Moreover, in 'at risk families' parents are likely to show the neuroendocrine, immunological, and cardiovascular correlates of persistent stressors.[31] Many of these physiological and psychological differences potentially explain changes in the brain, such as decreased hippocampus and amygdala volumes.[32,33] 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.[34] 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).[35] 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).[36,37]

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

1. Sameroff AJ, Chandler MJ. Reproductive risk and the continuum of caretaking casualty. *Review of child development research.* 1975;4:187-244.
2. Davies PT, Coe JL. Family relationship dynamics: A developmental perspective. 2019.
3. Rhoades KA. Children's responses to interparental conflict: a meta-analysis of their associations with child adjustment. *Child Dev.* 2008;79(6):1942-1956.
4. Connell AM, Goodman SH. The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis. *Psychol Bull.* 2002;128(5):746-773.
5. Amato. Children of divorce in the 1990s: an update of the Amato and Keith (1991) meta-analysis. *J Fam Psychol.* 2001;15(3):355-370.
6. Bernet W, Wamboldt MZ, Narrow WE. Child affected by parental relationship distress. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2016;55(7):571-579.
7. Harold GT, Sellers R. Annual Research Review: Interparental conflict and youth psychopathology: an evidence review and practice focused update. *Journal of child psychology and psychiatry.* 2018;59(4):374-402.
8. Nelson Iii CA, Gabard-Durnam LJ. Early Adversity and Critical Periods: Neurodevelopmental Consequences of Violating the Expectable Environment. *Trends in Neurosciences.* 2020;43(3):133-143.
9. Amato. Research on divorce: Continuing trends and new developments. *Journal of marriage and family.* 2010;72(3):650-666.
10. Knudsen EI. Sensitive periods in the development of the brain and behavior. *J Cogn Neurosci.* 2004;16(8):1412-1425.
11. Lupien SJ, Juster RP, Raymond C, Marin MF. The effects of chronic stress on the human brain: From neurotoxicity, to vulnerability, to opportunity. *Front Neuroendocrinol.* 2018;49:91-105.
12. Teicher MH, Tomoda A, Andersen SL. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? *Annals of the New York Academy of Sciences.* 2006;1071(1):313-323.
13. Hanson JL, Nacewicz BM, Sutterer MJ, et al. Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biol Psychiatry.* 2015;77(4):314-323.
14. Gould E, Tanapat P. Stress and hippocampal neurogenesis. *Biological psychiatry.* 1999;46(11):1472-1479.
15. Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience.* 1990;10(9):2897-2902.
16. Lupien, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience.* 2009;10:434.
17. Childs AW, Fite PJ, Moore TM, Lochman JE, Pardini DA. Bidirectional associations between parenting behavior and child callous-unemotional traits: does parental depression moderate this link? *Journal of abnormal child psychology.* 2014;42(7):1141-1151.
18. Combs-Ronto LA, Olson SL, Lunkenheimer ES, Sameroff AJ. Interactions between maternal parenting and children's early disruptive behavior: Bidirectional associations across the transition from preschool to school entry. *Journal of abnormal child psychology.* 2009;37(8):1151.
19. Sameroff. Transactional models in early social relations. *Human development.* 1975;18(1-2):65-79.
20. Paus T. Mapping brain maturation and cognitive development during adolescence. *Trends in cognitive sciences.* 2005;9(2):60-68.

21. McLanahan, Tach L, Schneider D. The Causal Effects of Father Absence. *Annu Rev Sociol.* 2013;399:399-427.
22. Morris T, Dorling D, Davey Smith G. How well can we predict educational outcomes? Examining the roles of cognitive ability and social position in educational attainment. *Contemporary Social Science.* 2016;11(2-3):154-168.
23. Roth B, Becker N, Romeyke S, Schäfer S, Domnick F, Spinath FM. Intelligence and school grades: A meta-analysis. *Intelligence.* 2015;53:118-137.
24. Teo AR, Lerrigo R, Rogers MAM. The role of social isolation in social anxiety disorder: A systematic review and meta-analysis. *Journal of Anxiety Disorders.* 2013;27(4):353-364.
25. Meltzer H, Bebbington P, Dennis MS, Jenkins R, McManus S, Brugha TS. Feelings of loneliness among adults with mental disorder. *Social psychiatry and psychiatric epidemiology.* 2013;48(1):5-13.
26. Cacioppo, Hawkley LC, Thisted RA. Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study. *Psychology and aging.* 2010;25(2):453.
27. Lebel C, Deoni S. The development of brain white matter microstructure. *Neuroimage.* 2018;182:207-218.
28. Katz LF, Woodin EM. Hostility, hostile detachment, and conflict engagement in marriages: Effects on child and family functioning. *Child development.* 2002;73(2):636-652.
29. Low SM, Stocker C. Family functioning and children's adjustment: associations among parents' depressed mood, marital hostility, parent-child hostility, and children's adjustment. *Journal of family psychology.* 2005;19(3):394.
30. Thompson RA. Stress and child development. *Future Child.* 2014;24(1):41-59.
31. Repetti RL, Taylor SE, Seeman TE. Risky families: family social environments and the mental and physical health of offspring. *Psychological bulletin.* 2002;128(2):330.
32. Whittle S, Vijayakumar N, Dennison M, et al. Observed measures of negative parenting predict brain development during adolescence. *PloS one.* 2016;11(1):e0147774.
33. Luby JL, Barch D, Whalen D, Tillman R, Belden A. Association between early life adversity and risk for poor emotional and physical health in adolescence: A putative mechanistic neurodevelopmental pathway. *JAMA pediatrics.* 2017;171(12):1168-1175.
34. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol.* 2016;31(12):1243-1264.
35. Costello, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of general psychiatry.* 2003;60(8):837-844.
36. Angold A, Costello EJ. A test-retest reliability study of child-reported psychiatric symptoms and diagnoses using the Child and Adolescent Psychiatric Assessment (CAPA-C). *Psychol Med.* 1995;25(4):755-762.
37. Angold A, Costello EJ. The Child and Adolescent Psychiatric Assessment (CAPA). *J Am Acad Child Adolesc Psychiatry.* 2000;39(1):39-48.

Chapter 2

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

Yllza Xerxa, Leslie A. Rescorla, Fadila Serdarevic, Marinus H. van IJzendoorn, Vincent W. Jaddoe, Frank C. Verhulst, Maartje P.C.M. Luijk, Henning Tiemeier

Journal of Clinical Child & Adolescent Psychology, 49(1), 79-93.

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 prsoblem 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.[1] Many children from separated families show difficulties in functioning, including frequent emotional and behavioral problems.[2-4] 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,[5] which increases the risk of separation as well as causing child maladjustment.[6,7] Furthermore, child maladjustment can often trigger or exacerbate family conflict.[8,9] 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.[10-12] 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.[13-15] 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.[16-18] When family conflict increases parental harshness, rejection, and inconsistency, it may lead to child maladjustment, such as internalizing and externalizing problems.[19,20] 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.[21,22] 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.[22]

Few studies have examined the stability of family conflict over time and even fewer have tested this stability starting prenatally. However, Kluwer and Johnson[23] 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.[24]

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

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 remaining 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 3years, respectively).

Measures

Family Assessment Device

Family functioning was assessed with the General Functioning (GF) subscale of the Family Assessment Device - FAD,[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; [40]), and the Child Behavior Checklist for Ages 6-18 (CBCL/6-18; [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,[40] and the scales were found to be generalizable across 23 societies, including The Netherlands.[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 [3], 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.[43,44] 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.[45]

Maternal and paternal age were assessed at intake. Parental ethnicity was categorized into Dutch, non-Western and other Western national origin.[46] 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

Table 1. Baseline Characteristics for Participants with Information on Family Conflict (FAD)

	Mother	Father
	(n=5,808)	*(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.

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'.[47,48] High validity and reliability have been reported for the Dutch translation.[49] Cronbach's alpha was α = 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

parental psychopathology, as they are often associated with family conflict, parental separation, and/or child maladjustment.[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.[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,[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 (INTref), 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 (INTmed), 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.[51] 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,[52] we posited and evaluated an unmeasured confounder in a sensitivity analysis. That is, an unobserbved 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 [53] 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.[54] Such a decomposition is important because, in many studies, the exposure and mediator do interact to affect the outcome.[55]

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.[56] 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	2	3	4	5	6	7	8	9	10
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.

Table 3. Associations between Mother and Father Reported Prenatal Family Conflict and Parental Separation

	Parental Separation							
	by age 3		between age 3-5		between age 5-9		by age 9	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
	(n = 4,174)		(n = 4,821)		(n = 3,771)		(n = 4,543)	
Mother Reported								
Prenatal family conflict (FAD), per score	2.80 (2.20, 3.56)	<.001	2.18 (1.74, 2.72)	<.001	1.32 (1.00,1.74)	.048	2.16 (1.84, 2.53)	<.001
Father Reported								
Prenatal family conflict (FAD), per score	3.14 (2.11, 4.66)	<.001	2.14 (1.51,3.02)	<.001	1.15 (0.77, 1.71)	.476	2.07 (1.62,2.64)	<.001

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%).

Table 4. The Association of Family Conflict and Child Problem Behavior

	Child problem behavior (CBCL –total score, per point)					
	age 3		age 5		age 9	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	
	(n=4,223)		(n=5,063)		(n=4,062)	
Mother Reported Family Conflict						
Prenatal Family conflict (FAD), per score	5.01 (4.01, 6.02)	<.001	4.20 (3.17, 5.22)	<.001	5.08 (4.01, 6.16)	<.001
Age 5 Family conflict (FAD), per score	-		8.53 (7.49, 9.57)	<.001	6.32 (5.17, 7.48)	<.001
Age 9 Family conflict (FAD), per score	-		-		9.26 (8.24, 10.2)	<.001
	(n=3,556)				(n=3,091)	
Father Reported Family Conflict						
Prenatal Family conflict (FAD), per score	3.87 (2.27, 5.47)	<.001	-		3.45 (1.73, 5.16)	<.001
Age 9 Family conflict (FAD), per score	-		-		10.84 (9.61, 12.0)	<.01

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.

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 5. The Association of Parental Separation and Child Problem Behavior

	Child problem behavior (CBCL - total score, per point)					
	age 3		age 5		age 9	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
			Mother reported			
	(n=4,223)		(n=5,063)		(n=4,062)	
Separation by age 3, (yes)						
Model 1	1.90 (0.28, 3.52)	.021	1.98 (0.68,3.89)	.042	3.01 (1.03,4.99)	.003
Model 2	1.08 (-1.14, 3.30)	.341	1.65 (-0.97, 4.28)	.218	0.94 (-1.79, 3.68)	.499
Separation between age 3 - 5, (yes)						
Model 1	-		2.58 (0.98, 4.18)	.002	2.24 (0.38, 4.10)	.018
Model 2			1.50 (-0.65, 3.66)	.172	0.84 (-1.55, 3.23)	.490
Separation between age 5 - 9, (yes)						
Model 1	-		-		3.93 (2.07, 5.80)	<.001
Model 2					1.21 (-1.06, 3.48)	.296
Separation by age 9, (yes)						
Model 1	-		-		3.28 (2.08, 4.48)	<.001
Model 2					1.67 (0.12, 3.22)	.034
	(n=3,556)		Father reported		(n=3,091)	
Separation by age 3, (yes)						
Model 1	3.29 (0.46, 6.13)	.023	-		4.88 (1.64, 8.12)	.003
Model 2	1.09 (-2.31, 4.49)	.530			2.78 (-1.08, 6.64)	.159
Separation between age 5-9, (yes)						
Model 1	-		-		3.40 (0.93, 5.87)	.007
Model 2					1.27 (-1.63, 4.18)	.391
Separation by age 9, (yes)						
Model 1	-		-		3.05 (1.34, 4.76)	<.001
Model 2					1.13 (-0.92, 3.18)	.280

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.

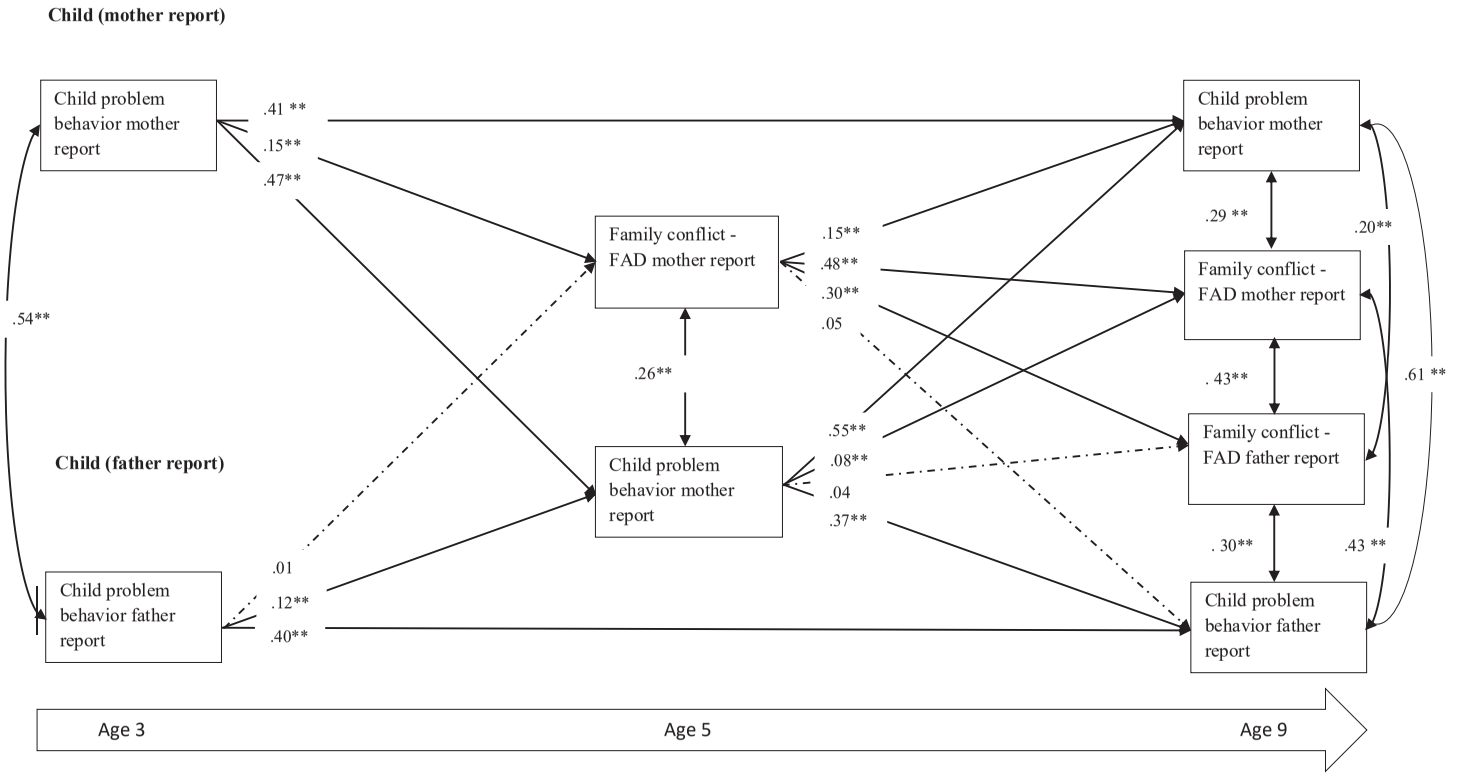
As shown in Table 6, a strong 'direct effect' (CDE) of prenatal family conflict on child problem behavior was present, with a large effect size. That is, in families with high levels of prenatal conflict, children had higher CBCL Total Problems scores at age 9. Second, there was evidence for a 'reference interaction effect' (INTref) 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 (INTmed). 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 6. Estimates of Direct and Indirect Effects Mediated Through Parental Separation of the Association Between Prenatal Family Conflict and Child Problem Behavior

Mediator: Parental separation	Child problem behavior (CBCL-total score, per point), (n=3,787) Mother reported									
	Controlled direct effect		Reference interaction		Mediated interaction		Pure indirect effect		Total effect	
	(95% CI)	p	(95% CI)	p	(95% CI)	p	(95% CI)	p	(95% CI)	p
Family conflict (FAD) prenatal, per score	2.90 (1.69, 4.10)	<.001	0.19 (0.03, 0.33)	.013	0.18 0.04, 0.31)	.008	-0.14 (-0.37, 0.08)	.206	3.12 (1.94, 4.29)	<.001

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 longitudinal 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 separation 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 studies 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 maladjustment 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,[6,7] 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.[25]

Generally, parental psychopathology and family conflict are closely interwoven and predispose each other.[58] 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,[13,59] and consequent negative parenting.[60,61] 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.[62] 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.[25,31,63] These longitudinal studies found that children of high conflict families that separated experienced improvement in well-being.[17,30] 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".[64] 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,[65,66] 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

1. Felitti VJ, Anda RF. The Relationship of Adverse Childhood Experiences to Adult Health, Well-being, Social Function, and Health Care. In: R. Lanius, E. Vermetten, Pain C, eds. *The Effects of Early Life Trauma on Health and Disease: the Hidden Epidemic.* Cambridge: Cambridge University Press.; 2010.
2. Lansford JE, Malone PS, Dodge KA, Crozier JC, Pettit GS, Bates JE. A 12-year prospective study of patterns of social information processing problems and externalizing behaviors. *J Abnorm Child Psychol.* 2006;34(5):715-724.
3. Amato. Children of divorce in the 1990s: an update of the Amato and Keith (1991) meta-analysis. *J Fam Psychol.* 2001;15(3):355-370.
4. Spruijt E, Kormos H. *Handboek scheiden en de kinderen [Handbook divorce and children].* Houten Bohn Stafleu van Loghum; 2014.
5. Goldthorpe JH. Causation, statistics, and sociology. *European sociological review.* 2001;17(1):1-20.
6. Bhrolch, xe, in M, xe, ire N, xed. 'Divorce Effects' and Causality in the Social Sciences. *European Sociological Review.* 2001;17(1):33-57.
7. McLanahan, Tach L, Schneider D. The Causal Effects of Father Absence. *Annu Rev Sociol.* 2013;399:399-427.
8. Schermerhorn AC, Cummings EM, DeCarlo CA, Davies PT. Children's influence in the marital relationship. *J Fam Psychol.* 2007;21(2):259-269.
9. Sturge-Apple ML, Davies PT, Cummings EM. Typologies of family functioning and children's adjustment during the early school years. *Child Dev.* 2010;81(4):1320-1335.
10. Cummings, Schermerhorn AC, Davies PT, Goeke-Morey MC, Cummings JS. Interparental Discord and Child Adjustment: Prospective Investigations of Emotional Security as an Explanatory Mechanism. *Child Development.* 2006;77(1):132-152.
11. Goeke-Morey MC, Cummings EM, Papp LM. Children and marital conflict resolution: implications for emotional security and adjustment. *J Fam Psychol.* 2007;21(4):744-753.
12. Rhoades KA. Children's responses to interparental conflict: a meta-analysis of their associations with child adjustment. *Child Dev.* 2008;79(6):1942-1956.
13. Camisasca E, Miragoli S, Di Blasio P. Families with Distinct Levels of Marital Conflict and Child Adjustment: Which Role for Maternal and Paternal Stress? *Journal of Child and Family Studies.* 2016;25(3):733-745.
14. Fosco GM, Grych JH. Emotional, cognitive, and family systems mediators of children's adjustment to interparental conflict. *J Fam Psychol.* 2008;22(6):843-854.
15. Pendry P, Adam EK. Child-Related Interparental Conflict in Infancy Predicts Child Cognitive Functioning in a Nationally Representative Sample. *Journal of Child and Family Studies.* 2013;22(4):502-515.
16. Amato, DeBoer DD. The Transmission of Marital Instability Across Generations: Relationship Skills or Commitment to Marriage? *Journal of Marriage and Family.* 2001;63(4):1038-1051.
17. Booth A, Amato PR. Parental Predivorce Relations and Offspring Postdivorce Well-Being. *Journal of Marriage and Family.* 2001;63(1):197-212.
18. Davies, Hentges RF, Coe JL, Martin MJ, Sturge-Apple ML, Cummings EM. The multiple faces of interparental conflict: Implications for cascades of children's insecurity and externalizing problems. *J Abnorm Psychol.* 2016;125(5):664-678.
19. Gryczkowski MR, Jordan SS, Mercer SH. Differential Relations between Mothers' and Fathers' Parenting Practices and Child Externalizing Behavior. *Journal of Child and Family Studies.* 2010;19(5):539-546.

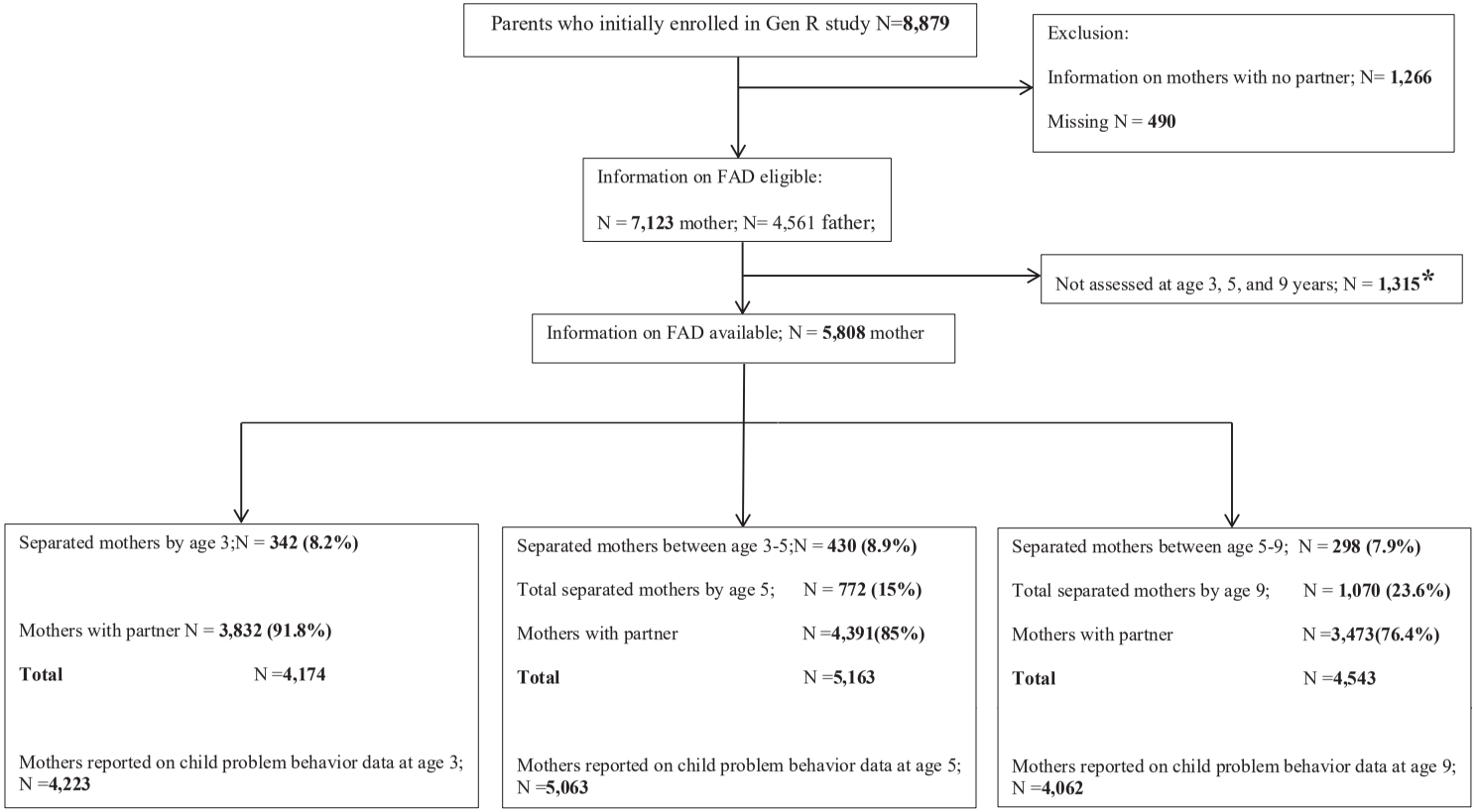
20. Laurin JC, Joussemet M, Tremblay RE, Boivin M. Early Forms of Controlling Parenting and the Development of Childhood Anxiety. *Journal of Child and Family Studies.* 2015;24(11):3279-3292.
21. Kelly, Lamb. Using child development research to make appropriate custody and access decisions for young children. *Family Court Review.* 2000;38(3):297-311.
22. McIntosh J. Enduring conflict in parental separation: Pathways of impact on child development. *Journal of Family Studies.* 2003;9(1):63-80.
23. Kluwer ES, Johnson MD. Conflict Frequency and Relationship Quality Across the Transition to Parenthood. *Journal of Marriage and Family.* 2007;69(5):1089-1106.
24. Howard KS, Brooks-Gunn J. Relationship Supportiveness During the Transition to Parenting Among Married and Unmarried Parents. *Parenting.* 2009;9(1-2):123-142.
25. Kelly, Emery RE. Children's Adjustment Following Divorce: Risk and Resilience Perspectives. *Family Relations.* 2003;52(4):352-362.
26. Stadelmann S, Perren S, Groeben M, von Klitzing K. Parental separation and children's behavioral/emotional problems: the impact of parental representations and family conflict. *Fam Process.* 2010;49(1):92-108.
27. Amato, Afifi TD. Feeling Caught Between Parents: Adult Children's Relations With Parents and Subjective Well-Being. *Journal of Marriage and Family.* 2006;68(1):222-235.
28. Strohschein L. Parental Divorce and Child Mental Health Trajectories. *Journal of Marriage and Family.* 2005;67(5):1286-1300.
29. Schoppe-Sullivan, Schermerhorn AC, Cummings EM. Marital Conflict and Children's Adjustment: Evaluation of the Parenting Process Model. *Journal of Marriage and Family.* 2007;69(5):1118-1134.
30. Amato, Kane JB, James S. Reconsidering the "Good Divorce". *Fam Relat.* 2011;60(5):511-524.
31. Amato. The Consequences of Divorce for Adults and Children. *Journal of Marriage and Family.* 2000;62(4):1269-1287.
32. Pardini DA. Novel insights into longstanding theories of bidirectional parent–child influences: Introduction to the special section. *Journal of abnormal child psychology.* 2008;36(5):627-631.
33. Shaw DS, Bell RQ. Developmental theories of parental contributors to antisocial behavior. *J Abnorm Child Psychol.* 1993;21(5):493-518.
34. Sameroff AJ, Mackenzie MJ. Research strategies for capturing transactional models of development: the limits of the possible. *Dev Psychopathol.* 2003;15(3):613-640.
35. De Los Reyes, Augenstein TM, Wang M, et al. The validity of the multi-informant approach to assessing child and adolescent mental health. *Psychol Bull.* 2015;141(4):858-900.
36. Achenbach, McConaughy SH, Howell CT. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychol Bull.* 1987;101(2):213-232.
37. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol.* 2016;31(12):1243-1264.
38. Byles J, Byrne C, Boyle MH, Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process.* 1988;27(1):97-104.
39. Epstein NB, Baldwin LM, Bishop DS. THE McMASTER FAMILY ASSESSMENT DEVICE*. *Journal of Marital and Family Therapy.* 1983;9(2):171-180.
40. Achenbach, Rescorla. *Manual for the ASEBA preschool forms & profiles: An integrated system of multi-informant assessment; Child behavior checklist for ages 1 1/2-5; Language development survey; Caregiver-teacher report form.* University of Vermont; 2000.
41. Achenbach, Rescorla. ASEBA school-age forms & profiles. Aseba Burlington, VT; 2001.

42. Ivanova MY, Achenbach TM, Rescorla LA, et al. Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *J Am Acad Child Adolesc Psychiatry.* 2010;49(12):1215-1224.
43. Choté AA, Koopmans GT, Redekop WK, et al. Explaining Ethnic Differences in Late Antenatal Care Entry by Predisposing, Enabling and Need Factors in the Netherlands. The Generation R Study. *Maternal and Child Health Journal.* 2011;15(6):689-699.
44. el Marroun H, Tiemeier H, Jaddoe VWV, et al. Demographic, emotional and social determinants of cannabis use in early pregnancy: The Generation R study. *Drug and Alcohol Dependence.* 2008;98(3):218-226.
45. Ellis EM. The legacy of divorce in the postmodern age. Divorce wars: *Interventions with families in conflict* (pp. 21-25). American Psychological Association. 2000a.
46. Netherlands Statistics. *Begrippen: Allochten.* 2006.
47. de Beurs. Brief symptom inventory. *Handleiding. Leiden (Netherlands): Pits Publishers.* 2004.
48. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983;13(3):595-605.
49. De Beurs, Zitman F. De Brief Symptom Inventory (BSI). *De betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL-90. Leiden: Leids universitair medisch centrum.* 2005.
50. Schunk D. A Markov chain Monte Carlo algorithm for multiple imputation in large surveys. *AStA Advances in Statistical Analysis.* 2008;92(1):101-114.
51. VanderWeele. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology.* 2014;25(5):749-761.
52. Imai K, Keele L, Yamamoto T. Identification, inference and sensitivity analysis for causal mediation effects. *Statistical science.* 2010:51-71.
53. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of personality and social psychology.* 1986;51(6):1173.
54. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, & Computers.* 2004;36(4):717-731.
55. Valeri L, Vanderweele. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods.* 2013;18(2):137-150.
56. Hartman RC, Bertsch DL, Bloom SD, et al. The third EGRET catalog of high-energy gamma-ray sources. *The Astrophysical Journal Supplement Series.* 1999;123(1):79.
57. Weaver JM, Schofield TJ. Mediation and moderation of divorce effects on children's behavior problems. *J Fam Psychol.* 2015;29(1):39-48.
58. De Los Reyes A, Youngstrom EA, Pabon SC, Youngstrom JK, Feeny NC, Findling RL. Internal consistency and associated characteristics of informant discrepancies in clinic referred youths age 11 to 17 years. *J Clin Child Adolesc Psychol.* 2011;40(1):36-53.
59. Anthony LG, Anthony BJ, Glanville DN, Naiman DQ, Waanders C, Shaffer S. The relationships between parenting stress, parenting behaviour and preschoolers' social competence and behaviour problems in the classroom. *Infant and Child Development.* 2005;14(2):133-154.
60. Deater-Deckard K. Parenting stress and children's development: Introduction to the special issue. *Infant and Child Development.* 2005;14(2):111-115.
61. Simons RL, Lin K-H, Gordon LC, Brody GH, Murry V, Conger RD. Community Differences in the Association Between Parenting Practices and Child Conduct Problems. *Journal of Marriage and Family.* 2002;64(2):331-345.

62. Robbers S, van Oort F, Huizink A, et al. Childhood problem behavior and parental divorce: evidence for gene-environment interaction. *Soc Psychiatry Psychiatr Epidemiol.* 2012;47(10):1539-1548.
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.
64. Ellis EM. Impact of parental conflict on children's adjustment following divorce. Divorce wars: *Interventions with families in conflict* (pp. 55-58). American Psychological Association. 2000b, p. 57.
65. Burke JD, Pardini DA, Loeber R. Reciprocal relationships between parenting behavior and disruptive psychopathology from childhood through adolescence. *J Abnorm Child Psychol.* 2008;36(5):679-692.
66. Jenkins J, Simpson A, Dunn J, Rasbash J, O'Connor TG. Mutual influence of marital conflict and children's behavior problems: shared and nonshared family risks. *Child Dev.* 2005;76(1):24-39.
67. Dawson-McClure SR, Sandler IN, Wolchik SA, Millsap RE. Risk as a moderator of the effects of prevention programs for children from divorced families: a six-year longitudinal study. *J Abnorm Child Psychol.* 2004;32(2):175-190.

SUPPLEMENTARY MATERIAL

Figure 1. Inclusion of the Study Sample



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 ρ between parental separation and child problem behavior regressions were tested.[52] 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 ρ is no longer zero. The sensitivity analysis was conducted by varying the value of ρ 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)

Average of NDE and NIE	Estimate	(95% CI)	*p*
Natural indirect effect - (NIE)	-0.30	(-0.007, 0.43)	.014
Natural direct effect - (NDE)	3.42	(2.08, 4.23)	.001
Total natural indirect efeffct	3.12	(1.70, 4.18)	<.001

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+INTref). Natural indirect effect estimated as follows: NIE = (PIE+INTmed).

Chapter 2.1

Compounded change: Poor family functioning, parental separation, and offspring school achievement

Yllza Xerxa, Nathalie Tamayo Martinez, Leslie A. Rescorla, Pauline W. Jansen, Henning Tiemeier

Manuscript submitted for publication

ABSTRACT

Family disruption is conceptualized as heightened exposure to events affecting continuity, consistency, and predictability of the family life for children. This study aimed to assess whether poor family functioning and parental separation from pregnancy onward are associated with less optimal child school achievement at age 12 years and whether this is explained by non-verbal IQ and attention problems in children exposed to family disruption. Follow-up measurements were performed in 3,025 children (M_{age} =11.8; 52.8% girls). Data for parents included 3.025 mothers (M_{age} at baseline =31.4), and 1723 fathers (M_{age} at baseline =33.6). All models were adjusted for baseline confounders, including maternal and paternal psychopathology and maternal intelligence. Children exposed to poor family functioning (either prenatal or during childhood) as well as parental separation had a lower school achievement. The associations of prenatal poor family functioning and parental separation with child school achievement were independent and each explained by childhood non-verbal IQ. Child attention problems also mediated the associations of both poor family functioning and parental separation with lower school achievement, independent of IQ. Overall, our findings indicate that in children exposed to early family disruption, a less optimal cognitive ability impacts school achievement later in childhood. Our findings suggest that interventions addressing poor family functioning and parental separation may help prevent low school achievement in children. Yet, these interventions would have to be implemented in young children as the impact of poor family functioning on child development occurs early. Possibly, interventions for children of disruptive families that target attention problems should be tested.

INTRODUCTION

Family disruption, defined as a change in the structural or social properties of the family environment including poor family functioning and parental separation, is conceptualized as heightened exposure to events impacting continuity, consistency, and predictability of the family life for children. Poor family functioning is associated with high levels of parenting stress and lower quality parent-child relationships, leading to poor long-term cognitive outcomes in children, such as lower cognitive abilities and poorer school achievement.[1-4] Likewise, parental separation negatively affects a variety of children's outcomes, including psychosocial well-being and school achievement, although this has sometimes been accounted for by poor family functioning and conflict.[5-10] The possibility that events cascade, in which one disruption magnifies the influence of other disruptions experienced simultaneously, means that parental separation might have second order effects on children's school achievement.[11] In particular, children of poor functioning families, unprepared for disruption, may experience considerable adjustment problems when parental separation occurs, leading to negative school achievement.[12] The transitions in household composition and family relationships, comprised economic resources, and children's own skills are most prominent mechanisms by which family disruption may limit children's cognitive function.[6,13,14] Despite the poor developmental outcomes, much less is known about the long-term pre- and postnatal associations of family disruption on offspring school achievement, and whether these associations are explained by effects on cognitive skills of the child early in life.

There also is evidence that poor family adjustment and separation more negatively impact the school achievement of elementary students than that of high school students.[8,15] Thus, the developmental period in childhood is a time of substantial cognitive change,[16] and may be especially sensitive to family disruption.[5] On this basis, McLanahan[17] formulated her seminal 'diverging destinies' thesis, suggesting that family instability, which is more common along low educated mothers, critically contributes to the disparities in children's access to resources and in their later socio-economic outcomes.[18] The 'diverging destinies' suggests that the changes in family behaviors associated with the second demographic transition are having negative consequences for parents, children, and society.[19]

A growing body of literature recognizes the importance of both cognitive and noncognitive abilities in children's school achievement in the context of developmental periods. Whereas some research suggests a symmetrical decline in children's psychosocial and cognitive skills in response to family disruption,[13] the developmental literature points to important asymmetry in which such skills (e.g., IQ and motivation) develop, and thus potentially also decline, throughout childhood. Although cognitive skills become relatively stable by early childhood, noncognitive skills, such as emotional stability and

motivation, change throughout childhood and thus may change in response to family disruption.[20-23]

Cognitive development is important to society and to children as individuals. In fact, IQ and school achievement has been shown to be a strong predictor of many outcomes, such as occupational status, happiness, health, and even life expectancy.[24-26] Moreover, a child's IQ and school achievement are strongly determined by the parent's IQ and socio-economic status (SES). Hidalgo et al.[4] showed that much of the associations between maternal stress and child IQ was explained by maternal IQ, and environmental factors such as family SES. The broad sense heritability of IQ, as observed in twin studies, reaches about H^2 = 0.7 - 0.8 after age 16 years and is thus higher than in many other traits. This broad sense heritability encompasses all genetic influences on variation of IQ, including additive, dominance, epistasis, and genetic-environmental interaction effects. However, a high heritability of a trait, does not necessarily mean that the trait is not susceptible to environmental influences; moreover, in less favorable environments lower heritability estimates are reported.[27,28]

Several gaps in our understanding remain. First, parental factors such as maternal IQ are implicated in child cognitive development. It thus cannot be ruled out that part of the observed associations between family disruption and child cognition is explained by parental factors such as parental intelligence and education, or psychopathology operating throughout childhood. Moreover, previous studies that included maternal IQ or psychopathology as covariate were limited to small sample sizes or were cross-sectional. Second, little is known about the possible associations of poor paternal-reported family functioning on child cognitive development. There is vis-á-vis evidence suggesting that father involvement contributes to maternal mental health and better family functioning,[29] and is associated with the child's cognitive functioning, in particular school attainment[30] as well. Third, cognitive skills may be associated with school achievement, and such skills may mediate part of the association between family disruption and children's achievement. Thus, child attention problems are more likely to reflect a relatively stable attribute of persistent environmental factors, that undermines the child's ability to attend. Fourth, it is unclear to what extent the associations of family disruption with child school achievement is explained by child IQ.

In the current population-based study, we investigated the associations between poor family functioning, separation, and child school achievement. In addition, we investigated whether school achievement is mediated by non-verbal IQ and attention problems in children exposed to family disruption. The present study had three main aims. First, we aimed to examine whether maternal and paternal reported poor family functioning and separation are independently associated with child non-verbal IQ and

school achievement. The second aim was to examine whether the association of poor family adjustment, separation and school achievement is mediated of early childhood non-verbal IQ. Third, we aimed to examine whether attention problems additionally mediate the association between poor family functioning, parental separation and child school achievement.

METHOD

Participants

Of the 8,879 pregnant women enrolled during pregnancy, we excluded 1,266 mothers with no partner data and 490 with missing parental conflict data, leaving 7,123 eligible mother-child pairs. We also excluded 4,098 children with no school achievement data. Reasons for missing data on school achievement were no consent to link the children's data to the national database, this test was not assessed at the school of the child or the linkage was not successful. We included dyads, if mothers reported child school achievement (N = 827) data. Our final sample consisted of 3,025 mother-child pairs with parental conflict, non-verbal IQ and educational attainment data (see Supplementary Figure 1 for a flow chart of the inclusion).

Measures

Family Assessment Device

Family functioning was assessed with the General Functioning (GF) subscale of the Family Assessment Device – FAD.[31,32] Family functioning refers to the social and structural properties of the global family environment. It includes interactions and relationships within the family, particularly levels of conflict and cohesion, adaptability, organization, and quality of communication. Both mothers and fathers completed this measure at 20 weeks pregnancy (prenatal time period, 18-25 weeks gestational age) and when their child was approximately 10 years old (late-childhood). In addition, mothers also filled out the questionnaire when their child was approximately six years old (mid-childhood). 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. 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 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.

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 three, six, and 10 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. First, we studied the exposure defined by parental separation during pregnancy. Second, we studied exposure to parental separation between birth and six years. 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 whether children were exposed to multiple separation/divorces or exposed to a single occurrence.

Attention Problems

The Child Behavior Checklist for older children (CBCL/6-18)[33,34] was used to obtain standardized parent reports of children's problem behaviors. The CBCL/6-18 contains 118 problems items. 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. For the current study, we used the continuous Attention Problems score at age 10 as our mediator measure, which comprised items such as: 'Can't concentrate', 'Can't sit still', and 'Wanders away'. Good reliability and validity have been reported for the CBCL/6-18.[33] The scales were found to be generalizable across 23 societies, including The Netherlands.[35]

Child non-verbal IQ

Children's non-verbal IQ was assessed by administering the Mosaics and Categories subtests when the child was six years old, from the Snijders-Oomen Non-Verbal Intelligence Test–Revised, a well-validated instrument developed in the Netherlands.[36] These two language-independent subtests include items that probe visuospatial and abstract reasoning abilities, and were selected because of the multiethnic composition of the Generation R Study. Subtest raw test scores were converted into age-standardized nonverbal IQ scores. The correlation between IQ derived from the whole test battery and IQ derived from just the "Mosaics" and "Categories" tests has been shown to be high ($r = 0.86$).[37] We chose a validated Dutch instrument and specifically investigated

non-verbal IQ, because our sample is multi-ethnic, and bilingualism is common; a valid assessment of verbal IQ before school age was not feasible.

School Achievement

School performance was operationalized into CITO-test scores, created by the Central Institute for Test Development (CITO). The CITO-test is a standardized, educational attainment score-test in the 8th grade (around 12-year-old) which informs about the most suitable type of secondary education.[38] The score is an indicator for the learning achievement of a child; like any performance measures, the score indirectly indicates the intelligence level, motivation, concentration, and the drives to learn. The CITO-test total score ranges from 501-550 and can be translated into specific levels of secondary education (e.g., pre-vocational secondary education, senior general secondary education, and pre-university education). In the Generation R Study, children's scores ranged from 505-550 and are non-normally distributed (left-skewed).

Test scores were obtained from CITO (n = 2,198), and, if not available, retrieved from maternal reports by questionnaire (n = 827). Mothers were queried about their child's CITO test score when the child was on average 13 years old. We assessed inter-rater reliability (ICC = 0.98) between maternal reported and CITO test scores from data linkage (overlap n = 975). We used the continuous CITO-test total score (the sum of ratings on all CITO-subtest language and math items) as our outcome measure because it broadly assesses the learning achievement of 13-year old children and is thus the best overall index of academic test in primary school.

Covariates

Descriptive statistics for parent and child characteristics are presented in Table 1. Child age (based on date of birth) and sex were obtained from study birth records. Maternal and paternal age were assessed at intake. Parental ethnicity was categorized into three groups: Dutch, non-Western, and other Western national origin.[39] 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) was assessed prenatally using self-report questionnaires. Maternal and paternal psychopathological symptoms were assessed at 20 weeks of pregnancy and when the child was three years old 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'*.[40,41] High validity and reliability have been reported for the Dutch translation.[42]

Table 1. Sociodemographic Characteristics of Participants at Baseline

	School achievement	
	Mother	Father
Age [a]	31.4 (4.6)	33.6 (5.2)
Ethnicity [b]		
Dutch	89.1	92.1
Other Western	8.0	4.6
Non Western	2.8	3.2
Education level [b]		
High	58.1	58.0
Middle	37.4	37.2
Low	4.5	4.8
Non-verbal maternal IQ-score [a]	102.0 (12.3)	
Age of the CITO, years, [a]	11.8 (0.4)	
Gender [b]	47.2	
Family functioning (FAD-score) prenatal [a]	1.50 (0.46)	1.48 (0.38)
Family functioning (FAD-score) at age 6 [a]	1.48 (0.41)	
Prenatal parental separation [b]		
Yes	8.4	
Parental separation by age 6 years [b]		
Yes	12.8	

Note. Total N = 3,025 mothers, total N = 1,725 fathers. Numbers denotes children included in one or more analyses.

[a] Values are frequencies for categorical measures.

[b] Means and standard deviations (M ±SD) for continuous measures.

Maternal non-verbal IQ was measured when mother-child pairs attended the six year examination, and was assessed using a computerized Ravens Advanced Progressive Matrices Test, set I.[43] The test is a 12-item reliable and validated short version of the Raven's Progressive Matrices to assess non-verbal cognitive ability.[44]

Statistical Analysis

First, we examined in separate linear regressions the associations of maternal and paternal reported poor family functioning during pregnancy and age six with child outcomes to examine period specific associations. Second we examined child exposure to parental separation. For these analyses we defined periods of separation, a) occurring during pregnancy, b) occurring between child birth and child age six years and examined these in different regression models. Non-verbal IQ and school achievement were studies as dependent variables. In model 1 we adjusted for child age and sex, while in model 2 we additionally adjusted for maternal age, ethnicity, education, maternal psychopathology and non-verbal IQ of the mother. Moreover, in analyses of family functioning at age six,

model 3 was additionally adjusted for prenatal maternal-reported poor family functioning to test independence of childhood associations. We also examined if family conflict and separation are independently associated with the different outcomes studied. To this aim we additional adjusted the models of separation and school achievement for family adjustment (model 3).

