8-2020

Maternal and Adolescent Depression: The Role of Genetic Variability and Telomere Length

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Recommended Citation
Thompson, Amanda, "Maternal and Adolescent Depression: The Role of Genetic Variability and Telomere Length." Thesis, Georgia State University, 2020.
doi: https://doi.org/10.57709/18170078

MATERNAL AND ADOLESCENT DEPRESSION: THE ROLE OF GENETIC VARIABILITY AND TELOMERE LENGTH

by

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Under the Direction of Christopher Henrich, PhD

ABSTRACT

Research has found an association between depression, telomere length, and poor health. Interestingly, research has found children of mothers with depression might also have shorter telomeres. A mother's depression increases a child's risk for depression through heritability and environmental factors, which has deleterious effects for child health. Further, the 5-HTT genotype could moderate the effects of maternal depression on child some socioemotional outcomes, but the moderating effect of maternal depression on child telomere length and depression has not been tested. This study tested the moderating effect of 5-HTT genotype and child sex for the effect of maternal depression on child and adolescent depression through child telomere length. From a subset (N=2,884) of the large and diverse Fragile Families and Child Wellbeing dataset, we found no support for the mediation or moderation hypotheses. Additional research is needed to better understand the mechanisms through which maternal depression affects child depressive outcomes.

INDEX WORDS: Maternal depression, Adolescent depression, Telomere, Serotonin, Genotype

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by

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Arts

in the College of Arts and Sciences

Georgia State University

2020

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August 2020

DEDICATION

I am dedicating this thesis to my loving mother and father who have supported me with unwavering encouragement. I thank my mother for demonstrating the resolve and strength that I now try to emulate for others. I thank my father for his selflessness and for his sacrifices so my siblings and I could have an education. Lastly, I dedicate this thesis to my loving partner, Christopher. He has supported me and loved me during every step of my academic journey. He encouraged me to keep knocking on the door until it finally opened.

ACKNOWLEDGEMENTS

First, I would like to acknowledge my advisor and thesis chair, Christopher Henrich. I appreciate the time and support he has given me, and I am ever grateful for his support in pursuing such an unfamiliar research topic. I would like to acknowledge my appreciation for Rose Sevcik and Erin Tully who also supported my endeavors to explore a research topic that was unfamiliar. I sincerely appreciate how each member of my committee brought and applied their unique expertise in order to help me succeed.

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1 INTRODUCTION

Negative child outcomes associated with maternal depression on children extend far beyond the socioemotional wellbeing of her child. Children whose mothers have suffered from depression are at risk for poor health and psychopathology through both environmental and inheritance of genetic risk factors. Maternal depression is associated with child stress reactivity (Kennedy et al., 2015; Nelson, Allen, & Laurent, 2018), child telomere length, (Beijers, Daehn, Shalev, Belsky, & de Weerth, 2020; Gotlib et al., 2015; Nelson et al., 2018), and child depressive outcomes (Hughes & Gullone, 2008; Sanger, Iles, Andrew, & Ramchandani, 2015). Telomeres are the protective caps at the end of the chromosomes, and a shorter telomere length (TL) is associated with greater risk for depression (Darrow et al., 2016) and disease (Smith et al., 2019). Some children may be genetically more sensitive to the stress of a mother's depression and consequently at greater risk for depression and shorter TL. According to the genetic differential susceptibility hypothesis, some children have a greater sensitivity to their environment and an increased risk for psychopathology in the context of stress (Boyce & Ellis, 2005). Child TL and later depressive outcomes might vary as a function of genotypic risk for depression, but this theory has not been tested. Using a large and diverse dataset, this research tested the effect of maternal depression on adolescent depression mediated through child telomere length. Using multigroup structural equation modeling, this research also tested the effect of TL on adolescent depression moderated by genotypic risk and child sex. This research aimed to identify potential mechanisms through which maternal depression effects both child mental and physical wellbeing.

1.1 Maternal Depression

According to the National Academy of Sciences, about 15 million children are living with parents experiencing major or severe depression (Child Trends, 2014). Children whose mothers are depressed are at risk for depression through hereditary mechanisms, maternal cognitions, and a stressful homelife (Goodman & Gotlib, 1999). For example, maternal dysphoria has been associated with her child's greater risk for depression through decreased parental warmth (Cummings, Keller, & Davies, 2005). Maternal depressive symptoms have also been associated with child internalizing behavior through parenting stress (Palmer Molina, Negriff, Monro, & Mennen, 2018).