We conducted a mediation analysis to test whether the association of poor family functioning, parental separation and child school achievement is due to child non-verbal IQ. Similarly, we examined with mediation analysis whether the association of poor family functioning, parental separation and child school achievement is explained by attention problems. To this aim, the overall effect was decomposed into natural direct effect (NDE), and the natural indirect effect (NIE). All models were adjusted for all potential confounding variables described in the previous section and child non-verbal IQ at six years.

The interaction of the child sex with parental conflict and separation were explored. Standardized coefficients were used throughout. All missing values of the potential confounding factors mentioned above were imputed using multiple imputations. With the Markov Chain Monte Carlo multiple imputation technique, 10 complete data sets were created.[45] Multivariate analyses were performed on each imputed data set, and effect estimates were pooled. All analyses were performed using SAS 9.4 software.

RESULTS

Parental and child characteristics of the sample are presented in Table 1. The mean age of the children when taking the school achievement test was 11.8 years. Half (47.2%) of the children were boys. In total, 8.4% of mothers reported separation from their partner in the prenatal period and another 14.9% reported separation by child age six years. Poor family functioning correlated negatively with child non-verbal IQ and child educational attainment (rs = -.09 to -.16). As expected, we observed a high positive correlation between child educational attainment and non-verbal IQ (rs = .41).

Table 2 shows the associations of the offspring's exposure to poor family functioning with school achievement. Results indicated that poor prenatal family functioning, whether reported by mother (β = -.26, CI: 95% [-.31, -.09], p <.001) or father (β = -.22, CI: 95% [-.33, -.11], p <.001), was associated with lower school achievement at age 12 years. We also observed that prenatal maternal-reported poor family functioning was associated with lower non-verbal IQ at age six (β = -.23, CI: 95% [-.32, -.13], p

<.001), as well as paternal-reported prenatal poor family functioning with lower child IQ at age six (β = -.20, CI: 95% [-.37, -.08], *p* <.001).

Table 2. The Associations of Poor Family Functioning with Offspring IQ and School Achievement

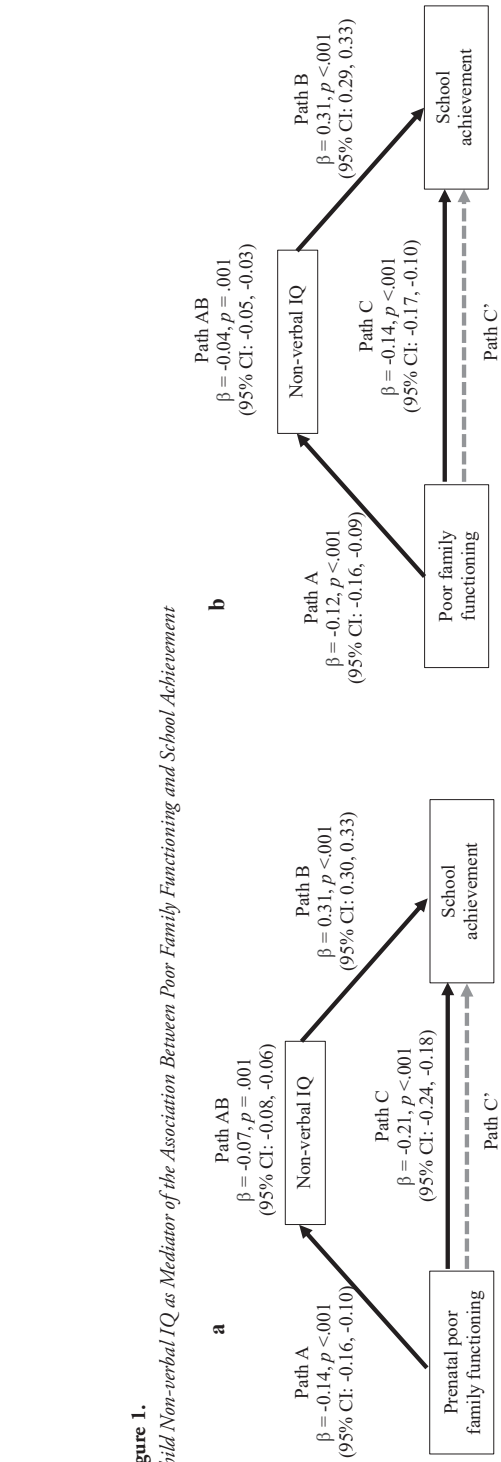
	Non-verbal IQ				School achievement			
	β	*95% CI*		*p*	β	*95% CI*		*p*
		LL	*UL*			*LL*	*UL*	
Mother-reported Poor Family Functioning (FAD), Prenatal								
Model 1	-.38	-.42	-.22	<.001	-.43	-.38	-.26	<.001
Model 2	-.23	-.32	-.13	<.001	-.26	-.31	-.09	<.001
Father-reported Poor Family Functioning (FAD), Prenatal								
Model 1	-.30	-.42	-.17	<.001	-.34	-.50	-.29	<.001
Model 2	-.20	-.37	-.08	.003	-.22	-.33	-.11	<.001
Mother-reported Poor Family Functioning (FAD), age 6								
Model 1	-.20	-.31	-.11	<.001	-.30	-.39	-.14	<.001
Model 2	-.13	-.20	-.03	.024	-.16	-.24	-.04	.009
Model 3	-.03	-.15	.08	.613	-.08	-.19	.02	.142

Note. Total N = 3,025. Linear regression analysis of poor family functioning and child outcomes. Standardized betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age and sex. Model 2 is additionally adjusted for maternal age, ethnicity, education, maternal or paternal psychopathology and non-verbal IQ of the mother. Model 3 is additionally adjusted for prenatal maternal-reported poor family functioning.
CI = confidence interval; LL = lower limit; UL = upper limit.

Next we examined poor family functioning in childhood. Poor family functioning reported at age six by the mother was associated with lower school achievement at age 12 even if adjusted for socio-economic factors, maternal non-verbal IQ and psychopathology (β = -.16, CI: 95% [-.24, -.04], *p* = .009). Similar associations were observed when we studied child IQ as the outcome: children exposed to poor family functioning had a lower non-verbal IQ at age six (β = -.13, CI: 95% [-.20, -.03], *p* = .024). However, if models of family functioning at child age six years were additionally adjusted for prenatal maternal-reported poor family functioning, neither the association of poor family functioning at age six with school achievement (β = -.08, CI: 95% [-.19, .02], *p* = .142) at age 12, nor the associations of poor family functioning at age six with child non-verbal IQ (β = -.03, CI: 95% [-.15, .08], *p* = .613) at age six remained.

As the Figure 1 illustrates, the association of prenatal poor family functioning and child school achievement was mediated by early childhood non-verbal IQ (β = -.07, 33% of the total effect; CI: 95% [-.08, -.06]). The child's non-verbal IQ also mediated the association between poor family functioning at age six and school achievement at age 12 (β = -.04, 33% of the total effect; CI: 95% [-.05, -.03]).

Figure 1.
Child Non-verbal IQ as Mediator of the Association Between Poor Family Functioning and School Achievement



Note. Total N = 3,025. Mediation analysis of child non-verbal IQ at age 6 in association of poor family functioning with child school achievement at age 12. (a) Mediation model for poor family functioning during pregnancy; (b) Mediation model for poor family functioning at age 6. Betas are averaged from 10 imputed datasets. Model is adjusted for child age and sex, maternal age, ethnicity, education, maternal psychopathology, non-verbal IQ of the mother. *Path "A" is the association of poor family functioning to child school achievement, and thus path "B" for the association of child non-verbal IQ to school achievement. Path C (in black) is the total effect of poor family functioning on school achievement with child non-verbal IQ not in the model. Path C' (in gray) is the direct effect of poor family functioning on child school achievement with non-verbal IQ in the model.

Second, we investigated the associations of parental separation and offspring school achievement (Table 3). Like poor family functioning, parental separation, whether before the birth of the child (β = -.30, CI: 95% [-.41, -.15], *p* = .003), or by age six (β = -.38, CI: 95% [-.52, -.25], *p* <.001), was associated with lower school achievement at age 12. In the fully adjusted models of non-verbal IQ, prenatal parental separation was not associated with lower child non-verbal IQ at age six (β = -.10, CI: 95% [-.28, .08], *p* = .12). However, we observed an association between parental separation occurring before age six years and lower child non-verbal IQ (β = -.22, CI: 95% [-.33, -.10], *p* = .009). Importantly, adjusting for prenatal maternal-reported poor family functioning did not meaningfully changed the associations. Similar to family adjustment, the associations of pre- and postnatal parental separation and school achievement were dependent of early childhood non-verbal IQ (Figure 2). Children whose parents had separated either before birth (β = -.03, 10% of the total effect; CI: 95% [-.04, -.01]) or up to age six years (β = -.06, 16% of the total effect; CI: 95% [-.08, -.05]) had lower school achievement scores mediated by non-verbal IQ.

Table 3. The Associations of Parental Separation with Offspring IQ and School Achievement

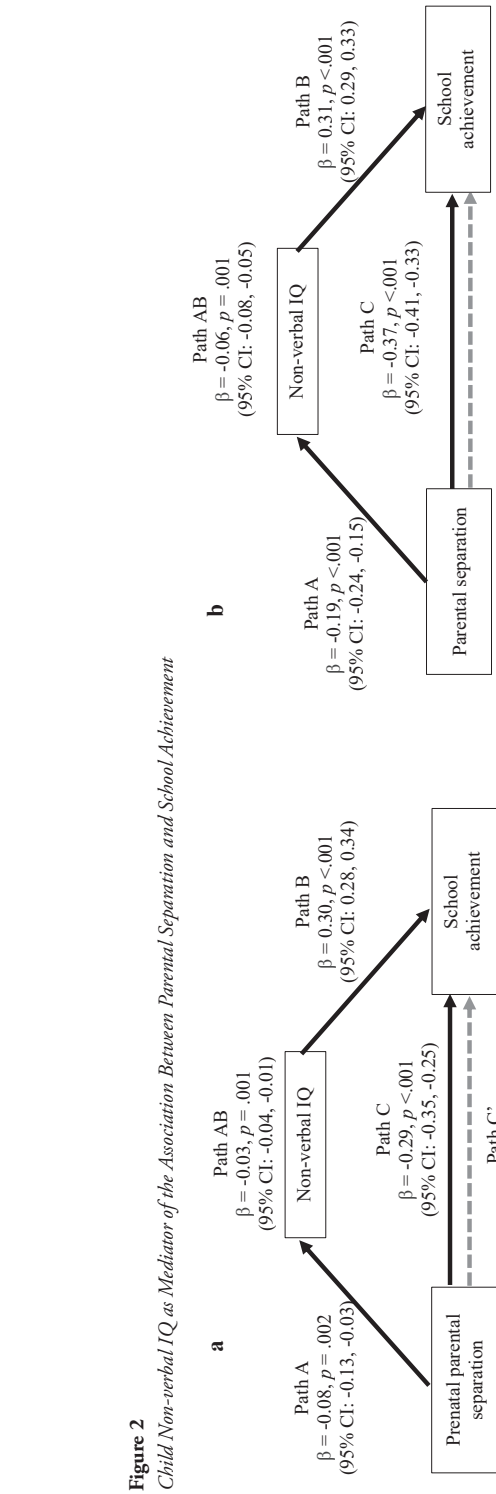
Mother reported	Non-verbal IQ				School Achievement			
	β	*95% CI*		*p*	β	*95% CI*		*p*
		LL	*UL*			*LL*	*UL*	
Separation - prenatal, (yes) [a]								
Model 1	-.25	-.40	-.17	.002	-.53	-.68	-.41	<.001
Model 2	-.10	-.28	.08	.121	-.30	-.41	-.15	.003
Model 3	-.04	-.20	.12	.646	-.23	-.38	-.09	.002
Separation by age 6, (yes) [b]								
Model 1	-.33	-.44	-.17	.001	-.61	-.70	-.49	<.001
Model 2	-.22	-.33	-.10	.009	-.38	-.52	-.25	.001
Model 3	-.15	-.30	-.04	.044	-.33	-.47	-.20	<.001

Note. Total N =3,025. Linear regression analysis of parental separation and child outcomes. Standardized betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age and sex. Model 2 is additionally adjusted for maternal age, ethnicity, education, maternal psychopathology and non-verbal IQ of the mother. Model 3 is additionally adjusted for prenatal maternal-reported poor family functioning. [a] Separated mothers prenatal, 179 (8.4%); [b] by age 6, 203 (12.8%). CI = confidence interval; LL = lower limit; UL = upper limit.

Lastly, we investigated whether child attention problems mediated the association between poor family functioning, parental separation and school achievement. As shown in Figure 3, the observed indirect effect suggests that child attention problems at age 10 mediated the association between poor prenatal family functioning and lower educational attainment at age 12 (β = -.07, 25% of the total effect; CI: 95% [-.08, -.05]), as well as with poor family functioning at age six and lower school achievement at age 12 (β = -.05, 70% of the total effect; CI: 95% [-.06, -.04]). Attention problems also

Figure 2

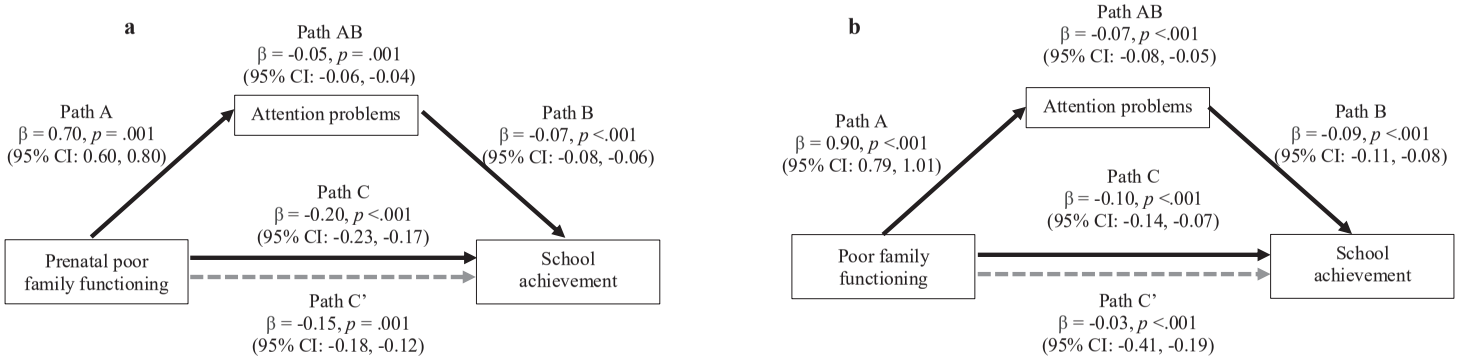
Child Non-verbal IQ as Mediator of the Association Between Parental Separation and School Achievement



Note. Total N = 3.025. Mediation analysis of child non-verbal IQ at age 6 in association of poor family functioning with child school achievement at age 12. (a) Mediation model for parental separation during pregnancy; (b) Mediation model for parental separation by age 6. Betas are averaged from 10 imputed datasets. Model is adjusted for child age and sex, maternal age, ethnicity, education, maternal psychopathology, non-verbal IQ of the mother. *Path "A" is the association of parental separation to child school achievement, and thus path "B" for the association of child non-verbal IQ to school achievement. Path C (in black) is the total effect of parental separation on school achievement with child non-verbal IQ not in the model. Path C' (in gray) is the direct effect of parental separation on child school achievement with non-verbal IQ in the model.

Figure 3

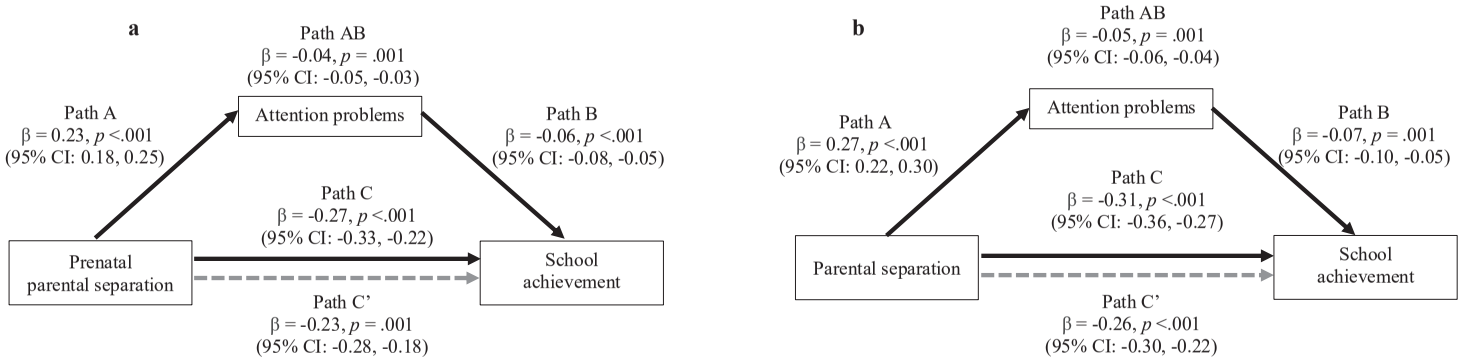
Child Attention Problems as Mediator of the Association Between Poor Family Functioning and School Achievement



Note. Total N = 3.025. Mediation analysis of child attention problems at age 10 in association of poor family functioning with child school achievement at age 12. (a) Mediation model for poor family functioning during pregnancy; (b) Mediation model for poor family functioning at age 6. Betas are averaged from 10 imputed datasets. Model is adjusted for child age and sex, maternal age, ethnicity, education, maternal psychopathology, non-verbal IQ of the mother. *Path "A" is the association of poor family functioning to child school achievement, and thus path "B" for the association of child attention problems to school achievement. Path C (in black) is the total effect of poor family functioning on school achievement with child attention problems not in the model. Path C' (in gray) is the direct effect of poor family functioning on child school achievement with child attention problems in the model.

Figure 4

Child Attention Problems as Mediator of the Association Between Parental Separation and School Achievement



Note. Total N = 3.025. Mediation analysis of child attention problems at age 10 in association of parental separation with child school achievement at age 12. (a) Mediation model for parental separation during pregnancy; (b) Mediation model for parental separation by age 6. Betas are averaged from 10 imputed datasets. Model is adjusted for child age and sex, maternal age, ethnicity, education, maternal psychopathology, non-verbal IQ of the mother. *Path "A" is the association of parental separation to child school achievement, and thus path "B" for the association of child attention problems to school achievement. Path C (in black) is the total effect of parental separation on school achievement with child attention problems not in the model. Path C' (in gray) is the direct effect of parental separation on child school achievement with child attention problems in the model.

mediated the association between parental separation and offspring school achievement (β = -.05, 14.8% of the total effect; CI: 95% [-.06, -.04]), as well as that of parental separation up to age six with school achievement (β = -.04, 16.1% of the total effect; CI: 95% [-.05, -.03]) (Figure 4). When we adjusted for child non-verbal IQ at six years, associations remained.

We found no interaction of sex of the child with poor family functioning or separation on child cognitive outcomes (results not shown).

DISCUSSION

This large population-based study examined the associations of poor pre- and postnatal family functioning, and parental separation with offspring school achievement while carefully controlling for indicators of innate cognitive ability of mothers. We highlight three main findings. First, poor prenatal family adjustment as well as parental separation were independently associated with lower school achievement. Moreover, poor prenatal family adjustment explained the association of childhood family adjustment with poor school outcomes. Second, we observed that these associations of poor family adjustment and parental separation with child school achievement at age 12 years were each mediated by childhood non-verbal IQ assessed at age six years. Third, child attention problems assessed at age 10 years mediated the associations of both poor family functioning and parental separation with lower school achievement independent of IQ. Overall, our findings indicate that in children exposed to family disruption, less optimal cognitive ability impacts school achievement.

Research results suggest that maternal stressors during pregnancy such as depression or anxiety have long-term cognitive problems in the offspring.[46] Similarly, our findings provided evidence that children exposed to poor family functioning during pregnancy perform less well in school. Our results, however, were independent of maternal depression. Thus, a potential explanation could be that the stress of poor reported family functioning directly influences child's cognitive outcomes through an intrauterine mechanism. There is evidence that maternal stress during pregnancy can induce alterations in fetal development but also increase the unborn child's risk of a range of cognitive outcomes in childhood or adulthood.[47,48] Yet, poor prenatal family functioning may also be a predictor of other environmental risks, such as negative parenting and postnatal depression. These may in turn exert their effects on their children's school achievement.[49] Our results could also reflect confounding, if independently of their exposure to family disruption in the prenatal period, exposed children would be more likely to experience an environment that does not facilitate school achievement. Differences in family economic resources is

such a mechanism that may account for a substantial share of the differences in child educational outcomes across family types.[6] However, adjustment for maternal education did not substantially attenuate the observed associations between family disruption and offspring cognitive development. In contrast, associations between poor family functioning in childhood and school achievement did not remain after adjustment for prenatal family functioning. This increases the plausibility that poor family functioning during pregnancy may lead to a suboptimal intrauterine environment with long-term risk in children's cognitive development.[47,48] Alternatively, the association and that of maternal and paternal poor functioning after childbirth with lower offspring school achievement may also indicate a contribution of genetic influences to the association.[50]

The association of poor family functioning with school achievement was mediated by early non-verbal IQ. It has been shown that different aspects of family functioning, such as parental organization, support and limit setting, predict better child executive functioning such as ability to plan and control emotions.[51] Much less is known about (non-verbal) child IQ. Our results indicate the lasting influence that early IQ development has on later academic functioning. To some extent, early child IQ could simply reflect continuity in basic competences, that may be largely genetically mediated.[52] Cognitive performance, educational attainment, and even neuropsychiatric phenotypes are phenotypically correlated, and several studies of twins and molecular genetics find that theses phenotypic correlations partly reflect genetic overlap. Although intelligence in childhood accounts for some of the variation in school achievement in adolescence, the differences between children in school achievement are relatively more environmentally influenced by factors related to the home and school situation.[53,54]

Our results indicate that poor family functioning and parental separation are uniquely associated with school achievement. Moreover, lower cognitive ability partly explains this difference in school achievement compared to children not exposed to family disruption. When parents separate, children's cognitive ability may develop less well or even deteriorate relative to peers, particularly when parental separation occurs in early childhood. Relationship transitions more likely occur after a parental separation and are potentially associated with high levels of parenting stress and lower quality of parent-child relationships. Moving away from former home and potentially change of the school may be a negative factor in child's adjustment. This may well lead to lower cognitive development among children of separated parents.[6,7,55] Disruptive events such as poor family functioning and separation probably interact to form their own dynamic relationship, in which consequences can be attributed to both or to a complex interplay of events. For example, if poor family functioning predicts a negative outcome, it could be that parental separation coinciding with poor family functioning is cause in the fallout. Prior research refers to such repeated instances as a 'cascade of instability',

in which one event prompts another event.[56,57] This is consistent with developmental research and theory positing that in early childhood, environmental influences interact with genetic predispositions to foster the acquisition of school achievement as well as other capacities.[58]

Prior studies suggested that children exposed to pre- and postnatal maternal stressors are more likely to have persistent attention problems.[59,60] In a study using six large longitudinal data sets, Duncan et al.[61] showed that children with attention problems performed less optimal in school in all six samples. The authors suggested that "…one explanation for this predictive power is that attention skills increase the time children are engaged and participating in academic endeavors and learning activities" (p. 1443). In the present study, we found that the associations of both poor family functioning and parental separation on school achievement were mediated by child attention problems. This mediation by attention problems indicates that environments likely characterized by family conflict, poor communication and disturbed interaction, may impede child attention and predict lower school attainment. Alternatively, lower school achievement in children with attention problems in elementary school may be explained by a failure to develop basic skills during the preschool years in more disrupted families.[62] Attention problems likely begin in the early school grades limiting the ability to develop cognitive skills later in school.[63,64]

Maternal IQ and psychopathology potentially are key confounders in the associations between family disruption and children's school attainment. In particular, both maternal intelligence and psychopathology may represent the influence of genetic factors as they may affect the transmission of risk.[65,66] For example, mothers with lower IQ are less able or have less resources to provide optimal environments for their children with lower IQ. Moreover, maternal IQ may not fully reflect all potentially relevant childhood cognitive development, and residual confounding by paternal IQ may exist. However, maternal IQ and psychopathology did not materially alter the overall associations between family disruption and school achievement in the present study.

Like most observational studies, the present study is not without limitations. First, the study was conducted in the Netherlands, and several specifics aspects of the Dutch school system, such as a long elementary school phase until age 12 years (when school achievement was assessed), may limit its generalizability of the results to other countries. Second, child non-verbal IQ and school achievement are not measured at the same time points, thus we were unable to examine concurrent assessment of each but rather studied non-verbal IQ as a potential mediator. Moreover, non-verbal IQ at age six years might not capture the full spectrum of cognitive abilities. The strengths of the current study lie in its large population-based sample and standardized assessments of child non-verbal

IQ and school achievement. The first school years of the child's life are a period of rapid cognitive development. Thus, our finding highlights the importance of considering early child non-verbal IQ and understanding its influence in particular child's development path. Because of our design and large number of measured covariates, we were able to adjust for multiple confounders, including maternal intelligence and psychopathology.

Our findings show that prenatal poor family functioning and parental separation were independently associated with lower school achievement. Specifically, the associations of poor family functioning and parental separation with child school achievement were accounted for by early childhood non-verbal IQ. Moreover, child attention problems independent of IQ also mediated the association of both poor family functioning and parental separation on school achievement. Collectively, our findings suggest that interventions addressing both poor family functioning and parental separation, may be an efficient way to prevent low school achievement in children. Yet, these would have to be implemented in young children, as the impact of poor family functioning on child development occurs early in life and can manifest in child non-verbal IQ. Possibly, interventions aimed at children of disruptive families with attention problems that include careful monitoring should be tested in systematic way.

REFERENCES

1. Harold GT, Sellers R. Annual Research Review: Interparental conflict and youth psychopathology: an evidence review and practice focused update. *Journal of child psychology and psychiatry.* 2018;59(4):374-402.
2. Harold GT, Aitken JJ, Shelton KH. Inter-parental conflict and children's academic attainment: A longitudinal analysis. *Journal of child psychology and psychiatry.* 2007;48(12):1223-1232.
3. Bernet W, Wamboldt MZ, Narrow WE. Child affected by parental relationship distress. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2016;55(7):571-579.
4. Cortes Hidalgo AP, Neumann A, Bakermans-Kranenburg MJ, et al. Prenatal Maternal Stress and Child IQ. *Child Dev.* 2020;91(2):347-365.
5. McLanahan, Tach L, Schneider D. The Causal Effects of Father Absence. *Annu Rev Sociol.* 2013;399:399-427.
6. Lee, McLanahan S. Family structure transitions and child development: Instability, selection, and population heterogeneity. *American sociological review.* 2015;80(4):738-763.
7. Halpern-Meekin S, Turney K. Relationship churning and parenting stress among mothers and fathers. *Journal of Marriage and Family.* 2016;78(3):715-729.
8. Amato. Children of divorce in the 1990s: an update of the Amato and Keith (1991) meta-analysis. *J Fam Psychol.* 2001;15(3):355-370.
9. Anthony CJ, DiPerna JC, Amato PR. Divorce, approaches to learning, and children's academic achievement: a longitudinal analysis of mediated and moderated effects. *J Sch Psychol.* 2014;52(3):249-261.
10. Xerxa Y, Rescorla LA, Serdarevic F, et al. The Complex Role of Parental Separation in the Association between Family Conflict and Child Problem Behavior. *J Clin Child Adolesc Psychol.* 2019:1-15.
11. Amato. Research on divorce: Continuing trends and new developments. *Journal of marriage and family.* 2010;72(3):650-666.
12. Brand JE, Moore R, Song X, Xie Y. Parental divorce is not uniformly disruptive to children's educational attainment. *Proceedings of the National Academy of Sciences.* 2019;116(15):7266-7271.
13. Kim HS. Consequences of Parental Divorce for Child Development. *American Sociological Review.* 2011;76(3):487-511.
14. McLanahan, Percheski. Family Structure and the Reproduction of Inequalities. *Annual Review of Sociology.* 2008;34(1):257-276.
15. Cox BE, Reason RD, Nix S, Gillman M. Life happens (outside of college): Non-college life-events and students' likelihood of graduation. *Research in Higher Education.* 2016;57(7):823-844.
16. Paus T. Mapping brain maturation and cognitive development during adolescence. *Trends in cognitive sciences.* 2005;9(2):60-68.
17. McLanahan. Diverging destinies: how children are faring under the second demographic transition. *Demography.* 2004;41(4):607-627.
18. Bernardi F, Comolli CL. Parental separation and children's educational attainment: heterogeneity and rare and common educational outcomes. *Zeitschrift für Familienforschung.* 2019;31(1):3-26.
19. McLanahan, Jacobsen W. Diverging Destinies Revisited. In: Amato PR, Booth A, McHale SM, Van Hook J, eds. *Families in an Era of Increasing Inequality: Diverging Destinies*. Cham: Springer International Publishing; 2015:3-23.
20. Borghans L, Duckworth AL, Heckman JJ, Ter Weel B. The economics and psychology of personality traits. *Journal of human Resources.* 2008;43(4):972-1059.
21. Hsin A, Xie Y. Hard Skills, Soft Skills: The Determinants and Consequences of Cognitive and Socio-behavioral Skills. *Social Science Research.* 2016.

22. Roberts BW, Wood D, Caspi A. The development of personality traits in adulthood. *Handbook of personality: Theory and research.* 2008;3:375-398.
23. Cunha F, Heckman JJ. Human capital formation in childhood and adolescence. *CESifo DICE Report.* 2009;7(4):22-28.
24. Furnham A, Cheng H. Childhood cognitive ability predicts adult financial well-being. *Journal of Intelligence.* 2017;5(1):3.
25. Gottfredson LS, Deary IJ. Intelligence predicts health and longevity, but why? *Current Directions in Psychological Science.* 2004;13(1):1-4.
26. Arendt JN. Does education cause better health? A panel data analysis using school reforms for identification. *Economics of Education review.* 2005;24(2):149-160.
27. Turkheimer E, Haley A, Waldron M, d'Onofrio B, Gottesman II. Socioeconomic status modifies heritability of IQ in young children. *Psychological science.* 2003;14(6):623-628.
28. Scarr-Salapatek S. Race, social class, and IQ. *Science.* 1971;174(4016):1285-1295.
29. Hook JL. Care in context: Men's unpaid work in 20 countries, 1965–2003. *American sociological review.* 2006;71(4):639-660.
30. Cano T, Perales F, Baxter J. A matter of time: Father involvement and child cognitive outcomes. *Journal of Marriage and Family.* 2019;81(1):164-184.
31. Byles J, Byrne C, Boyle MH, Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process.* 1988;27(1):97-104.
32. Epstein NB, Baldwin LM, Bishop DS. THE McMASTER FAMILY ASSESSMENT DEVICE*. *Journal of Marital and Family Therapy.* 1983;9(2):171-180.
33. Achenbach, Rescorla. *Manual for the ASEBA preschool forms & profiles: An integrated system of multi-informant assessment; Child behavior checklist for ages 1 1/2-5; Language development survey; Caregiver-teacher report form.* University of Vermont; 2000.
34. Achenbach, Rescorla. ASEBA school-age forms & profiles. Aseba Burlington, VT; 2001.
35. Ivanova MY, Achenbach TM, Rescorla LA, et al. Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *J Am Acad Child Adolesc Psychiatry.* 2010;49(12):1215-1224.
36. Tellegen P, Winkel M, Wijnberg-Williams B, Laros J. Snijders-Oomen Niet-verbale intelligentietest. SON-R 2½–7. Handleiding. Tweede gereviseerde editie [Snijders-Oomen Non-verbal test of intelligence. SON-R 2½–7. Manual. Göttingen, Germany: Hogrefe Verlag; 1998.
37. Ghassabian A, El Marroun H, Peeters RP, et al. Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children. *J Clin Endocrinol Metab.* 2014;99(7):2383-2390.
38. van der Lubbe M. *The End of Primary School Test.* 2007.
39. Netherlands Statistics. *Begrippen: Allochten.* 2006.
40. de Beurs. Brief symptom inventory. *Handleiding. Leiden (Netherlands): Pits Publishers.* 2004.
41. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983;13(3):595-605.
42. De Beurs, Zitman F. De Brief Symptom Inventory (BSI). *De betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL-90. Leiden: Leids universitair medisch centrum.* 2005.
43. Prieler J. Raven's advanced progressive matrices. *Schufried, Mödling, Austria.* 2003.
44. Chiesi F, Ciancaleoni M, Galli S, Primi C. Using the Advanced Progressive Matrices (Set I) to assess fluid ability in a short time frame: an item response theory-based analysis. *Psychol Assess.* 2012;24(4):892-900.

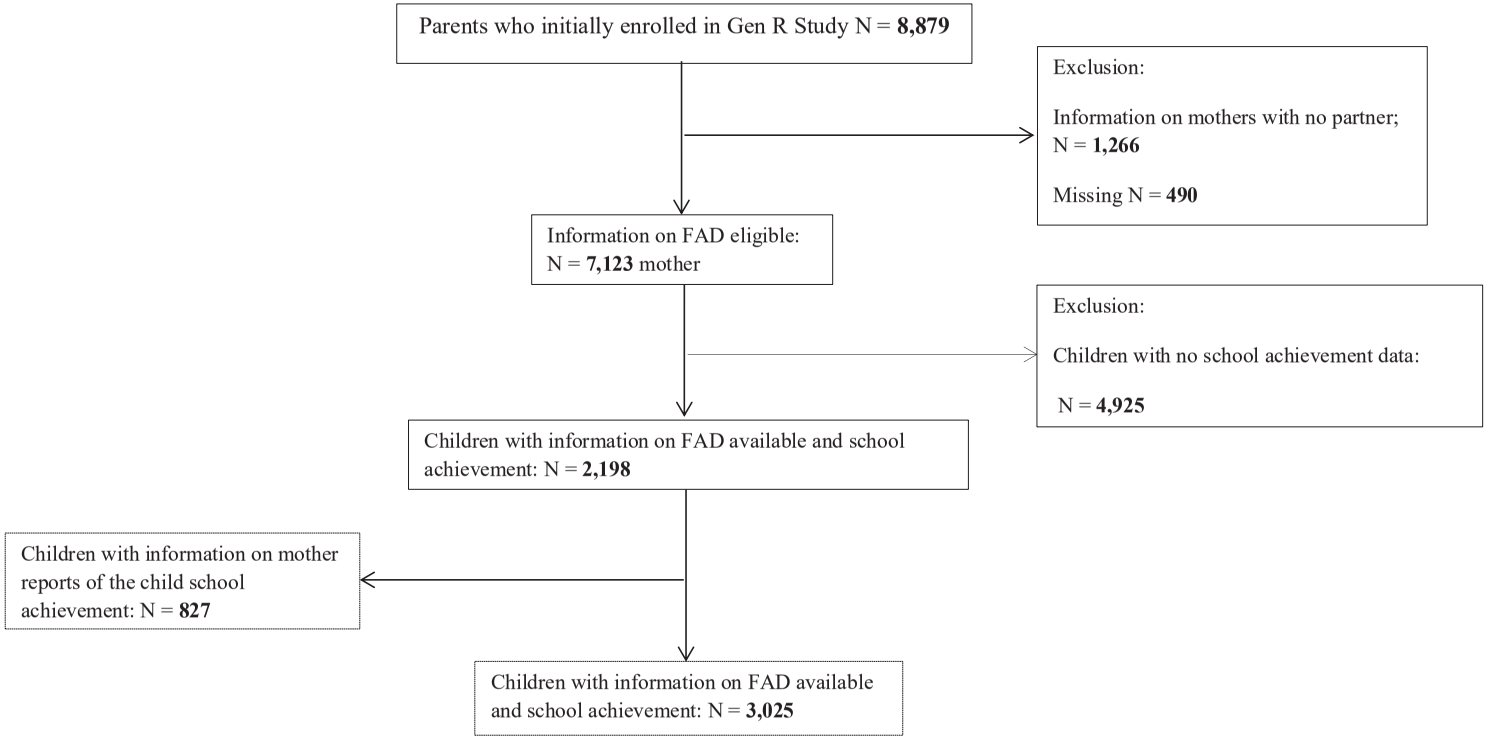
45. Schunk D. A Markov chain Monte Carlo algorithm for multiple imputation in large surveys. *AStA Advances in Statistical Analysis.* 2008;92(1):101-114.
46. Pearson RM, Bornstein MH, Cordero M, et al. Maternal perinatal mental health and offspring academic achievement at age 16: the mediating role of childhood executive function. *Journal of Child Psychology and Psychiatry.* 2016;57(4):491-501.
47. Lewis AJ, Austin E, Galbally M. Prenatal maternal mental health and fetal growth restriction: a systematic review. *J Dev Orig Health Dis.* 2016;7(4):416-428.
48. Weinstock M. The long-term behavioural consequences of prenatal stress. *Neurosci Biobehav Rev.* 2008;32(6):1073-1086.
49. Psychogiou L, Russell G, Owens M. Parents' postnatal depressive symptoms and their children's academic attainment at 16 years: Pathways of risk transmission. *British Journal of Psychology.* 2020;111(1):1-16.
50. Plomin R, von Stumm S. The new genetics of intelligence. *Nature Reviews Genetics.* 2018;19(3):148.
51. Schroeder VM, Kelley ML. Family environment and parent-child relationships as related to executive functioning in children. *Early child development and care.* 2010;180(10):1285-1298.
52. Krapohl E, Rimfeld K, Shakeshaft NG, et al. The high heritability of educational achievement reflects many genetically influenced traits, not just intelligence. *Proceedings of the national academy of sciences.* 2014;111(42):15273-15278.
53. Nye B, Konstantopoulos S, Hedges LV. How large are teacher effects? *Educational evaluation and policy analysis.* 2004;26(3):237-257.
54. Asbury K, Plomin R. *G is for genes: The impact of genetics on education and achievement.* Vol 24: John Wiley & Sons; 2013.
55. Thompson RA. Stress and child development. *Future Child.* 2014;24(1):41-59.
56. Thomas JS. Dimensions of family disruption: Coincidence, interactions, and impacts on children's educational attainment. *Longitudinal and Life Course Studies.* 2018;9(2):157-187.
57. Wheaton B, Gotlib IH. Trajectories and turning points over the life course: Concepts and themes. *Stress and adversity over the life course: Trajectories and turning points.* 1997:1-25.
58. Phillips DA, Shonkoff JP. *From neurons to neighborhoods: The science of early childhood development.* National Academies Press; 2000.
59. Clavarino AM, Mamun AA, O'Callaghan M, et al. Maternal anxiety and attention problems in children at 5 and 14 years. *Journal of Attention Disorders.* 2010;13(6):658-667.
60. Van den Bergh BRH, Mulder EJH, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neuroscience & Biobehavioral Reviews.* 2005;29(2):237-258.
61. Duncan GJ, Magnuson K. The nature and impact of early achievement skills, attention skills, and behavior problems. *Whither opportunity.* 2011:47-70.
62. Latimer WW, August GJ, Newcomb MD, Realmuto GM, Hektner JM, Mathy RM. Child and familial pathways to academic achievement and behavioral adjustment: A prospective six-year study of children with and without ADHD. *Journal of Attention Disorders.* 2003;7(2):101-116.
63. Rabiner DL, Carrig MM, Dodge KA. Attention Problems and Academic Achievement: Do Persistent and Earlier-Emerging Problems Have More Adverse Long-Term Effects? *J Atten Disord.* 2016;20(11):946-957.
64. Breslau J, Miller E, Breslau N, Bohnert K, Lucia V, Schweitzer J. The impact of early behavior disturbances on academic achievement in high school. *Pediatrics.* 2009;123(6):1472-1476.
65. Sameroff. *The transactional model.* American Psychological Association; 2009.

66. Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychological review.* 1999;106(3):458.

SUPPLEMENTARY MATERIAL

Figure 1

Inclusion of the Study Sample



Chapter 2.2

The double advantage of high parental education for offspring's educational achievement: The role of parenting practices

Nathalie Tamayo Martinez, Yllza Xerxa, James Law, Pauline W. Jansen, Henning Tiemeier

Manuscript submitted for publication

ABSTRACT

Background: Parental education is one of the best predictors of child school achievement. Higher parental education is not only associated with higher child intelligence, but additionally children from highly educated parents perform better in school due to other family related factors. This study evaluates the relation between parental education, child non-verbal intelligence and parenting practices with child school achievement.

Methods: Longitudinal data from a large population-based, multi-ethnic cohort of children in the Netherlands (63% Dutch origin) followed from birth to age 12 years (3,547 children; 52.3% girls) was analysed. School achievement was measured at the end of primary school (twelve years of age) with a national Dutch academic test score. The non-verbal intelligence of the child was measured at age 6 years. Parental education was assessed at age 3 years. Maternal and paternal parenting measures were assessed in early and mid-childhood.

Results: Child intelligence partially mediated (B indirect effect= 1.55 95% CI [1.30, 1.79] $p<0.001$) of the association between parental education and child school achievement. Additionally, mother and father family routines in and mid-childhood partially mediated (B indirect effect= 0.08 95% CI [0.04, 0.14] $p<0.01$) the association between parental education and child school achievement. We did not find a mediated effect of corporal punishment in the association between parental education and child school achievement.

Conclusion: Higher parental education was associated with better school achievement through two mechanisms, a higher intelligence in the child and independently through parenting practices which contribute to better performance.

INTRODUCTION

Parental education is a consistent predictor of offspring school achievement, physical health, mental health, cognitive abilities, school achievement and final offspring academic attainment.[1,2] School achievement is an important developmental outcome, is a predictor of the final academic attainment, socioeconomic status throughout life[3] and health.[4] One of the most important child characteristic contributing to school achievement is child intelligence.[5]

Parental education is associated with school achievement by mechanisms related to child intelligence[2] and by mechanisms independent of child intelligence. Parents with a higher intelligence will have children with higher intelligence,[6] due to a high genetic heritability of intelligence. The heritability of intelligence in childhood is only around 20%, but increases to about 70% in adolescence and up to 80% in adulthood.[7] Additionally, the family environment has lasting consequences on the development of a child's intelligence, as indicated by adopted children having a higher intelligence than non-adopted biological siblings and non-adopted peers.[8] Somewhat surprisingly, few studies have attempted to quantify the effect of the association between parental education and child school achievement through child intelligence.

Independent of child intelligence, parents with a high education are more able than lower educated parents to provide social and material resources promoting a higher school achievement in the offspring, through their involvement with school activities.[9] Higher educated parents also tend to live in higher quality neighbourhoods,[10] are more likely to provide cognitive enriched environments to their children[11] and tend to express expectations that children complete higher education.[12] Parental education is known to be related to parenting practices. Parenting practices like parental involvement in childhood have been associated with better school achievement[13] and less behavioural and emotional problems.[14] It has been shown that higher parental education is associated with more consistent family routines.[15] Family routines are associated with less anxiety, depressive symptoms[16] and less behavioural problems in children.[17] The association of family routines with school achievement has hardly been studied. In contrast to family routines, corporal punishment[18] and harsh discipline tend to occur more amongst parents with a lower education.[19] Corporal punishment in childhood has been associated with the presence of internalizing and externalizing problems, low self-esteem, a negative parent–child relationship and lower cognitive abilities in children.[20] In addition, harsh discipline, which includes the use of harsh verbal discipline or mild physical punishmen,[19] often precedes emotional and behavioral problems in children[21] as well as a lower academic attainment.[22]

In the present study, we aimed to investigate mechanisms that differentially underlie the association of parental education with children's school achievement. Specifically, we focus on quantifying the mediated effect of child intelligence and parenting practices in the association of parental education and child school achievement.

METHOD

Participants

Participants were drawn from the Generation R Study, a population-based prospective birth cohort that enrolled 9,778 women living in Rotterdam with an expected delivery date between April 2002 and January 2006. The study has been described extensively elsewhere.[23] This study has been approved by the Medical Ethical Committee of the Erasmus Medical Centre, and written informed consent was obtained from all participants parents. The eligible population for the present study consisted of the 7,393 children who participated in the school period (see flow chart, Supplementary Figure 1). Information on school achievement was obtained in 3,547 children, either by accessing the national database (n = 2,655) or the mother report when there was no link to the database (n = 892). Reasons for missing data on school achievement were: no consent to link the child's data to the national database; the test was not used at the school of the child; the linkage was not successful, or there was no mother report available. For the analyses, we included only children who had information on school achievement and parental education. Of the 3,547 children, 3,477 children had available data for maternal education and 3,218 for paternal education.

Maternal and Paternal Education

Information on their own educational attainment was provided by the mother and by the father during pregnancy, at child age three, and at age five years. Education was scored as: primary education not completed; primary education completed; up to three years of secondary school; intermediate vocational training; higher vocational training, or university degree. For the present analysis, we used the items from the three-year assessment.

Offspring School Achievement

The school achievement of the child was based on a test created by the Central Institute for Test Development (in Dutch: Centraal Instituut voor Test Ontwikkeling, CITO), the CITO score. In the Netherlands, is compulsory to administer an academic test in the final grade of primary school, to guide the appropriate choice for secondary education (i.e., pre-vocational secondary education, higher general secondary education and pre-university level). Of the different available academic tests, the CITO test is the most

frequently used. The test evaluates school achievement at the end of primary education, when children are 11-12 years old, by assessing language (e.g. In which sentence there is a word spelled incorrectly? This is the eightst long jumper.) and mathematics skills (e.g. 7.7 + 3,07 = 10.14; 10.77; 10.707; or 11.40). The standardized test score ranges between 500 and 550, with higher scores pointing at a higher school achievement. For 1,295 children, we had information on the school achievement score both by linkage through the national database and the mother report. The correlation between these two assessment types was .97. Of these combined reports, 79.5% of the mothers reported the correct school achievement score. This comparison suggests that mothers reliably report on their children's CITO score. Therefore, for children with a maternal report only we used this score to replace the missing value of the CITO test.

Offspring Intelligence

We measured children's intelligence at two time points. A non-verbal IQ was determined when children were age six using the Dutch Snijders-Oomen non-verbal intelligence test.[24,25] The subsets of the non-verbal IQ test used in Generation R are Mosaics and Categories. We chose a validated Dutch instrument and specifically investigated non-verbal IQ, because our sample is multi-ethnic, and bilingualism is common; a valid assessment of verbal IQ before school age was therefore not feasible. Additionally, this assessment focuses on fluid intelligence [25], which allowed us to distinguish between intelligence characteristics that are more innate and less amenable to learning. At age 13 the WISC-V, a full intelligence scale was assessed, it comprises of Vocabulary, Matrix Reasoning, Digit Span and Coding scales.[26] To do this analysis we assume the IQ before 12 years is the same as the IQ assessment at 13 years.

Parenting Practices

We selected maternal and paternal parenting measures assessed in different childhood periods. Early Childhood: Harsh discipline was assessed with a Dutch adapted version of the Parent-Child Conflict Tactics Scale.[19] Mothers and fathers completed this measure at child age three years. The harsh discipline scale is a validated self-report measure consisting of six items (e.g., "I shouted or screamed angrily at him/her"). Parents were asked to rate their use of this discipline practice in the last two weeks on a six-point scale ranging from never to five times or more (0 to 5). The six items were summed if there were no missing values, higher scores indicate more harsh discipline. In the current study, internal consistencies (Cronbach's alpha) were 0.63 for the mother rated scale and 0.57 for the father rated scale.

Family routines were reflected in a composite score derived from seven items about domains of family regularity reported by mothers when children were between two and four years old as described previously.[17] The measure included two items on bedtime

routines (e.g. 'Do you have a set pattern or ritual with your child at bedtime?') at age two years. At age four, the measure included two items on family meal locations (e.g. 'How often do you have breakfast/evening meal around the table together with your child/children?') and three items on meal frequency (i.e. 'how often does your child eat breakfast/lunch/evening meals?'). A Confirmatory Factor Analysis was employed to combine these items into a single construct. The model fit was acceptable with a root mean square error of approximation = .05 and the comparative fit index and the Tucker–Lewis index being 0.94).

Middle Childhood: Corporal punishment was assessed with two questions from the Alabama Parenting Questionnaire.[27] The mothers completed this questionnaire when the children were eight years old. The questions were "Do you slap your child when he/she does something wrong?" and "Do you spank your child with your hand when he/she has done something wrong?". Mothers were asked how often this discipline type is used in the house, on a five-point scale ranging from never to often (0 to 4). The items were summed if there were no missing values, higher scores indicate the use of more corporal punishment. The internal consistency (Cronbach's alpha) was 0.67.

Family routines was measured with a subscale from the Stability of Activities in the Family Environment (SAFE) questionnaire.[28] Both mothers and fathers completed this measure when children were nine years of age. The scale is a validated self-report measure consisting of six questions (e.g., "How regular is your child's homework routine after school"). Parents were asked to rate the regularity of the activities in the family during the last six months on a four-point scale. The items were summed up allowing for 25% missing data. Higher scores mean more regularity in the family routines. In the current study, the internal consistencies (Cronbach's alpha) were 0.63 for the mother rated scale and 0.65 for the father rated scale.

Covariates

The following possibly confounding factors were included. Maternal age was assessed at enrolment. Maternal national origin was categorized as Dutch, other Western and non-Western, based on their parents' country of birth. A parent was categorized as Dutch origin if both her/his parents were born in the Netherlands, the Western category was created if either reported European or American Western origin, and the non-Western category included Surinamese, Dutch Antillean, Turkish, and all African descent amongst other origins. Mother's IQ was estimated at child age six years, with the set I from the Raven's Advanced Progressive Matrices Test[29] which is a nonverbal ability test used to assess fluid intelligence.

Statistical modelling

Missing values on the parenting practices, the covariates, and IQ of the children were imputed using chained equations with mice package[30] in R 3.5.3.[31] Twenty imputed data sets were created. Additionally, we imputed parental education at age three years, carrying the information from the pregnancy assessment forward or the information from the five-year assessment backwards. We did not impute the school achievement score data. We performed an attrition analysis comparing the 3,547 included children to the 3,846 children with missing information. We also examined the correlation between the parenting practices with the Pearson's correlation coefficient.

We performed mediation analysis using Lavaan package[32] in R. We assessed the relationship of parental education, children's intelligence and parenting practices with school achievement in four models. In the models one to three we evaluated the mediated effect of child full IQ, family routines in mid-childhood, and corporal punishment in the relationship of parental education and the child school achievement with each mediator in a separate model (see Figure 1). In the fourth model, we evaluated all the mediation paths in a single model. Models were fitted in the last imputed dataset with a maximum likelihood estimation and the standard errors were bootstrapped 1,000 times, the confidence intervals were calculated with the percentile bootstrap method and the p values were corrected for multiple testing with Benjamini and Yekutieli control, that takes into account the dependency between measurements.[33] Unstandardized coefficients are presented.

Maternal and paternal education and the maternal and paternal scores of harsh discipline in early childhood and family routines in middle childhood each were combined with the mixed model approach[34] using the Linear and Nonlinear Mixed Effects Models ('nlme') package.[35] This approach yielded combined latent variables for parental education (N = 3,490) and parenting variables, which were used in all analysis.

All the models were adjusted for age at enrolment and national origin of the mother and maternal IQ. Compared with the children not included in this analysis (n = 3,846), the included children (n = 3,547) had a higher non-verbal IQ (mean = 104.0, SD = 14.4) than children not included (mean = 98.2, SD = 15.1). The mothers and fathers included in the analysis were higher educated (31.3% university degree for the mothers and 37.3% for the fathers) (see Supplementary Table 1).

We performed two secondary analyses. In the first, we evaluated sequential mediation paths, going through the early childhood measure of each mediator and then through IQ and parenting practices in mid-childhood. In the second, we estimated the association between parenting practices and child full IQ, in the children with information

on school achievement and in all children regardless if they had information on school achievement to increase power in the analysis.

Figure 1. Mediation Models

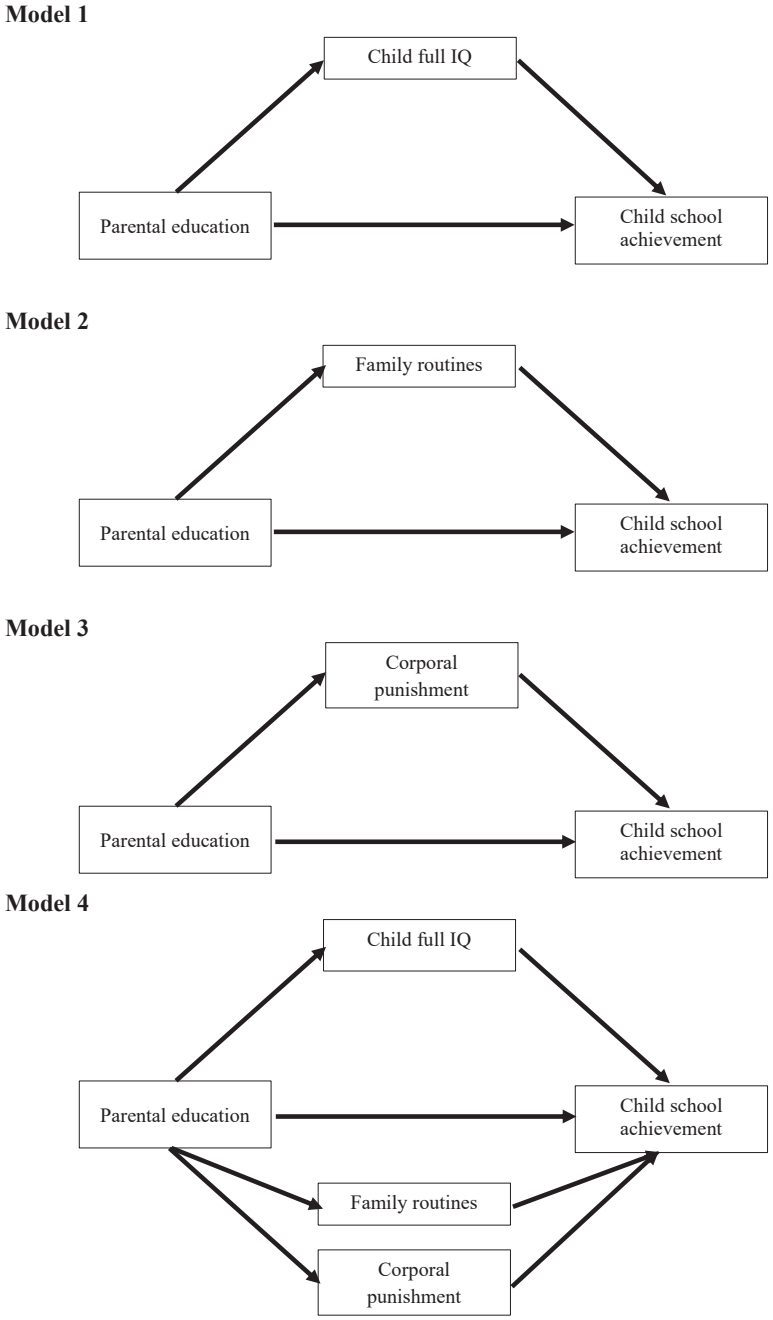


Table 1. *Characteristics of the Study Population*

Characteristics of the child	School achievement
Gender, boy, %	47.7
Age at academic test (in years), Mean (SD)	11.9 (.4)
School achievement test (score), Mean (SD)	538.4 (9.4)
Child non-verbal IQ (score), Mean (SD)	104.0 (14.4)
Child full IQ (score), Mean (SD)	104.6 (12.9)
Characteristics of the parents	
Mother's age at intake (in years), Mean (SD)	31.4 (4.7)
Mother IQ (score), Mean (SD)	98.3 (14.8)
Maternal education, %	
Secondary school only, less than 3 years	14.4
Secondary school only, more than 3 years and less	27.2
Higher vocational training	27.0
University degree	31.3
Paternal education, %	
Secondary school only, less than 3 years	16.3
Secondary school only, more than 3 years	24.3
Higher vocational training	22.0
University degree	37.3
National origin of the mother, %	
Dutch	63.0
Western	8.0
Non-Western	29.0
Parenting practices	
Harsh discipline mother age 3, Median (IQR)	2 (2)
Harsh discipline father age 3, Median (IQR)	2 (3)
Family routines mother age 4, Median (IQR)	0.1 (0.6)
Corporal punishment mother age 8, Median (IQR)	0 (1)
Regularity in routines mother age 9, Mean (SD)	18.4 (3.2)
Regularity in routines father age 9, Mean (SD)	17.8 (3.4)

Note. Total N= 3,547. Numbers denotes children included in one or more analyses.
SD= Standard deviation
IQR= Inter quartile range

RESULTS

The characteristics of the population are shown in Table 1. Of the participants, 47.7% were boys. The mean non-verbal IQ of the children was 104.0 (SD = 14.4) and of the mother 98.3 (SD = 14.8). The national origin of most mothers was Dutch, 63.0%. The correlations between the parenting practices are presented in Supplementary Table 2.

Table 2. *Child full IQ and Parenting Practices in Mid-childhood as Mediators of the Association between Parental Education and Child School Achievement.*

	Model 1			*Model 2*			*Model 3*			*Model 4*		
	β	*95% CI*	*p*	β	*95% CI*	*p*	β	*95% CI*	*p*	β	*95% CI*	*p*[a]
Indirect effect through full IQ	1.55	(1.30, 1.79)	<0.001							1.55	(1.30, 1.79)	<0.001
Indirect effect through family routines				0.11	(0.03, 0.18)	<0.01				0.08	(0.04, 0.14)	<0.01
Indirect effect through corporal punishment							0.04	(-0.01, 0.09)	0.06	0.01	(-0.02, 0.04)	1.00
Direct effect	2.56	(2.19, 2.97)	<0.001	4.03	(3.55, 4.46)	<0.001	4.06	(3.59, 4.52)	<0.001	2.47	(2.10, 2.88)	<0.001
Total effect	4.11	(3.65, 4.56)	<0.001	4.13	(3.68, 4.58)	<0.001	4.10	(3.69, 4.56)	<0.001	4.11	(3.65, 4.56)	<0.001

Note. N= 3,490. Models are adjusted for child age and sex, maternal age, ethnicity, and non-verbal IQ of the mother.

[a] p values are adjusted for multiple testing.

Family routines in early and mid-childhood were positively correlated (ranging from r=0.19 to 0.26). Similarly, harsh discipline in early childhood and corporal punishment in mid-childhood were correlated (ranging from r=0.23 to 0.33). Family routines in early and mid-childhood were negatively correlated with harsh discipline and corporal punishment (ranging from r=-0.04 to -0.14).

The outputs of the four mediation models are presented in Table 2. We describe model 4, as the results are similar to models 1 to 3. Child full IQ mediated 38% (B indirect effect= 1.55 95% CI [1.30, 1.79] p<0.001) of the association between parental education and child school achievement. Additionally, regularity in the routines at ages four and nine years mediated 2% (B indirect effect= 0.08 95% CI [0.04, 0.14] p<0.01) of the association between parental education and child school achievement. We did not find a statistically significant mediated effect of corporal punishment (B indirect effect= 0.01 95% CI [-0.02, 0.04] p= 1.0) and child school achievement.

In the secondary analysis, sequential mediation paths were evaluated. We found that 30% of the mediated effect of mid-childhood full IQ in the association of parental education and child school achievement goes through non-verbal intelligence in early childhood. Additionally 40% of the mediated effect of regularity in the routines in mid-childhood goes through regularity in the routines in early childhood (see Supplementary Table 3). Finally, we contrasted the association of parenting practices with the child's full IQ both in the dataset of children with school achievement score and in the complete data set of children who participated in the school period (see Supplementary Table 4). Results very similar, harsh parenting and corporal punishment were negatively associated with IQ in both datasets.

DISCUSSION

In this study, using data from a population-based prospective birth cohort, we examined the association between parental education, children's intelligence, parenting practices in early and mid-childhood, and children's school achievement at age 12 years. Our study results are in line with the positive association of parental education with the child's intelligence and better school achievements. Additionally, we highlight two main findings. First, the child's intelligence partially mediates the association between parental education and the child's school achievement. Second, parental education is also related to offspring school achievement through parenting practices, family routines mediated the relation between parental education and the child's school achievement. In addition, we found that some effect of parenting practices may occur via child intelligence.

The positive association between parental education and offspring school achievement has been reported in numerous studies in over 50 years of research, across cultures and in countries with different levels of economic development.[1] We found that parental education was related to better school achievement of the child due the relation with offspring intelligence, the child's intelligence mediated 38% of the association of parental education and the child's school achievement. These analyses were controlled for maternal fluid intelligence to further minimize the impact of intellectual endowment from the mother and because intelligence is a highly heritable genetic trait.[7] The association between parental education and child IQ reflects the role of environmental and genetic factors in the association of parental education with the child's intelligence in line with prior literature. For instance, intelligence is a highly heritable trait.[7] Nonetheless, children adopted by parents with a higher socioeconomic status have a higher intelligence than the not adopted siblings and peers.[8]

In the present study, higher educated parents also were more likely than lower educated parents to provide more family routines and these routines partially mediated the association between parental education and child school achievement. Contrary to our hypothesis, there was no mediation by harsh discipline and corporal punishment in the relation between parental education and the child school achievement. This may be a result of the relatively low prevalence of harsh parenting and corporal punishment in the present study. Corporal punishment may not be very frequent in the Netherlands,[36] more so because of a ban of some of these practices, like beating. Nonetheless, we found that harsh discipline and corporal punishment were associated with lower intelligence, which is in line with previous literature.[20] Given the consistent association between IQ and school achievement, harsh parenting and corporal punishment cannot be ruled out as possible mediators of the relation of parental education and offspring school achievement.

These results should be viewed against the background of some limitations. First, we did not have a father report for two parenting practices measures as we found it more difficult to motivate fathers to complete frequently mailed questionnaires. Therefore, family routines in early childhood were only rated by the mother, as was corporal punishment in mid-childhood. Second, the mediated effect by parenting practices was not large, it was 2% of the total effect. Arguably, this is an important finding as school achievement is a complex outcome with numerous determinants and it points out to parenting practices as possible avenues for public health interventions. Parenting practices are a broad construct that encompasses multiple behaviours in a wide time span that are hard to assess comprehensively, for instance, 40% of the mediated effect of family routines in mid-childhood and school achievement goes through family routines in early childhood.

Third, school achievement data was only available in part of the sample. However, this selection was largely determined by the choice of schools for the specific test we linked.

This study has notable strengths, including the prospective nature of the data collection and the multiple ages at which parenting practices were collected minimizes recall bias from parental reports. The large number of children and the multi-ethnic composition of the sample improves the generalizability of the results. Further, both IQ and school achievement were objectively obtained in standardized settings.

These results illustrate that higher maternal and paternal education are important indicators of inequality in school achievement for two different reasons; firstly, through the positive effect on the child intelligence which mediates the child's school achievement, and secondly, by an additional effect on the child's performance in school, which is related to parenting practices. Importantly, implementing more routines, including morning, mealtime and bedtime routines, homework and school activities, household responsibilities and cultural activities, could improve the child's school achievement and may be a potential mechanism to narrow the gap between the children's school achievement of higher and lower educated parents and hence social inequality. This, however, remains speculative as our study is no intervention study demonstrating causality. Also, based on our findings, we carefully postulate that some aspects of routines are amenable to school and community interventions and can be addressed by educational institutions, for example with supervised homework routines at school. The findings should be replicated in a randomized trial to better account for unknown confounders that could explain these results. Additionally, the components of routines should be meticulously dissected to understand what components of the family routines hold the positive association found.

Key points

- Parental education is an important determinant of offspring education and is source of inequality through two different mechanisms. Children from highly educated parents are more intelligent and have a higher school achievement. Additionally, highly educated parents provide more regular routines at home and this regularity is associated to a higher school achievement.
- Promoting routines in the activities at home might be a way to decrease school achievement inequality.

REFERENCES

1. Hertz T, Jayasundera T, Piraino P, Selcuk S, Smith N, Verashchagina A. The inheritance of educational inequality: International comparisons and fifty-year trends. *The BE Journal of Economic Analysis & Policy.* 2008;7(2).
2. Morris T, Dorling D, Davey Smith G. How well can we predict educational outcomes? Examining the roles of cognitive ability and social position in educational attainment. *Contemporary Social Science.* 2016;11(2-3):154-168.
3. Chen, Kaplan HB. School failure in early adolescence and status attainment in middle adulthood: A longitudinal study. *Sociology of Education.* 2003:110-127.
4. Dundas R, Leyland AH, Macintyre S. Early-Life School, Neighborhood, and Family Influences on Adult Health: A Multilevel Cross-Classified Analysis of the Aberdeen Children of the 1950s Study. *American Journal of Epidemiology.* 2014;180(2):197-207.
5. Roth B, Becker N, Romeyke S, Schäfer S, Domnick F, Spinath FM. Intelligence and school grades: A meta-analysis. *Intelligence.* 2015;53:118-137.
6. Anger S. The Intergenerational Transmission of Cognitive and Non-Cognitive Skills During Adolescence and Young Adulthood. *SSRN Electronic Journal.* 2011.
7. Plomin R, Deary IJ. Genetics and intelligence differences: five special findings. *Mol Psychiatry.* 2015;20(1):98-108.
8. Ijzendoorn MHv, Juffer F, Poelhuis CWK. Adoption and cognitive development: a meta-analytic comparison of adopted and nonadopted children's IQ and school performance. *Psychological bulletin.* 2005;131 2:301-316.
9. Núñez JC, Suárez N, Rosário P, Vallejo G, Valle A, Epstein JL. Relationships between perceived parental involvement in homework, student homework behaviors, and academic achievement: differences among elementary, junior high, and high school students. *Metacognition and learning.* 2015;10(3):375-406.
10. Patacchini E, Zenou Y. Neighborhood effects and parental involvement in the intergenerational transmission of education*. *Journal of Regional Science.* 2011;51(5):987-1013.
11. Sammons P, Toth K, Sylva K, Melhuish E, Siraj I, Taggart B. The long-term role of the home learning environment in shaping students' academic attainment in secondary school. *Journal of Children's Services.* 2015;10(3):189-201.
12. Froiland JM, Peterson A, Davison ML. The long-term effects of early parent involvement and parent expectation in the USA. *School Psychology International.* 2013;34(1):33-50.
13. Castro M, Expósito-Casas E, López-Martín E, Lizasoain L, Navarro-Asencio E, Gaviria JL. Parental involvement on student academic achievement: A meta-analysis. *Educational Research Review.* 2015;14:33-46.
14. Wang MT, Hill NE, Hofkens T. Parental involvement and African American and European American adolescents' academic, behavioral, and emotional development in secondary school. *Child Development.* 2014;85(6):2151-2168.
15. Anderson PM. Parental employment, family routines and childhood obesity. *Economics & Human Biology.* 2012;10(4):340-351.
16. Ivanova M, Israel AC. Family stability as a protective factor against the influences of pessimistic attributional style on depression. *Cognitive Therapy and Research.* 2005;29:243-251.
17. Rijlaarsdam J, Tiemeier H, Ringoot AP, et al. Early family regularity protects against later disruptive behavior. *European Child & Adolescent Psychiatry.* 2016;25(7):781-789.
18. Barkin S, Scheindlin B, Ip EH, Richardson I, Finch S. Determinants of parental discipline practices: A national sample from primary care practices. *Clinical Pediatrics.* 2007;46(1):64-69.

19. Jansen P, Raat H, Mackenbach J, et al. Early Determinants of Maternal and Paternal Harsh Discipline: The Generation R Study. *Family Relations.* 2012;61:253-270.
20. Gershoff ET, Grogan-Kaylor A. Spanking and child outcomes: Old controversies and new meta-analyses. *Journal of Family Psychology.* 2016;30(4):453-469.
21. Di Giunta L, Rothenberg WA, Lunetti C, et al. Longitudinal associations between mothers' and fathers' anger/irritability expressiveness, harsh parenting, and adolescents' socioemotional functioning in nine countries. *Developmental Psychology Journal.* 2020;56(3):458-474.
22. Hentges RF, Wang MT. Gender Differences in the Developmental Cascade From Harsh Parenting to Educational Attainment: An Evolutionary Perspective. *Child Development Journal.* 2018;89(2):397-413.
23. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *European Journal of Epidemiology.* 2016;31(12):1243-1264.
24. Tellegen PJ, Laros JA, Petermann F. *SON-R 2 1/2-7: non-verbaler Intelligenztest; Testmanual mit deutscher Normierung und Validierung.* Hogrefe; 2007.
25. Tellegen PJ, Winkel M, Laros JA, Wijnberg-Williams BJ. *Snijders-Oomen Nonverbal Intelligence Test SONR 2,5-7: Manual and Research Report.* HOGREFE; 1998.
26. Kaufman AS, Raiford SE, Coalson DL. *Intelligent testing with the WISC-V.* John Wiley & Sons; 2015.
27. Essau CA, Sasagawa S, Frick PJ. Psychometric Properties of the Alabama Parenting Questionnaire. *J Child Fam Stud.* 2006;15(5):595-614.
28. Israel AC, Roderick HA. A measure of the stability of family activities: an initial examination. *Assessment.* 2001;8(4):417-424.
29. Chiesi F, Ciancaleoni M, Galli S, Primi C. Using the Advanced Progressive Matrices (Set I) to assess fluid ability in a short time frame: an item response theory-based analysis. *Psychological Assessment.* 2012;24(4):892-900.
30. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software.* 2011;45(3):1-67.
31. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computingienna, Austria. 2018; URL http://www.R-project.org/. Accessed 0403, 2020.
32. Rosseel Y. lavaan: An R Package for Structural Equation Modeling. *2012.* 2012;48(2):36.
33. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *The Annals of Statistics.* 2001;29(4):1165-1188, 1124.
34. Kenny DAKDACWL. Using Multilevel Modeling to Study Dyads. In: Kenny DA, ed. *Dyadic Data Analysis*. New York: The Guilford Press; 2006:78-100.
35. Pinheiro J, Bates D, DebRoy S, Sarkar D, Team RC. nlme: Linear and nonlinear mixed effects models. *R package version.* 2015;3(2).
36. Lansford JE, Alampay LP, Al-Hassan S, et al. Corporal Punishment of Children in Nine Countries as a Function of Child Gender and Parent Gender. *International Journal of Pediatrics.* 2010;2010:672780.

Supplementary Table 1. *Attrition Analysis*

	Included participants	Excluded participants
Characteristics of the child		
Gender, boy, %	47.7	52.1
Age at academic test (in years), Mean (SD)	11.9 (.4)	-
School achievement test (score), Mean (SD)	538.4 (9.4)	-
Child IQ (score) , Mean (SD)	104.0 (14.4)	98.2(15.1)
Characteristics of the parents:		
Mother's age at intake (in years), Mean (SD)	31.4 (4.7)	29.8 (5.3)
Mother IQ (score), Mean (SD)	98.3 (14.8)	93.4 (15.4)
Maternal education, %		
Secondary school only, less than 3 years	14.4	28.9
Secondary school only, more than 3 years and less	27.2	32.2
Higher vocational training	27.0	19.9
University degree	31.3	19.0
Paternal education, %		
Secondary school only, less than 3 years	16.3	26.7
Secondary school only, more than 3 years	24.3	28.4
Higher vocational training	22.0	20.2
University degree	37.3	24.7
National origin of the mother, %		
Dutch	63.0	48.1
Western	8.0	8.1
Non Western	29.0	43.8
Parenting practices		
Harsh discipline mother age 3, Median (IQR)	2 (2)	3 (2)
Harsh discipline father age 3, Median (IQR)	2 (3)	3 (2)
Family routines mother age 4, Median (IQR)	.1 (.6)	-.03 (.7)
Corporal punishment mother age 8, Median (IQR)	0 (1)	0 (1)
Regularity in routines mother age 9, Mean (SD)	18.4 (3.2)	17.9 (3.5)
Regularity in routines father age 9, Mean (SD)	17.8 (3.4)	17.5 (3.7)

Note. Total N included participants = 3,547, total N excluded participants = 3,846.
SD= Standard deviation.
IQR= Inter quartile range.

Supplementary Table 2. *Correlation Coefficients Between Parenting Practices.*

	1	2	3	4	5	6	7	8
Early childhood								
1. Harsh discipline mother rating	1	0.42	0.85	-0.14	0.33	-0.08	-0.07	-0.09
2. Harsh discipline father rating		1	0.83	-0.09	0.23	-0.04	-0.08	-0.07
3. Harsh discipline combined, mother and father rating			1	-0.14	0.33	-0.07	-0.09	-0.09
4. Family routines mother rating				1	-0.16	0.25	0.19	0.26
Middle childhood								
5. Corporal punishment mother rating					1	-0.12	-0.11	-0.14
6. Family routines mother rating						1	0.45	0.87
7. Family routines father rating							1	0.83
8. Family routines combined, mother and father rating								1

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

Supplementary Table 3. *Child full IQ and parenting practices in early and mid-childhood as mediators of the association between parental education and child school achievement.*

	Model 4		
	β	*95% CI*	*p*
Indirect effect through child non-verbal IQ and full IQ	0.30	(0.23, 0.38)	<0.001
Indirect effect through family routines in early and mid-childhood	0.02	(0.01, 0.04)	<0.01
Indirect effect through harsh parenting and corporal punishment	0.0005	(-0.004, 0.01)	0.80
Direct effect	2.31	(1.94, 2.72)	<0.001
Total effect	2.63	(2.26, 3,03)	<0.001

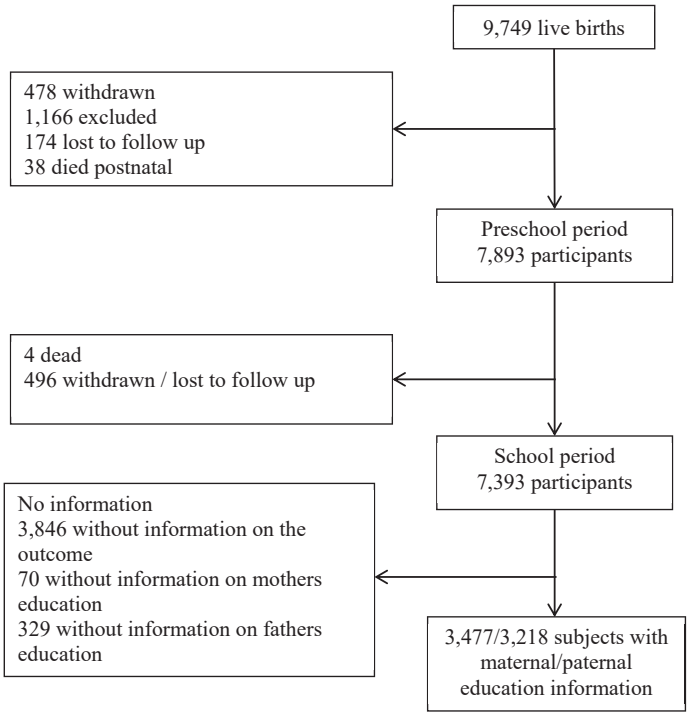
Note. N= 3,490. Models are adjusted for child age and sex, maternal age, ethnicity, and non-verbal IQ of the mother.

Supplementary Table 4. *Associations of parenting practices and child full IQ in the dataset of children with school achievement measure and in the dataset of all the children who participated in the school period.*

	Full IQ in children with school achievement data			Full IQ in all children		
	β	*95% CI*	*p*	β	*95% CI*	*p*
Early childhood						
Harsh discipline combined, mother and father rating	-0.56	(-1.10, -0.02)	0.04	-0.56	(-0.97, -0.15)	<0.01
Family routines mother rated	0.48	(-0.78, 1.74)	0.45	0.89	(-0.02, 1.80)	0.05
Middle childhood						
Corporal punishment mother rating	-0.75	(-1.23, -0.27)	<0.01	-0.77	(-1.12, -0.41)	<0.001
Family routines combined, mother and father rating	0.21	(-0.07, 0.49)	0.14	0.15	(-0.04, 0.35)	0.13

Note. N= 3,490 for the dataset of children with school achievement measure and 7,393 for the dataset of all the children who participated in the school period. Models are adjusted for child age and sex, maternal age, ethnicity, and non-verbal IQ of the mother.

Supplementary Figure 1. Flowchart of the study population



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

Child Development, 92(1), 291-307.

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.[23] 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.[21,24] Much less is known about the bidirectional relationship between child problem behavior and parental psychopathology, such as depression and anxiety.[25]

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.[26] and Gross et al.[27] provided some support for bidirectional associations between parental depression and adolescent disruptive behaviors. However, Gross et al.[25] 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.[28] 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.[29] 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.[29] 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.[30] 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.[31] 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,[28,29] with only some indicating that parent to child influences were greater than child to parent influences.[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.[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.[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.[34] 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'.[35,36] 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; [35]), 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.[36] High validity and reliability have been reported for the Dutch translation.[37] 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)[38,39] 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.[38] The scales were found to be generalizable across 23 societies, including The Netherlands.[40]

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.[41] Since that time, many other instruments assessing child psychopathology have adopted these broadband groups of problems.[42] 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.[43] 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%,[47] and therefore, if confidence intervals of two estimates do not overlap, they differ significantly.[47,48]

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)[32,49] 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 Ψstandardized 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.[49-51] 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.

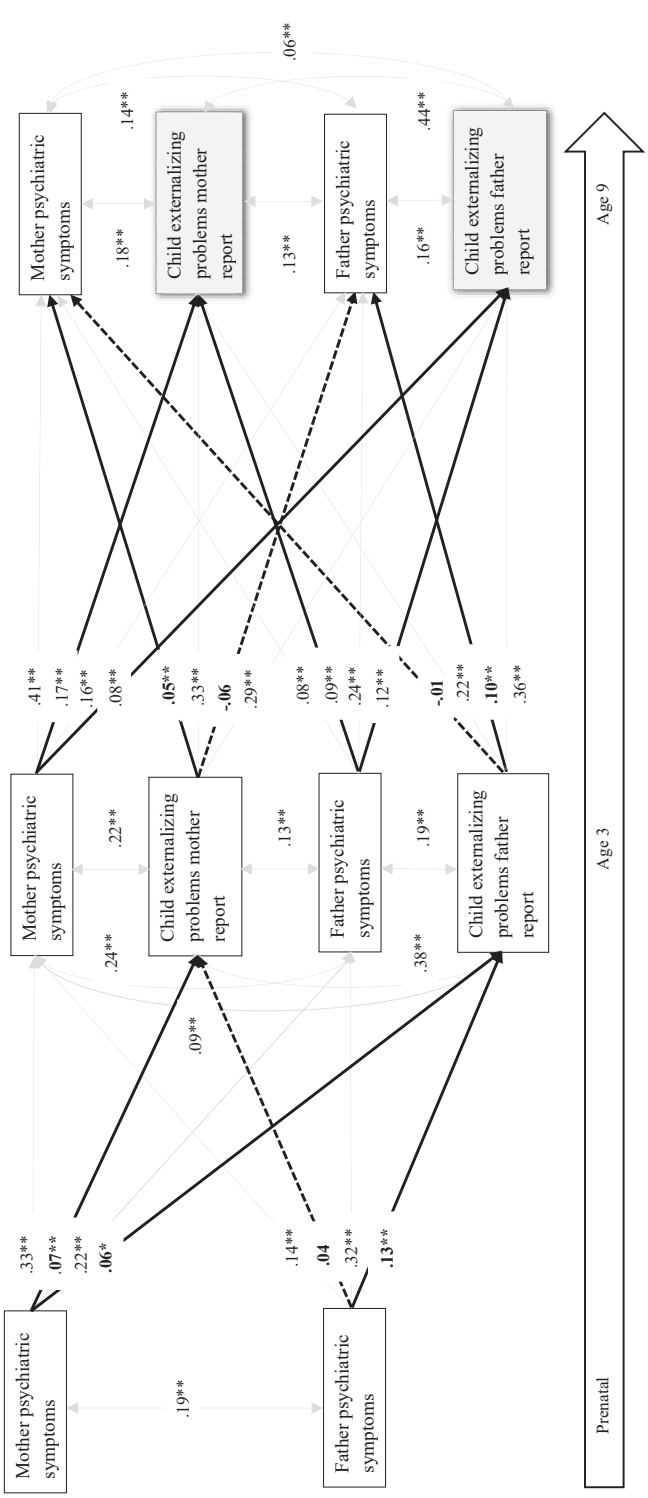


Figure 1. Structural equation modeling of parental psychopathology and child externalizing problems. Numeric values are standardized path regression coefficients. The models are adjusted for parental age, ethnicity, education, child sex and age, smoking, alcohol consumption and prenatal parental psychopathology 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.

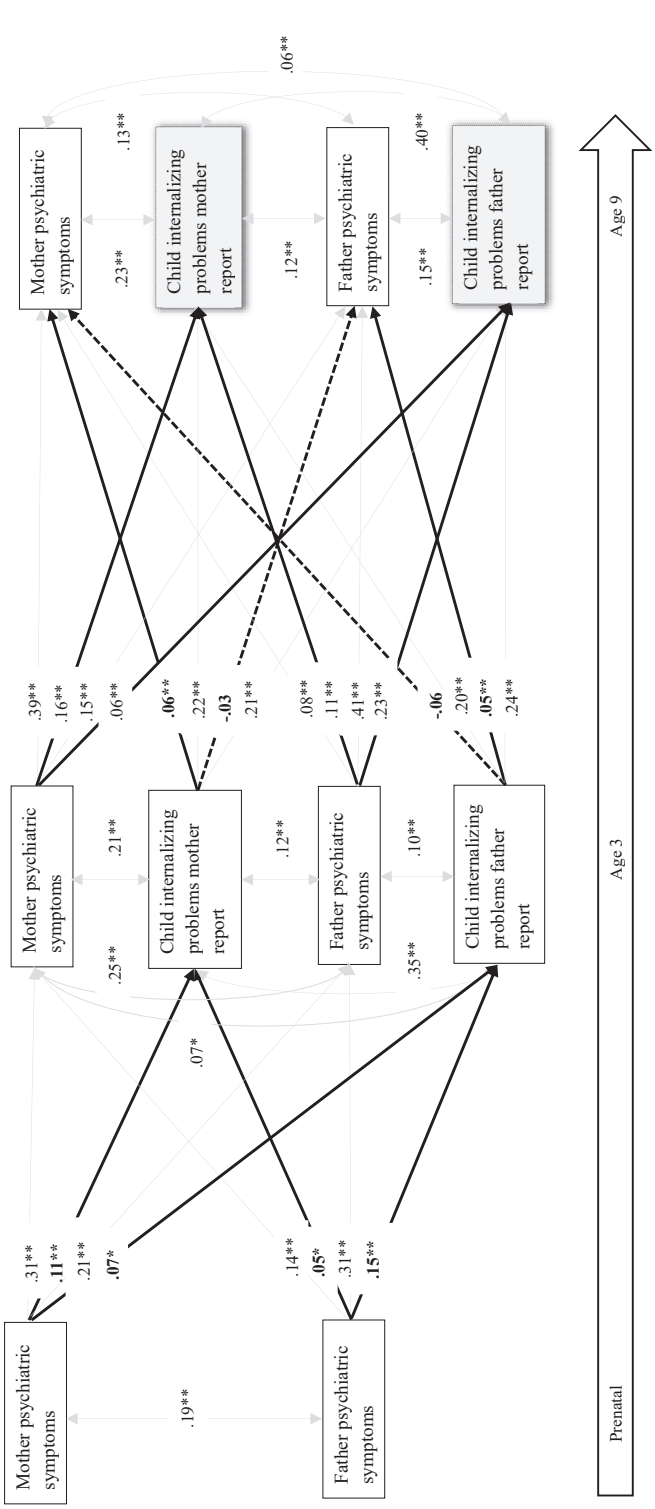


Figure 2. Structural equation modeling of parental psychopathology and child internalizing problems. Numeric values are standardized path regression coefficients. The models are adjusted for parental age, ethnicity, education, child sex and age, smoking, alcohol consumption and prenatal parental psychopathology reported by mother and father. (RMSEA=0.02; CFI=0.99; TLI=0.92). The dotted line represents the non-significant associations 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 (ΔCFI) and root mean square error of approximation (ΔRMSEA).[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. 8[56] 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 χ^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)

	Mother	Father
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
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)	49.5	
Age, years, M (SD)	10.1 (0.6)	

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.

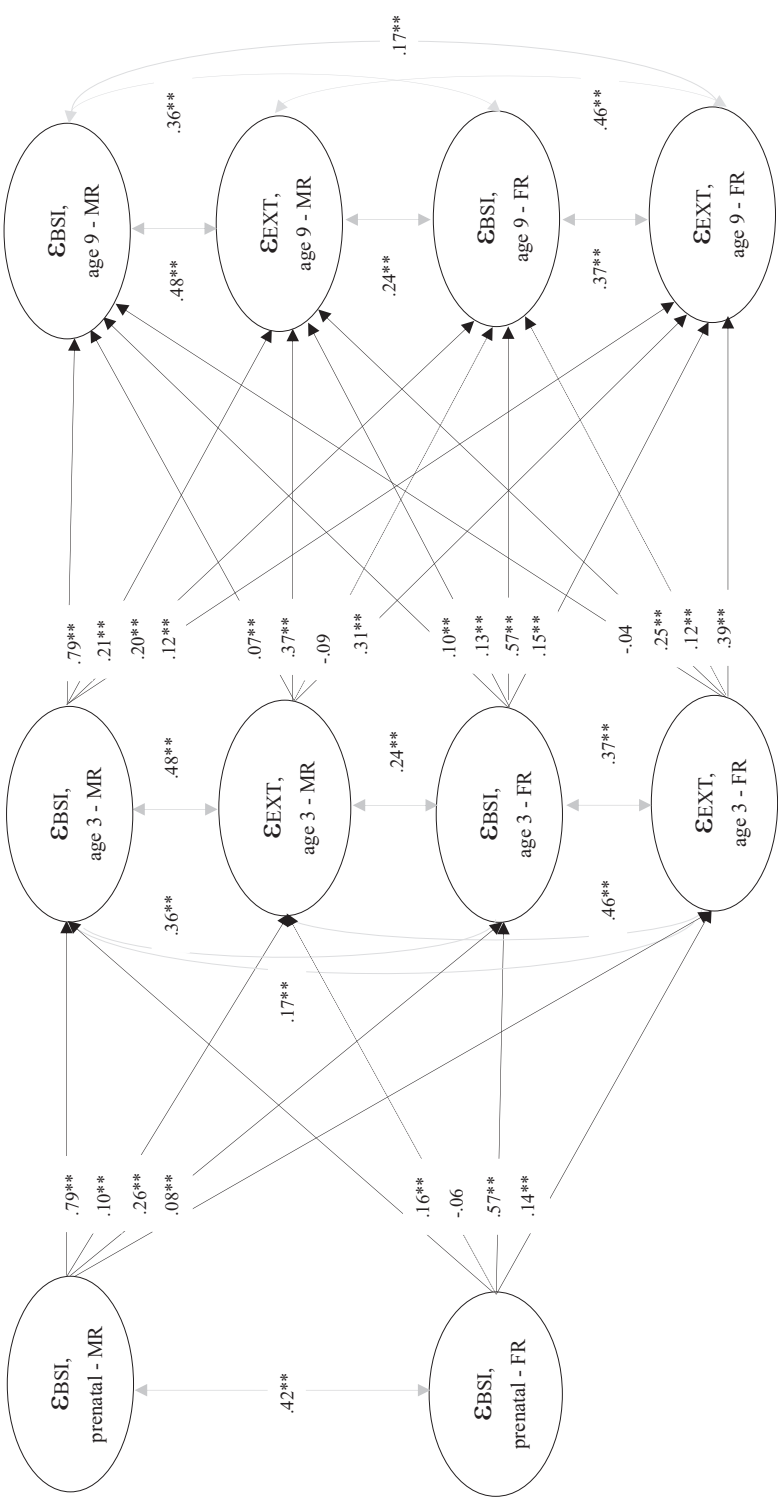


Figure 3. Autoregressive latent trajectory model with structured residuals (ALT-SR), disaggregating the within- and between-person associations of parental and offspring psychopathology. Numeric values are standardized path coefficients. The dotted lines represent the non-significant associations. The 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.