The effect of maternal depression can have larger implications for child wellbeing through both heritable and environmental pathways. This added stress of depression can impede a mother's ability to parent effectively hindering healthy child development (Goodman & Gotlib, 1999). For example, mothers experiencing depression can be withdrawn and emotionally unavailable or unresponsive to children (Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Further, maternal depression is associated with hostile parenting behaviors which has been linked to later depressive outcomes in both pre-school children (Dougherty, Klein, Rose, & Laptook, 2011) and adolescents (McLeod, Weisz, & Wood, 2007). Children of depressed mothers are vulnerable to depressive outcomes through multiple pathways because behavioral traits and psychopathology are both highly heritable.

The coping behaviors and cognitions of a mother with depression can be both inherited and learned by her children (Thompson, Kazantseva, & Gaysina, 2017). It remains unclear how much these inherited traits contribute to child depressive outcomes, but children who are genetically pre-disposed toward depression would theoretically be at greater risk when their

mothers are depressed during the early stages of development. Research has found that adolescents of mothers who experienced post-natal depression were at greater risk for affective disorders, but the risk was significantly higher among adolescents whose mother experienced post-natal and later depression (Halligan, Murray, Martins, & Cooper, 2007). This research suggests there are both inherited biological mechanisms as well as environmental effects that contribute to adolescent depression. There is also evidence to support an association between shorter TL and having a mother with depression (Gotlib et al., 2015; Nelson et al., 2018). TL is also both highly heritable (Costa et al., 2015; Njajou et al., 2007) and affected by early-life stress (Ridout et al., 2019). The stress of having a depressed mother could be a mechanism through which maternal depression affects child TL, but this stress likely also interacts with the child's genetic makeup. Given the high prevalence and consequences of maternal depression, the mechanisms underlying this increased risk for poor child outcomes deserve further investigation.

To cope with the stress of a mother suffering from depression, children have been found to develop emotion regulatory strategies that quickly alleviate stress at the cost of long-term functioning (Thompson, 2011; Thompson, Lewis, & Calkins, 2008). Children whose mothers experienced depression have been found to suppress their emotions (Goodman & Gotlib, 1999; Zahn-Waxler et al., 1984). These regulatory strategies and cortisol levels, interrupt the biological feedback loop that signals a restoration to baseline cortisol levels (Boyce & Ellis, 2005; Holsboer, 2000; Joos, McDonald, & Wadsworth, 2019). Overtime, this exposure to unhealthy cortisol levels can lead to greater oxidative stress and accelerated telomere attrition (Bucci, Marques, Oh, & Harris, 2016; Lee, Kim, & Choi, 2015).

Oxidative stress (Beijers et al., 2020; Nelson et al., 2018) refers to an imbalance of harmful free radicals caused by repeated activation of the body's stress response systems. High

levels of oxidative stress result from chronic or repeated activation of the body's stress response systems, specifically, the Hypothalamic Pituitary-Adrenal Axis. Oxidative stress promotes inflammation and impede the body's ability to maintain and repair telomeres by decreasing levels of the restorative enzyme telomerase (Betteridge, 2000). In a literature review, Michel and colleagues (2012) found higher levels of oxidative stress was associated with various forms of depression. This association between oxidative stress and depression could be a mechanism through which individuals with depression are at greater risk for poor health (Michel, Pülschen, & Thome, 2012). With repeated exposure to a mother's depressive behavior, a child's response may inadvertently increase the levels of oxidative stress through dysregulated psychobiological stress reactivity leading to unhealthy levels of cortisol, greater oxidative stress, and inability to maintain TL. Research has established an association between TL and risk for various diseases, but tests TL as a risk factor for depression is unclear given the lack of support for TL as a predictor of depression. Given the mounting support for associations between depression and TL, this study tested associations of maternal depression on child and adolescent depression mediated by child TL.

1.2 Stress and depression

The effects of maternal postpartum depression and maternal depressive symptoms are believed to affect child TL through repeated activation of the child's psychobiological response to stressors (Gotlib et al., 2015; Nelson et al., 2018). The stress-response system is largely comprised of the hypothalamic-pituitary adrenal axis (HPA) and the sympathetic adrenal medullary (SAM) system. These systems coordinate the body's psychobiological response to stressors through glucocorticoids, or corticosteroid hormones like cortisol. Chronic exposure to elevated levels of glucocorticoids in the early stages of development can increase the number of

glucocorticoid receptors in the amygdala and hippocampus are associated with an increased sensitivity to depression in the context of stress (Chen et al., 2019; Shonkoff, Boyce, & McEwen, 2009).