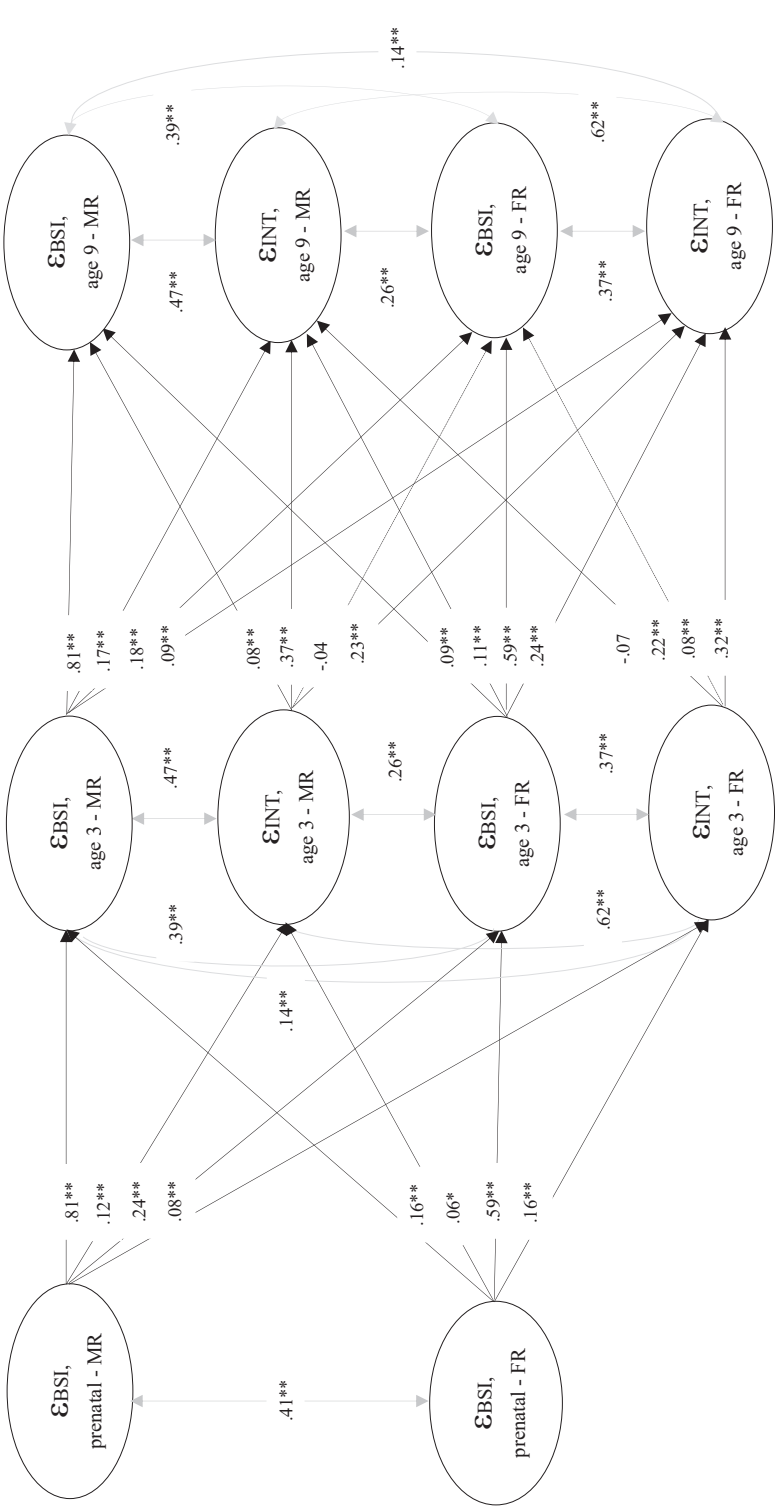


Figure 4. Autoregressive latent trajectory model with structured residuals (ALT-SR), disaggregating the within- and between-person associations of parental and offspring psychopathology. Numeric values are standardized path coefficients. The dotted lines represent the non-significant associations. The 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. ε (epsilon) = 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 (Ψstandardized = 2.94, p <.001), as well as higher initial levels of paternal BSI scores were associated with higher initial levels of Externalizing scores (Ψstandardized = 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 (Ψstandardized = 2.63, p <.001), and paternal BSI and child Internalizing scores (Ψstandardized = 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,[1,16] 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.[21] 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.[3] 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.[58] 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.[9] 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,[59,60] 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.[61] 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,[62,63] information bias, and importantly, shared-rater variance, which is a particular form of information bias.[64-66] 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.[62,63,67] It is likely that mothers and fathers have different kinds of relationships with children that evoke different behaviors.[62] For example, fathering practices in terms of coaching and team sport typically differ from maternal parenting, which more occurs at home.[68] 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.[69] 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.[70] 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,[71] and spend more time with children relative to fathers.[72,73] 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.[67,74] However, discrepant reports with some evidence of moderation by child gender have also been published. For example, Choe, Olson, Sameroff[29] 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.[75] 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,[76] 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.[77] 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

1. Connell AM, Goodman SH. The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis. *Psychol Bull.* 2002;128(5):746-773.
2. Sameroff, Chandler MJ. Reproductive risk and the continuum of caretaking casualty. *Review of child development research.* 1975;4:187-244.
3. Sameroff. Transactional models in early social relations. *Human development.* 1975;18(1-2):65-79.
4. Pettit GS, Arsiwalla DD. Commentary on Special Section on "Bidirectional Parent–Child Relationships": The Continuing Evolution of Dynamic, Transactional Models of Parenting and Youth Behavior Problems. *Journal of Abnormal Child Psychology.* 2008;36(5):711.
5. Bell RQ. A reinterpretation of the direction of effects in studies of socialization. *Psychological review.* 1968;75(2):81.
6. Cicchetti, Toth SL, Luthar SS, Burack JA, Weisz JR. Developmental psychopathology: Perspectives on adjustment, risk, and disorder. 1997.
7. Sameroff. *The transactional model.* American Psychological Association; 2009.
8. O'Connor. Annotation: Theeffects' of parenting reconsidered: findings, challenges, and applications. *Journal of Child Psychology and Psychiatry.* 2002;43(5):555-572.
9. Perlman M, Ross HS. The Benefits of Parent Intervention in Children's Disputes: An Examination of Concurrent Changes in Children's Fighting Styles. *Child Development.* 1997;68(4):690-700.
10. Cowan PA, Cowan CP. Developmental psychopathology from family systems and family risk factors perspectives: Implications for family research, practice, and policy. *Developmental psychopathology: Theory and method, Vol 1, 2nd ed*. Hoboken, NJ, US: John Wiley & Sons Inc; 2006:530-587.
11. Sameroff, Fiese BH. Transactional regulation: The developmental ecology of early intervention. *Handbook of early childhood intervention.* 2000;2:135-159.
12. Childs AW, Fite PJ, Moore TM, Lochman JE, Pardini DA. Bidirectional associations between parenting behavior and child callous-unemotional traits: does parental depression moderate this link? *Journal of abnormal child psychology.* 2014;42(7):1141-1151.
13. Combs-Ronto LA, Olson SL, Lunkenheimer ES, Sameroff AJ. Interactions between maternal parenting and children's early disruptive behavior: Bidirectional associations across the transition from preschool to school entry. *Journal of abnormal child psychology.* 2009;37(8):1151.
14. Pardini DA, Fite PJ, Burke JD. Bidirectional associations between parenting practices and conduct problems in boys from childhood to adolescence: The moderating effect of age and African-American ethnicity. *Journal of abnormal child psychology.* 2008;36(5):647-662.
15. Shaffer A, Lindhiem O, Kolko DJ, Trentacosta CJ. Bidirectional relations between parenting practices and child externalizing behavior: A cross-lagged panel analysis in the context of a psychosocial treatment and 3-year follow-up. *Journal of abnormal child psychology.* 2013;41(2):199-210.
16. Breaux RP, Harvey EA, Lugo-Candelas CI. The role of parent psychopathology in the development of preschool children with behavior problems. *J Clin Child Adolesc Psychol.* 2014;43(5):777-790.
17. Joelsson P, Chudal R, Uotila J, et al. Parental psychopathology and offspring attention-deficit/hyperactivity disorder in a nationwide sample. *J Psychiatr Res.* 2017;94:124-130.
18. Middeldorp CM, Wesseldijk LW, Hudziak JJ, Verhulst FC, Lindauer RJ, Dieleman GC. Parents of children with psychopathology: psychiatric problems and the association with their child's problems. *Eur Child Adolesc Psychiatry.* 2016;25(8):919-927.
19. Nath S, Russell G, Kuyken W, Psychogiou L, Ford T. Does father–child conflict mediate the association between fathers' postnatal depressive symptoms and children's adjustment problems at 7 years old? *Psychological medicine.* 2016;46(8):1719-1733.

20. Dodge KA. Developmental psychopathology in children of depressed mothers. *Developmental Psychology.* 1990;26(1):3.
21. Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychological review.* 1999;106(3):458.
22. McCarty CA, McMahon RJ. Mediators of the relation between maternal depressive symptoms and child internalizing and disruptive behavior disorders. *Journal of Family Psychology.* 2003;17(4):545.
23. Pardini DA. Novel insights into longstanding theories of bidirectional parent–child influences: Introduction to the special section. *Journal of abnormal child psychology.* 2008;36(5):627-631.
24. Forbes EE, Shaw DS, Silk JS, et al. Children's affect expression and frontal EEG asymmetry: transactional associations with mothers' depressive symptoms. *J Abnorm Child Psychol.* 2008;36(2):207-221.
25. Gross, Shaw DS, Moilanen KL, Dishion TJ, Wilson MN. Reciprocal models of child behavior and depressive symptoms in mothers and fathers in a sample of children at risk for early conduct problems. *J Fam Psychol.* 2008b;22(5):742-751.
26. Gross, Shaw DS, Burwell RA, Nagin DS. Transactional processes in child disruptive behavior and maternal depression: a longitudinal study from early childhood to adolescence. *Dev Psychopathol.* 2009;21(1):139-156.
27. Gross, Shaw DS, Moilanen KL. Reciprocal associations between boys' externalizing problems and mothers' depressive symptoms. *J Abnorm Child Psychol.* 2008a;36(5):693-709.
28. Nicholson JS, Deboeck PR, Farris JR, Boker SM, Borkowski JG. Maternal depressive symptomatology and child behavior: Transactional relationship with simultaneous bidirectional coupling. *Developmental Psychology.* 2011;47(5):1312.
29. Choe DE, Olson SL, Sameroff AJ. Effortful control moderates bidirectional effects between children's externalizing behavior and their mothers' depressive symptoms. *Child Dev.* 2014;85(2):643-658.
30. Antúnez Z, la Osa N, Granero R, Ezpeleta L. Reciprocity between parental psychopathology and oppositional symptoms from preschool to middle childhood. *Journal of clinical psychology.* 2018;74(3):489-504.
31. Brooker RJ, Neiderhiser JM, Leve LD, Shaw DS, Scaramella LV, Reiss D. Associations between infant negative affect and parent anxiety symptoms are bidirectional: evidence from mothers and fathers. *Frontiers in psychology.* 2015;6:1875.
32. Curran PJ, Howard AL, Bainter SA, Lane ST, McGinley JS. The separation of between-person and within-person components of individual change over time: a latent curve model with structured residuals. *J Consult Clin Psychol.* 2014;82(5):879-894.
33. Ringoot AP, Tiemeier H, Jaddoe VW, et al. Parental depression and child well-being: young children's self-reports helped addressing biases in parent reports. *J Clin Epidemiol.* 2015;68(8):928-938.
34. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol.* 2016;31(12):1243-1264.
35. de Beurs. Brief symptom inventory. *Handleiding. Leiden (Netherlands): Pits Publishers.* 2004.
36. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983;13(3):595-605.
37. De Beurs, Zitman F. De Brief Symptom Inventory (BSI). *De betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL-90. Leiden: Leids universitair medisch centrum.* 2005.
38. Achenbach, Rescorla. *Manual for the ASEBA preschool forms & profiles: An integrated system of multi-informant assessment; Child behavior checklist for ages 1 1/2-5; Language development survey; Caregiver-teacher report form.* University of Vermont; 2000.
39. Achenbach, Rescorla. ASEBA school-age forms & profiles. Aseba Burlington, VT; 2001.

40. Ivanova MY, Achenbach TM, Rescorla LA, et al. Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *J Am Acad Child Adolesc Psychiatry.* 2010;49(12):1215-1224.
41. Achenbach. The classification of children's psychiatric symptoms: a factor-analytic study. *Psychol Monogr.* 1966;80(7):1-37.
42. Achenbach, Ivanova MY, Rescorla LA, Turner LV, Althoff RR. Internalizing/externalizing problems: Review and recommendations for clinical and research applications. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2016;55(8):647-656.
43. Netherlands Statistics. *Begrippen: Allochten.* 2006.
44. Goelman H, Zdaniuk B, Boyce WT, Armstrong JM, Essex MJ. Maternal mental health, child care quality, and children's behavior. *Journal of Applied Developmental Psychology.* 2014;35(4):347-356.
45. Harvey EA, Metcalfe LA. The interplay among preschool child and family factors and the development of ODD symptoms. *Journal of Clinical Child & Adolescent Psychology.* 2012;41(4):458-470.
46. Ramchandani P, Psychogiou L. Paternal psychiatric disorders and children's psychosocial development. *The Lancet.* 2009;374(9690):646-653.
47. Julious SA. Using confidence intervals around individual means to assess statistical significance between two means. *Pharmaceutical Statistics: The Journal of Applied Statistics in the Pharmaceutical Industry.* 2004;3(3):217-222.
48. Payton ME, Greenstone MH, Schenker N. Overlapping confidence intervals or standard error intervals: what do they mean in terms of statistical significance? *J Insect Sci.* 2003;3:34.
49. Berry D, Willoughby MT. On the practical interpretability of cross-lagged panel models: Rethinking a developmental workhorse. *Child Development.* 2017;88(4):1186-1206.
50. Hoffman L. *Longitudinal analysis: Modeling within-person fluctuation and change.* Routledge; 2015.
51. Hoffman L, Stawski RS. Persons as contexts: Evaluating between-person and within-person effects in longitudinal analysis. *Research in Human Development.* 2009;6(2-3):97-120.
52. Hernán MA. The C-word: scientific euphemisms do not improve causal inference from observational data. *American journal of public health.* 2018;108(5):616-619.
53. Satorra A, Bentler PM. Corrections to test statistics and standard errors in covariance structure analysis. 1994.
54. Chen FF. Sensitivity of goodness of fit indexes to lack of measurement invariance. *Structural Equation Modeling: A Multidisciplinary Journal.* 2007;14(3):464-504.
55. Enders CK. *Applied missing data analysis.* Guilford press; 2010.
56. Muthén LK, Muthen B. *Mplus user's guide: Statistical analysis with latent variables, user's guide.* Muthén & Muthén; 2017.
57. Kline RB. *Principles and practice of structural equation modeling.* Guilford publications; 2015.
58. Maccoby EE. Parenting and its effects on children: On reading and misreading behavior genetics. *Annual review of psychology.* 2000;51(1):1-27.
59. Cicchetti. *Developmental psychopathology, risk, resilience, and intervention.* Vol 4: John Wiley & Sons; 2016.
60. Ingoldsby EM, Shaw DS. Neighborhood contextual factors and early-starting antisocial pathways. *Clinical child and family psychology review.* 2002;5(1):21-55.
61. Fergusson DM, Lynskey MT, Horwood LJ. The effect of maternal depression on maternal ratings of child behavior. *Journal of abnormal child psychology.* 1993;21(3):245-269.
62. Achenbach. As Others See Us:Clinical and Research Implications of Cross-Informant Correlations for Psychopathology. *Current Directions in Psychological Science.* 2006;15(2):94-98.

63. De Los Reyes, Kazdin. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. *Psychological bulletin.* 2005;131(4):483.
64. Collishaw S, Goodman R, Ford T, Rabe-Hesketh S, Pickles A. How far are associations between child, family and community factors and child psychopathology informant-specific and informant-general? *Journal of Child Psychology and Psychiatry.* 2009;50(5):571-580.
65. Geiser C, Eid M, Nussbeck FW, Courvoisier DS, Cole DA. Analyzing true change in longitudinal multitrait-multimethod studies: application of a multimethod change model to depression and anxiety in children. *Dev Psychol.* 2010;46(1):29-45.
66. Jaffee SR, Poulton R. Reciprocal effects of mothers' depression and children's problem behaviors from middle childhood to early adolescence. *Developmental contexts in middle childhood: Bridges to adolescence and adulthood.* 2006:107-129.
67. Achenbach, McConaughy SH, Howell CT. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychol Bull.* 1987;101(2):213-232.
68. Gavanas A. Domesticating masculinity and masculinizing domesticity in contemporary US fatherhood politics. *Social Politics: International Studies in Gender, State & Society.* 2004;11(2):247-266.
69. Spector PE. Method variance in organizational research: truth or urban legend? *Organizational research methods.* 2006;9(2):221-232.
70. Podsakoff PM, MacKenzie SB, Podsakoff NP. Sources of method bias in social science research and recommendations on how to control it. *Annu Rev Psychol.* 2012;63:539-569.
71. Pleck, Hofferth SL. Mother Involvement as an Influence on Father Involvement with Early Adolescents. *Fathering.* 2008;6(3):267-286.
72. Lamb ME. How do fathers influence children's development? Let me count the ways. *The role of the father in child development.* 2010:1.
73. Pleck. Integrating father involvement in parenting research. *Parenting.* 2012;12(2-3):243-253.
74. Duhig AM, Renk K, Epstein MK, Phares V. Interparental agreement on internalizing, externalizing, and total behavior problems: A meta-analysis. *Clinical Psychology: Science and Practice.* 2000;7(4):435-453.
75. Caspi A, Houts RM, Belsky DW, et al. The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clin Psychol Sci.* 2014;2(2):119-137.
76. Goodman SH, Rouse MH, Connell AM, Broth MR, Hall CM, Heyward D. Maternal depression and child psychopathology: A meta-analytic review. *Clinical child and family psychology review.* 2011;14(1):1-27.
77. Parent J, Forehand R, Pomerantz H, Peisch V, Seehuus M. Father participation in child psychopathology research. *Journal of abnormal child psychology.* 2017;45(7):1259-1270.

SUPPLEMENTARY MATERIAL

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

			1	2	3	4	5	6	7	8	9	10	11
	M	(SD)											
Child externalizing problems													
1 Age 1.5, mother report	10.6	6.73	-										
2 Age 3, mother report	8.13	6.14	.56**	-									
3 Age 3, father report	9.20	6.45	.36**	.56**	-								
4 Age 9, mother report	3.59	4.56	.32**	.44**	.32**	-							
5 Age 9, father report	3.71	4.61	.23**	.32**	.40**	.61**	-						
Parental psychopathology													
6 Prenatal, mother report	.24	.32	.20**	.19**	.11**	.14**	.07**	-					
7 Prenatal, father report	.13	.19	.11**	.10**	.11**	.07**	.13**	.24**	-				
8 Age 3, mother report	.15	.25	.22**	.31**	.19**	.20**	.11**	.35**	.14**	-			
9 Age 3, father report	.13	.23	.18**	.21**	.29**	.16**	.20**	.19**	.26**	.39**	-		
10 Age 9, mother report	.22	.29	.17**	.21**	.10**	.25**	.13**	.33**	.11**	.45**	.21**	-	
11 Age 9, father report	.16	.24	.06**	.11**	.18**	.17**	.25**	.09**	.23**	.16**	.37**	.25**	-

**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

			1	2	3	4	5	6	7	8	9	10	11
	M	(SD)											
Child internalizing problems													
1 Age 1.5, mother report	5.12	4.77	-										
2 Age 3, mother report	4.83	4.65	.56**	-									
3 Age 3, father report	5.23	4.84	.36**	.56**	-								
4 Age 9, mother report	4.51	4.76	.32**	.44**	.32**	-							
5 Age 9, father report	4.44	4.58	.23**	.32**	.40**	.61**	-						
Parental psychopathology													
6 Prenatal, mother report	.24	.32	.20**	.19**	.11**	.14**	.07**	-					
7 Prenatal, father report	.13	.19	.11**	.10**	.11**	.07**	.13**	.24**	-				
8 Age 3, mother report	.15	.25	.22**	.31**	.19**	.20**	.11**	.35**	.14**	-			
9 Age 3, father report	.13	.23	.18**	.21**	.29**	.16**	.20**	.19**	.26**	.39**	-		
10 Age 9, mother report	.22	.29	.17**	.21**	.10**	.25**	.13**	.33**	.11**	.45**	.21**	-	
11 Age 9, father report	.16	.24	.06**	.11**	.18**	.17**	.25**	.09**	.23**	.16**	.37**	.25**	-

**Correlation is significant at the0.01 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).

	Compared with	χ^2	*df*	RMSEA	CFI	*p*	$\Delta\chi^2$	Δdf	ΔRMSEA	ΔCFI	*p*
Externalizing problems, mother and father reports											
Model 1: Parent reported psychopathology and child externalizing problems		269.8	89	.009	.97	.65					
Model 2: Parental psychopathology à child externalizing problems	Model 1						128.9	44.5	.003	.02	.42
Model 3: Child externalizing problems à parental psychopathology	Model 1						122.4	44.5	.006	.01	.51
Internalizing problems, mother and father reports											
Model 1: Parent reported psychopathology and child internalizing problems		284.7	89	.006	.99	.38					
Model 2: Parental psychopathology à child internalizing problems	Model 1						132.1	44.5	.001	.03	.24
Model 3: Child internalizing problems à parental psychopathology	Model 1						118.9	44.5	.004	.02	.37

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: χ^2 = chi-square difference test; RMSEA = Root mean square error of approximation; CFI = Comparative fit index; Δ = change in statistical values.

Supplementary Table 4. ALT-SR Model: Bidirectional Associations between Parent and Offspring Psychopathology (N=5,536).

	Externalizing problems[a]	Internalizing problems[b]
ALT-SR effects	Parameter estimate (SE)	Parameter estimate (SE)
Within-person cross-laggs		
BSI_{t+1} on $CBCL_t$ - MR	0.40 (0.09)**	0.43 (0.08)**
BSI_{t+1} on $CBCL_t$ - FR	0.36 (0.07)**	0.33 (0.07)**
Auto-regressive		
BSI_{t+1} on BSI_t - MR	0.79 (0.10)**	0.81 (0.11)**
$CBCL_{t+1}$ on $CBCL_t$ - MR	0.37 (0.07)**	0.37 (0.06)**
BSI_{t+1} on BSI_t - FR	0.57 (0.09)**	0.59 (0.08)**
$CBCL_{t+1}$ on $CBCL_t$ - FR	0.39 (0.06)**	0.32 (0.06)**
(Co)variances (between- person)		
BSI_{int} with $CBCL_{int}$ - MR	2.94 (0.15)**	2.63 (0.14)**
BSI_{int} with $CBCL_{slope}$ - MR	1.95 (0.13)**	1.72 (0.11)**
$CBCL_{int}$ with BSI_{slope} - MR	2.25 (0.15)**	2.27 (0.13)**
BSI_{slope} with $CBCL_{slope}$ - MR	1.13 (0.09)**	1.19 (0.09)**
BSI_{int} with $CBCL_{int}$ - FR	2.83 (0.14)**	2.55 (0.14)**
BSI_{int} with $CBCL_{slope}$ - FR	1.87 (0.11)**	1.54 (0.12)**
$CBCL_{int}$ with BSI_{slope} - FR	1.99 (0.12)**	2.15 (0.14)**
BSI_{slope} with $CBCL_{slope}$ - FR	1.10 (0.10)**	1.13 (0.11)**
Residual (co)variances		
BSI $\varepsilon_{it1\_}\ \varepsilon_{it3}$ - MR	4.21 (0.45)**	4.07 (0.44)**
CBCL$\varepsilon_{it1_}\ \varepsilon_{it2}$ - MR	3.89 (0.37)**	3.83 (0.38)**
BSI $\varepsilon_{it1\_}\ \varepsilon_{it3}$ - FR	4.15 (0.43)**	3.87 (0.39)**
CBCL$\varepsilon_{it1_}\ \varepsilon_{it2}$ - FR	3.26 (0.33)**	3.12 (0.32)**
Fit statistics		
χ^2	438.53	429.77
df	144	144
RMSEA	.003	.009
SRMR	.009	.010
CFI	.97	.96

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 constraint 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 ($\varepsilon it1$) 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. **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.[1] As such, perceived loneliness can exist for individuals who are not socially isolated.[2] 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[3,4] and depression.[5]

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,[6,7] while more than 40% of Americans of all ages reported feeling lonely.[8] Perceived loneliness is also associated with a substantial increase in the risk of premature mortality, independent of income, education, sex, and ethnicity.[9-11] 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.[12] 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 (M_{age} below 21 years).[3] 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.[5] 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.[13,14] 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.

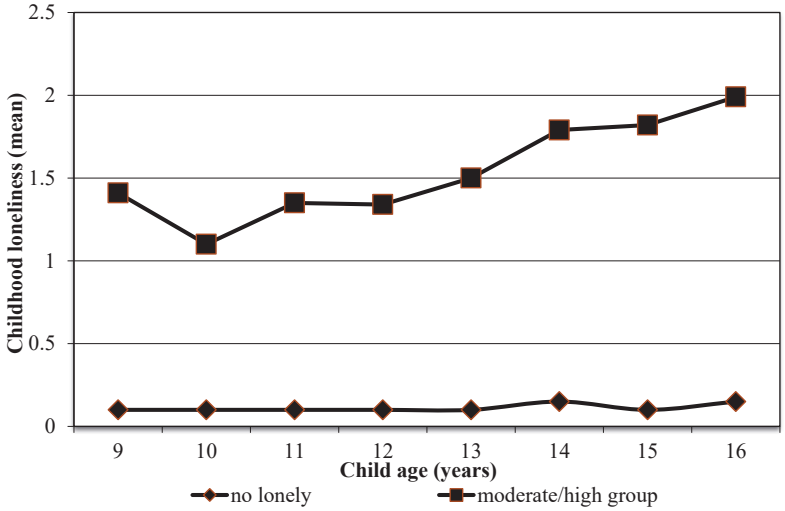
METHOD

Participants

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.[15] 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.[16] 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 1420 participants (630 girls [weighted percentage, 49.0%]).[16] 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[16-18] 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.

Figure 1. Childhood loneliness trajectories



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.[19] 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.[20] Subjective loneliness has been linked to psychological consequences

(e.g., Weiss[21] and Peplau and Perlman[22] Other studies of loneliness have used a similar construct.[5,23]

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 uncontrollable', 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),[24] 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.[16-18] 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.[19,25] 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.[26] 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 s 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

	Never lonely N (%)	*Ever lonely* N (%)	*p value* [a]
Overall childhood loneliness	1230 (86.6)	190 (13.4)	
Sex, girl	529 (43)	101 (53.2)	0.042
Rural areas	739 (60.1)	100 (52.6)	0.863
Psychosocial risk			
Low socioeconomic status	489 (39.8)	84 (44.2)	0.131
Single parent	491 (39.9)	105 (44.7)	0.256
Change in parent structure	386 (31.4)	76 (40)	0.305
Maltreatment	262 (21.3)	74 (38.9)	0.136
Depression mother	193 (15.7)	64 (33.7)	0.001

Numbers denotes children included in one or more analyses. Numbers are unweighted, and percentages are weighted. [a] *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

	Child-report loneliness		
	Never lonely N (%)	*Ever lonely* N (%)	*p value* [a]
Overall childhood loneliness	1342 (94.5)	78 (5.5)	
Psychiatric disorders			
Any anxiety diagnosis	86 (6.4)	22 (28.2)	<0.001
Any depression diagnosis	28 (2.1)	18 (23.1)	<0.001
Disruptive behavior disorder	122 (9.1)	19 (24.4)	0.001
Psychiatric symptoms	M (SD)	M (SD)	
Any anxiety symptoms	1.7 (2.2)	4.9 (3.9)	<0.001
Any depression symptoms	0.2 (0.1)	0.2 (0.4)	<0.001
Disruptive behavior	0.1 (0.3)	0.2 (0.4)	<0.001
	Parent-report loneliness		
Psychiatric 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. [a] *p* value from binary logistic regression of childhood loneliness and childhood psychiatric disorder outcomes. The models (Odd 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

	Psychiatric disorders							
			Any anxiety diagnosis		Any depression diagnosis		Substance use disorder	
		Overall	OR (95% CI)	*p value*	OR (95% CI)	*p value*	OR (95% CI)	*p value*
Child-report loneliness	Never lonely n (%)	1260 (94.4)	184 (14.6)		137 (10.9)		398 (31.6)	
	Ever lonely n (%)	74 (5.6)	33 (44.6)		20 (27.0)		34 (45.9)	
Model 1			5.95 (2.77 to 12.7)	<0.0001	2.72 (1.08 to 6.83)	0.033	1.95 (0.95 to 3.97)	0.067
Model 2			3.53 (1.55 to 8.04)	0.002	1.86 (0.73 to 4.71)	0.190	1.65 (0.73 to 3.74)	0.227
Parent-report loneliness	Never lonely n (%)	1215 (91.1)	177 (14.6)		136 (11.2)		392 (32.3)	
	Ever lonely n (%)	119 (8.9)	40 (33.6)		21 (17.6)		40 (33.6)	
Model 1			2.95 (1.51 to 5.75)	0.001	1.61 (0.61 to 4.23)	0.331	1.25 (0.62 to 2.54)	0.530
Model 2			1.43 (0.67 to 3.04)	0.354	0.91 (0.32 to 2.57)	0.861	0.94 (0.42 to 2.12)	0.887
	Psychiatric symptoms							
			Any anxiety symptoms		Any depression symptoms		Substance use symptoms	
			B (95% CI)	*p value*	B (95% CI)	*p value*	B (95% CI)	*p value*
Child-report loneliness	Never lonely, M (SD)		2.5 (3.2)		2.1 (2.0)		1.1 (1.4)	
	Ever lonely, M (SD)		4.5 (4.2)		3.4 (2.6)		1.5 (1.7)	
Model 1			1.91 (1.16 to 2.66)	<0.0001	1.25 (0.76 to 1.72)	<0.0001	0.38 (0.06 to 0.72)	0.020
Model 2[a]			1.20 (0.43 to 1.97)	0.002	0.76 (0.27 to 1.25)	0.002	0.20 (-0.14 to 0.54)	0.246
Parent-report loneliness	Never lonely, M (SD)		2.4 (3.2)		2.1 (2.0)		1.1 (1.4)	
	Ever lonely, M (SD)		4.4 (4.1)		3.2 (2.4)		1.3 (1.5)	
Model 1			1.78 (1.17 to 2.40)	<0.0001	0.93 (0.54 to 1.32)	<0.0001	0.09 (-0.17 to 0.37)	0.478
Model 2[a]			1.12 (0.49 to 1.75)	0.001	0.48 (0.08 to 0.88)	0.019	-0.06 (-0.33 to 0.22)	0.684

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.

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

	Psychiatric disorders					
	Any anxiety diagnosis		Any depression diagnosis		Substance use disorder	
Child-report loneliness	OR (95% CI)	*p value*	OR (95% CI)	*p value*	OR (95% CI)	*p value*
Model 1						
No lonely	Ref		Ref		Ref	
Moderate/ high group	6.34 (2.78 to 9.94)	<0.0001	3.71 (1.09 to 7.01)	0.010	2.75 (0.91 to 4.52)	0.040
Model 2						
No lonely	Ref		Ref		Ref	Ref
Moderate/ high group	3.82 (1.45 to 7.24)	0.001	1.34 (0.72 to 4.99)	0.193	1.89 (0.60 to 3.54)	0.127
	Psychiatric symptoms					
	Any anxiety symptoms		Any depression symptoms		Substance use symptoms	
Child-report loneliness	B (95% CI)	*p value*	B (95% CI)	*p value*	B (95% CI)	*p value*
Model 1						
No lonely	Ref		Ref		Ref	
Moderate/ high group	2.65 (1.21 to 2.76)	<0.0001	2.34 (0.70 to 1.82)	<0.0001	0.81 (0.05 to 0.85)	0.010
Model 2[a]						
No lonely	Ref		Ref		Ref	
Moderate/high group	2.31 (0.55 to 2.05)	0.001	1.68 (0.21 to 1.41)	0.001	0.43 (-0.10 to 0.73)	0.212

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.

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.

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.[5,6,23,29] 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[30] 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,[31] neuroendocrine,[9] genetic mechanisms,[32] 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).[33] 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.[31] 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.[34] 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.[35] 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,[36] 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.[37] 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).[38]

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.[32] For example, McGuire et al. showed significant heritability and non-shared environmental influences for children's loneliness using adoption and twin studies.[39] 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.

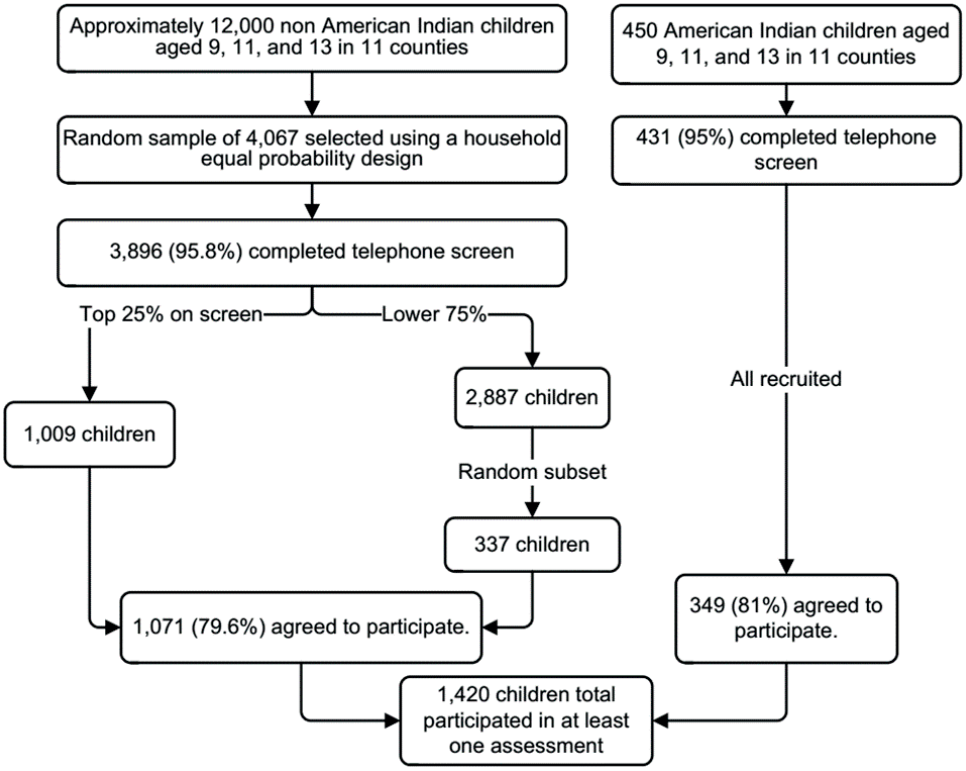
REFERENCES

1. Perlman D, Peplau LA. Toward a social psychology of loneliness. *Personal relationships.* 1981;3:31-56.
2. Cacioppo, Hawkley LC, Ernst JM, et al. Loneliness within a nomological net: An evolutionary perspective. *Journal of research in personality.* 2006;40(6):1054-1085.
3. Maes M, Nelemans SA, Danneel S, et al. Loneliness and social anxiety across childhood and adolescence: Multilevel meta-analyses of cross-sectional and longitudinal associations. *Developmental psychology.* 2019;55(7):1548.
4. Teo AR, Lerrigo R, Rogers MAM. The role of social isolation in social anxiety disorder: A systematic review and meta-analysis. *Journal of Anxiety Disorders.* 2013;27(4):353-364.
5. Qualter, Brown SL, Munn P, Rotenberg KJ. Childhood loneliness as a predictor of adolescent depressive symptoms: an 8-year longitudinal study. *European Child & Adolescent Psychiatry.* 2010;19(6):493-501.
6. Yang, Petersen KJ, Qualter P. Undesirable social relations as risk factors for loneliness among 14-year-olds in the UK: Findings from the Millennium Cohort Study. *International Journal of Behavioral Development.* 2020:0165025420965737.
7. Snape D, Manclossi S. Children's and young people's experiences of loneliness: 2018, London. 2018.
8. Cacioppo, Grippo AJ, London S, Goossens L, Cacioppo JT. Loneliness:Clinical Import and Interventions. *Perspectives on Psychological Science.* 2015;10(2):238-249.
9. Cacioppo, Cacioppo S, Capitanio JP, Cole SW. The neuroendocrinology of social isolation. *Annu Rev Psychol.* 2015;66:733-767.
10. Miller G. Why loneliness is hazardous to your health. American Association for the Advancement of Science; 2011.
11. Holt-Lunstad J, Smith TB. Loneliness and social isolation as risk factors for CVD: implications for evidence-based patient care and scientific inquiry. BMJ Publishing Group Ltd and British Cardiovascular Society; 2016.
12. Yang, Boen C, Gerken K, Li T, Schorpp K, Harris KM. Social relationships and physiological determinants of longevity across the human life span. *Proceedings of the National Academy of Sciences.* 2016;113(3):578-583.
13. De Los Reyes A, Youngstrom EA, Pabon SC, Youngstrom JK, Feeny NC, Findling RL. Internal consistency and associated characteristics of informant discrepancies in clinic referred youths age 11 to 17 years. *J Clin Child Adolesc Psychol.* 2011;40(1):36-53.
14. Achenbach, McConaughy SH, Howell CT. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychol Bull.* 1987;101(2):213-232.
15. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Annals of internal medicine.* 2007;147(8):573-577.
16. Costello, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of general psychiatry.* 2003;60(8):837-844.
17. Costello, Angold A, Burns BJ, et al. The Great Smoky Mountains Study of Youth: goals, design, methods, and the prevalence of DSM-III-R disorders. *Archives of general psychiatry.* 1996;53(12):1129-1136.

18. Copeland WE, Angold A, Shanahan L, Costello EJ. Longitudinal patterns of anxiety from childhood to adulthood: the Great Smoky Mountains Study. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2014;53(1):21-33.
19. Angold A, Costello EJ. The Child and Adolescent Psychiatric Assessment (CAPA). *J Am Acad Child Adolesc Psychiatry.* 2000;39(1):39-48.
20. Victor C, Scambler S, Bond J, Bowling A. Being alone in later life: loneliness, social isolation and living alone. *Reviews in Clinical Gerontology.* 2000;10(4):407-417.
21. Weiss RS. Loneliness: The experience of emotional and social isolation. 1973.
22. Peplau LA, Perlman D. Blueprint for a social psychological theory of loneliness. Paper presented at: Love and attraction: An interpersonal conference1979.
23. Qualter, Brown SL, Rotenberg KJ, et al. Trajectories of loneliness during childhood and adolescence: Predictors and health outcomes. *Journal of Adolescence.* 2013;36(6):1283-1293.
24. Angold A, Cox A, Prendergast M, et al. The Young Adult Psychiatric Assessment (YAPA). *Durham, NC: Duke University Medical Center.* 1999.
25. Angold A, Costello EJ. A test-retest reliability study of child-reported psychiatric symptoms and diagnoses using the Child and Adolescent Psychiatric Assessment (CAPA-C). *Psychol Med.* 1995;25(4):755-762.
26. Copeland WE, Wolke D, Angold A, Costello EJ. Adult psychiatric outcomes of bullying and being bullied by peers in childhood and adolescence. *JAMA psychiatry.* 2013;70(4):419-426.
27. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural equation modeling: A multidisciplinary Journal.* 2007;14(4):535-569.
28. Schunk D. A Markov chain Monte Carlo algorithm for multiple imputation in large surveys. *AStA Advances in Statistical Analysis.* 2008;92(1):101-114.
29. Vanhalst J, Luyckx K, Goossens L. Experiencing loneliness in adolescence: A matter of individual characteristics, negative peer experiences, or both? *Social Development.* 2014;23(1):100-118.
30. Offord DR, Kraemer HC. Risk factors and prevention. *Evidence-Based Mental Health.* 2000;3(3):70-71.
31. Cacioppo, Capitanio JP, Cacioppo JT. Toward a neurology of loneliness. *Psychol Bull.* 2014;140(6):1464-1504.
32. Goossens L, Van Roekel E, Verhagen M, et al. The genetics of loneliness: Linking evolutionary theory to genome-wide genetics, epigenetics, and social science. *Perspectives on Psychological Science.* 2015;10(2):213-226.
33. Boomsma DI, Cacioppo JT, Muthén B, Asparouhov T, Clark S. Longitudinal genetic analysis for loneliness in Dutch twins. *Twin Research and Human Genetics.* 2007;10(2):267-273.
34. Heinrich LM, Gullone E. The clinical significance of loneliness: A literature review. *Clinical psychology review.* 2006;26(6):695-718.
35. Cacioppo, Cacioppo, Boomsma D. Evolutionary mechanisms for loneliness. *Cognition & emotion.* 2014;28(1):3-21.
36. Vazire S. Who knows what about a person? The self–other knowledge asymmetry (SOKA) model. *Journal of personality and social psychology.* 2010;98(2):281.
37. Qualter, Vanhalst J, Harris R, et al. Loneliness across the life span. *Perspectives on Psychological Science.* 2015;10(2):250-264.
38. Cacioppo, Cacioppo S, Cole SW, Capitanio JP, Goossens L, Boomsma DI. Loneliness across phylogeny and a call for comparative studies and animal models. *Perspectives on Psychological Science.* 2015;10(2):202-212.

39. McGuire S, Clifford J. Genetic and environmental contributions to loneliness in children. *Psychological Science.* 2000;11(6):487-491.

Supplementary Figure 1. Ascertainment of the original Great Smoky Mountains study sample



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?

When did s/he start to feel lonely like that?

LONELINESS

0 = Absent

2 = The subject definitely feels intrusively and uncontrollably lonely, in at least 2 activities.

3 = S/he feels lonely almost all the time.

PDB9I01
Intensity

PDB9O01
Onset
/ /

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

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

Numbers denotes children included in one or more analyses. Numbers are unweighted, and percentages are weighted. [a]*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

	Fit indices			
	Entropy[a]	AIC[b]	BIC[c]	*BLRTp value*[d]
Number of class				
2	0.91	175.86	180.21	<0.001

[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% 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.[1-3] oor family functioning often includes, but is not limited to, high levels of conflict and lack of cohesion, disorganization, and poor quality of communication.[4] 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.[5] 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.[6]

Prenatal stressful life events and maternal anxiety and depression during pregnancy increase children's risk for socioemotional and cognitive problems.[7,8] 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.[9-12] Furthermore, brain imaging research suggests that maternal stress is associated with changes in the limbic and frontotemporal structures of children.[13] 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.[14] Animal studies suggest that this may be accomplished, in part, by changing the structure of neurons, especially in the hippocampus, amygdala, and prefrontal cortex.[15] Overall, preclinical studies during pregnancy and childhood indicate that the hippocampus is highly susceptible to early stressful experiences,[16,17] because of its high density of glucocorticoid receptors[18,19] and persistent postnatal neurogenesis.[16]

In a clinical study of monozygotic twins discordant for trauma exposure, Gilbertson et al.[20] 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.[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.[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.[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.[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.[27,28] 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[29] and the Child Behavior Checklist for Ages 6 to 18[30] 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 Acquisition

All images were acquired using the same sequence on the same 3-T 750w Discovery scanner (GE Healthcare) when children were aged 10 years.[26] 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[31] (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[32,33] 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 outcomes[36,37] (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[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 β 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.[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 × exposure period interaction P = .01), but no other brain outcomes varied by the timing of family functioning measurement (eResults in the Supplement).

Table 1. Baseline charachtersitics

	Mother	Father
	(n=2,583)	*(n=1,788)*
Age, M (SD)	31.1 (4.7)	33.5 (5.3)
Ethnicity		
Dutch, (%)	62.6	69.3
Other Western, (%)	9.3	5.8
Non Western, (%)	28.1	24.9
Education level		
High, (%)	52.4	56.4
Middle, (%)	28.9	27.4
Low, (%)	18.7	16.2
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	
Parental psychopathology score, M (SD)	0.26 (0.3)	0.13(0.2)
Marital status, prenatal, Yes (%)	90.6	
Child age at the MRI scan, years, M (SD)	10.1 (0.6)	
Gender, (% boy)	49.1	
Harsh parenting score, M (SD)	1.73 (1.57)	1.74 (1.57)
Poor family functioning - FAD		
Poor family functioning (FAD-score) prenatal, M (SD)	1.48 (0.4)	1.49 (0.4)
Poor family functioning (FAD-score) at age 5, M (SD)	1.50 (0.4)	
Poor family functioning (FAD-score) at age 9, M (SD)	1.51 (0.4)	1.48 (0.4)
Child problem behavior		
CBCL total problems score at age 10, M (SD)	17.2 (15.0)	17.3 (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.

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 2. Associations of poor family functioning with brain morphology.

	Brain morphology (N = 2,583)														
	Global brain measures									*Specific brain volumetric measures*					
***Mother reported* poor family functioning**	**Total brain volume (cm3)**			**Cerebral white matter, (cm^3)**			**Total gray volume, (cm^3)**			**Amygdala volume, (cm^3)**			**Hippocampus volume, (cm^3)**		
	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}
Poor prenatal family functioning (FAD), per score															
Model 1	-26.8 (-34.6 to -18.9)	<.001	.002	-9.76 (-13.3 to -6.20)	<.001	.002	-16.7 (-21.3 to -12.2)	<.001	.002	-0.01 (-0.03 to 0.02)	.593	.741	-0.04 (-0.09 to 0.04)	.075	.107
Model 2	-9.54 (-17.9 to -1.19)	.025	.087	-4.15 (-8.01 to -0.29)	.035	.087	-5.24 (-10.1 to -0.41)	.034	.088	-0.02 (-0.05 to 0.06)	.129	.258	-0.08 (-0.13 to -0.02)	.004	.040
Model 3	-9.13 (-17.4 to -0.74)	.033	.105	-4.05 (-7.92 to -0.18)	.041	.105	-5.05 (-9.93 to -0.19)	.042	.105	-0.02 (-0.04 to 0.09)	.192	.384	-0.07 (-0.13 to -0.03)	.003	.030
Age 5 poor family functioning (FAD), per score															
Model 1	-15.6 (-24.9 to -6.36)	.001	.002	-5.05 (-9.27 to -0.83)	.019	.031	-10.4 (-15.8 to -4.97)	<.001	.002	0.01 (-0.02 to 0.03)	.938	.938	-0.01 (-0.06 to 0.05)	.872	.938
Model 2	-5.47 (-14.7 to 3.81)	.248	.354	-1.86 (-6.14 to 2.45)	.400	.500	-3.52 (-8.90 to 1.86)	.199	.574	-0.01 (-0.03 to 0.03)	.823	.823	-0.02 (-0.07 to 0.04)	.528	.586
Model 3	-4.18 -14.1 to 4.50)	.311	.444	-1.47 (-5.80 to 2.83)	.499	.586	-2.91 (-8.31 to 2.49)	.292	.444	-0.01 (-0.03 to 0.03)	.933	.933	-0.02 (-0.08, to 0.04)	.528	.586
p Homogeneity for age of FAD assessment*		.234			.011			.180			.133			.001	

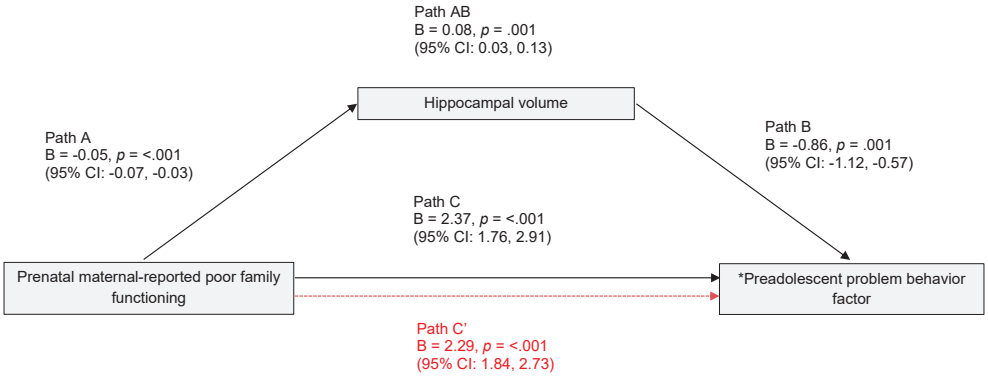
Note: Linear regression analysis of FAD and brain morphology outcome. Betas are averaged from 10 imputed datasets. Model 1 is adjusted for child age at brain MRI scan, child sex and total ICV (total intracranial volume). Model 2 is additionally adjusted for maternal age, ethnicity, education, marital 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 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.

[a]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.

[b]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.[41,42] 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.[43] Other research supports this inference. For example, higher levels of early-life maternal support have been linked to increased volume of the hippocampus.[44,45] 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.[46]

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[56] 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.[57] 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,[13] 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:

1. Davies PT, Coe JL. Family relationship dynamics: A developmental perspective. 2019.
2. Cummings EM, Keller PS, Davies PT. Towards a family process model of maternal and paternal depressive symptoms: exploring multiple relations with child and family functioning. *J Child Psychol Psychiatry.* 2005;46(5):479-489.
3. Davies PT, Cummings EM, Winter MA. Pathways between profiles of family functioning, child security in the interparental subsystem, and child psychological problems. *Development and psychopathology.* 2004;16(3):525-550.
4. Alderfer MA, Fiese BH, Gold JI, et al. Evidence-based Assessment in Pediatric Psychology: Family Measures. *Journal of Pediatric Psychology.* 2007;33(9):1046-1061.
5. Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology.* 2011;214(1):55-70.
6. Thompson RA. Stress and child development. *Future Child.* 2014;24(1):41-59.
7. O'Connor, Heron J, Golding J, Beveridge M, Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *Br J Psychiatry.* 2002;180:502-508.
8. O'Donnell KJ, Glover V, Barker ED, O'Connor TG. The persisting effect of maternal mood in pregnancy on childhood psychopathology. *Development and psychopathology.* 2014;26(2):393-403.
9. Catherine M, Claudia L-C, Caroline T. Prenatal Developmental Origins of Future Psychopathology: Mechanisms and Pathways. *Annual Review of Clinical Psychology.* 2019;15(1):317-344.
10. Maccari S, Krugers HJ, Morley-Fletcher S, Szyf M, Brunton PJ. The consequences of early-life adversity: neurobiological, behavioural and epigenetic adaptations. *Journal of neuroendocrinology.* 2014;26(10):707-723.
11. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience & biobehavioral reviews.* 2003;27(1-2):33-44.
12. Teicher MH, Tomoda A, Andersen SL. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? *Annals of the New York Academy of Sciences.* 2006;1071(1):313-323.
13. Qiu A, Rifkin-Graboi A, Chen H, et al. Maternal anxiety and infants' hippocampal development: timing matters. *Translational psychiatry.* 2013;3(9):e306.
14. Lupien, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience.* 2009;10:434.
15. Kolb B, Harker A, Mychasiuk R, de Melo SR, Gibb R. Stress and prefrontal cortical plasticity in the developing brain. *Cognitive development.* 2017;42:15-26.
16. Gould E, Tanapat P. Stress and hippocampal neurogenesis. *Biological psychiatry.* 1999;46(11):1472-1479.
17. Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience.* 1990;10(9):2897-2902.
18. Sapolsky RM, McEwen BS, Rainbow TC. Quantitative autoradiography of [3H] corticosterone receptors in rat brain. *Brain research.* 1983;271(2):331-334.
19. Patel PD, Lopez JF, Lyons DM, Burke S, Wallace M, Schatzberg AF. Glucocorticoid and mineralocorticoid receptor mRNA expression in squirrel monkey brain. *Journal of psychiatric research.* 2000;34(6):383-392.
20. Gilbertson MW, Shenton ME, Ciszewski A, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci.* 2002;5(11):1242-1247.

21. Hanson JL, Nacewicz BM, Sutterer MJ, et al. Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biol Psychiatry.* 2015;77(4):314-323.
22. Hair NL, Hanson JL, Wolfe BL, Pollak SD. Association of Child Poverty, Brain Development, and Academic Achievement. *JAMA Pediatr.* 2015;169(9):822-829.
23. Tavassolie T, Dudding S, Madigan AL, Thorvardarson E, Winsler A. Differences in perceived parenting style between mothers and fathers: implications for child outcomes and marital conflict. *Journal of Child and Family Studies.* 2016;25(6):2055-2068.
24. Lamb ME. How do fathers influence children's development? Let me count the ways. *The role of the father in child development.* 2010:1.
25. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol.* 2016;31(12):1243-1264.
26. White T, Muetzel RL, El Marroun H, et al. Paediatric population neuroimaging and the Generation R Study: the second wave. *Eur J Epidemiol.* 2018;33(1):99-125.
27. Byles J, Byrne C, Boyle MH, Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process.* 1988;27(1):97-104.
28. Epstein NB, Baldwin LM, Bishop DS. THE McMASTER FAMILY ASSESSMENT DEVICE*. *Journal of Marital and Family Therapy.* 1983;9(2):171-180.
29. Achenbach, Rescorla. *Manual for the ASEBA preschool forms & profiles: An integrated system of multi-informant assessment; Child behavior checklist for ages 1 1/2-5; Language development survey; Caregiver-teacher report form.* University of Vermont; 2000.
30. Achenbach, Rescorla. ASEBA school-age forms & profiles. Aseba Burlington, VT; 2001.
31. Fischl B, van der Kouwe A, Destrieux C, et al. Automatically parcellating the human cerebral cortex. *Cereb Cortex.* 2004;14(1):11-22.
32. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983;13(3):595-605.
33. de Beurs. Brief symptom inventory. *Handleiding. Leiden (Netherlands): Pits Publishers.* 2004.
34. Straus MA, Hamby SL, Finkelhor D, Moore DW, Runyan D. Identification of child maltreatment with the Parent-Child Conflict Tactics Scales: Development and psychometric data for a national sample of American parents. *Child abuse & neglect.* 1998;22(4):249-270.
35. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the royal statistical society. Series B (Methodological).* 1995:289-300.
36. Litman HJ, Horton NJ, Hernandez B, Laird NM. Incorporating missingness for estimation of marginal regression models with multiple source predictors. *Stat Med.* 2007;26(5):1055-1068.
37. Sanchez, Hu H, Litman HJ, Tellez-Rojo MM. Statistical methods to study timing of vulnerability with sparsely sampled data on environmental toxicants. *Environ Health Perspect.* 2011;119(3):409-415.
38. Valeri L, Vanderweele. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods.* 2013;18(2):137-150.
39. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology.* 2012;23(1):119-128.
40. Schunk D. A Markov chain Monte Carlo algorithm for multiple imputation in large surveys. *AStA Advances in Statistical Analysis.* 2008;92(1):101-114.
41. Jabès A, Nelson CA. 20 years after "The ontogeny of human memory: A cognitive neuroscience perspective," where are we? *International Journal of Behavioral Development.* 2015;39(4):293-303.

42. Casey BJ, Giedd JN, Thomas KM. Structural and functional brain development and its relation to cognitive development. *Biol Psychol.* 2000;54(1-3):241-257.
43. Knudsen EI. Sensitive periods in the development of the brain and behavior. *J Cogn Neurosci.* 2004;16(8):1412-1425.
44. Luby JL, Barch DM, Belden A, et al. Maternal support in early childhood predicts larger hippocampal volumes at school age. *Proc Natl Acad Sci U S A.* 2012;109(8):2854-2859.
45. Luby JL, Belden A, Harms MP, Tillman R, Barch DM. Preschool is a sensitive period for the influence of maternal support on the trajectory of hippocampal development. *Proc Natl Acad Sci U S A.* 2016;113(20):5742-5747.
46. Bick J, Nelson CA. Early experience and brain development. *Wiley Interdiscip Rev Cogn Sci.* 2017;8(1-2).
47. Calem M, Bromis K, McGuire P, Morgan C, Kempton MJ. Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. *Neuroimage Clin.* 2017;14:471-479.
48. Curtis WJ, Cicchetti D. Affective facial expression processing in young children who have experienced maltreatment during the first year of life: an event-related potential study. *Dev Psychopathol.* 2011;23(2):373-395.
49. Lieslehto J, Kiviniemi V, Maki P, et al. Early adversity and brain response to faces in young adulthood. *Hum Brain Mapp.* 2017;38(9):4470-4478.
50. Nagy K, Greenlee MW, Kovacs G. The lateral occipital cortex in the face perception network: an effective connectivity study. *Front Psychol.* 2012;3:141.
51. Hibar, Adams HHH, Jahanshad N, et al. Novel genetic loci associated with hippocampal volume. *Nature Communications.* 2017;8:13624.
52. Lewis AJ, Austin E, Galbally M. Prenatal maternal mental health and fetal growth restriction: a systematic review. *J Dev Orig Health Dis.* 2016;7(4):416-428.
53. Weinstock M. The long-term behavioural consequences of prenatal stress. *Neurosci Biobehav Rev.* 2008;32(6):1073-1086.
54. Li J, Wang Z-N, Chen Y-P, et al. Late gestational maternal serum cortisol is inversely associated with fetal brain growth. *Neuroscience & Biobehavioral Reviews.* 2012;36(3):1085-1092.
55. Hompes T, Vrieze E, Fieuws S, et al. The influence of maternal cortisol and emotional state during pregnancy on fetal intrauterine growth. *Pediatr Res.* 2012;72(3):305-315.
56. Lindsay KL, Buss C, Wadhwa PD, Entringer S. The Interplay between Maternal Nutrition and Stress during Pregnancy: Issues and Considerations. *Annals of Nutrition and Metabolism.* 2017;70(3):191-200.
57. Luby J, Belden A, Botteron K, et al. The effects of poverty on childhood brain development: the mediating effect of caregiving and stressful life events. *JAMA pediatrics.* 2013;167(12):1135-1142.

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.
eTable 1. Concurrent associations of poor family functioning and brain morphology
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
eTable 9. The associations of poor family functioning and lobar measures stratified by hemispheres
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).[1,2] 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,[3] and the scales have been found to be generalizable across 23 societies, including The Netherlands.[4] 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.[5] 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.[6] 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[7] (eFigure 1 in the Supplement).

Covariates

Parental ethnicity was categorized into three groups: Dutch, non-Western, and other Western national origin.[8] 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 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'.[9,10] High validity and reliability have been reported for the Dutch translation.[11] Harsh parenting was assessed when the child was 3 years old using the Parent-Child Conflict Tactics Scale,[12] a validated self-report questionnaire completed by mother and father. In our research group,[13] 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.[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.[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[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.[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),[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.

	Brain morphology (N = 2,583)														
	Global brain measures									***Specific brain volumetric measures***					
***Mother reported* poor family functioning**	**Total brain volume (cm3)**			**Cerebral white matter, (cm^3)**			**Total gray volume, (cm^3)**			**Amygdala volume, (cm^3)**			**Hippocampus volume, (cm^3)**		
	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}
Age 9 poor family functioning (FAD), per score															
Model 1	-9.13 (-17.7 to -0.59)	.036	.081	-4.10 (-7.98 to -0.22)	.038	.081	-5.05 (-10.1 to -0.03)	.049	.081	0.02 (-0.01 to 0.04)	.234	.234	0.03 (-0.02 to 0.09)	.194	.234
Model 2	-1.13 (-9.61 to 7.34)	.793	.886	-1.60 (-5.51 to 2.31)	.423	.823	0.36 (-4.57 to 5.29)	.886	.886	0.01 (-0.02 to 0.04)	.834	.834	0.02 (-0.03 to 0.07)	.463	.834
Model 3	-0.50 (-3.17 to 4.07)	.789	.790	-1.27 (-5.20 to 2.66)	.527	.658	0.90 (-4.04 to 5.85)	.720	.720	0.01 (-0.01 to 0.04)	.359	.658	0.02 (-0.03 to 0.08)	.425	.658

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.

eTable 2. The associations of poor family functioning and lobar measures.

	Brain morphology (N = 2,583)											
	Lobar measures											
***Mother reported* poor family functioning**	**Temporal lobe, (cm^3)**			**Frontal lobe, (cm^3)**			**Parietal lobe, (cm^3)**			**Occipital lobe, (cm^3)**		
	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}
Poor prenatal family functioning (FAD), per score												
Model 1	-0.16 (-0.8 to 0.53)	.652	.869	0.31 (-0.68 to 1.31)	.534	.854	-1.25 (-2.01 to -0.49)	.001	.004	-0.80 (-1.25 to-0.35)	<.001	.004
Model 2	0.05 (-0.71 to 0.80)	.903	.903	0.70 (-0.38 to 1.78)	.206	.408	-0.58 (-1.40 to 0.24)	.167	.408	-0.70 (-1.19 to -0.21)	.005	.040
Age 5 poor family functioning (FAD), per score												
Model 1	-0.04 (-0.85 to 0.77)	.928	.928	-0.91 (-2.07, 0.26)	.127	.254	-0.09 (-0.98 to 0.81)	.851	.928	-0.48 (-1.01 to 0.48)	.074	.197
Model 2	0.05 (-0.78 to 0.89)	.898	.903	-0.80 (-2.00, 0.39)	.189	.408	0.33 (-0.59 to 1.24)	.486	.648	-0.32 (-0.86 to 0.23)	.255	.408
p Homogeneity for age of FAD assessment*		093			.148			.091			.030	

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. **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 3. The associations of poor family functioning and occipital lobe stratified by regions.

	Brain morphology (N = 2,583)							
	Occipital lobe anatomical region							
Mother reported **poor family functioning**	**Lateral occipital, (cm^3)**		**Lingual occipital, (cm^3)**		**Cuneus occipital, (cm^3)**		**Pericalcarine occipital, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Poor prenatal family functioning (FAD), per score								
Model 1	-0.54 (-0.79 to -0.29)	<.001	-0.12 (-0.28 to 0.04)	.138	-0.09 (-0.19 to 0.02)	.056	-0.05 (-0.12 to 0.02)	.176
Model 2	-0.47 (-0.61 to -0.09)	.007	-0.11 (-0.28 to 0.06)	.223	-0.07 (-0.16 to 0.04)	.247	-0.04 (-0.11 to 0.03)	.242
Age 5 poor family functioning (FAD), per score								
Model 1	-0.27 (-0.56 to 0.02)	.066	-0.09 (-0.29, 0.09)	.328	-0.06 (-0.18 to 0.05)	.246	-0.05 (-0.13 to 0.03)	.240
Model 2	-0.15 (-0.45 to 0.14)	.311	-0.07 (-0.27, 0.13)	.483	-0.05 (-0.16 to 0.07)	.402	-0.04 (-0.13 to 0.04)	.296

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.

eTable 4. The associations of poor family functioning and subcortical brain morphology.

	Brain morphology (N = 2,583)							
	Global brain measures				***Specific brain volumetric measures***			
Mother reported **poor family functioning**	**Thalamus volume, (cm^3)**		**Accumbens volume, (cm^3)**		**Caudate volume, (cm^3)**		**Putamen volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Poor prenatal family functioning (FAD), per score								
Model 1	0.02 (-13.3 to -6.20)	.623	-0.01 (-0.02 to -0.01)	.243	-0.07 (-0.14 to -0.01)	.038	0.06 (-0.02 to 0.14)	.140
Model 2	0.03 (-0.05 to 0.11)	.433	-0.01 (-0.02 to 0.01)	.323	-0.04 (-0.12 to 0.03)	.236	0.01 (-0.08 to 0.09)	.870
Age 5 poor family functioning (FAD), per score								
Model 1	-0.04 (-0.13 to 0.05)	.356	-0.01 (-0.02 to 0.01)	.298	-0.05 (-0.13 to 0.03)	.241	0.06 (-0.03 to 0.15)	.210
Model 2	-0.04 (-0.13 to 0.05)	.528	-0.01 (-0.02 to 0.01)	.392	-0.02 (-0.10 to 0.06)	.605	-0.04 (-0.13 to 0.05)	.528

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.

	Brain morphology (N = 2,583)														
	Global brain measures									*Specific brain volumetric measures*					
***Father reported* poor family functioning**	**Total brain volume, (cm^3)**			**Cerebral white matter, (cm^3)**			**Total gray volume, (cm^3)**			**Amygdala volume, (cm^3)**			**Hippocampus volume,(cm^3)**		
	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}
Poor prenatal family functioning (FAD), per score															
Model 1	-23.1 (-34.3 to -12.1)	<.001	.005	-7.98 (-13.1 to -2.92)	.002	.005	-15.2 (-21.7 to -8.69)	<.001	.005	-0.03 (-0.04 to 0.03)	.881	.881	-0.01 (-0.08 to 0.05)	.664	.772
Model 2	-7.34 (-18.9 to 4.16)	.211	.422	-2.40 (-7.72 to 2.91)	.375	.564	-5.08 (-11.8 to 1.61)	.137	.387	-0.04 (-0.04 to0.03)	.842	.842	-0.02 (-0.09 to 0.06)	.668	.808
Age 9 poor family functioning (FAD), per score															
Model 1	-13.2 (-23.7 to -2.73)	.013	.026	-5.82 (-10.6 to -1.03)	.002	.005	-7.19 (-13.3 to -1.06)	.021	.035	0.007 (-0.02 to 0.04)	.695	.772	0.03 (-0.03 to 0.09)	.359	.513
Model 2	-8.95 (-19.3 to 1.45)	.092	.387	-4.39 (-9.20 to 0.42)	.074	.387	-4.37 (-10.4 to 1.65)	.155	.387	0.06 (-0.03 to 0.04)	.728	.808	0.03 (-0.04 to 0.09)	.395	.564
p Homogeneity for age of FAD assessment*		.069			.055			.132			.600			.162	

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.

eTable 6. The associations of paternal-reported poor family functioning and lobar measures.

	Brain morphology (N = 2,583)											
	Lobar measures											
***Father reported* poor family functioning**	**Temporal lobe, (cm^3)**			**Frontal lobe, (cm^3)**			**Parietal lobe, (cm^3)**			**Occipital lobe, (cm^3)**		
	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}	B (95% CI)	*p*	p_{FDR}
Poor prenatal family functioning (FAD), per score												
Model 1	-0.87 (-1.85 to 0.11)	.083	.226	-1.10 (-2.52 to 0.32)	.128	.260	-1.09 (-2.17 to -0.01)	.166	.266	-0.25 (-1.25 to -0.35)	.442	.593
Model 2	0.51 (-1.56 to 0.53)	.334	.605	-0.75 (-2.26 to 0.75)	.327	.605	-0.61 (-1.76 to 0.52)	.288	.845	0.09 (-0.58 to -0.77)	.783	.845
Age 9 poor family functioning (FAD), per score												
Model 1	0.28 (-0.64 to 1.20)	.552	.791	0.17 (-1.12 to 1.47)	.791	.791	0.38 (-0.62 to 1.39)	.453	.791	-0.14 (-0.74 to -0.47)	.658	.791
Model 2	0.38 (-0.55 to 1.31)	.426	.686	0.33 (-0.98 to 1.65)	.620	.827	0.54 (-0.48 to 1.56)	.300	.686	-0.03 (-0.63 to -0.58)	.930	.930
p Homogeneity for age of FAD assessment*		.122			.376			.110			.930	

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.

	Brain morphology (N = 2,583)									
	Global brain measure						*Specific brain volumetric measures*			
Mother reported poor family functioning	**Total brain volume, (cm^3)**		**Cerebral white matter, (cm^3)**		**Total gray volume, (cm^3)**		**Amygdala volume, (cm^3)**		**Hippocampus volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Poor prenatal family functioning FAD, per score	-9.50 (-17.9 to -1.13)	.026	-4.19 (-8.07 to -0.32)	.034	-5.16 (-10.1 to -0.31)	.037	-0.02 (-0.05 to 0.005)	.107	-0.08 (-0.13 to -0.02)	.004
Age 5 poor family functioning (FAD), per score	-5.47 (-14.7 to 3.81)	.248	-1.86 (-6.19 to 2.40)	.388	-3.59 (-8.98 to 1.78)	.190	-0.004 (-0.03 to 0.03)	.798	-0.02 (-0.07 to 0.04)	.518

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.

	Brain morphology (N = 2,583)							
	Specific brain volumetric measures							
Mother reported poor family functioning	**Amygdala volume, (cm^3)**				**Hippocampus volume, (cm^3)**			
	Left amygdala		**Right amygdala**		**Left hippocampus**		**Right hippocampus**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Poor prenatal family functioning (FAD), per score	-.012 (-0.27 to 0.03)	.110	-.009 (-.025 to .006)	.243	.039 (-.066 to -.012)	.005	-.037 (-.066 to -.009)	.011
Age 5 poor family functioning (FAD), per score	-.006 (-.023 to .010)	.444	.003 (-.015 to .020)	.748	-.005 (-.035 to .025)	.828	-.014 (-.046 to .018)	.391

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.

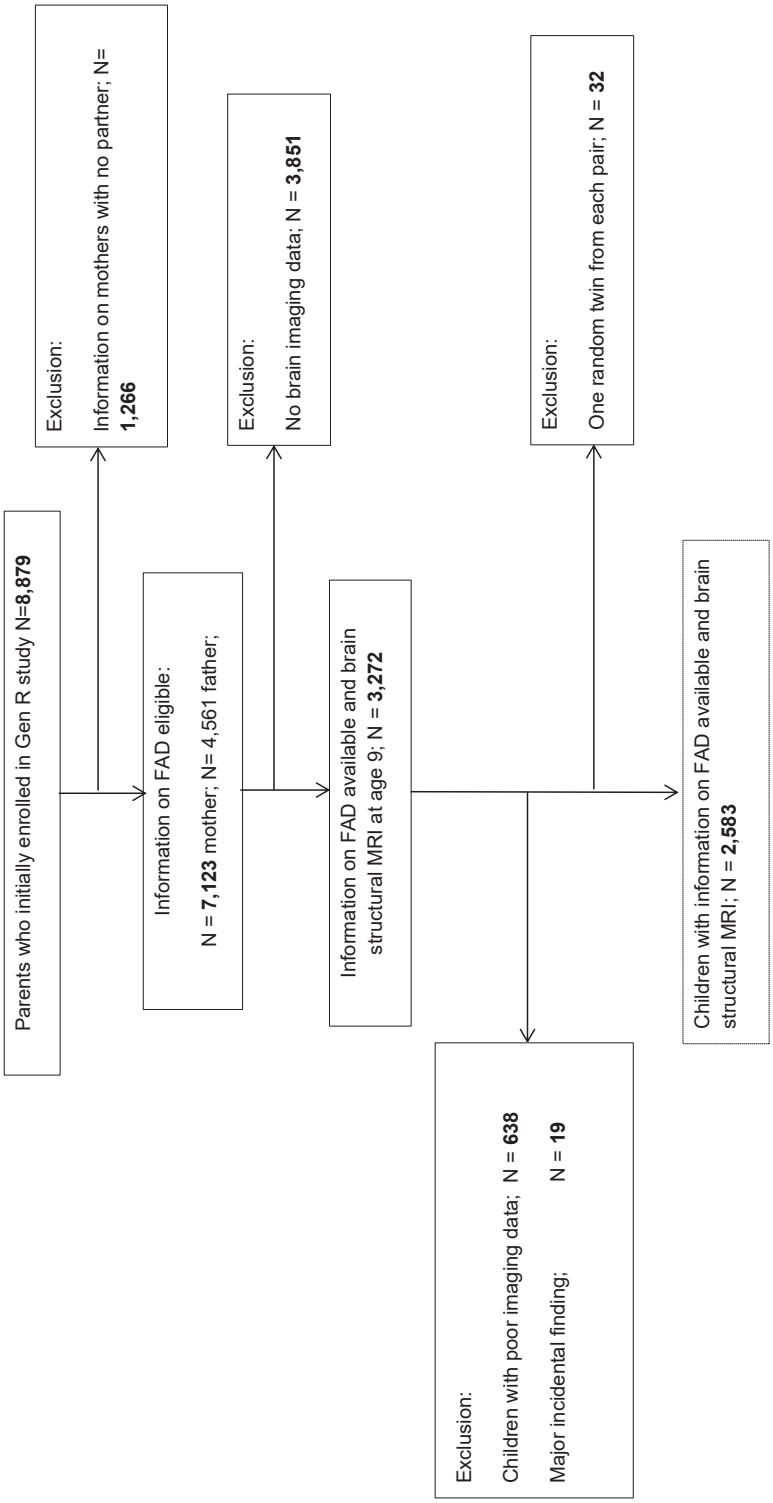
	Brain morphology (N = 2,583)							
	Lobar measures							
Mother reported poor family functioning	**Temporal lobe, (cm^3)**		**Frontal lobe, (cm^3)**		**Parietal lobe, (cm^3)**		**Occipital lobe, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
	Left lobar measures							
Poor prenatal family functioning (FAD), per score	-.120 (-.289 to .529)	.566	.478 (-.066 to 1.02)	.085	-.309 (-.747 to .128)	.165	-.252 (-.503 to .001)	.050
	Right lobar measures							
	-.062 (-.473 to .349)	.768	.221 (-.370 to .812)	.464	-.271 (-.709 to .167)	.225	-.450 (-.721 to -.179)	.001
	Left lobar measures							
Age 5 poor family functioning (FAD), per score	-.127 (-.582 to .328)	.584	-.201 (-.805 to .402)	.513	-.040 (-.443 to .524)	.870	-.103 (-.383 to .176)	.469
	Right lobar measures							
	-.182 (-.273 to .637)	.434	-.602 (-1.25 to .050)	.070	.286 (-.203 to .775)	.251	-.213 (-.514 to .087)	.164

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.

eTable 10. Correlation coefficients between maternal and paternal report of poor family functioning.

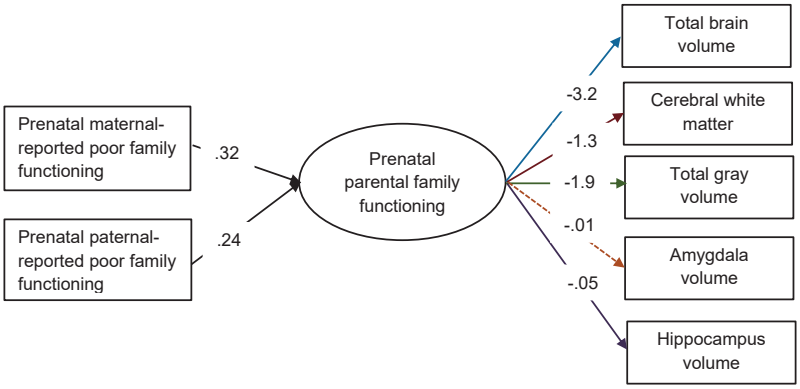
	1	2	3	4	5
Poor family functioning					
1 Prenatal, mother report	-				
2 Prenatal, father report	.45**	-			
3 Age 5, mother report	.38**	.26**	-		
4 Age 9, mother report	.37**	.22**	.52**	-	
5 Age 9, father report	.25**	.39**	.35**	.45**	-

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



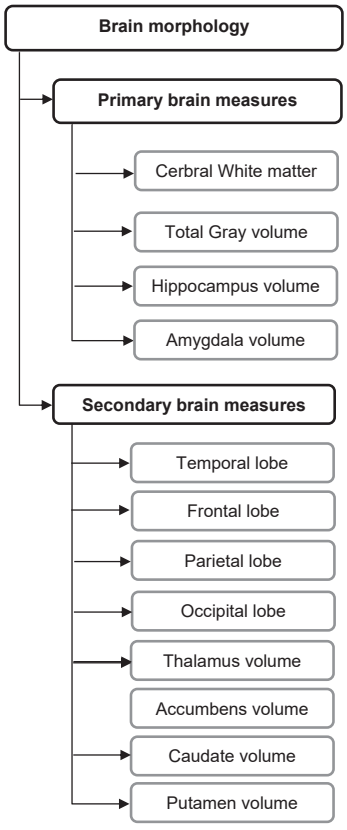
eFigure 1. Inclusion of the study sample

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.[17] 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).

eReferences:

1. Byles J, Byrne C, Boyle MH, Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process.* 1988;27(1):97-104.
2. Epstein NB, Baldwin LM, Bishop DS. THE McMASTER FAMILY ASSESSMENT DEVICE*. *Journal of Marital and Family Therapy.* 1983;9(2):171-180.
3. Achenbach, Rescorla. *Manual for the ASEBA preschool forms & profiles: An integrated system of multi-informant assessment; Child behavior checklist for ages 1 1/2-5; Language development survey; Caregiver-teacher report form.* University of Vermont; 2000.
4. Ivanova MY, Achenbach TM, Rescorla LA, et al. Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *J Am Acad Child Adolesc Psychiatry.* 2010;49(12):1215-1224.
5. Fischl B, van der Kouwe A, Destrieux C, et al. Automatically parcellating the human cerebral cortex. *Cereb Cortex.* 2004;14(1):11-22.
6. White T, Jansen PR, Muetzel RL, et al. Automated quality assessment of structural magnetic resonance images in children: Comparison with visual inspection and surface-based reconstruction. *Hum Brain Mapp.* 2018;39(3):1218-1231.
7. Muetzel RL, Blanken LME, van der Ende J, et al. Tracking Brain Development and Dimensional Psychiatric Symptoms in Children: A Longitudinal Population-Based Neuroimaging Study. *Am J Psychiatry.* 2018;175(1):54-62.
8. Netherlands Statistics. *Begrippen: Allochten.* 2006.
9. de Beurs. Brief symptom inventory. *Handleiding. Leiden (Netherlands): Pits Publishers.* 2004.
10. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983;13(3):595-605.
11. De Beurs, Zitman F. De Brief Symptom Inventory (BSI). *De betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL-90. Leiden: Leids universitair medisch centrum.* 2005.
12. Straus MA, Hamby SL, Finkelhor D, Moore DW, Runyan D. Identification of child maltreatment with the Parent-Child Conflict Tactics Scales: Development and psychometric data for a national sample of American parents. *Child abuse & neglect.* 1998;22(4):249-270.
13. Jansen PW, Raat H, Mackenbach JP, et al. Early determinants of maternal and paternal harsh discipline: The generation R study. *Family relations.* 2012;61(2):253-270.
14. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the royal statistical society. Series B (Methodological).* 1995:289-300.
15. Litman HJ, Horton NJ, Hernandez B, Laird NM. Incorporating missingness for estimation of marginal regression models with multiple source predictors. *Stat Med.* 2007;26(5):1055-1068.
16. Sanchez, Hu H, Litman HJ, Tellez-Rojo MM. Statistical methods to study timing of vulnerability with sparsely sampled data on environmental toxicants. *Environ Health Perspect.* 2011;119(3):409-415.
17. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology.* 2012;23(1):119-128.
18. McDonald RP, Ho M-HR. Principles and practice in reporting structural equation analyses. *Psychological methods.* 2002;7(1):64.
19. Hu Lt, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural equation modeling: a multidisciplinary journal.* 1999;6(1):1-55.

Chapter 5.1

Long-term associations between early-life family functioning and preadolescent white matter microstructure.

Scott W. Delaney, Yllza Xerxa, Ryan L. Muetzel, Tonya White, Sebastien Haneuse, Kerry J. Ressler, Henning Tiemeier, Laura D. Kubzansky

Manuscript submitted for publication

ABSTRACT

Objective: Causes of childhood behavior problems remain poorly understood. Enriched family environments and corresponding brain development may protect against their onset, but research investigating white matter neurodevelopmental pathways explaining associations between the family environment and behavior remains limited. We tested whether healthier early-life family functioning would be associated with lower global mean diffusivity (MD) and higher global fractional anisotropy (FA) in preadolescence, which have been associated previously with reduced problem behaviors.

Methods: Data are from 2,653 children in the Generation R Study in Rotterdam, the Netherlands. Mothers reported family functioning using the McMaster Family Assessment Device (range 1 – 4, higher scores indicate healthier functioning) both prenatally and in mid-childhood (mean age 6.0 years). In preadolescence (mean age 10.1), the study collected diffusion-weighted scans. We computed standardized global (i.e., multi-tract mean) MD and FA values by averaging metrics from 27 white matter tracts and used adjusted OLS models to examine global and tract-specific outcomes.

Results: Estimates from fully adjusted, weighted models for a one-unit increase in prenatal family functioning score were $\beta_{\text{global MD}}$ = -0.13 (95% CI: -0.25, -0.02) and $\beta_{\text{global FA}}$ = 0.10 (95% CI: -0.01, 0.21). These magnitudes were 76% and 57% of estimates associated with a one-year increase in age at scan for global MD and FA, respectively. Tract-specific analyses supported these global findings. We found no evidence of an association between mid-childhood functioning and global outcomes.

Conclusion: Healthy early-life family functioning may induce white matter microstructural differences in preadolescence linked previously to reduced problem behaviors.

INTRODUCTION

The origins of child behavior disorders remain poorly understood. Increasingly, investigators have called for a population neuroscience approach both to identify factors shaping brain structure and function, and to understand how variations in the brain cause child behavior problems.[1–3] Empirical studies suggest elements of the social environment impact brain development in both positive and negative ways, with effects on aspects of brain function that have been associated with behavior problems.[4–6] Neuroscience research often characterizes the childhood social environment as a monolithic experience measured by parental socioeconomic status. In contrast, social scientific models of the social environment include experiences related to one's family, friends, schools, organized activities, neighborhood, and place of worship.[7] The relative importance of these domains may change throughout childhood, with the family environment most influential early in life. As such, a healthy early-life family environment may drive healthy brain development and protect against behavior disorders.

However, the neurodevelopmental effects of family-based exposures have not been thoroughly explored. Among studies in this area, most focus on family dysfunction and its link to poor outcomes.[8] For example, a broad spectrum of research links child maltreatment, which occurs most often within the family environment, to structural alterations in corticolimbic regions of the brain involved in cognitive and affective processes underlying behavior problems.[9–11] Similarly, functional imaging studies report that family conflict is associated with increased adolescent risk-taking behavior.[12,13]

In contrast to research on family dysfunction, some neurodevelopmental studies assess positive family-based experiences, which may confer benefits beyond those associated with a mere absence of negative exposures. For example, greater maternal support and positive parenting behavior have been associated with brain structural changes thought to be advantageous, including accelerated hippocampal growth in childhood and adolescence, and attenuated amygdala growth in adolescence.[14,15] Some functional imaging studies also report associations between healthy parent-child relationships, decreased risk taking behavior, and increased cognitive control in adolescence and early adulthood.[16–18]

These studies are limited insofar as they focus on parenting practices—typically maternal practices—rather than on broader measures of overall family functioning that may capture important characteristics within a complex family ecology. Many of these studies also assess aspects of the family environment during a narrow time period in a child's life. As a result, they cannot quantify how the family environment's influence may change throughout childhood. And despite the importance of white matter to

healthy brain development, prior imaging studies of family-based exposures assess only brain function or gray matter structural outcomes.

Studies suggest both negative and positive experiences occurring prenatally, postnatally, and in childhood alter white matter structural development.[19,20] These studies generally report associations between negative exposures (e.g., maternal prenatal anxiety) and properties of white matter microstructure that may decrease neural efficiency, and between positive ones (e.g., breastfeeding) and the opposite.[21–25] Studies associating childhood experiences with white matter microstructure differences are complemented by a separate body of mostly cross-sectional research associating white matter microstructure with behavioral outcomes. In these studies, 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 antisocial behavior, attention deficit hyperactivity disorder, bipolar disorder, and disruptive behavior problems.[20,26,27]

To investigate whether a positive family environment may impact white matter microstructure, this study used prospective data from the Generation R Study, a population-based birth cohort tracking child development from pregnancy through adolescence. Study staff collected data on family functioning from mothers prenatally and in mid-childhood, and their children completed an MRI brain scan in preadolescence. We hypothesized that more positive family functioning at each time point would be associated with more organized white matter microstructure across all areas of the brain (i.e., global effects), even after extensive adjustment for plausible confounders selected based on prior literature and theory.[20]

METHODS

Participants

This study uses data from the Generation R Study, a prospective, population-based birth cohort in Rotterdam, the Netherlands, seeking to identify social, environmental, and genetic factors affecting child health and development.[28] The Generation R Study enrolled 8,879 pregnant women living in Rotterdam between 2002 and 2006 and another 898 women at the birth of their child during the same time period. Study researchers have collected data through clinic visits and postal questionnaires from children and their caregivers at multiple time points through the present after securing written informed consent and assent from all participants. All study protocols are approved by the Medical Ethics Committee of the Erasmus University Medical Center.

Women completed a postal questionnaire about their family functioning prior to the birth of their enrolled child (gestational age range 18 – 25 weeks) and again when their child was in mid-childhood (mean age 6.0 years; range 4.0 – 9.1 years). Mothers enrolled at the birth of their child (i.e., not while pregnant) completed only the mid-childhood questionnaire. In sum, 8,271 women completed at least one of these questionnaires. Later, study researchers obtained diffusion-weighted magnetic resonance imaging (DWI) scans from 3,992 children in preadolescence (mean age 10.1 years; range 8.6 – 12.0 years).[29] The current study included participants if they had a usable DWI scan with no missing tract-specific scalar data (described below) and either prenatal or mid-childhood family functioning data. Among these participants, we excluded those whose mothers reported using cocaine or heroin while pregnant. And because Generation R includes a number of twins and triplets, we randomly selected only one sibling for inclusion in these cases. Our final analysis sample included 2,653 children. Supplement Section 1 details selection into our analysis sample.

Measures

Family Functioning

To measure family functioning, parents completed the McMaster Family Assessment Device, General Functioning Subscale.[30] This is a self-report survey of established reliability and validity in Dutch and several other populations, in which parents respond on a 4-point Likert scale to 6 positively framed and 6 negatively framed items.[31–33] Representative questions include, "If there are problems, we can count on each other for support," and, "There are a lot of unpleasant and painful feelings in our family." Because these questions do not reference specific family members or roles, parents can respond regardless of their family's structure. We derived a family functioning score at each time point by reverse-scoring negatively framed items, then averaging response scores across all 12 items to yield a family functioning score range of 1 to 4 for each participant and time period, where higher scores indicated more positive functioning. Cronbach's alpha in the analytic sample was strong (0.89) at both prenatal and mid-childhood time periods.

Brain Imaging

Generation R researchers have described diffusion-weighted imaging collection protocols and preprocessing pipelines elsewhere.[29,34] All DWI images were acquired using a 3T GE MR-750W scanner (General Electric, Milwaukee, Wisconsin) and an eight-channel head coil. Sequence parameters yielded 2 mm isotropic resolution and 35 diffusion-weighted volumes. Study staff preprocessed the resulting images using the FMRIB Software Library (FSL), version 5.0.9, and the FSL AutoPtx plugin to compute tract-specific scalar metrics of white matter microstructure, including mean diffusivity

(MD), fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) for 27 white matter tracts. These included three brainstem tracts (middle cerebellar peduncle; left and right medial lemniscus), ten projection fibers (left and right corticospinal tracts and acoustic radiations, and bilateral anterior, posterior, and superior thalamic radiations), eight association fibers (bilateral superior and inferior longitudinal fasciculi, and bilateral inferior fronto-occipital and uncinate fasciculi), four limbic system fibers (left and right cingulate gyrus part of the cingulum and parahippocampal part of the cingulum), and two callosal fibers (forceps major and forceps minor).[35] Supplement Section 2 further details scan acquisition and processing. Researchers inspected all raw images, selected tractography data, and slice signal intensities to assess scan quality. Scans deemed poor quality were excluded from analysis.

Following prior research on white matter microstructure, we focused our primary analyses on two measures, MD and FA.[36,37] MD is a measure of the extent to which water molecules in white matter tissue move freely in all directions. FA assesses the extent to which white matter microstructure constrains water molecule diffusion in a single direction. In post hoc analyses, we also assessed AD and RD, which quantify how much water molecules are able to move in certain directions.[38] All four measures provide complementary information from which inferences about white matter microstructural anatomy can be made. As children age, MD values decrease, and FA values increase.[20] Lower MD and higher FA values suggest more organized white matter, which in turn may enable more efficient neural functioning.[20]

Because complex human behavior manifests from coordinated neural activity across many distinct brain regions connected by many different white matter tracts, we constructed multi-tract mean measures of white matter microstructure incorporating information from all 27 tracts delineated by AutoPtx by averaging and standardizing all tract-specific MD, FA, AD, and RD values (hereafter referred to as "global" or "multi-tract mean" values). While tracts vary substantially in size, calculating arithmetic means ensured each tract contributed equal information to our "global" outcomes regardless of its size, which enabled us to test our primary hypothesis that family functioning affects all (or nearly all) white matter tracts in the brain.

Separately, for the 24 tracts with analogues in both hemispheres (e.g., left and right uncinate fasciculus), we averaged and standardized measures from both hemispheres. For example, we averaged left and right MD values for each participant's uncinate fasciculi, resulting in a single mean MD value for the uncinate fasciculus. Because three tracts (middle cerebellar peduncle, forceps major, and forceps minor) do not have independent analogues in both hemispheres, this process resulted in 15 sets of tract-specific values used in our analyses.

Covariates

Researchers retrieved child birthdate and sex data from birth records. Parents self-reported the following: their country of origin and ethnicity, which we used to categorize child ethnicity as European (including Dutch but excluding Turkish), Turkish, Moroccan, and Other Ethnicity; household income during pregnancy (more or less than €2200 / month); highest maternal and paternal completed education level at study enrollment (< high school equivalent; high school or intermediate vocational training; advanced vocational training, bachelor's degree, or higher); maternal and paternal history of psychotic episodes (yes, no); maternal age at childbirth; maternal smoking history during pregnancy (never, until pregnancy was known, or through pregnancy); and parental psychopathology symptoms at two time points: (1) prenatally, included in models of prenatal family functioning and measured using the full 53-item Brief Symptom Inventory (BSI); and (2) at child age 3 years, included in models of mid-childhood family functioning and measured using a subset of the 21 items from the BSI available at that time point.[39] We calculated continuous BSI sum scores for each parent at each time point. We considered paternal-report education, psychosis, and psychopathology symptoms in addition to the maternal factors as covariates because paternal factors may also confound the relationship between maternal-report family functioning and child white matter structure.

Statistical Analyses

We assessed and removed as appropriate outliers in MD, FA, AD, and RD using standard methods (n = 162 removed). Supplement Section 3 details our methods and rationale.

To investigate whether family functioning was associated with our primary measures of white matter microstructure (i.e., MD and FA only), we used ordinary least squares linear regression. We imposed a hierarchical structure to these analyses with initial models examining global multi-tract mean outcomes and subsequent models evaluating specific tracts. We adjusted p-values for multiple comparisons in tract-specific models via the Simes procedure.[40] For each outcome, we fit (1) minimally adjusted models accounting for each child's age at scan, sex, and ethnicity; and (2) fully adjusted models adding all other covariates listed above. We ran separate models to assess associations with prenatal and mid-childhood family functioning, after which we considered models including functioning scores from both time points simultaneously. We also fit fully adjusted models weighted to account for differential loss to follow-up by important sociodemographic characteristics (see below for details of inverse probability weights). In post hoc analyses, we followed the same analysis plan for global AD and global RD.

We conducted several sensitivity analyses with respect to our primary outcomes (i.e., global multi-tract mean MD and FA). First, we evaluated whether prenatal family

Figure 1. Associations between prenatal family functioning and tract-specific FA and MD.

Figure 1. Associations between prenatal family functioning and tract-specific FA and MD.

Estimates are from fully adjusted and weighted models accounting for child age at MRI scan, sex, ethnicity, household income, highest level of parental education achieved, maternal and partner history of psychosis, prenatal maternal and partner psychopathology symptoms, maternal age at child's birth, and child in utero exposure to smoking.

Coefficient plot estimates are standard deviation differences associated with a one-point increase in prenatal family functioning score (score range 1 - 4).

functioning modified effects of mid-childhood family functioning by incorporating an interaction term between prenatal and mid-childhood functioning scores using continuous measures in fully adjusted models. Second, we evaluated associations between both global outcomes and mean family functioning by averaging functioning scores from both prenatal and mid-childhood time points. Third, because there was substantial left skew in the functioning score distributions (see below for more detail), we fit fully adjusted piecewise continuous linear spline models of prenatal functioning and both global outcomes. Based on *a priori* considerations of the family functioning scale and score distributions in our sample, we initially modeled a knot at a score of 3.0, after which we iteratively modeled alternative knots below 3.0 in score decrements of 0.1.

Missing data.

To account for differential loss to follow-up by sociodemographic characteristics, we calculated inverse probability of attrition weights (IPWs). We deemed lost to follow-up participants enrolled at baseline but excluded from our analytic sample for any reason. We multiply imputed missing exposure and covariate data using chained equations to construct 50 imputed datasets, then combined imputation-specific mean and variance measures using Rubin's Rules.[41] Supplement Sections 4 and 5 include additional details of our IPWs and imputation models.

RESULTS

Analytic sample characteristics

Included versus excluded participants were more likely to be of European ethnicity (71% versus 58%); to have parents with at least advanced vocational training or a bachelor's degree (63% versus 44%); to be from higher-income households (65% versus 49%); and to be born to older mothers (mean maternal age at birth 31.7 years versus 29.8 years).

Table 1 details sociodemographic characteristics in our analytic sample according to family functioning scores. Mothers of European children reported higher family functioning scores at both time points than mothers of children of other ethnicities, as did mothers of higher-income or education households. Prenatal and mid-childhood scores were moderately correlated, r = 0.38. Functioning scores at both time points were left skewed. Prenatal mean and median scores were 3.48 and 3.58, respectively, with 75% of mothers in the analysis sample reporting scores greater than or equal to 3.0 (scale range 1.0 – 4.0). Similarly, mid-childhood mean and median scores were 3.50 and 3.58, respectively, with fully 83% of mothers reporting mid-childhood scores 3.0 or higher. Supplement Section 6 details mean outcome values (global FA and MD) by sociodemographic characteristics.

Table 1. Distribution of exposure measures by participant characteristics in the final analysis sample. n = 2,653.

		Prenatal Family Functioning		Mid-Childhood Family Functioning	
	%	$\bar{x}$	*s*	$\bar{x}$	*s*
Total Sample	100	3.48	0.46	3.50	0.42
Child biological sex					
Female	51	3.49	0.46	3.51	0.41
Male	49	3.47	0.46	3.49	0.43
Child race / ethnicity / country of origin					
Dutch / Other European	71	3.56	0.42	3.55	0.40
Turkish	5	3.26	0.48	3.29	0.49
Moroccan	4	3.26	0.47	3.27	0.40
Surinamese	7	3.25	0.50	3.39	0.45
Other	13	3.30	0.53	3.40	0.43
Highest Household Education					
Less than high school equivalent	4	3.18	0.49	3.22	0.47
High school or intermediate vocational trainin	33	3.36	0.49	3.44	0.43
Adv. vocational training, bachelor's, or higher	63	3.60	0.41	3.56	0.40
Household Income					
€2200 / month or less	35	3.30	0.51	3.38	0.46
More than €2200 / month	65	3.59	0.40	3.57	0.38

a. This table is based on observed values for each characteristic and does not account for missing data.
b. Family functioning scores are based on the McMaster Family Assessment Device - General Functioning Subscale and range from 1 to 4.

Global multi-tract mean outcomes.

In both weighted and unweighted fully adjusted models, prenatal family functioning was negatively associated with preadolescent global multi-tract mean MD (Table 2), with more modest evidence of a positive association with global multi-tract mean FA. For comparison, the magnitudes of the prenatal functioning effect estimates were approximately 76% and 57% of those associated with a one-year increase in age at scan in our weighted, fully adjusted models for global MD and global FA, respectively. Effect estimates from weighted and unweighted models were nearly identical, though standard errors were greater in weighted versus unweighted models. In contrast, we found no evidence of an association between mid-childhood functioning and either global measure of white matter microstructure. Notably, in models of mid-childhood functioning adjusting for prenatal functioning, prenatal functioning remained statistically significantly associated with both outcomes. For example, in weighted, fully adjusted models of mid-childhood functioning, effect estimates for prenatal functioning were $\beta_{\text{global MD}}$ = -0.13 (95% CI: -0.25, -0.00), and $\beta_{\text{global FA}}$ = 0.14 (95% CI: 0.03, 0.26). Supplement Section 7 includes post hoc model results for global multi-tract mean RD and AD, which suggest global RD—but not AD—is associated with prenatal family functioning.

Table 2. Associations between family functioning and global multi-tract mean measures of white matter microstructure in preadolescence. n = 2,653.

		Global FA			Global MD		
		β	95% CI	*p*	β	95% CI	*p*
Prenatal Family Functioning							
Min. adjusted	Unweighted	0.13	(0.04, 0.22)	0.01	-0.10	(-0.19, -0.01)	0.03
Fully adjusted	Unweighted	0.10	(0.00, 0.19)	0.04	-0.13	(-0.23, -0.04)	0.01
Fully adjusted	Weighted	0.10	(-0.01, 0.21)	0.07	-0.13	(-0.25, -0.02)	0.03
Mid-Childhood Family Functioning - Baseline Unadjusted							
Min. adjusted	Unweighted	0.00	(-0.10, 0.09)	0.93	0.00	(-0.10, 0.09)	0.95
Fully adjusted	Unweighted	-0.02	(-0.12, 0.08)	0.70	-0.01	(-0.11, 0.09)	0.81
Fully adjusted	Weighted	-0.04	(-0.17, 0.08)	0.48	0.00	(-0.12, 0.12)	0.98
Mid-Childhood Family Functioning - Baseline Adjusted							
Min. adjusted	Unweighted	-0.06	(-0.16, 0.04)	0.24	0.04	(-0.06, 0.14)	0.46
Fully adjusted	Unweighted	-0.06	(-0.16, 0.04)	0.27	0.03	(-0.07, 0.13)	0.59
Fully adjusted	Weighted	-0.08	(-0.21, 0.04)	0.19	0.03	(-0.09, 0.16)	0.58

a. Minimally adjusted models include covariates for child age at scan, sex, and ethnicity.
b. Fully adjusted models account for child age at scan, sex, ethnicity, household income, highest level of parental education achieved, maternal and partner history of psychosis, prenatal maternal and partner psychopathology symptoms (for prenatal models), early-childhood maternal and partner psychopathology symptoms (for mid-childhood models), maternal age at child's birth, and child in utero exposure to smoking.
c. "Global" measures are standardized mean values of weighted-average FA and MD across all 27 tracts delineated by AutoPtx.

Tract-specific outcomes.

Exploratory tract-specific models revealed associations between prenatal functioning and MD in the uncinate fasciculus, medial lemniscus, and both parts (parahippocampal and gyral) of the cingulum bundle; however, the latter two associations did not survive adjustment for multiple testing (Figure 1, Supplement Section 8). The remaining tract-specific MD effect estimates had larger standard errors and thus did not evince associations based on statistical significance, but all MD effect estimates were uniform in direction (Figure 1). A similar pattern emerged from models assessing prenatal functioning and tract-specific FA. Effect estimates were mostly uniform in direction, though only the association with medial lemniscus FA remained statistically significant after adjustment for multiple testing (Figure 1, Supplement Section 8).

Sensitivity analyses.

In weighted, fully adjusted models of global multi-tract mean MD and FA, we found no evidence of statistical interaction between prenatal and mid-childhood functioning scores. Interaction terms were $\beta_{\text{global MD}}$ = -0.08 (95% CI: -0.33, 0.18) and $\beta_{\text{global FA}}$ = 0.15 (95% CI: -0.09, 0.40). Separately, weighted, fully adjusted models of mean family functioning scores yielded only marginal or no evidence that mean functioning was associated with either outcome: $\beta_{\text{global MD}}$ = -0.11 (95% CI: -0.23, 0.01); and $\beta_{\text{global FA}}$ = 0.05 (95% CI: -0.06, 0.17). Piecewise continuous linear spline models suggested

effects of greater magnitudes for lower prenatal functioning scores, i.e., scores between 1.0 and 3.0. However, given the relatively fewer number of participants with lower functioning scores, these effect estimates were uncertain. Among the relatively greater number of participants with higher functioning scores (i.e., above 3.0), effect estimates were smaller. See Supplement Section 9 for estimates from these models.

DISCUSSION

This study provides evidence to support our hypothesis that early-life family functioning may affect white matter neurodevelopment. Specifically, more positive prenatal family environments (i.e., supportive and accepting families with high problem-solving capacity) were associated with lower MD and higher FA, on average, across the brain's white matter tracts in preadolescence. While the effect estimate magnitudes were relatively small in absolute terms, they can be compared to other known contributors to white matter microstructure. For example, the difference in global MD associated with a one-unit increase in prenatal family functioning score was about three-quarters of the difference associated with a one-year increase in scan age. The three-unit range of the family functioning scale (i.e., from 1 to 4) renders these estimates more substantial when comparing children of families with exceedingly low scores to those with very high scores. In contrast to our prenatal findings, we found no evidence suggesting a relationship between mid-childhood family functioning and our global outcomes. One possible explanation for the diverging results between prenatal and mid-childhood functioning relates to the decreasing relative importance of the family environment to children's broader social environment (and thus to their neurodevelopment) over time. As children grow older, they attend school, spend more time with friends, and establish influential relationships outside the family.

Secondary analyses suggest effects of prenatal family functioning on white matter microstructure may be widespread throughout the brain. For example, with respect to MD, only associations with the uncinate fasciculus and medial lemniscus among the 15 tract-specific outcomes tested remained statistically significant after adjustment for multiple testing, but the uniform direction and similar magnitude of the remaining tracts' estimates suggest a model of global effects rather than one in which effects are targeted at specific tracts. Moreover, if effects were tract-specific (rather than global), one might postulate the uncinate fasciculus and medial lemniscus would share a common structural feature or functional role. However, the uncinate fasciculus connects the brain's temporal and frontal lobes and is involved in memory, language, and social-emotional processing, while the medial lemniscus is a brainstem tract involved in sensory information transport to the brain.[42,43] While both tracts emerge at around 15 gestational weeks,

many other tracts for which effect estimates were not strictly statistically significant also appear to emerge between 13 and 19 gestational weeks.[44] Thus, taken together, our tract-specific analyses suggest prenatal family functioning may have global rather than targeted effects.

Our findings are consistent with the limited available prior work in this area. The only other study to assess prenatal and early childhood life experiences and white matter microstructure in a population-based cohort also found lasting effects of prenatal exposures. Using diffusion-weighted images obtained when participants were in early adulthood, Jensen et al. (2018) reported maternal prenatal stressful experiences were associated with a decrease in the magnetization transfer ratio (MTR) in the splenium, a marker of lower white matter microstructure.[21] Thus, our findings correspond with those of Jensen et al. (2018) because they reported *stressful* prenatal experiences were associated with *less* microstructure, while our study reports *enriched* prenatal environments are associated with *more* microstructure.

Moreover, our results support findings from prior studies reporting that positive parenting practices or healthy parent-child relationships confer neurodevelopmental advantages associated with decreased risky behavior. Because many of these studies assess the family environment after the children are born, they are vulnerable to reverse causation, since child behavior likely influences family functioning. Our study, however, found similar effects using a measure of prenatal family functioning obtained before the child's birth, thereby reducing concerns about recall bias and reverse causation. Together, these findings suggest additional investigation is warranted to explore whether, how, and to what extent prenatal and early-life experiences induce lasting white matter microstructural changes.

The period from the last weeks of gestation through the first years of life is critical to a number of foundational white matter developmental processes, which may be affected by the family environment and may also explain lasting microstructural differences. Our prenatal measure of the family environment is unlikely to measure the prenatal environment exclusively. More likely, it captures the perinatal and early-childhood family environment, spanning some time period both before and after the child's birth. Interestingly, we found prenatal and mid-childhood functioning scores were only moderately correlated ($r = 0.38$), suggesting that the family environment may change modestly through the child's first six years of life. Follow-up research may investigate whether and to what extent family functioning fluctuates during this time period. Measures of prenatal and immediate postnatal functioning may be particularly interesting as families adjust to the presence of a new infant while the infant continues rapid white matter development.

Jensen et al. (2018) propose at least three complementary mechanisms that could explain how prenatal stress may affect white matter microstructure. The first is the balance between neurogenesis (neuron production) and apoptosis (neuron death). Both processes occur in the prenatal and, at least within the hippocampus, the very early postnatal period. The balance between these processes affects neuronal density by influencing the number of neurons (and thus axons) that comprise the brain's white matter. Studies in humans and other animals suggest both processes are in part experience dependent. For example, maternal psychological stress—and the resulting increase in stress hormones—may reduce neuronal density by decreasing neurogenesis and increasing apoptosis, while enriched environments may increase neuronal density by doing the opposite.[20,21] Increased neuronal density could result in higher FA and lower MD values.[21] Importantly, if the associations observed in this study are both (1) reflective of biological reality and (2) caused by a change in balance between neurogenesis and apoptosis, then neuroplastic processes in childhood and adolescence that enable the brain to reorganize itself might able to compensate partially for these prenatal effects later in a child's life, but they would be unable to undo them entirely because neurogenesis largely ends prior to or just after birth.

Another possible mechanism is altered developmental myelination, or the process by which axons develop an insulating myelin sheath to enhance their efficiency. Myelination begins in the late prenatal period and extends well into childhood. Enriched environments have been associated with increased FA and decreased MD, which suggest greater myelination. Likewise, stressful environments have been associated with decreased FA and increased MD, which suggest lesser myelination.[21] Positive family functioning may have effects similar to those of enriched environments.

A third potential mechanism relates to changes in axonal diameter and the thickness of the myelin sheath. Larger axons have thinner myelin sheaths compared to smaller axons, resulting in different microstructural profiles. Because enriched environments entail novel and healthy stimuli, they may increase neuronal activity and promote axonal growth.[21] Both FA and MD may be influenced by these changes, such that a greater density of large-diameter axons (perhaps resulting from enriched environments) would manifest as higher FA and lower MD.

Our study has limitations. First, the sample included few families reporting low functioning scores, perhaps due either to selection or social desirability bias. This inhibits our ability to examine effects of scores at the low end of the continuum. Second, with only one DWI scan per participant, we cannot fully assess changes in neurodevelopmental trajectories due to our exposures. Third, as with all observational studies, confounding and reverse causation may bias our results. For example, certain parental genetic profiles

may predispose parents to report higher or lower family functioning while also affecting their child's white matter structure. We partly addressed this concern by adjusting for maternal and paternal psychopathology symptoms and psychosis history. Fourth, our study is limited by challenges inherent in large, population-based pediatric neuroimaging studies. For example, we excluded several participants due to poor scan quality, which can be patterned by child behavior and sociodemographic profiles. Relatedly, the study's generalizability is limited by differential attrition in the cohort by sociodemographic characteristics, although our use of inverse probability weights to account for attrition helps to address this concern. Selection in utero may also induce survival bias, wherein frail fetuses of mothers reporting high prenatal family functioning may have survived and been included in our analyses when they would not have done so if they were from lower functioning families.[45] In turn, prenatal functioning effect estimate magnitudes are likely to be underestimated. Finally, our analyses do not account for possible partial volume effects related to head size that may influence DTI scalar metrics.[46]

Our study also has several strengths. First, we used a longitudinal design, leveraging prospectively collected exposure data predating the child's birth and linking it to outcomes measured fully ten years later, which enabled us to investigate relatively long-term effects of the perinatal family environment. This mitigates concerns about reverse causation and recall bias. We also avoid many challenges associated with studies using maternal reports of both exposures and outcomes (e.g., behavior measures) by using objective outcomes constructed from DWI scans. Finally, this study is nested within a large, population-based birth cohort, which reduces the risk of selection bias common to many neuroimaging studies relying on case-control designs.

CONCLUSION

In a sample of 2,653 children, more positive prenatal family functioning—a measure of the perinatal family environment—was associated with greater white matter microstructure in preadolescents, suggesting healthy perinatal family functioning may confer lasting neurodevelopmental advantages. Our results also suggest the emphasis on parenting practices in family-focused child neurodevelopmental research may be too narrow, and that more general measures of family functioning agnostic to family structure may capture important health-relevant dimensions of the family environment. Subsequent studies of family functioning and its neurodevelopmental effects should consider developing new tools to assess better variation at both the lower and the higher end of the scale, and they should emphasize participation of low-functioning families. Capturing positive aspects of early-life family functioning may provide important in-

sight into novel pathways by which facets of the social environment become biologically embedded and link to child health and well-being.

REFERENCES

1. Paus T. Population neuroscience: why and how. *Hum Brain Mapp*. 2010;31(6):891-903. doi:10.1002/hbm.21069
2. Falk EB, Hyde LW, Mitchell C, et al. What is a representative brain? Neuroscience meets population science. *PNAS*. 2013;110(44):17615-17622. doi:10.1073/pnas.1310134110
3. Tiemeier H, Muetzel R. Population Neuroscience. In: Taylor E, Verhulst FC, Wong J, Yoshida K, Nikapota A, eds. *Mental Health and Illness of Children and Adolescents*. Mental Health and Illness Worldwide. Springer; 2020:1-22. doi:10.1007/978-981-10-0753-8_12-1
4. Liu J. Childhood Externalizing Behavior: Theory and Implications. *J Child Adolesc Psychiatr Nurs*. 2004;17(3):93-103.
5. Mason CA, Cauce AM, Gonzales N, Hiraga Y, Grove K. An Ecological Model of Externalizing Behaviors in African-American Adolescents: No Family Is an Island. *Journal of Research on Adolescence*. 1994;4(4):639-655. doi:10.1207/s15327795jra0404_12
6. Plybon LE, Kliewer W. Neighborhood Types and Externalizing Behavior in Urban School-Age Children: Tests of Direct, Mediated, and Moderated Effects. *Journal of Child and Family Studies*. 2001;10(4):419-437. doi:10.1023/A:1016781611114
7. Bronfenbrenner U. Ecology of the Family as a Context for Human Development: Research Perspectives. *Developmental psychology*. 1986;22(6):723-742.
8. Xerxa Y, Delaney SW, Rescorla LA, et al. Association of Poor Family Functioning From Pregnancy Onward With Preadolescent Behavior and Subcortical Brain Development. *JAMA Psychiatry*. Published online September 16, 2020. doi:10.1001/jamapsychiatry.2020.2862
9. Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. *Nat Rev Neurosci*. 2016;17(10):652-666. doi:10.1038/nrn.2016.111
10. Rogers JC, De Brito SA. Cortical and Subcortical Gray Matter Volume in Youths With Conduct Problems: A Meta-analysis. *JAMA Psychiatry*. 2016;73(1):64-72. doi:10.1001/jamapsychiatry.2015.2423
11. Thijssen S, Ringoot AP, Wildeboer A, et al. Brain morphology of childhood aggressive behavior: A multi-informant study in school-age children. *Cogn Affect Behav Neurosci*. 2015;15(3):564-577. doi:10.3758/s13415-015-0344-9
12. Guassi Moreira JF, Telzer EH. Family conflict is associated with longitudinal changes in insular-striatal functional connectivity during adolescent risk taking under maternal influence. *Dev Sci*. 2018;21(5):e12632. doi:10.1111/desc.12632
13. McCormick EM, Qu Y, Telzer EH. Adolescent neurodevelopment of cognitive control and risk-taking in negative family contexts. *NeuroImage*. 2016;124:989-996. doi:10.1016/j.neuroimage.2015.09.063
14. Luby JL, Belden A, Harms MP, Tillman R, Barch DM. Preschool is a sensitive period for the influence of maternal support on the trajectory of hippocampal development. *Proc Natl Acad Sci USA*. 2016;113(20):5742-5747. doi:10.1073/pnas.1601443113
15. Whittle S, Simmons JG, Dennison M, et al. Positive parenting predicts the development of adolescent brain structure: a longitudinal study. *Dev Cogn Neurosci*. 2014;8:7-17. doi:10.1016/j.dcn.2013.10.006
16. Kim-Spoon J, Maciejewski D, Lee J, Deater-Deckard K, King-Casas B. Longitudinal associations among family environment, neural cognitive control, and social competence among adolescents. *Dev Cogn Neurosci*. 2017;26:69-76. doi:10.1016/j.dcn.2017.04.009

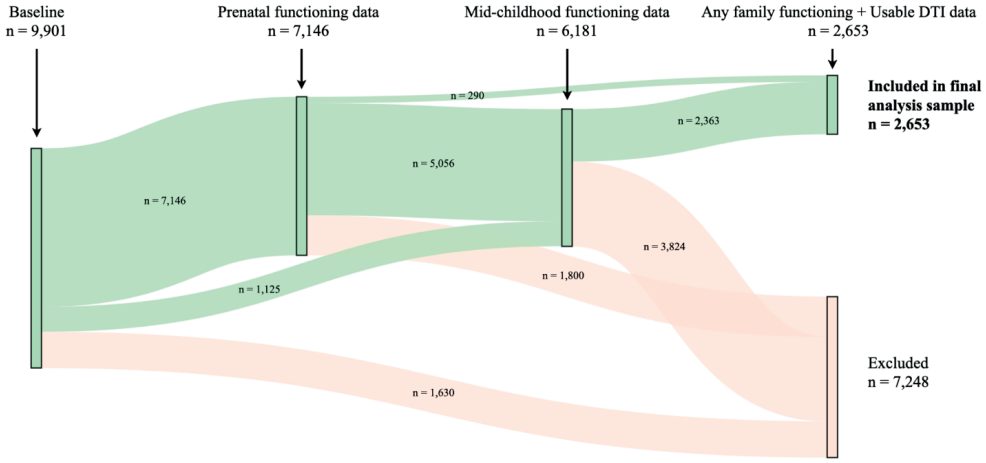
17. Qu Y, Fuligni AJ, Galvan A, Telzer EH. Buffering effect of positive parent-child relationships on adolescent risk taking: A longitudinal neuroimaging investigation. *Dev Cogn Neurosci*. 2015;15:26-34. doi:10.1016/j.dcn.2015.08.005
18. Holmes CJ, Barton AW, MacKillop J, et al. Parenting and Salience Network Connectivity Among African Americans: A Protective Pathway for Health-Risk Behaviors. *Biol Psychiatry*. 2018;84(5):365-371. doi:10.1016/j.biopsych.2018.03.003
19. Paus T, Pesaresi M, French L. White matter as a transport system. *Neuroscience*. 2014;276:117-125. doi:10.1016/j.neuroscience.2014.01.055
20. Lebel C, Deoni S. The development of brain white matter microstructure. *Neuroimage*. 2018;182:207-218. doi:10.1016/j.neuroimage.2017.12.097
21. Jensen SKG, Pangelinan M, Björnholm L, et al. Associations between prenatal, childhood, and adolescent stress and variations in white-matter properties in young men. *NeuroImage*. 2018;182:389-397. doi:10.1016/j.neuroimage.2017.10.033
22. Hanson JL, Knodt AR, Brigidi BD, Hariri AR. Lower structural integrity of the uncinate fasciculus is associated with a history of child maltreatment and future psychological vulnerability to stress. *Dev Psychopathol*. 2015;27(4 0 2):1611-1619. doi:10.1017/S0954579415000978
23. Rifkin-Graboi A, Meaney MJ, Chen H, et al. Antenatal Maternal Anxiety Predicts Variations in Neural Structures Implicated in Anxiety Disorders in Newborns. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2015;54(4):313-321.e2. doi:10.1016/j.jaac.2015.01.013
24. Deoni SCL, Dean DC, Piryatinsky I, et al. Breastfeeding and early white matter development: A cross-sectional study. *Neuroimage*. 2013;82:77-86. doi:10.1016/j.neuroimage.2013.05.090
25. Bick J, Zhu T, Stamoulis C, Fox NA, Zeanah C, Nelson CA. Effect of early institutionalization and foster care on long-term white matter development: a randomized clinical trial. *JAMA Pediatr*. 2015;169(3):211-219. doi:10.1001/jamapediatrics.2014.3212
26. Waller R, Dotterer HL, Murray L, Maxwell AM, Hyde LW. White-matter tract abnormalities and antisocial behavior: A systematic review of diffusion tensor imaging studies across development. *Neuroimage Clin*. 2017;14:201-215. doi:10.1016/j.nicl.2017.01.014
27. Bolhuis K, Muetzel RL, Stringaris A, et al. Structural Brain Connectivity in Childhood Disruptive Behavior Problems: A Multidimensional Approach. *Biol Psychiatry*. 2019;85(4):336-344. doi:10.1016/j.biopsych.2018.07.005
28. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol*. 2016;31(12):1243-1264. doi:10.1007/s10654-016-0224-9
29. White T, Muetzel RL, El Marroun H, et al. Paediatric population neuroimaging and the Generation R Study: the second wave. *Eur J Epidemiol*. 2018;33(1):99-125. doi:10.1007/s10654-017-0319-y
30. Epstein NB, Baldwin LM, Bishop DS. The McMaster Family Assessment Device. *Journal of Marital and Family Therapy*. 1983;9(2):171-180. doi:10.1111/j.1752-0606.1983.tb01497.x
31. Byles J, Byrne C, Boyle MH, Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process*. 1988;27(1):97-104.
32. Boterhoven de Haan KL, Hafekost J, Lawrence D, Sawyer MG, Zubrick SR. Reliability and validity of a short version of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process*. 2015;54(1):116-123. doi:10.1111/famp.12113
33. Wenniger WFM d. B, Hageman WJJM, Arrindell WA. Cross-national validity of dimensions of family functioning: First experiences with the Dutch version of the McMaster Family Assessment Device (FAD). *Personality and Individual Differences*. 1993;14(6):769-781. doi:10.1016/0191-8869(93)90090-P

34. Muetzel RL, Blanken LME, van der Ende J, et al. Tracking Brain Development and Dimensional Psychiatric Symptoms in Children: A Longitudinal Population-Based Neuroimaging Study. *Am J Psychiatry*. 2018;175(1):54-62. doi:10.1176/appi.ajp.2017.16070813
35. de Groot M, Vernooij MW, Klein S, et al. Improving alignment in Tract-based spatial statistics: evaluation and optimization of image registration. *Neuroimage*. 2013;76:400-411. doi:10.1016/j.neuroimage.2013.03.015
36. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*. 2006;31(4):1487-1505. doi:10.1016/j.neuroimage.2006.02.024
37. Lebel C, Beaulieu C. Longitudinal Development of Human Brain Wiring Continues from Childhood into Adulthood. *J Neurosci*. 2011;31(30):10937-10947. doi:10.1523/JNEUROSCI.5302-10.2011
38. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed*. 2002;15(7-8):435-455. doi:10.1002/nbm.782
39. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med*. 1983;13(3):595-605.
40. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. *Biometrika*. 1986;73(3):751-754. doi:10.1093/biomet/73.3.751
41. Rubin DB. Multiple Imputation After 18+ Years. *Journal of the American Statistical Association*. 1996;91(434):473-489. doi:10.2307/2291635
42. Von Der Heide RJ, Skipper LM, Klobusicky E, Olson IR. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. *Brain*. 2013;136(Pt 6):1692-1707. doi:10.1093/brain/awt094
43. Purves D, Augustine GJ, Fitzpatrick D, et al. The Major Afferent Pathway for Mechanosensory Information: The Dorsal Column-Medial Lemniscus System. In: *Neuroscience. 2nd Edition*. ; 2001. Accessed February 6, 2020. https://www.ncbi.nlm.nih.gov/books/NBK11142/
44. Huang H, Xue R, Zhang J, et al. Anatomical Characterization of Human Fetal Brain Development with Diffusion Tensor Magnetic Resonance Imaging. *J Neurosci*. 2009;29(13):4263-4273. doi:10.1523/JNEUROSCI.2769-08.2009
45. Nobles J, Hamoudi A. Detecting the Effects of Early-Life Exposures: Why Fecundity Matters. *Popul Res Policy Rev*. 2019;38(6):783-809. doi:10.1007/s11113-019-09562-x
46. Vos SB, Jones DK, Viergever MA, Leemans A. Partial volume effect as a hidden covariate in DTI analyses. *Neuroimage*. 2011;55(4):1566-1576. doi:10.1016/j.neuroimage.2011.01.048

APPENDIX OF SUPPLEMENTAL INFORMATION

Section 1.

Supplement Figure 1.



Supplement Table 1. Bases for excluding participants from analysis sample.

1,630	Missing both prenatal and mid-childhood family functioning data
4,063	No MRI / DTI scan data
1,282	Unusable DTI scan (poor quality image)
12	Incidental finding on MRI scan
8	In utero exposure to heroin or cocaine
55	Missing DTI data for some tracts
162	Outlier DTI data
36	Randomly selected twin removed
7,248	**Total excluded participants**

Section 2. Brain imaging details.

All MRI and DTI brain scans were acquired by a GE MR-750W scanner (General Electric Healthcare, Chicago, IL) at 3T with an eight-channel head coil.[29] Sequence parameters included 2 mm isotropic resolution and 35 diffusion-weighted volumes. Study staff preprocessed the resulting images using the FMRIB Software Library (FSL), version 5.0.9, which stripped non-brain tissue, corrected for artifacts from eddy currents and head motion, and fit a diffusion tensor to each voxel using the RESTORE method from the Camino diffusion MRI toolkit. This pipeline calculated fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) metrics for each voxel.

Next, study researchers conducted fully automated probabilistic fiber tractography on each participant's diffusion-weighted image in native space using the AutoPtx plugin for FSL.[35] This method generates subject-specific, probabilistic representations of 27 large white matter tracts that can be consistently and robustly identified across brain regions. The process identifies each tract's connectivity distribution, normalizes it given the number of successful seed-to-target attempts, and then removes voxels unlikely to be part of the tract's distribution. Thereafter, the process automatically computes tract-specific scalar metrics (MD, FA, AD, RD) of microstructural properties by weighting voxel-specific metrics by the probability that each voxel is part of the specific tract. To ensure the quality of all scans and reconstructions, researchers visually inspected all raw images and examined signal intensity in each slice to assess attenuation by various artifacts. They also visually inspected all probabilistic tractography data. Scans deemed poor at any point in the quality control process were excluded from analysis.

Section 3. Outlier analyses.

We assessed statistical outliers in four measures of white matter microstructure: tract-specific MD, FA, AD, and RD. Though our primary outcomes are composite MD and FA metrics, we included AD and RD outcomes in the outlier analyses because they are based more directly on tensor eigenvalues describing diffusion anisotropy than MD and FA and therefore may be less likely to obscure extreme values. For example, while MD is the mean of all three tensor eigenvalues (λ_1, λ_2, and λ_3), RD is merely the mean of two (λ_2 and λ_3), and AD is simply λ_1, where $\lambda_1 > \lambda_2 > \lambda_3$.

In our first outlier identification strategy, we excluded participants with any tract-specific MD, FA, AD, or RD value greater than 5 standard deviations from the mean value for each respective tract because such values are either (1) biologically implausible or (2) so far from the sample means that they likely represent significant pathology or brain structural abnormality. Next, we calculated jackknife residuals of minimally adjusted models for the associations between prenatal and mid-childhood family functioning and tract-specific MD, FA, AD, and RD outcomes. Using Tukey's formula, we then excluded participants with any jackknife residual beyond Tukey's outer fences, i.e., greater than a cutoff value at 3 interquartile ranges above the respective residual distribution's 75th percentile or below its 25th percentile. When this test identified statistical outliers, we re-ran the original models after excluding the outliers and repeated diagnostic testing until the process revealed no additional outlier values. Finally, we visually inspected quantile-quantile plots of all outcomes and excluded any remaining participants with outlier outcome metrics.

Section 4. Inverse probability of attrition weights.

We defined participants lost to follow up as those enrolled at baseline (either prior to or at birth) but excluded from our analysis sample for any reason. To calculate our IPWs, we identified a broad set of variables theorized to predict who among originally enrolled participants satisfied our inclusion criteria. We used multiple imputation by chained equations (regression models for continuous dependent variables; predictive mean matching for all other variables, knn = 10, burn-in = 25) to address missing data in these variables, resulting in 50 imputed datasets. Thereafter, we fit a logistic regression model using these variables to predict the likelihood of each enrolled participant's inclusion in our analysis sample. The predictive accuracy of this model yielded an area under the receiver operating characteristic curve (AUC of ROC curve) of 0.800 (SE = 0.005). Last, we calculated IPWs for use in later analyses. Unstabilized weights had a mean of 3.40 and ranged from 1.00 to 22.72.

Section 5. Multiple imputation models.

We imputed missing exposure and covariate data. The proportion of missing data for most covariates was low to moderate (e.g., 12% for paternal age at birth), with the exception of household income, for which we were missing 20% of data. We used the 'mi impute chained' package in Stata 16.0/MP. For continuous variables, we specified linear OLS regression models. For ordinal and categorical variables, we specified predictive mean matching models, knn = 10 (i.e., 10 donor values). We specified a 25-iteration burn-in period for each chain to ensure convergence to a stationary distribution. Models included all outcomes as right-hand side variables with no missing data. We imputed 50 imputed datasets and combined the resulting estimates using Rubin's Rules.[41]

Section 6. Mean FA and MD values by sociodemographic characteristics.

On average, girls had lower global MD and FA scores than boys (p-values < 0.001 for both outcomes). European children had higher global FA values than children of other ethnicities (p < 0.001). Children of more socially advantaged households had higher global FA values than their less advantaged counterparts (p = 0.002 and < 0.001 for parental education and household income, respectively). No differences in global MD by ethnicity, parental education, or household income were evident.

Supplement Section 6. Distribution of standardized outcome measures by participant characteristics in the final analytic sample. n = 2,653.

	%	Mean Global FA	*p*	Mean Global MD	*p*
Total Sample	100	0.00		0.00	
Child biological sex			< 0.001		< 0.001
Female	51	-0.11		-0.13	
Male	49	0.11		0.13	
Child race / ethnicity / country of origin			< 0.001		0.229
Dutch / Other European	71	0.06		-0.01	
Turkish	5	-0.21		0.04	
Moroccan	4	-0.13		0.21	
Surinamese	7	-0.24		0.00	
Other	13	-0.10		0.01	
Highest Household Education			0.002		0.484
Less than high school equivalent	4	-0.11		-0.08	
High school or intermediate vocational trainin	33	-0.07		-0.03	
Adv. vocational training, bachelor's, or higher	63	0.07		0.01	
Household Income			< 0.001		0.955
€2200 / month or less	35	-0.12		0.00	
More than €2200 / month	65	0.06		0.00	

1. This table is based on observed values for each characteristic and does not account for missing data.
2. p-values are from one-way ANOVA F-tests for differences in outcomes by each respective participant characteristic.

Section 7. Global axial diffusivity and global radial diffusivity.

Supplement Section 7. Associations between family functioning and global measures (AD and RD) of white matter microstructure in preadolescence.

		Axial Diffusivity			Radial Diffusivity		
		β	95% CI	*p*	β	95% CI	*p*
Prenatal Family Functioning							
Min. adjusted	Unweighted	-0.01	(-0.09, 0.08)	0.90	-0.13	(-0.22, -0.04)	< 0.01
Fully adjusted	Unweighted	-0.07	(-0.17, 0.02)	0.13	-0.14	(-0.23, -0.04)	< 0.01
Fully adjusted	Weighted	-0.07	(-0.20, 0.06)	0.29	-0.15	(-0.26, -0.03)	0.01
Mid-Childhood Family Functioning - Baseline Unadjusted							
Min. adjusted	Unweighted	0.00	(-0.10, 0.09)	0.95	0.00	(-0.10, 0.09)	0.96
Fully adjusted	Unweighted	-0.03	(-0.12, 0.07)	0.56	0.00	(-0.10, 0.10)	0.99
Fully adjusted	Weighted	-0.04	(-0.16, 0.09)	0.57	0.02	(-0.10, 0.14)	0.74
Mid-Childhood Family Functioning - Baseline Adjusted							
Min. adjusted	Unweighted	0.00	(-0.10, 0.10)	0.99	0.05	(-0.05, 0.15)	0.30
Fully adjusted	Unweighted	-0.01	(-0.11, 0.09)	0.80	0.05	(-0.06, 0.15)	0.38
Fully adjusted	Weighted	-0.03	(-0.16, 0.10)	0.68	0.06	(-0.06, 0.18)	0.29

1. Minimally adjusted models include covariates for child age at scan, sex, and ethnicity.
2. Fully adjusted models account for child age at scan, biological sex, ethnicity, household income, highest level of parental education achieved, maternal and partner history of psychosis, prenatal maternal and partner psychopathology symptoms (for prenatal models), early-childhood maternal and partner psychopathology symptoms (for mid-childhood models), maternal age at child's birth, and child in utero exposure to smoking.
3. Global measures are standardized mean values of weighted-average AD and RD across all 27 tracts delineated by AutoPtx.

Section 8. Prenatal functioning score and tract-specific MD and FA.

Supplement Section 8. Weighted associations between prenatal family functioning and tract-specific measures of white matter microstructure.

	Fractional Anisotropy			Mean Diffusivity		
	β	95% CI	*p*	β	95% CI	*p*
Association Fibers						
Superior Longitudinal Fasciculus	0.10	(-0.02, 0.22)	0.11	-0.07	(-0.20, 0.05)	0.24
Inferior Longitudinal Fasciculus	0.06	(-0.06, 0.17)	0.31	-0.07	(-0.18, 0.05)	0.25
Inferior Fronto-Occipital Fasciculus	-0.02	(-0.15, 0.10)	0.68	-0.03	(-0.15, 0.10)	0.68
Uncinate Fasciculus	0.00	(-0.12, 0.12)	0.99	-0.17	(-0.30, -0.05)	< 0.01 *
Limbic System Fibers						
Cingulum (Cingulate Gyrus Part)	0.02	(-0.09, 0.13)	0.75	-0.12	(-0.24, -0.00)	0.04
Cingulum (Parahippocampal Part)	0.10	(-0.02, 0.21)	0.09	-0.14	(-0.26, -0.02)	0.02
Projection Fibers						
Corticospinal Tract	0.13	(0.02, 0.24)	0.03	-0.03	(-0.16, 0.09)	0.59
Acoustic Radiation	0.04	(-0.08, 0.17)	0.49	-0.06	(-0.18, 0.06)	0.32
Anterior Thalamic Radiation	0.04	(-0.08, 0.16)	0.55	-0.08	(-0.21, 0.04)	0.19
Superior Thalamic Radiation	0.07	(-0.05, 0.19)	0.24	-0.09	(-0.21, 0.03)	0.15
Posterior Thalamic Radiation	-0.02	(-0.14, 0.10)	0.74	0.00	(-0.12, 0.12)	0.99
Callosal Fibers						
Forceps Major	0.08	(-0.05, 0.20)	0.23	-0.12	(-0.25, 0.01)	0.07
Forceps Minor	0.07	(-0.04, 0.19)	0.21	-0.07	(-0.19, 0.05)	0.26
Brainstem Tracts						
Middle Cerebellar Peduncle	0.09	(-0.03, 0.21)	0.14	-0.01	(-0.13, 0.11)	0.91
Medial Lemniscus	0.22	(0.11, 0.33)	< 0.001 *	-0.20	(-0.32, -0.08)	< 0.01 *

1. Fully adjusted models account for child age at scan, sex, ethnicity, household income, highest level of parental education achieved, maternal and partner history of psychosis, maternal and partner psychopathology symptoms, maternal age at child's birth, and child in utero exposure to smoking.

2. MD and FA values are averaged across hemispheres where appropriate and standardized.

** Starred results remain statistically signficant after adjustment for multiple comparisons.*

Section 9. Prenatal functioning and global FA and MD – spline model results.

Supplement Section 9. Piecewise continuous linear spline model results for the association between prenatal family functioning, global MD, and global FA.

Global mean diffusivity

	Pre-knot slope		Post-knot slope	
Knot	β	95% CI	β	95% CI
No knot	-0.13	(-0.25, -0.02)	-0.13	(-0.25, -0.02)
3.0	-0.21	(-0.54, 0.11)	-0.10	(-0.26, 0.05)
2.9	-0.24	(-0.62, 0.14)	-0.10	(-0.25, 0.04)
2.8	-0.25	(-0.70, 0.19)	-0.11	(-0.25, 0.03)
2.7	-0.23	(-0.76, 0.30)	-0.12	(-0.26, 0.02)
2.6	-0.26	(-0.89, 0.36)	-0.12	(-0.25, 0.01)
2.5	-0.39	(-1.12, 0.33)	-0.11	(-0.24, 0.01)

Global fractional anisotropy

Knot	β	95% CI	β	95% CI
No knot	0.10	(-0.01, 0.21)	0.10	(-0.01, 0.21)
3.0	0.20	(-0.09, 0.49)	0.07	(-0.09, 0.22)
2.9	0.20	(-0.13, 0.53)	0.08	(-0.07, 0.22)
2.8	0.23	(-0.15, 0.61)	0.08	(-0.06, 0.22)
2.7	0.31	(-0.12, 0.73)	0.07	(-0.06, 0.21)
2.6	0.42	(-0.05, 0.91)	0.07	(-0.06, 0.20)
2.5	0.59	(0.05, 1.13)	0.06	(-0.06, 0.19)

1. Fully adjusted models account for child age at scan, biological sex, ethnicity, household income, highest level of parental education achieved, maternal and partner history of psychosis, maternal and partner psychopathology symptoms, maternal age at child's birth, and child in utero exposure to smoking.
2. The post-knot β is the estimated absolute slope, i.e., not merely the change in slope relative to the pre-knot β.

Chapter 6

The interrelation of maternal and paternal hostility with both child and parent brain morphology in the association with child aggressive behavior. A population-based neuroimaging study

Yllza Xerxa, Sander Lamballais, Ryan L. Muetzel, M. Arfan Ikram, Henning Tiemeier

Manuscript to be submitted for publication

ABSTRACT

Background: Parental hostility is associated with differential aspect of child and family functioning including high levels of parental conflict, depression, and parental-child relationship quality. In children, parental hostility can lead to prolonged disruption in emotional security and heightened levels of aggression. However, little is known whether parental hostility is associated with long-term disruption on parents and child brain using magnetic resonance imaging (MRI).

Objectives: We aimed to investigate the degree to which associations of prenatal and childhood parental hostility would be associated with differences in maternal, paternal and child brain structure if analyzed together, i.e. as triads.

Methods: This population-based cohort study was embedded in Generation R, a multiethnic population-based cohort from fetal life onward. Mother- and father-rated hostility was repeatedly measured by the Brief Symptom Inventory. High-resolution structural neuroimaging data of children aged 10 years, and the parental brain (mothers M_{age} = 41.6, and fathers M_{age} = 43.6), were collected with a single 3-T magnetic resonance imaging system. Child aggressive behavior were assessed with the Child Behavior Checklist.

Results: Prenatal maternal-reported hostility but not mid- or late childhood was associated with smaller total white matter, gray matter, and hippocampal volumes in adolescents. Our findings highlight the role of each parent's ability to transpire hostile behaviors to his or her partner and the child. The contribution of prenatal parental hostility to child aggressive behavior was partially mediated by both hippocampal volumes of children and, importantly, also of mothers.

Conclusion: This population-based neuroimaging study suggests that parental hostility from pregnancy onward is associated not only with differences in the behavior of other family members but also their brain morphology.

INTRODUCTION

Parental hostility is defined as an overt behavior and communication between parents and children characterized by arguing, angry comments, contempt, yelling, swearing, name-calling and or physical aggression.[1,2] Hostile behavior of a parent is associated with different aspects of child and family functioning including high levels of parental conflict, depression, and parental-child relationship quality. In children, parental hostility can lead to prolonged disruption in emotional security and heightened levels of aggression.[3,4] which in turn increases the risk for a wide variety of other negative mental health outcomes.[5,6] Children exposed to family hostility appear to live in a state of chronic psychological stress[7] and recent evidence suggests that this may be associated with disruption in brain development.[8] Although the interest on the effects of parental hostility and child adjustment dates back to early 20th century, the parent and child brain affected by early-life events is a recent area of inquiry. Brain imaging studies can deepen our understanding of the neurobiological underpinnings of parent-child functioning.

Reviews of the literature within the framework of 'risky' family environments have shown that aggression, conflict, and disengagement in the family, parent-child, or interparental context are risk factors for the persistence of negative mental health outcomes.[9,10] Parental hostility often co-occurs in the parents.[4] This can be due to socio-economic and other demographic factors, assortative mating, and one parent's hostility may induce the other parent's hostility. Research suggests that what transpires in one family subsystem, e.g. hostility among parents, is related to what transpires in other subsystems, e.g. mother-child or father-child, and can negatively child development, either directly or indirectly.[11] A large body of evidence shows that family relationships function as unitary systems and are built on the ongoing transactions between family members.[12,13] Childhood behavioral problems, and in particular aggression, are often the result of interparental conflict and interrelated parental psychopathology.[14] When one parent is hostile, the child is at risk developmentally; when both parents are hostile, the risk increases further.[15] Although mothers and fathers have different kinds of relationships with children that evoke different behaviors,[16] one parent's hostility is thus likely to affect all members of the family and relationships within family.

Functional imaging studies suggest that stress and psychopathology in mothers after the birth of a child correlate with pronounced long-term changes in the mother's brain.[17,18] Differences are most marked in the limbic and frontotemporal brain structures implicated in maternal motivation and behaviors. The amygdala and the hippocampus are two major components of the limbic system implicated in learning, memory, and emotion.[19] A recent study that assessed brain-to-brain synchrony between mothers and their children at age 3-4 and its association with stress suggests that higher parenting stress experienced

by mothers associated with reduced brain-to-brain synchrony.[20] Finally, research is beginning to address the effects of parenthood on the father's brain suggesting different and similar responses as found in mothers.[21] In 'risky families', parents and children often experience some form of psychopathology, and parents as well as children are likely to exhibit similar or different neuroendocrine, immunological, and cardiovascular correlates of persistent stress.[22] Thus, the environmental and biological changes that occur in pregnancy and early childhood may potentially be accompanied by maternal, paternal and offspring brain differences in specific brain areas such as limbic and frontotemporal brain regions.[17] While suggestive, previous brain imaging studies, however, did not examine these pathways of family psychopathology and disruption jointly in parents and children.

No study to date addressed the key question of whether parental hostility is associated with long-term disruption on parents and child brain using magnetic resonance imaging (MRI).

In the present study, we aimed to investigate the degree to which associations of prenatal and childhood parental hostility would be associated with differences in maternal, paternal and child brain structure if analyzed together, i.e. as triads. In addition, we investigated whether the associations between parental hostility and child brain morphology differed between mothers and fathers. We examined both global brain outcome measures including total gray and cerebral white matter volumes, and hippocampal and amygdala volumes. The current study had three main aims. First, we aimed to examine the associations of parental hostility measured repeatedly over time with child brain development. Second, we aimed to examine whether each parent's hostility would be associated with differences in parental brain structure outcomes (within-parent analyses), and whether these associations would be associated with his or her partner's brain characteristics (across parent analyses). Our third aim was to investigate to what extent the persistent association of prenatal parental hostility with preadolescent aggressive behavior is mediated by subcortical brain volumes of mothers, fathers, or children.

Methods

Participants

Data were collected 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.[23] Briefly, all pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. Neuroimaging data were obtained for 3,937 children from the late-childhood (M_{age} = 10 years) assessment wave from 2012 till 2015.[24] We excluded 657 children with poor imaging data (n = 638) quality or incidental findings (n = 19).[25] Between 2017

and 2019, neuroimaging data for parents were obtained as part of the Generation R Parent Scan Study. T_1-weighted data were available for 958 parents (630 mothers, 328 fathers/partners). We excluded 30 parents because of insufficient quality of the scans. Of the remaining 605 mothers and 323 fathers, those with no data on parental hostility or missing partner imaging (409 mothers and 127 fathers) were excluded. That is, all individuals were nested within families. For the current study, families were included if mother, father and their child had neuroimaging data in a triadic family. The final sample consisted of 196 mother-father-child triads (Supplementary Figure 1).

The study was conducted in accordance with the guidelines as set by the World Medical Association Declaration of Helsinki. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam (registration number MEC 02.1015). Written informed consent was obtained from all adult participants and from both the parents of minors.

Parental hostility

Parental hostility was assessed with the Brief Symptom Inventory (BSI). Mothers and fathers reported their hostile symptoms at 20 weeks pregnancy and again when their child was 3 and 10 years old. The BSI is widely used instrument to measure self-reported psychological symptoms in samples of psychiatric patients and community non-patients.[24] We used the hostility subscale of the BSI, a validated self-report questionnaire answered on a five-point scale, ranging from 0 = 'not at all' to 4 = 'extremely'.[26,27] This instrument encompasses symptom dimensions covering clinically relevant psychiatric and psychosomatic symptoms.[26] The hostility subscale consists of 5 items: "easily becoming bored or feeling irritable", "uncontrollable bursts of anger", "an urge to hit, injure or cause pain to others", "an urge to damage or break things", and "often getting involved in arguments". High validity and reliability were reported for the Dutch translation.[28] In the current study, internal consistencies (Cronbach's alpha) for parental hostility ranged from 0.60 to 0.71.

Child aggressive behavior

The Child Behavior Checklist for older children (CBCL/6-18)[29,30] was used to obtain standardized parent report s of children's problem behaviors. The CBCL/6-18 contains 118 problems items. 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. We used the continuous Aggressive Problems score at age 10 as outcome measure, which comprised items such as: "My child gets in many fights", and "My child destroys others' things". This scale consists of 19 items scored on a three-point Likert scale, in our sample (α = .85). Good reliability and validity have been reported for the CBCL/6-18.[29] The scales were generalizable across 23 societies, including the Netherlands.[31]

Image Acquisition

Neuroimaging data were acquired with a 3 Tesla GE Discovery MR750w MRI System (General Electric, Milwaukee, WI, USA) and an 8-channel receive-only head coil.[24] T_1-weighted images were acquired in the children with a coronal inversion recovery fast spoiled gradient recalled sequence (T_R = 8.77 ms, T_E=3.4 ms, T_I = 600 ms, flip angle = 10°, field of view = 220 mm × 220 mm, acquisition matrix = 220 × 220, slice thickness = 1 mm, number of slices = 230). The parental images were collected with a similar sequence but with an axial orientation.[32]

Morphological Image Processing

The T_1-weighted images were processed through the FreeSurfer analysis suite, version 6.0. The details of the processing steps for the child data have been described elsewhere[33], and the parental images were processed with the exact same protocol. 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. Global metrics of volume were extracted (e.g., total brain volume and subcortical volume), and a number of cortical and subcortical structures (amygdala, hippocampus, etc.) were automatically labeled. All measures were averaged across the left and right hemispheres. Surface reconstructions were visually inspected for accuracy and data not suitable for statistical analysis were excluded.[33] We also used a metric of image quality which automatically characterizes the amount of motion/artifact based on signal intensities outside of the brain.[34]

Covariates

Child and parental age at MRI (based on date of birth) and sex were obtained from birth records. Maternal and paternal age were assessed at intake. Parental ethnicity was categorized into three groups: Dutch, other Western, and non-Western national origin.[35] 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 during pregnancy (three categories: no smoking; smoked until pregnancy recognized; and continued smoking), alcohol intake during pregnancy (four categories: no alcohol consumption; alcohol consumption until pregnancy recognized; continued occasionally (<1 glass/week); and continued frequently (>=1 glass/week)) was assessed prenatally using self-report questionnaires.

Statistical Analysis

To study the associations of parental hostility and structural brain morphology of both parent and children, we have primarily created a data file in which mother, father, and child were treated as a family unit.[36] That means, we focused on the triads of mother,

father, and child. Analyses defined the parental hostility measures paired with each other as independent variables and maternal, paternal, and children brain measures (including total white matter, gray matter, hippocampus or amygdala volumes) as the dependent variables (i.e., all individuals were nested within families).

In a first step, however, we examined in separate linear regressions the associations of maternal and paternal reported hostility during pregnancy and ages 6 and 10 with parents and child brain measures to examine period-specific exposure associations. In all models, we adjusted for age of the parents at baseline, but performed no additional adjustment for parental age at MRI scan as the results remained essentially unchanged.

We then used structural equation models (SEM) path analysis to test whether maternal and paternal hostility from pregnancy onward is associated with maternal, paternal, and child brain morphology. The general strategy in specifying path models with triadic data is that each parent's hostility score used as predictor variable for her or his own outcomes, her or his partner's outcomes, as well as child outcomes, i.e., brain structures. We correlated all variables across triad members, and correlations across parents (i.e., maternal and paternal hostility) were added to the model (Supplementary Table 5). Maternal, paternal, and child brain outcomes were not nested within one family score. As such, we examined the extent to which one parent hostility is associated independently of the other parent's and child brain morphology.

The parameter estimates were used to create a variance-covariance matrix among the observed variables. The fit of the model was tested by comparing this variance-covariance matrix with a chi-square test based on parent's hostility and parent and child brain discrepancies. We performed all models adjusting for the confounders described above and intracranial volume.

Finally, we examined whether brain morphology of mothers, fathers, or children mediated the association between prenatal maternal- and paternal-reported hostility and preadolescent aggressive behavior at age 10 years. No association were found between parental hostility and child amygdala volumes. Based on the results, we only examined mediation for the hippocampus, a subcortical brain measure in the relation between parental hostility and preadolescent aggressive behavior related. The mediation analysis framework provides estimates of the natural direct effect, the natural indirect effect, and the total effect.[37] All models were adjusted for baseline confounders and child aggressive behavior when the child was 1.5 years old to help rule out a reverse association.[38] A latent construct based on maternal and paternal hostility reported by mothers and fathers was used in relation with child hippocampal volume and aggressive behavior (Methods in the Supplement).

False Discovery Rate (FDR) was applied to adjust for multiple comparisons.[39] We adjusted for multiple hypothesis testing of 3 outcomes such as maternal, paternal, and child brain structures (total white matter, gray matter, hippocampus or amygdala volumes), and the 3 relevant exposure periods (prenatal mid- and late childhood) in the multiple testing correction (9 comparisons). The unstandardized β coefficients (B) and 95% confidence intervals (CIs) were calculated. All analyses were performed using SAS 9.4 software.

Results

The descriptive sample characteristics regarding triadic parental socio-economic factors, child and parental age at the MRI are described in Table 1. The mean age of the children at scanning was 10.1 years (standard deviation (SD) = 0.6). Half (49.1%) of the children were boys. In total, 28.1% of mothers and 24.9% of fathers had a non-Western national origin. The mean age of the mothers at scanning was 41.6 years (SD = 23.5); fathers were 43.6 years (SD = 17.9).

Table 1. Child and parents' sociodemographic characteristics (N = 196 triads).

	Mother	Father
Age, M (SD)	31.1 (4.7)	33.5 (5.3)
Ethnicity		
Dutch, (%)	62.6	69.3
Other Western, (%)	9.3	5.8
Non Western, (%)	28.1	24.9
Education level		
High, (%)	42.9	50.7
Middle, (%)	45.9	41.0
Low, (%)	11.2	8.3
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	
Parents' age at the MRI scan, years, M (SD)	41.6 (23.5)	43.6 (17.9)
Child sex, (% boy)	49.1	
Child age at the MRI scan, years, M (SD)	10.1 (0.6)	

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 hostility with parent and child brain morphology

The associations of the child's exposure to parental hostility with brain morphology are shown in Supplementary Table 1 and 2. Prenatal maternal but not paternal hostility was associated with differences in child white matter, gray matter, as well as hippocampus volumes. In contrast, in mid- or late-childhood parental hostility scores was not related to any brain measure in fully adjusted models. Mothers and fathers with higher levels of hostility during offspring pregnancy or early childhood had smaller white matter, gray matter, amygdala and hippocampal volumes (Supplementary Table 3 and 4).

Parental hostility and child brain morphology

In the triadic model, the association of maternal and paternal hostility from pregnancy onward were examined in relation to children's brain structures. We observed that prenatal maternal but not paternal hostility was associated with differences in child cortical white matter volumes (B = -0.05; 95% CI, -0.07, -0.03) and gray matter volumes (B = -0.06; 95% CI, -0.08, -0.03) (Figure 1 and 2), as well as with smaller child hippocampal volumes after adjusting for intracranial volume (B = -0.03; 95% CI, -0.05, -0.02), (Figure 3). These associations survived multiple testing correction. In contrast, no associations were observed for mid- and late childhood mother hostility or any father hostility measure with the child's cortical white matter, gray matter, or hippocampal volumes. Adjusting for baseline confounders and parental smoking and alcohol consumption did not meaningfully change this association. No associations were observed between prenatal and early childhood parental hostility and child amygdala volume (Figure 4).

Parental hostility and parents brain morphology

Next, we found that maternal and paternal hostility measured during pregnancy and earlier child's life were associated with smaller white matter, gray matter, amygdala and hippocampal volumes of that parent (i.e., within-parent analyses). Moreover, both maternal and paternal hostility scores were associated with their partner's smaller white matter and gray matter volumes brain morphology 10 years later (across parent analysis) (Figure 1 and 2). However, no associations were observed between parental hostility with hippocampal and amygdala volumes of the partner (i.e., across parents)(Figure 3 and 4). That is, maternal and paternal hostility score were related to their own subcortical brain measures, but not partner's subcortical brain outcomes.

Taken together, these results indicate that the observed associations of maternal and paternal hostility co-occur and were related to individual differences of parent and child brain outcomes in the triadic model.

The associations between parental hostility and white matter microstructure for parents and children (N = 196 triads).

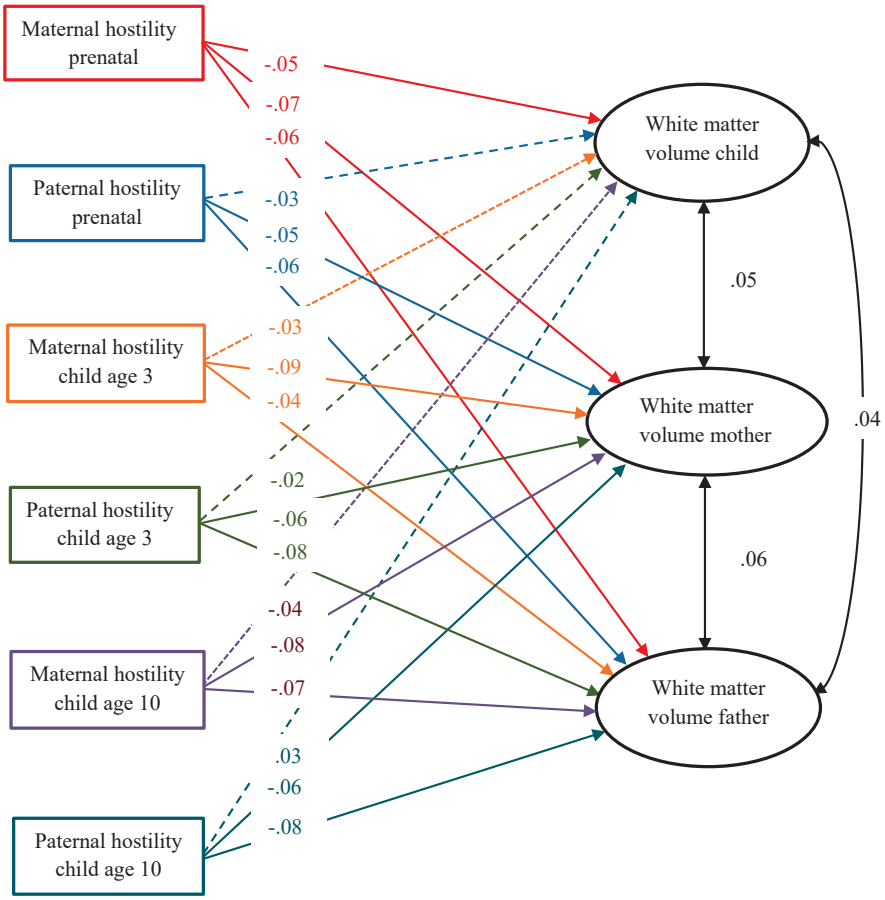


Figure 1. Structural equation modeling of parental hostility and cortical white matter volumes of parents and children. Numeric values are unstandardized path regression coefficients. Models are adjusted for child age at brain MRI scan, child sex, age, ethnicity and education, smoking and alcohol consumption reported by mother and father. The dotted line represents the non-significant associations. (RMSEA=0.01; CFI=0.97; TLI=0.90). Mother father-child triadic data (n = 196). Associations survived the false discovery rate correction for multiple testing. Number of tests = 3 outcomes and the 3 relevant exposure periods (prenatal, mid- and late childhood). Critical value for FDR = 0.05.

Mediation analysis

Lastly, we investigated the potential mediating role of hippocampal volumes of the mothers, fathers, and their children each separately in the association between prenatal parental hostility and child aggressive behavior at age 10. As Figure 5 illustrates, hippocampal volumes of the mother, but not the father, partially mediated the association of prenatal parental hostility (latent construct) and preadolescent aggressive behavior (B = 0.01; 6.25% of the total effect; 95% CI, 0.01, 0.03). In addition, we found evidence that smaller hippocampal volumes of the child also partly account of the observed pre-

The associations between parental hostility and cortical gray matter microstructure for parents and children (N = 196 triads).

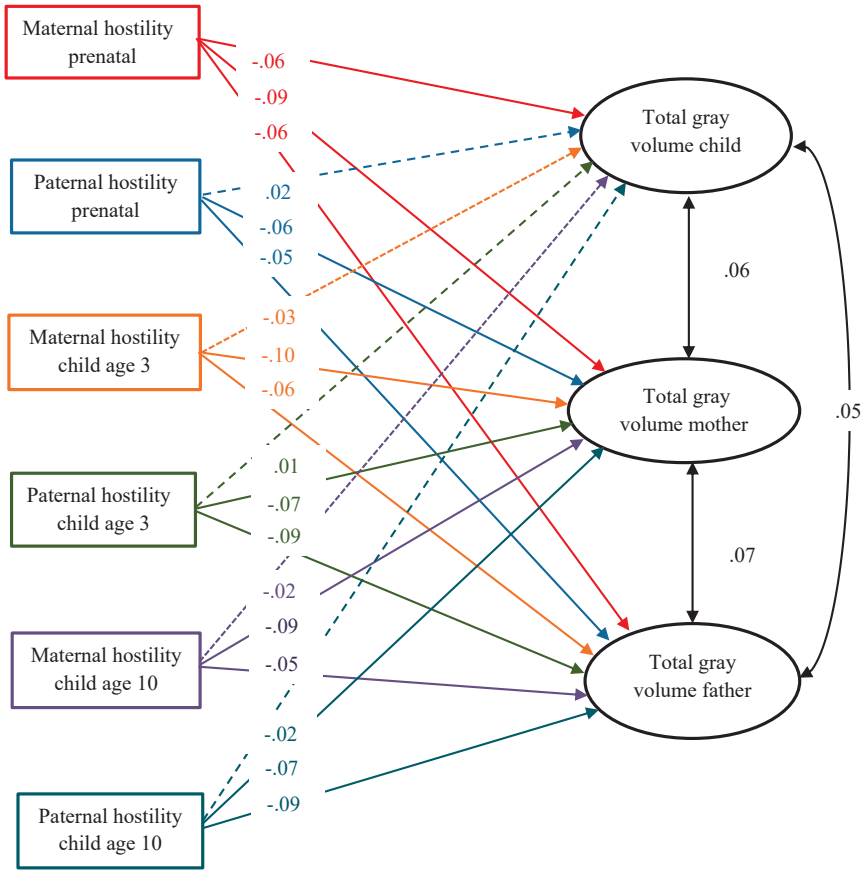


Figure 2. Structural equation modeling of parental hostility and cortical gray matter volumes of parents and children. Numeric values are unstandardized path regression coefficients. Models are adjusted for child age at brain MRI scan, child sex, age, ethnicity, education, smoking and alcohol consumption reported by mother and father. The dotted line represents the non-significant associations. (RMSEA=0.01; CFI=0.94; TLI=0.90). Mother father-child triadic data (n = 196). Associations survived the false discovery rate correction for multiple testing. Number of tests = 3 outcomes and the 3 relevant exposure periods (prenatal, mid- and late childhood). Critical value for FDR = 0.05.

adolescent problem behavior during late childhood (B = 0.02; 10% of the total effect; 95% CI, 0.01, 0.05). Additional adjustment for pre-existing child aggressive behavior at 1.5 years, resulted in no meaningful change in mediation results, suggesting that the behavioral changes did not precede the observed brain differences in the child.

The associations between parental hostility and hippocampus volume for parents and children (N = 196 triads).

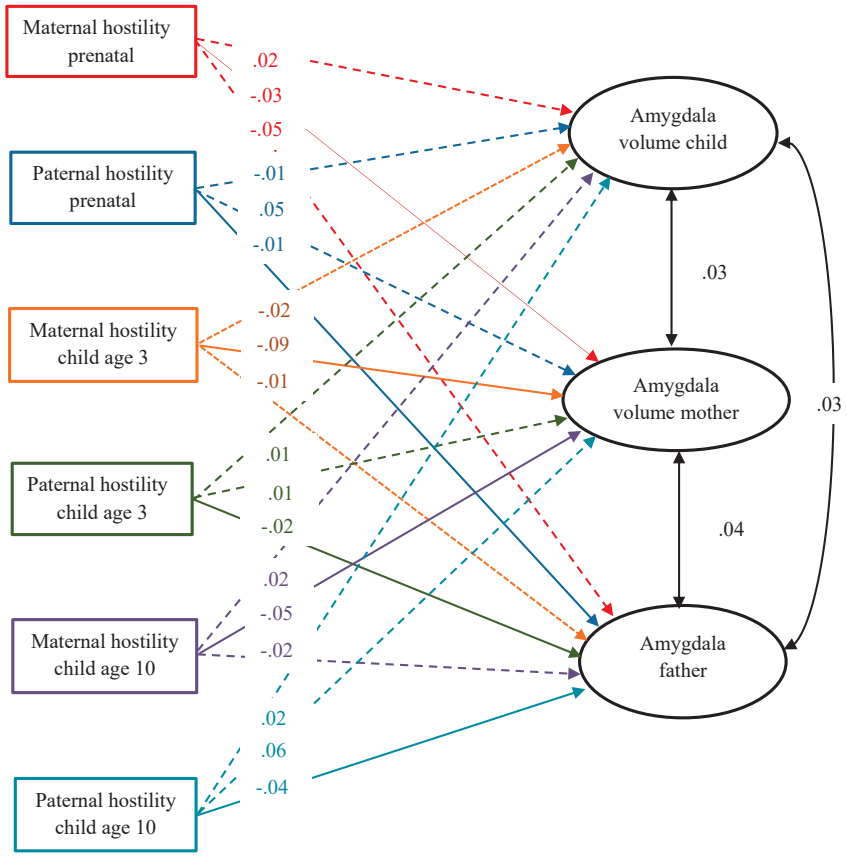


Figure 3. Structural equation modeling of parental hostility and hippocampus volumes of parents and children. Numeric values are unstandardized path regression coefficients. Models are adjusted for child age at brain MRI scan, child sex, total ICV, age, ethnicity, education, smoking and alcohol consumption reported by mother and father. The dotted line represents the non-significant associations. (RMSEA=0.01; CFI=0.95; TLI=0.90). Mother, father, and child triadic data (n = 196). Associations survived the false discovery rate correction for multiple testing. Number of tests = 3 outcomes and the 3 relevant exposure periods (prenatal, mid- and late childhood). Critical value for FDR = 0.05.

DISCUSSION

This population-based neuroimaging study suggests that parental hostility from pregnancy onward is associated not only with differences in the behavior of other family members but also their brain morphology. We highlight four main findings. First, we observed smaller total white matter, gray matter, and hippocampal volumes in children exposed to maternal hostility occurring during pregnancy. Second, our findings highlight the role of each parent's ability to transpire hostile behaviors to his or her partner and the child. Third, our results suggest that within parents, parental hostility

The associations between parental hostility and amygdala volumes for parents and children (N = 196 triads).

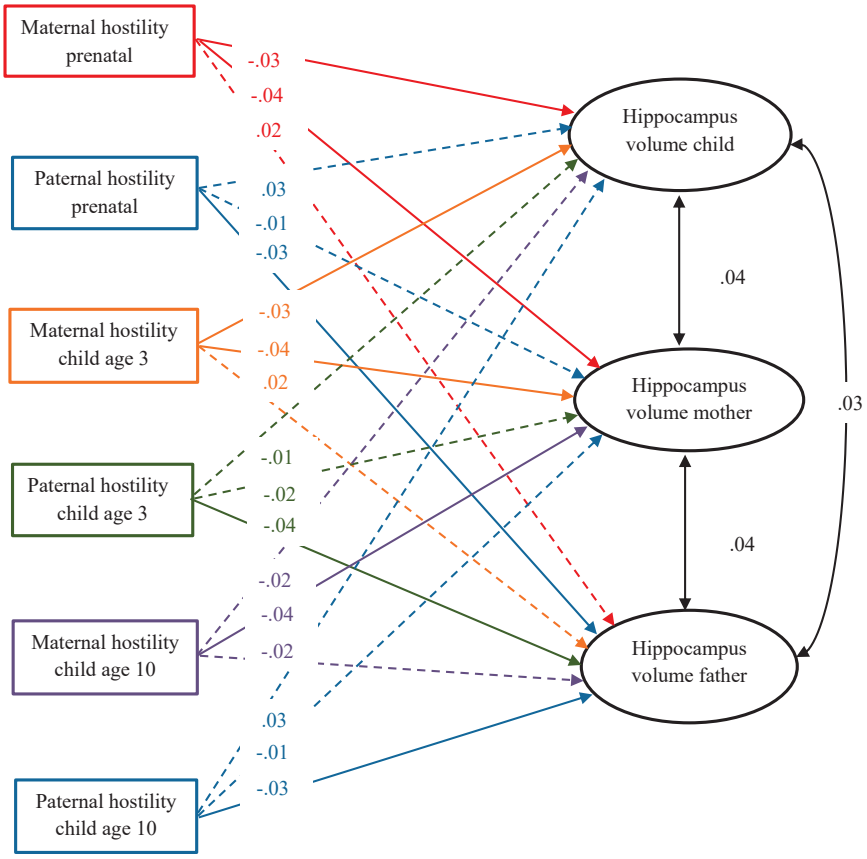
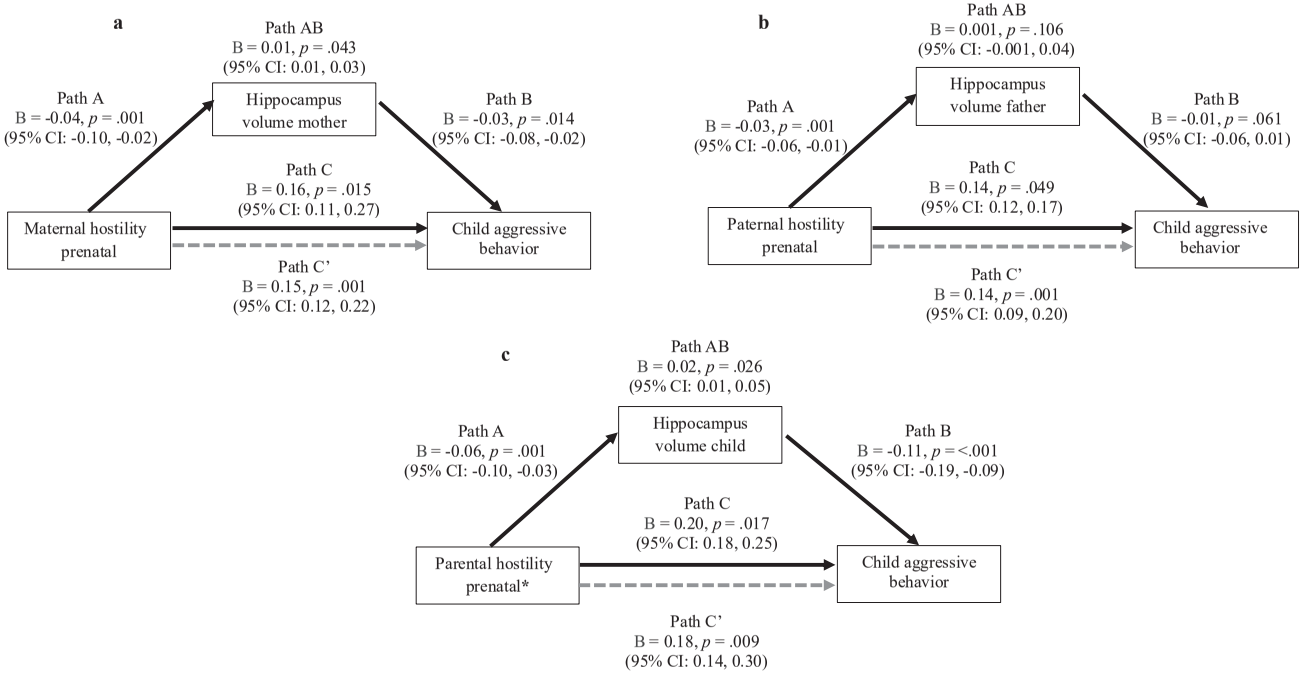


Figure 4. Structural equation modeling of parental hostility and amygdala volumes of parents and children. Numeric values are unstandardized path regression coefficients. Models are adjusted for child age at brain MRI scan, child sex, total ICV, age, ethnicity, education, smoking and alcohol consumption reported by mother and father. The dotted line represents the non-significant associations. (RMSEA=0.01; CFI=0.92; TLI=0.90). Mother father-child triadic data (n = 196). Associations survived the false discovery rate correction for multiple testing. Number of tests = 3 outcomes and the 3 relevant exposure periods (prenatal, mid- and late childhood). Critical value for FDR = 0.05.

is associated with differences in parental total white matter, gray matter, hippocampus, and amygdala volumes. Moreover, parental hostility is associated with differences in parental total white matter and gray matter volumes across parents. Last, we showed that prenatal parental hostility to child aggressive behavior was partially mediated by both hippocampal volumes of children and, importantly, also of mothers. These associations remained after adjusting for baseline family factors and multiple testing. Overall, the findings elucidate how hostility of a parent negatively relates to different family subsystems.

Figure 5. Hippocampal volumes of parents and children as mediator of the association between prenatal parental hostility and child aggressive behavior.



Mediation analysis of hippocampal volumes of parents and children in association with maternal and paternal hostility during pregnancy with preadolescent aggressive behavior at age 10. Model is adjusted for child age at brain MRI scan, child sex, total ICV, maternal age, race/ethnicity, education, smoking and alcohol consumption, and prior child aggressive behavior when child was aged 1.5 years.

a Path A is the association of prenatal maternal- or paternal-reported hostility with maternal or paternal hippocampal volumes, and path B is for the association of maternal or paternal or child hippocampal volumes with preadolescent aggressive behavior. Path C (in black) is the total association between prenatal maternal or paternal hostility and preadolescent aggressive behavior with hippocampal volumes not in the model. Path C′ (in gray) 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 hostility. Parental hostility factor captures covariation across raters, or the extent to which a given dimension is reflected across parents (i.e., a between-rater dimension factor).

Parental to child associations

Previous studies indicate that the development of brain structures and function is shaped by a complex interaction between pre- and postnatal environmental factors continuously affecting the neural architecture throughout lifetime.[40,41] Brain development might be vulnerable and these environmental factors thus particularly significant early in life.[38] Our findings provide evidence that prenatal maternal but not paternal hostility was associated with smaller white matter, gray matter and hippocampal volumes of the child. Thus, it is likely that hostility is associated with the intrauterine environment, which in turn impairs child development.[42-44] Several mechanisms could explain this association. First, mothers with high levels of intrusive behavior during interactions with partners likely experience stress, which in turn dysregulates the hypothalamic-pituitary-adrenal axis and in turn affects child development, but it may also affect brain development through inflammatory responses and changes in the balance of the autonomic nervous system.[45] Another potential mechanism is an unhealthy maternal diet during pregnancy by which a variation in maternal nutrition (either a surplus or paucity of maternal nutrition) is significantly related to child's future neurodevelopment.[46]

Maternal hostility and differences in maternal brain

There is some evidence that maternal depression and anxiety during pregnancy and early childhood are related to structural changes in the maternal brain.[17] Similarly, our findings underscores that differences maternal hostile behavior were associated with maternal brain morphology. In a previous study, positive experiences during early postpartum period co-occurred with structural changes in mothers' brain regions susceptive to stress exposure including, gray matter volumes and prefrontal cortex in a study of 19 women.[47] Several mechanisms could explain the observed associations between parental hostility of both parent and child brain morphology. Pre-existing familial vulnerability factors such as parental psychopathology might be one mechanism that explaining the association with parental brain differences, which in turn increase child's aggressive behavior. Importantly, such associations could also be explained by genetic influences. Genetic predisposition could underlie difference in parent and child brain morphology. Recently, a genome-wide association meta-analysis identified a few genetic loci associated with hippocampal volume,[48] which could be (indirectly) associated with parental psychopathology. The co-occurrence in parents could possibly reflect assortative mating, while the association with the child could signal direct genetic or indirect transmission, the latter being dynastic effects.

Paternal hostility and differences in paternal brain

The present study extends the available neuroimaging data on parents and underscores the multiple pathways by which not only maternal but also paternal hostile behaviors during prenatal and earlier child's life may impact family life. We found fathers who

were more hostility during pre- and postnatal period had lower total white matter, gray matter and hippocampal volumes. Indeed, the accumulating evidence suggests that fathers' psychopathology poses many challenges to men's lives and mental health.[49] The timing of paternal psychopathology before and after child's birth is just recently being studied and placed into a biological framework that could involve brain morphology.[21] Researchers have consistently reported that adults with psychopathology have smaller hippocampus and amygdala volumes, two major components of the limbic system implicated in learning, memory, and emotion.[50] For example, smaller amygdala and hippocampus have been shown in mothers with postpartum depression, trauma, or substance use.[51-53] The present findings indicate that in addition to pre-existing familial factors and genetic predisposition, different influences of environment such as learning through observation, parenting practices and emotional climate in the family (triadic model) can affect both parents and children psychopathology.[54,55]

Within and between parents findings

Our findings show that one parent's hostility occur together with his or her partner's hostility, which has important implication for family health and well-being. A potential mechanism for the correlation of hostile behaviors between parents is assortative mating,[56] which suggests that mothers' and fathers' psychopathology may be similar before engaging in a relation.[57] That is, both partners may, for example, share common environments affecting the main trait with genetic and phenotypic resemblance. As such, partner resemblance arises because 'like mates with like' rather than 'mates become alike'. Such parental concordance for hostility is known to be related to more child aggressive behavior in children.[58] Poverty is another factor that could be associated not only to parents mental health but also to their functioning and brain characteristics. The stress experienced by maternal low socio-economic status may result in brain changes, and in turn increase risk for parental psychopathology.[59] However, in our study this remains speculative as a clear temporal direction was lacking; parents were imaged only once.

Mediation findings

The association between prenatal parental hostility and child aggressive behavior was partially mediated by the child's hippocampal volumes. Although the common variance is shared across mother and father-reported hostility, the association with prenatal exposure suggests that direct maternal physiological influences may underlie the findings. This is consistent with prior research in the present cohort showing that smaller offspring hippocampal volumes partially mediate the association between prenatal family disruption and child adjustment problems.[60] However, maternal, but not paternal hippocampal volumes partially also mediated the associations of prenatal parental hostility with child aggressive behavior. This could be explained in part due to the specific role of the mother

in the postnatal period which together with the intrauterine period is considered a critical period for optimal child development.[61] As infants are highly dependent, this critical period of nurturance and care requires a tremendous maternal investment. Whether this reflects that pregnancy has a long-lasting impact on maternal brain or background risk factors is unclear. However, the maternal hippocampal volume is related both to maternal hostility and may underlie the child problems. We cannot conclude which of these mechanisms contributed most to these associations, but our findings help guide a more comprehensive understanding of interrelated familial mechanisms.

There are several limitations of this study. First, as with all observational studies, the relative homogeneity of the population limits its generalizability. Second, given the lack of the repeated measures of both parents and child brain morphology, we cannot assess the directionality of the associations between parental hostility and the brain characteristics of the parents. Third, parental genetic variation could possibly predispose parents to higher levels of hostility while also affecting their child's brain structure. The strengths of the study lie in its large population-based sample and the SEM approach in the unique triadic data to testing the associations of prospectively measured exposure data with two parents' and child brain outcomes measured at 10 years of age. Furthermore, we included both maternal and paternal reports hostility and therefore could examine how one parent's hostility affects all members of the family. The methodology used in this study enabled us to separate associations of mother-related risk of hostility from those of father-related risk of hostility and assess their differential associations on the parent-child and family associations.

In conclusion, our findings suggest 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. Moreover, 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 volumes. Our findings suggest that parental hostility has the potential to compromise child neurodevelopment and well-being long-term. The association of parental hostility during pregnancy and child aggressive behavior was partially mediated by the child's as well as maternal hippocampal volumes. Further research with repeated neuroimaging is required to identify distinctive changes in both parent and child brain structures among 'at-risk' parents and their children, in order to test the directionality and to direct specific and early interventions appropriately.

REFERENCES

1. Davies PT, Martin MJ, Cicchetti D. Delineating the sequelae of destructive and constructive interparental conflict for children within an evolutionary framework. *Developmental Psychology.* 2012;48(4):939.
2. Cummings JS, Pellegrini DS, Notarius CI, Cummings EM. Children's responses to angry adult behavior as a function of marital distress and history of interparent hostility. *Child development.* 1989:1035-1043.
3. Katz LF, Woodin EM. Hostility, hostile detachment, and conflict engagement in marriages: Effects on child and family functioning. *Child development.* 2002;73(2):636-652.
4. Low SM, Stocker C. Family functioning and children's adjustment: associations among parents' depressed mood, marital hostility, parent-child hostility, and children's adjustment. *Journal of family psychology.* 2005;19(3):394.
5. Card NA, Little TD. Proactive and reactive aggression in childhood and adolescence: A meta-analysis of differential relations with psychosocial adjustment. *International journal of behavioral development.* 2006;30(5):466-480.
6. Card NA, Stucky BD, Sawalani GM, Little TD. Direct and indirect aggression during childhood and adolescence: A meta-analytic review of gender differences, intercorrelations, and relations to maladjustment. *Child development.* 2008;79(5):1185-1229.
7. Gottman JM, Katz LF. Effects of marital discord on young children's peer interaction and health. *Developmental psychology.* 1989;25(3):373.
8. Hanson JL, Nacewicz BM, Sutterer MJ, et al. Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biol Psychiatry.* 2015;77(4):314-323.
9. Repetti RL, Robles TF, Reynolds B. Allostatic processes in the family. *Development and psychopathology.* 2011;23(3):921-938.
10. Davies PT, Sturge-Apple ML. Family context in the development of psychopathology. *Handbook of developmental psychopathology*: Springer; 2014:143-161.
11. Schermerhorn AC, Mark Cummings E. Transactional Family Dynamics: A New Framework for Conceptualizing Family Influence Processes. In: Kail RV, ed. *Advances in Child Development and Behavior.* Vol 36: JAI; 2008:187-250.
12. Peltz JS, Rogge RD, Sturge-Apple ML. Transactions within the family: Coparenting mediates associations between parents' relationship satisfaction and the parent–child relationship. *Journal of Family Psychology.* 2018;32(5):553.
13. Schermerhorn AC, Cummings EM. Transactional family dynamics: A new framework for conceptualizing family influence processes. *Advances in child development and behavior.* Vol 36: Elsevier; 2008:187-250.
14. Erel O, Burman B. Interrelatedness of marital relations and parent-child relations: a meta-analytic review. *Psychological bulletin.* 1995;118(1):108.
15. Goodman JH. Paternal postpartum depression, its relationship to maternal postpartum depression, and implications for family health. *Journal of advanced nursing.* 2004;45(1):26-35.
16. Achenbach. As Others See Us:Clinical and Research Implications of Cross-Informant Correlations for Psychopathology. *Current Directions in Psychological Science.* 2006;15(2):94-98.
17. Feldman R. The adaptive human parental brain: implications for children's social development. *Trends Neurosci.* 2015;38(6):387-399.
18. Kim P, Strathearn L, Swain JE. The maternal brain and its plasticity in humans. *Hormones and Behavior.* 2016;77:113-123.

19. Lupien SJ, Juster RP, Raymond C, Marin MF. The effects of chronic stress on the human brain: From neurotoxicity, to vulnerability, to opportunity. *Front Neuroendocrinol.* 2018;49:91-105.
20. Azhari A, Leck WQ, Gabrieli G, et al. Parenting stress undermines mother-child brain-to-brain synchrony: A hyperscanning study. *Scientific reports.* 2019;9(1):1-9.
21. Swain JE, Dayton CJ, Kim P, Tolman RM, Volling BL. Progress on the paternal brain: theory, animal models, human brain research, and mental health implications. *Infant Ment Health J.* 2014;35(5):394-408.
22. Repetti RL, Taylor SE, Seeman TE. Risky families: family social environments and the mental and physical health of offspring. *Psychological bulletin.* 2002;128(2):330.
23. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol.* 2016;31(12):1243-1264.
24. White T, Muetzel RL, El Marroun H, et al. Paediatric population neuroimaging and the Generation R Study: the second wave. *Eur J Epidemiol.* 2018;33(1):99-125.
25. Jansen PR, Dremmen M, Berg Avd, et al. Incidental findings on brain imaging in the general pediatric population. *New England Journal of Medicine.* 2017;377(16):1593-1595.
26. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983;13(3):595-605.
27. de Beurs. Brief symptom inventory. *Handleiding. Leiden (Netherlands): Pits Publishers.* 2004.
28. De Beurs, Zitman F. De Brief Symptom Inventory (BSI). *De betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL-90. Leiden: Leids universitair medisch centrum.* 2005.
29. Achenbach, Rescorla. *Manual for the ASEBA preschool forms & profiles: An integrated system of multi-informant assessment; Child behavior checklist for ages 1 1/2-5; Language development survey; Caregiver-teacher report form.* University of Vermont; 2000.
30. Achenbach, Rescorla. ASEBA school-age forms & profiles. Aseba Burlington, VT; 2001.
31. Ivanova MY, Achenbach TM, Rescorla LA, et al. Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *J Am Acad Child Adolesc Psychiatry.* 2010;49(12):1215-1224.
32. Lamballais S, Adank MC, Hussainali RF, et al. Design and overview of the Origins of Alzheimer's Disease Across the Life course (ORACLE) study. *Eur J Epidemiol.* 2021;36(1):117-127.
33. Muetzel RL, Mulder RH, Lamballais S, et al. Frequent Bullying Involvement and Brain Morphology in Children. *Front Psychiatry.* 2019;10:696.
34. White T, Jansen PR, Muetzel RL, et al. Automated quality assessment of structural magnetic resonance images in children: Comparison with visual inspection and surface-based reconstruction. *Hum Brain Mapp.* 2018;39(3):1218-1231.
35. Netherlands Statistics. *Begrippen: Allochten.* 2006.
36. Kenny DA, Kashy DA, Cook WL. *Dyadic data analysis.* Guilford press; 2020.
37. Valeri L, Vanderweele. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods.* 2013;18(2):137-150.
38. VanderWeele TJ, Mathur MB, Chen Y. Outcome-wide longitudinal designs for causal inference: A new template for empirical studies. *Statistical Science.* 2020;35(3):437-466.
39. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the royal statistical society. Series B (Methodological).* 1995:289-300.
40. Fox SE, Levitt P, Nelson CA, 3rd. How the timing and quality of early experiences influence the development of brain architecture. *Child Dev.* 2010;81(1):28-40.

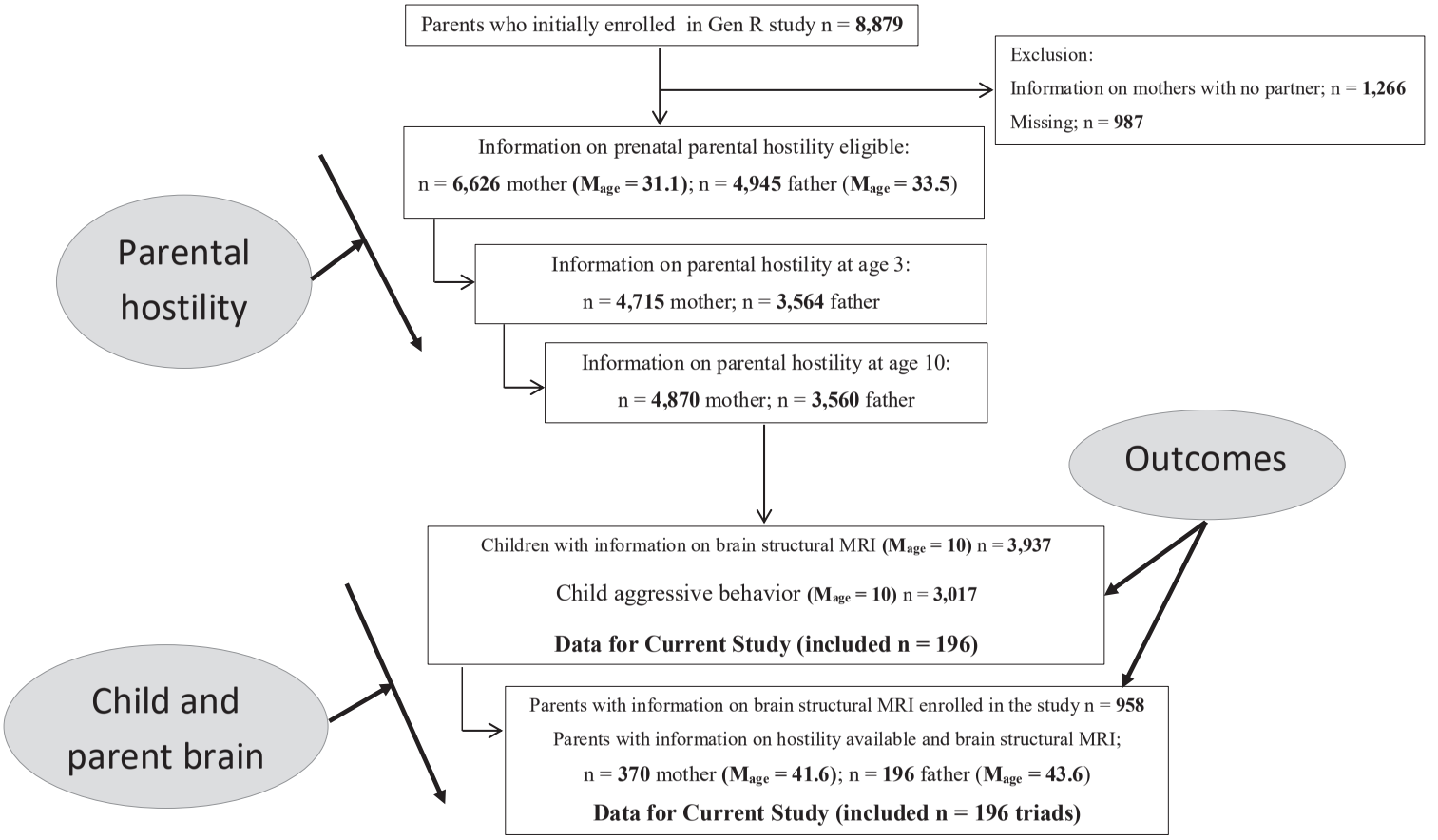
41. Belsky J, De Haan M. Annual research review: Parenting and children's brain development: The end of the beginning. *Journal of Child Psychology and Psychiatry.* 2011;52(4):409-428.
42. Lewis AJ, Austin E, Galbally M. Prenatal maternal mental health and fetal growth restriction: a systematic review. *J Dev Orig Health Dis.* 2016;7(4):416-428.
43. Weinstock M. The long-term behavioural consequences of prenatal stress. *Neurosci Biobehav Rev.* 2008;32(6):1073-1086.
44. Li J, Wang Z-N, Chen Y-P, et al. Late gestational maternal serum cortisol is inversely associated with fetal brain growth. *Neuroscience & Biobehavioral Reviews.* 2012;36(3):1085-1092.
45. Hompes T, Vrieze E, Fieuws S, et al. The influence of maternal cortisol and emotional state during pregnancy on fetal intrauterine growth. *Pediatr Res.* 2012;72(3):305-315.
46. Lindsay KL, Buss C, Wadhwa PD, Entringer S. The Interplay between Maternal Nutrition and Stress during Pregnancy: Issues and Considerations. *Annals of Nutrition and Metabolism.* 2017;70(3):191-200.
47. Kim P, Leckman JF, Mayes LC, Feldman R, Wang X, Swain JE. The plasticity of human maternal brain: longitudinal changes in brain anatomy during the early postpartum period. *Behavioral neuroscience.* 2010;124(5):695.
48. van der Meer D, Rokicki J, Kaufmann T, et al. Brain scans from 21,297 individuals reveal the genetic architecture of hippocampal subfield volumes. *Molecular Psychiatry.* 2020;25(11):3053-3065.
49. Kim P, Swain JE. Sad dads: paternal postpartum depression. *Psychiatry (Edgmont).* 2007;4(2):35-47.
50. Besteher B, Gaser C, Nenadić I. Brain Structure and Subclinical Symptoms: A Dimensional Perspective of Psychopathology in the Depression and Anxiety Spectrum. *Neuropsychobiology.* 2020;79(4):270-283.
51. Chase HW, Moses-Kolko EL, Zevallos C, Wisner KL, Phillips ML. Disrupted posterior cingulate–amygdala connectivity in postpartum depressed women as measured with resting BOLD fMRI. *Social cognitive and affective neuroscience.* 2014;9(8):1069-1075.
52. Kim S, Fonagy P, Allen J, Strathearn L. Mothers' unresolved trauma blunts amygdala response to infant distress. *Social neuroscience.* 2014;9(4):352-363.
53. Landi N, Montoya J, Kober H, et al. Maternal neural responses to infant cries and faces: relationships with substance use. *Frontiers in psychiatry.* 2011;2:32.
54. Morris AS, Silk JS, Steinberg L, Myers SS, Robinson LR. The role of the family context in the development of emotion regulation. *Social development.* 2007;16(2):361-388.
55. Rutherford HJV, Wallace NS, Laurent HK, Mayes LC. Emotion regulation in parenthood. *Developmental Review.* 2015;36:1-14.
56. Maes HH, Neale MC, Kendler KS, et al. Assortative mating for major psychiatric diagnoses in two population-based samples. *Psychol Med.* 1998;28(6):1389-1401.
57. Frisell T, Pawitan Y, Langstrom N, Lichtenstein P. Heritability, assortative mating and gender differences in violent crime: results from a total population sample using twin, adoption, and sibling models. *Behav Genet.* 2012;42(1):3-18.
58. Merikangas KR, Prusoff BA, Weissman MM. Parental concordance for affective disorders: psychopathology in offspring. *Journal of Affective Disorders.* 1988;15(3):279-290.
59. Pilyoung KIM, Blanco H. Understanding how motherhood and poverty change the brain. *Zero to Three.* 2014:29-36.
60. Xerxa Y, Delaney SW, Rescorla LA, et al. Association of Poor Family Functioning From Pregnancy Onward With Preadolescent Behavior and Subcortical Brain Development. *JAMA Psychiatry.* 2020.
61. Lisofsky N, Gallinat J, Lindenberger U, Kühn S. Postpartal neural plasticity of the maternal brain: Early renormalization of pregnancy-related decreases? *Neurosignals.* 2019;27:12-24.

SUPPLEMENTARY METHOD.

Latent factor analysis

Latent factors analysis maternal- and paternal-reported parental hostility were modeled as latent variable via common confirmatory factor analytic (CFA) methods. The models were allowed to correlate, and were estimated with the robust maximum likelihood estimator using standardized latent variables. The latent parental hostility factor was used in mediation model to test whether the associations between prenatal parental hostility factor and child aggressive behavior was mediated by hippocampal volumes (Figure 5). The association between the latent construct of parental hostility with child hippocampal volumes and aggressive behavior captures covariation across raters, or the extent to which a given dimension is reflected both across parents (i.e., a "between-rater" dimension factor). The latent constructs showed good model fit as judged with the comparative fit index (CFI, acceptable fit ≥ .90).[1] 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.[2]

Supplementart Figure 1. Inclusion of the Study Sample



Supplementary Table 1. The associations between maternal-reported hostility and child brain morphology (N = 196 triads).

	Child brain morphology (N = 196)							
	Global brain measures				***Specific brain volumetric measures***			
***Mother-reported* hostility**	**Cerebral white matter, (cm^3)**		**Total gray volume, (cm^3)**		**Amygdala volume, (cm^3)**		**Hippocampus volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Hostility, prenatal								
Model 1	-0.23 (-1.81 to -0.12)	.001	-0.38 (-1.44 to -0.15)	.001	0.07 (-0.09 to 0.02)	.362	-0.12 (-0.24 to -0.04)	.001
Model 2	-0.10 (-1.17 to -0.04)	.016	-0.13 (-1.12 to -0.02)	.009	0.03 (-0.13 to 0.09)	.537	-0.07 (-0.21 to -0.02)	.001
Hostility, child age 3								
Model 1	-0.11 (-1.12 to 0.07)	.312	-0.14 (-1.01 to 0.09)	.122	-0.06 (-0.05 to 0.04)	.331	-0.11 (-0.31 to -0.01)	.026
Model 2	-0.03 (-1.28 to 0.03)	.723	-0.03 (-1.13 to 0.07)	.443	-0.03 (-0.06 to 0.04)	.504	-0.04 (-0.30 to -0.01)	.035
Hostility, child age 10								
Model 1	-0.07 (-0.85 to 0.02)	.159	-0.08 (-0.93 to 0.02)	.067	0.05 (-0.02 to 0.03)	.938	0.05 (-0.02 to 0.11)	.165
Model 2	-0.05 (-0.74 to 0.06)	.663	-0.02 (-0.69 to 0.07)	.299	0.02 (-0.04 to 0.04)	.811	0.03 (-0.07 to 0.05)	.644

Linear regression analysis of maternal-reported hostility and child brain morphology outcome. B statistics are averaged from 10 imputed data sets. Model 1 is adjusted for child age at brain MRI scan, child sex, and total ICV. Model 2 is additionally adjusted for maternal age, race/ethnicity, education, and smoking and alcohol consumption. Global brain measures are not adjusted for total ICV.

Supplementary Table 2. The associations between paternal-reported hostility and child brain morphology (N = 196 triads).

	Child brain morphology (N = 196)							
	Global brain measures				***Specific brain volumetric measures***			
***Father-reported* hostility**	**Cerebral white matter, (cm^3)**		**Total gray volume, (cm^3)**		**Amygdala volume, (cm^3)**		**Hippocampus volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Hostility, prenatal								
Model 1	-0.08 (-0.35 to -0.05)	.019	-0.03 (-0.34 to 0.01)	.046	-0.01 (-0.05 to 0.03)	.774	-0.03 (-0.11 to 0.06)	.507
Model 2	-0.05 (-0.21 to 0.17)	.385	0.04 (-0.25 to 0.01)	.179	-0.01 (-0.05 to 0.04)	.843	0.01 (-0.10 to 0.07)	.787
Hostility, child age 3								
Model 1	-0.04 (-0.19 to 0.07)	.403	-0.03 (-0.33 to 0.08)	.343	0.02 (-0.03 to 0.03)	.371	0.03 (-0.07 to 0.01)	.601
Model 2	-0.02 (-0.15 to 0.06)	.591	0.02 (-0.27 to 0.01)	.199	0.01 (-0.05 to 0.07)	.741	-0.01 (-0.13 to 0.02)	.305
Hostility, child age 10								
Model 1	0.05 (-0.17 to 0.02)	.217	-0.05 (-0.41 to 0.03)	.177	0.05 (-0.03 to 0.01)	.540	0.05 (-0.09 to 0.03)	.079
Model 2	0.04 (-0.16 to 0.03)	.432	-0.04 (-0.34 to 0.02)	.307	0.03 (-0.04 to 0.01)	.459	0.03 (-0.08 to 0.03)	.095

Linear regression analysis of paternal hostility and child brain morphology outcome. B statistics are averaged from 10 imputed data sets. Model 1 is adjusted for child age at brain MRI scan, child sex, and total ICV. Model 2 is additionally adjusted for paternal age, race/ethnicity, education, and smoking and alcohol consumption. Global brain measures are not adjusted for total ICV.

Supplementary Table 3. The associations between maternal-reported hostility and maternal brain morphology (N = 196 triads).

	Maternal brain morphology (N = 196)							
	Global brain measures				*Specific brain volumetric measures*			
Parental hostility, mother rating	**Cerebral white matter, (cm^3)**		**Total gray volume, (cm^3)**		**Amygdala volume, (cm^3)**		**Hippocampus volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Hostility, prenatal								
Model 1	-0.11 (-0.39 to -0.02)	.001	-0.15 (-0.47 to -0.06)	.001	-0.04 (-0.12 to -0.01)	.009	-0.07 (-0.12 to -0.04)	.001
Model 2	-0.10 (-0.36 to -0.04)	.014	-0.13 (-0.41 to -0.05)	.003	-0.04 (-0.13 to -0.01)	.010	-0.06 (-0.10 to -0.02)	.001
Hostility, child age 3								
Model 1	-0.12 (-0.27 to -0.03)	.001	-0.16 (-0.38 to -0.04)	.001	-0.08 (-0.14 to -0.03)	.010	-0.06 (-0.12 to -0.02)	.004
Model 2	-0.12 (-0.34 to -0.03)	.003	-0.15 (-0.32 to -0.05)	.001	-0.07 (-0.13 to -0.02)	.017	-0.06 (-0.15 to -0.02)	.016
Hostility, child age 10								
Model 1	-0.09 (-0.47 to -0.03)	.001	-0.12 (-0.29 to -0.04)	.001	-0.07 (-0.15 to -0.02)	.004	-0.05 (-0.09 to -0.02)	.001
Model 2	-0.09 (-0.49 to -0.02)	.002	-0.12 (-0.33 to -0.03)	.001	-0.06 (-0.16 to -0.03)	.003	-0.05 (-0.10 to -0.02)	.003

Linear regression analysis of maternal-reported hostility and maternal brain morphology outcome. B statistics are averaged from 10 imputed data sets. Model 1 is adjusted for maternal age at intake, race/ethnicity, education, and total ICV. Model 2 is additionally adjusted for maternal smoking and alcohol consumption. Global brain measures are not adjusted for total ICV.

Supplementary Table 4. The associations between paternal-reported hostility and paternal brain morphology (N = 196 triads).

	Paternal brain morphology (N = 196)							
	Global brain measures				***Specific brain volumetric measures***			
***Father-reported* hostility**	**Cerebral white matter, (cm^3)**		**Total gray volume, (cm^3)**		**Amygdala volume, (cm^3)**		**Hippocampus volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Hostility, prenatal								
Model 1	-0.08 (-0.46 to -0.01)	.001	-0.09 (-0.43 to -0.02)	.001	-0.03 (-0.15 to -0.01)	.026	-0.05 (-0.09 to -0.01)	.009
Model 2	-0.07 (-0.41 to -0.02)	.002	-0.08 (-0.39 to -0.02)	.001	-0.03 (-0.12 to -0.01)	.040	-0.04 (-0.10 to -0.01)	.002
Hostility, child age 3								
Model 1	-0.09 (-0.37 to -0.05)	.001	-0.12 (-0.52 to -0.04)	.001	-0.04 (-0.09 to -0.01)	.024	-0.06 (-0.11 to -0.02)	.001
Model 2	-0.09 (-0.38 to -0.04)	.001	-0.11 (-0.47 to -0.04)	.002	-0.04 (-0.08 to -0.01)	.038	-0.05 (-0.13 to -0.03)	.014
Hostility, child age 10								
Model 1	-0.10 (-0.27 to -0.04)	.001	-0.13 (-0.39 to -0.03)	.001	-0.05 (-0.16 to -0.02)	.001	-0.05 (-0.11 to -0.05)	.010
Model 2	-0.09 (-0.17 to -0.04)	.001	-0.13 (-0.34 to -0.05)	.002	-0.04 (-0.13 to -0.03)	.001	-0.05 (-0.13 to -0.04)	.019

Linear regression analysis of paternal-reported hostility and paternal brain morphology outcome. B statistics are averaged from 10 imputed data sets. Model 1 is adjusted for paternal age at intake, race/ethnicity, education, and total ICV. Model 2 is additionally adjusted for paternal smoking and alcohol consumption. Global brain measures are not adjusted for total ICV.

Supplementary Table 5. Correlation coefficients between maternal and paternal report of hostility.

	1	2	3	4	5	6
Parental hostility						
1 Prenatal, mother report	-					
2 Prenatal, father report	.27**	-				
3 Age 3, mother report	.32**	.13**	-			
4 Age 3, father report	.14**	.34**	.25**	-		
5 Age 10, mother report	.31**	.09**	.39**	.12**	-	
6 Age 10, father report	.11**	.29**	.14**	.37**	.18**	-

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

Chapter 7

General discussion

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.[1] 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.[2,3] 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.[4] 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.[5] 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.[6] 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.[7] 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,[8,9] 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.[10,11] 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.[16] 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.[17,18] 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.[19] 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.[23] 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.[24] That is, a sensitive period describes the effects an experience has on the development during narrow windows of time.[23] 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.[25,26] 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.[27] 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,[28] and yield estimates that are difficult to interpret meaningfully. Moreover, the parameters are typically interpreted as between-person effect.[34,35] 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)[10] 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.[36,37] 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.[38,39] 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.[40] 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.[41] However, inconsistencies often arise among multiple informants referred to as 'informant discrepancies',[42] even when informants complete parallel or identical measures.[43]

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,[42,44] information bias, and importantly, shared-rater variance, which is a particular form of information bias.[45-47] 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).[44] 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 suggests 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.

REFERENCES

1. Rutter M. Epidemiological Approaches to Developmental Psychopathology. *Archives of General Psychiatry.* 1988;45(5):486-495.
2. Rutter M, Cox A, Tupling C, Berger M, Yule W. Attainment and adjustment in two geographical areas. I--The prevalence of psychiatric disorder. *Br J Psychiatry.* 1975;126:493-509.
3. Rutter M, Quinton D. Psychiatric disorder: ecological factors and concepts of causation. *Ecological factors in human development.* 1977;173:87.
4. Barker DJP. The developmental origins of adult disease. *European journal of epidemiology.* 2003:733-736.
5. Amato. Children of divorce in the 1990s: an update of the Amato and Keith (1991) meta-analysis. *J Fam Psychol.* 2001;15(3):355-370.
6. Goldthorpe JH. Causation, statistics, and sociology. *European sociological review.* 2001;17(1):1-20.
7. Booth A, Amato PR. Parental Predivorce Relations and Offspring Postdivorce Well-Being. *Journal of Marriage and Family.* 2001;63(1):197-212.
8. Bernet W, Wamboldt MZ, Narrow WE. Child affected by parental relationship distress. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2016;55(7):571-579.
9. Harold GT, Aitken JJ, Shelton KH. Inter-parental conflict and children's academic attainment: A longitudinal analysis. *Journal of child psychology and psychiatry.* 2007;48(12):1223-1232.
10. Curran PJ, Howard AL, Bainter SA, Lane ST, McGinley JS. The separation of between-person and within-person components of individual change over time: a latent curve model with structured residuals. *J Consult Clin Psychol.* 2014;82(5):879-894.
11. Berry D, Willoughby MT. On the practical interpretability of cross-lagged panel models: Rethinking a developmental workhorse. *Child Development.* 2017;88(4):1186-1206.
12. Cacioppo, Cacioppo S. Loneliness in the modern age: an evolutionary theory of loneliness (ETL). *Advances in experimental social psychology.* Vol 58: Elsevier; 2018:127-197.
13. Lewis AJ, Austin E, Galbally M. Prenatal maternal mental health and fetal growth restriction: a systematic review. *J Dev Orig Health Dis.* 2016;7(4):416-428.
14. Weinstock M. The long-term behavioural consequences of prenatal stress. *Neurosci Biobehav Rev.* 2008;32(6):1073-1086.
15. Hompes T, Vrieze E, Fieuws S, et al. The influence of maternal cortisol and emotional state during pregnancy on fetal intrauterine growth. *Pediatr Res.* 2012;72(3):305-315.
16. Luby J, Belden A, Botteron K, et al. The effects of poverty on childhood brain development: the mediating effect of caregiving and stressful life events. *JAMA pediatrics.* 2013;167(12):1135-1142.
17. Paus T, Pesaresi M, French L. White matter as a transport system. *Neuroscience.* 2014;276:117-125.
18. Rifkin-Graboi A, Meaney MJ, Chen H, et al. Antenatal maternal anxiety predicts variations in neural structures implicated in anxiety disorders in newborns. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2015;54(4):313-321. e312.
19. Kenny DA. Commentary: Dyadic analyses of family data. *Journal of pediatric psychology.* 2011;36(5):630-633.
20. Rutter M. Developmental catch-up, and deficit, following adoption after severe global early privation. *Journal of Child Psychology and Psychiatry.* 1998;39(4):465-476.
21. Litman HJ, Horton NJ, Hernandez B, Laird NM. Incorporating missingness for estimation of marginal regression models with multiple source predictors. *Stat Med.* 2007;26(5):1055-1068.
22. Sanchez, Hu H, Litman HJ, Tellez-Rojo MM. Statistical methods to study timing of vulnerability with sparsely sampled data on environmental toxicants. *Environ Health Perspect.* 2011;119(3):409-415.

23. Knudsen EI. Sensitive periods in the development of the brain and behavior. *J Cogn Neurosci.* 2004;16(8):1412-1425.
24. Sanchez, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Dev Psychopathol.* 2001;13(3):419-449.
25. Greenough WT, Black JE, Wallace CS. Experience and brain development. *Child Dev.* 1987;58(3):539-559.
26. Black JE, Jones TA, Nelson CA, Greenough WT. Neuronal plasticity and the developing brain. *Handbook of child and adolescent psychiatry.* 1998;6:31-53.
27. Nelson Iii CA, Gabard-Durnam LJ. Early Adversity and Critical Periods: Neurodevelopmental Consequences of Violating the Expectable Environment. *Trends in Neurosciences.* 2020;43(3):133-143.
28. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology.* 1992:143-155.
29. Pearl J. Direct and indirect effects. *arXiv preprint arXiv:1301.2300.* 2013.
30. VanderWeele. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology.* 2014;25(5):749-761.
31. Robins JM. Semantics of causal DAG models and the identification of direct and indirect effects. *Oxford Statistical Science Series.* 2003:70-82.
32. VanderWeele TJ. Policy-relevant proportions for direct effects. *Epidemiology (Cambridge, Mass.).* 2013;24(1):175.
33. Sameroff. *The transactional model.* American Psychological Association; 2009.
34. Curran PJ, Lee T, Howard AL, Lane S, MacCallum R. Disaggregating within-person and between-person effects in multilevel and structural equation growth models. 2012.
35. Bollen KA, Brand JE. A general panel model with random and fixed effects: A structural equations approach. *Social Forces.* 2010;89(1):1-34.
36. Curran PJ, Bauer DJ. The disaggregation of within-person and between-person effects in longitudinal models of change. *Annual review of psychology.* 2011;62:583-619.
37. Hertzog C, Dixon RA, Hultsch DF, MacDonald SWS. Latent change models of adult cognition: Are changes in processing speed and working memory associated with changes in episodic memory? *Psychology and aging.* 2003;18(4):755.
38. Muthén BO, Curran PJ. General longitudinal modeling of individual differences in experimental designs: a latent variable framework for analysis and power estimation. *Psychological methods.* 1997;2(4):371.
39. Snijders TAB, Bosker RJ. *Multilevel analysis: An introduction to basic and advanced multilevel modeling.* Sage; 2011.
40. Roberts BW, Caspi A. Personality Development and the Person-Situation Debate: It's D7éjà Vu All Over Again. *Psychological Inquiry.* 2001;12(2):104-109.
41. Hunsley J, Mash EJ. Evidence-based assessment. *Annu. Rev. Clin. Psychol.* 2007;3:29-51.
42. Achenbach. As Others See Us:Clinical and Research Implications of Cross-Informant Correlations for Psychopathology. *Current Directions in Psychological Science.* 2006;15(2):94-98.
43. De Los Reyes. Introduction to the special section: More than measurement error: Discovering meaning behind informant discrepancies in clinical assessments of children and adolescents. *J Clin Child Adolesc Psychol.* 2011;40(1):1-9.

44. De Los Reyes, Kazdin. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. *Psychological bulletin.* 2005;131(4):483.
45. Collishaw S, Goodman R, Ford T, Rabe-Hesketh S, Pickles A. How far are associations between child, family and community factors and child psychopathology informant-specific and informant-general? *Journal of Child Psychology and Psychiatry.* 2009;50(5):571-580.
46. Geiser C, Eid M, Nussbeck FW, Courvoisier DS, Cole DA. Analyzing true change in longitudinal multitrait-multimethod studies: application of a multimethod change model to depression and anxiety in children. *Dev Psychol.* 2010;46(1):29-45.
47. Jaffee SR, Poulton R. Reciprocal effects of mothers' depression and children's problem behaviors from middle childhood to early adolescence. *Developmental contexts in middle childhood: Bridges to adolescence and adulthood.* 2006:107-129.
48. van der Ende J, Verhulst FC, Tiemeier H. Multitrait-multimethod analyses of change of internalizing and externalizing problems in adolescence: Predicting internalizing and externalizing DSM disorders in adulthood. *Journal of Abnormal Psychology.* 2020;129(4):343.
49. Dawson-McClure SR, Sandler IN, Wolchik SA, Millsap RE. Risk as a moderator of the effects of prevention programs for children from divorced families: a six-year longitudinal study. *J Abnorm Child Psychol.* 2004;32(2):175-190.

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 ontwrichte 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 gerapporteerd 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 samenhing 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
About the Author

ACKNOWLEDGEMENTS

The work presented in this thesis was conducted at the Erasmus MC, University Medical Center Rotterdam, Department of Child and Adolescent Psychiatry and The Generation R Study Group, Rotterdam, 3015 CN, the Netherlands. The Generation R Study is conducted by the Erasmus Medical Center, Rotterdam, in close collaboration with the Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service, Rotterdam Homecare Foundation and Stichting Trombosedienst & Artsenlaboratorium Rijnmond. The authors thankfully acknowledge the contribution of the participating parents and their children, general practitioners, hospitals, midwives, and pharmacies in Rotterdam. The general design of the Generation R Study is supported by the Erasmus Medical Center-Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), Netherlands Organization for Scientific Research (NOW), and the Ministry of Health, Welfare and Sport, the Municipal Health Service Rotterdam area, and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond. The work presented in the thesis was conducted at the Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center, Rotterdam, the Netherlands. Studies were financially supported by grants from, ERAWEB, the European Commission (2013-2548/001-001-EMA2), and the Royal Netherlands Academy of Arts and Sciences (KNAW) Ter Meulen (KNAWWF/DA/2061/TMB367). Financial support for the publication of this thesis was provided by the Generation R Study, and the Erasmus Medical Center.

AUTHOR AFFILIATIONS

Erasmus MC, University Medical Center Rotterdam, Department of Child and Adolescent Psychiatry, Rotterdam, 3015 CN, the Netherlands
Yllza Xerxa, Ryan L. Muetzel, Jan van der Ende, Maartje P.C.M. Luijk, Nathalie Tamayo Martinez, Fadila Serdarevic, Pauline W. Jansen, Tonya White, Manon H.J. Hillegers, Frank C. Verhulst, Henning Tiemeier

Erasmus MC, University Medical Center Rotterdam, The Generation R Study Group, Rotterdam, 3015 CN, the Netherlands
Yllza Xerxa, Ryan L. Muetzel, Nathalie Tamayo Martinez, Tonya White, Vincent W. V. Jaddoe

Erasmus MC, University Medical Center Rotterdam, Department of Epidemiology, Rotterdam, 3015 CN, the Netherlands
M. Arfan Ikram

Erasmus MC, University Medical Center Rotterdam, Department of Pediatrics, Rotterdam, 3015 CN, the Netherlands
Vincent W. V. Jaddoe

Erasmus MC, University Medical Center Rotterdam, Department of Radiology and Nuclear Medicine, Rotterdam, 3015 CN, the Netherlands
Tonya White

Department of Psychology, Education and Child Studies, Erasmus School of Social and Behavioral Sciences, Erasmus University Rotterdam, 3062 PA, the Netherlands
Pauline W. Jansen, Maartje P.C.M. Luijk, Marinus H. van IJzendoorn

Erasmus MC, University Medical Center Rotterdam, Department of Clinical Genetics, Rotterdam, 3015 CN, the Netherlands
Sander Lamballais

Department of Psychology, Bryn Mawr College, Bryn Mawr, Pennsylvania, 19010, USA
Leslie A. Rescorla

Child and Adolescent Mental Health Center, Mental Health Services, the Capital Region of Denmark, Copenhagen, 2200, Denmark
Frank C. Verhulst

Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, 2200, Denmark
Frank C. Verhulst

School of Education, Communication and Language Sciences, Newcastle University, Newcastle-Upon-Tyne, NE1 7RU, United Kingdom
James Law

Vermont Center for Children, Youth and Families, Department of Psychiatry, University of Vermont, Burlington, VT 05401, USA
William E. Copeland

Jacobs Center for Productive Youth Development, Department of Psychology, University of Zürich, Zürich, 8050, Switzerland
Lilly Shanahan

Department of Social and Behavioral Sciences, Harvard T. H. Chan School of Public Health, Boston, MA, 02115, USA
Scott W. Delaney, Laura D. Kubzansky, Henning Tiemeier

Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, 02115, USA
Sebastien Haneuse

Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA, 02478, USA
Kerry J. Ressler

Lee Kum Sheung Center for Health and Happiness, Harvard T.H. Chan School of Public Health, Boston, MA, 02115, USA
Laura D. Kubzansky

LIST OF PUBLICATIONS NOT PART OF THIS THESIS

Serdarevic, F., Tiemeier, H., Jansen, PR., Alemany, S., **Xerxa, Y.**, Neumann, A., Robinson, E., Hillegers, MHJ., Verhulst, FC., Ghassabian, A. Polygenic Risk Scores for Developmental Disorders, Neuromotor Functioning During Infancy, and Autistic Traits in Childhood. (2019) *Biological Psychiatry,* 87(2), 132-138.

Kocevska, D., Lysen, TS., Dotinga, A., Koopman-Verhoeff, ME., Luijk, MPCM., Antypa, N., Biermasz, NR., Blokstra, A., Brug, J., Burk, WJ., Comijs, HC., Corpeleijn, E., Dashti, HS., de Bruin, EJ., de Graaf, R., Derks, IPM., Dewald-Kaufmann, JF., Elders, PJM., Gemke, RJBJ., Grievink, L., Hale, L., Hartman, CA., Heijnen, CJ., Huisman, M., Huss, A., Ikram, MA., Jones, SE., Velderman, MK., Koning, M., Meijer, AM., Meijer, K., Noordam, R., Oldehinkel, AJ., Groeniger, JO., Penninx, BWJH., Picavet, HSJ., Pieters, S., Reijneveld, SA., Reitz, E., Renders, CM., Rodenburg, G., Rutters, F., Smith, MC., Singh, AS., Snijder, MB., Stronks, K., Ten Have, M., Twisk, JWR., Van de Mheen, D., van der Ende, J., van der Heijden, KB., van der Velden, PG., van Lenthe, FJ., van Litsenburg, RRL., van Oostrom, SH., van Schalkwijk, FJ., Sheehan, CM., Verheij, RA., Verhulst, FC., Vermeulen, MCM., Vermeulen, RCH., Verschuren, WMM., Vrijkotte, TGM., Wijga, AH., Willemen, AM., Ter Wolbeek, M., Wood, AR., **Xerxa, Y.**, Bramer, WM., Franco, OH., Luik, AI., Van Someren, EJW., Tiemeier, H. (2020). Sleep Characteristics Across the Lifespan in 1.1 Million People from the Netherlands, United Kingdom and United States: A Systematic Review and Meta-analysis. *Nature Human Behavior,* 5(1), 113-122.

PHD PORTFOLIO

Name PhD student:	Yllza Xerxa
Erasmus MC Department:	Child & Adolescent Psychiatry/Psychology
PhD period:	Aug 2015 - Jun 2020
Promotors:	Prof. Dr. H. Tiemeier
	Prof. Dr. F.C. Verhulst

1. PhD training	Year	ECTS
MSc-program Epidemiology, NIHES:		
Study Design	2015	4.3
Biostatistical Methods I: Basic Principles	2015	5.7
Development Research Proposal	2015	2.5
Biostatistical Methods II: Classical Regression Models	2015	4.3
Introduction to Medical Writing	2015	2.0
Methodologic Topics in Epidemiologic Research	2015	1.4
Principles of Research in Medicine and Epidemiology	2015	0.7
Methods of Public Health Research	2015	0.7
Introduction to Public Health	2015	0.7
Primary and Secondary Prevention Research	2015	0.7
Social Epidemiology	2015	0.7
Fundamental of Medical Decision Making	2015	0.7
Elective Courses, NIHES		
Clinical Epidemiology	2016	5.7
Causal Inference	2016	0.7
Causal Mediation Analysis	2016	0.7
Methods of Clinical Research	2016	0.7
Women's Health	2016	0.9
Conceptual Foundation of Epidemiologic Study Design	2016	0.7
History of Epidemiologic Ideas	2016	0.7
Advances in Epidemiologic Analysis	2016	0.4
Preventing Failed Interventions in Behavioral Research	2016	1.4
Public Health in Low and Middle Income Countries	2016	3.0
Markers in Prediction Research	2016	0.4
Advances in Genomics Research	2016	0.4
Skills courses		
Intermediate Course in R, Erasmus MC	2018	1.4
Bayesian Statistics, Erasmus MC	2018	0.7
Principles of Epidemiologic Data Analysis, Erasmus MC	2018	0.7

A

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 Teeuw-De Kwart, (Clinical Psychology, Erasmus University Rotterdam). *Association of Maternal Childhood Trauma and Child Behavioral Problems"*	2018-2019	3.0
Duifje M.B. Wurzer, (Clinical Psychology, Erasmus University Rotterdam). *Prenatal Organophosphate Pesticide Exposure and Academic Achievement in Preadolescence: A Population-based Cohort Study in the Netherlands*	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		
Eraweb, European Commission Grant	2015	
The Royal Netherlands Academy of Arts and Sciences (KNAW) Ter Meulen Grant	2019	

1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours

WORDS OF GRATITUDE / DANKWOORD

"*None of us got to where we are alone. Whether the assistance we received was obvious or subtle, acknowledging someone's help is a big part of understanding the importance of saying thank you.*" - Harvey Mackay

Graag zou ik als eerste alle moeders, vaders en kinderen die deelnemen aan het Generation R onderzoek willen bedanken. Dit onderzoek zou onmogelijk geweest zijn zonder jullie hulp en trouwe participatie. Dankzij jullie bijdragen is de wetenschappelijke kennis wederom gegroeid. To the Generation R team, Professor Vincent Jaddoe and the MT, thank you for all the efforts and leadership. Claudia, Marjolein, Ronald, Patricia, Sunayna, and many others of the Generation R team, thank you to for all of your help and support.

This adventure would not have come to a successful ending without confidence and support of Professor Henning Tiemeier, from whom I learned psychiatric epidemiology and without whose teaching and supervision I would not have been able to take on the work presented in this thesis. Henning, you have guided my progress with a keen eye for detail and style, never fearing to suggest an idea that merely sounded good, and reminding me of the big picture at every turn. I thank you for reading every word I wrote and for providing me with careful feedback I always needed to hear. I am grateful for your supervision, for countless meetings and many insightful discussions, but most of all, for the support you have given me throughout every day of this process.

Professor Frank Verhulst, I am most grateful to having had the opportunity to study under your supervision over the past years. Frank, you have taught me pretty much everything about writing and countless other topics in academia as well. Thank you for mentoring me through this endeavor, for your valuable comments, and for your kind guidance and encouragement.

I dedicate this thesis to the late Professor Leslie A. Rescorla, who has been a mentor of mine since my studies in Kosovo. I was fortunate of having available the best support there can be. She was the cornerstone, the lighthouse and the guiding star of this whole process. If you could see me now! In particular, I would like to thank Professor Thomas Achenbach for making me feel so welcome at the department in Burlington. Tom, your profound knowledge and passion for research have humbled and inspired me, and I can only wish to develop into such inspiring mentor to others, as you have been to me. Thank you for everything. It has truly been an honor and a pleasure.

I would also like to thank all members of the reading committee and opposition. Professor M. Arfan Ikram, Professor Renske Keizer, and Professor Carlo Schuengel, I am honored that you agreed to be part of the reading committee. Professor Joan L. Luby, Professor Pol van Lier, and Professor Marinus H. van IJzendoorn, I am honored that you agreed to be part of the opposition committee. I appreciate the time and expertise devoted to the appraisal of this thesis.

I would like to express my deepest gratitude to my co-authors. Professor Vincent Jaddoe, thank you for your valuable comments and support. Professor Manon Hillegers, thank you for our wonderful collaboration and your valuable contributions. Dr. Tonya White, I am grateful for all of the helpful suggestions and comments I have received on the neuroimaging project. Professor Arfan Ikram, thank you for all of your help, advice, and support. Dr. Jan van der Ende, thank you for being a calm, patient, and steady compass in the multidimensional world of statistics. Professor Jansen, Pauline, thank you for numerous helpful suggestions and comments, and warm support when I needed most. Professor Copeland, Bill, thank you for giving me the opportunity to work in your group, and for believing in me. I am grateful for many insightful discussions, suggestions, and for all of your support. You have truly been an inspiring mentor. Professor Lilly Shanahan, I am exceedingly grateful for all of the helpful feedback and support.

I would also like to thank some people of outstanding importance for my research. Ryan, you have been such a great support and one of my valuable guides in the neuroimaging world. With your confidence and kindness, you are one of my great examples. Thank you for all your feedback and encouragement, and most of all for your friendship. Scott, I feel lucky to have been able to work with you. I am grateful for your genuine interests in our projects, and your willingness to help. Thank you for investing time and providing interesting and valuable feedback. Sander (Snafer), thank you for your interest in my project and discussing it with me on many occasions. I am ever grateful for your friendship, for support, and most importantly for all the laughs. Nathalie, you are an incredibly kind, and genuine person. Thank you for all of the interesting discussions, and for the emotional support. Fadila, thank you so much for thinking with me, and for statistical support. Being able to bring across and discuss my work with you has been invaluable for developing my ideas. I have learned so much from your input.

Michiel, you have always been there for me. I am grateful in more ways than I can express for your support and encouragement over the years. Thank you for your wonderful friendship; I treasure and consider invaluable. Also, thank you for providing the most welcome sort of distraction when necessary, and most importantly for all the laughter. I greatly admire how you have integrated into the environmental and chemical world, and along the way have taught me all the truly important things.

For support, balance, focus, and timely distraction, I would like to thank my wonderful colleagues of the Behavioral group. Rosa, you make everyone around you better, without even realizing it. Many thanks for your constant support since the beginning of this journey. Desi, I have enjoyed many useful and entertaining discussions. Thank you for all of your support. Ivonne, you are simply amazing. Your patience and confidence continue to inspire me. Koen, my favorite Dutch teacher! Thank you for all of the fun conversations (Tot de grond,…!). Elize and Clair, thank you for all the nice conversations and support. Deborah, I already miss you! Thank you for providing me with support and friendship that I needed. Andrea, I still remember all emails about our syntaxes, great work. The trip to New York was better than I ever could have hoped, and I thank you for all that. Gosia, thank you for providing me with a friendly and inspiring environment to work and have fun. Runyu, thank you for many insightful discussions and rock steady support in the final stretch. Maria and Fernando, one of my favorite couples! It is always wonderful to see you and exchange views. Monica Lopez, your support and friendship over the last year have been invaluable. Alex, Annemarie, Cees, Charlotte, Elisabet, Hanan, Holly, Isabel, Jeremy, Laura P., Lisa, Lisanne, Lizzy, Lorenza, Louk, Mannan, Monica G., Moud, Nienke, Novika, Patricia, Philip, Sara, Serena, Tessa, thank you for all the great conversations, and I owe you a deep dept of gratitude for making it worth going into the department every day.

Carolina Silva, a truly positive force throughout this process. You have always been there for me, and I am lucky to call you my friend. Your friendship and support over the years have been truly a blessing.

Kathy, you were the first person I met when I came at the department, and I will never forget how welcome you made me feel from the outset. I deeply appreciate the fact that you always made room for my interests during our discussions. I'll be forever grateful for all of your support, and will always remember fondly the occasions when you and Peter opened your home to me. Thank you for patiently reading my Discussion, and for making sure to keep in touch every weekend. Linda, you made my life in Burlington incredibly easy and enjoyable. Thank you for everything and especially for having me over for your delicious dinners, and coffee breaks. Our discussions were always lively and although generally longer than planned, always ended too soon. Marina, I love your enthusiasm and look very much forward to how your career will develop. I am grateful to you and Victor for your friendship, for all delicious dinners, coffee breaks, and most of all for showing me the best of Vermont.

Arjola, Asdren, Blerim, Bruna, Emi, Enisa, Eralda, Fjorda, Gera, Jana, Kaltrina, Klea, Najada, Natyra, Olta, Qendrim, dhe Taulant, faleminderit për kohën, mbështetjen, dhe gjitha momentet që kemi kaluar bashkë.

Arta, Blerina, Eta, Freski, Nora B., Nora Rr., Rina, Shkelqim, Tina, Xhevi, dhe Zana, shumë faleminderit për shoqërinë e mrekullueshme dhe mbështetjen që më keni ofruar ndër vite.

Rreze, faleminderit për gjithë mbështetjen dhe shoqërinë e mirë që më ke ofruar gjithmonë. Faleminderit ty dhe familjes tënde të mrekullueshme për mikëpritjen dhe eksperiencen e paharruar që kalova në New York. Ti je vërtet një shoqe që une e admiroj! Je një dashuri!

Mimoza, Roland, Debora, dhe Denis, jeni familje e mrekullueshme. Shumë faleminderit për mikëpritjen, mbështetjen, dhe shoqërinë e mire që na ofroni në Rotterdam.

Dita, Vela, Albu, Zana, Enki, faleminderit shumë për mbështetjen që më keni dhënë, dhe veçanërisht për kujdesin ndaj mamit Tikit.

Gjithçka që kam arritur është falë mbështëtjes që më keni dhënë gjatë viteve, mami dhe babi. Kjo punë është rezultat i drejtpërdrejt i përgjegjësisë dhe edukimit të mrekullueshëm që më keni dhënë për të shfrytëzuar sa më mirë talentet e mia. Unë gjithmonë do të përpiqem të udhëhiqem nga ky mësim. Ju dua shumë! Agi, Flori, Nushi, Loli, Altina, jeni dashuria ime më e madhe. E di që nuk mund të vija në fund të këtij procesi pa mbështetjen e juaj pa kushte. Estri, Malda, Enes, Ergen, Eden, xuxat e mi më të mirë. Jam pafundësisht e lumtur për dashurinë që më jepni çdo ditë të jetës. Eneda, je mrekullia vet! Si ka mundësi që bisedat me ty çdo ditë me kanë sjell kaq shumë gëzim, edhe në momentet kur nuk isha e motivuar.

Tiki, ne kaq shumë vite që ne kemi ndarë bashkë, ti më ke mësuar, korigjuar, inkurajuar, dhe mbështetur mua në të gjitha gjërat. Faleminderit njëmijë herë! Përjetësisht!

ABOUT THE AUTHOR

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.