Children whose mothers experienced depression are at greater risk for altered atypical corticotropic reactivity. For example, an atypical cortisol response during stressful challenges was found among infants of mothers with Maternal Depressive Disorder (Azak, Murison, Wentzel-Larsen, Smith, & Gunnar, 2013). Research has also found atypical corticotropic stress reactivity among preschool children of parents with a history of depression and hostile parenting behavior (Dougherty, Klein, Rose, & Laptook, 2011). This body of research suggests that maternal depression may indirectly increase a child's risk for later mental and physical illness by altering the child's psychobiological response to stressors. This altered HPA reactivity may negatively impact telomere maintenance leaving the child vulnerable to psychopathology and illness.

1.3 Telomere biology and depression

Telomeres naturally degrade, or shorten, across the lifespan during a process of cellular replication known as mitosis (Ly et al., 2018). Unhealthy HPA reactivity can promote oxidative stress, dampening the body's ability to maintain and repair telomeres (Aschbacher et al., 2013; Şimşek, Yüksel, Kaplan, Uysal, & Aktaş, 2016). Currently, TL has not been found predictive of depression, but research has found depression is predictive of TL (Darrow et al., 2016; Shalev et al., 2014). Some have theorized the relation between depression and TL could be transactional, but few studies have considered the dynamic relation between TL and depressive symptoms (Verhoeven et al., 2018). The cellular damage caused by stress could theoretically lead to

depression, which could lead to even more cellular damage creating a cycle of poor mental and physical health.

Several meta-analyses find that shorter TL is associated with depression (Darrow et al., 2016; Ridout, Ridout, Price, Sen, & Tyrka, 2016; Schutte & Malouff, 2015; Smith et al., 2019). Research has also found an effect of depressive symptoms and symptom severity on later TL in adults (Verhoeven et al., 2014, 2018), but research has not reached a consensus on the role of TL prior to depressive symptoms. In a literature review, Epel and Prather (2018) concluded that TL, stress, and depression share a dynamic transactional relation, and TL could potentially mediate the effects of stress on depression, but this is unclear (Epel & Prather, 2018). Additionally, in a ten-year longitudinal investigation, Verhoeven and colleagues found no transactional relation between depressive symptoms and TL. However, there was a significant association between depressive symptoms and TL within each time point (Verhoeven et al., 2018, 2016).

Other research has aimed to unpack the transactional relation between TL and depression. In a prospective longitudinal study of Danish adults, those diagnosed with clinical depression had shorter TL cross-sectionally, but prospective TL data did not predict later depression (Wium-Andersen, Ørsted, Rode, Bojesen, & Nordestgaard, 2017). While research among adults mostly does not find shorter TL prior to depression, interesting research by Gotlib and colleagues (2015) found that adolescent daughters of mothers with MDD had shorter TL prior to their own experience with depression. In another study, Beijers and colleagues (2020) found no evidence of mediation by TL in the effect of maternal postpartum depression on child behavior, but this research did find that child TL predicted later rates of internalizing behavior (Beijers et al., 2020). Lastly, Nelson and colleagues (2018) found that maternal postpartum depression predicted shorter infant TL, mediated by HPA reactivity. Given the growing evidence that

children exposed to maternal depression are at risk for shorter TL, we hypothesized that children with greater exposure to maternal depression would have shorter TL. We also hypothesized, that child TL would mediate the effect of maternal depression on adolescent depression while accounting for previous child depressive symptoms.

It is important to note that not all children of depressed mothers experience depression. These differences may be a factor of genetic sensitivity toward depression. Individual differences at the genetic level could moderate the effect of maternal depression on adolescent depression, but this effect of genetic sensitivity is unclear. The genetic sensitivity to context hypothesis posits that some genotypes were more evolutionarily successful, thus creating a predisposition toward certain biological and behavioral traits. These traits can be evolutionarily advantageous in certain contexts but harmful in other circumstances (Boyce & Ellis, 2005). A predisposition toward heightened reactivity would be evolutionarily advantageous in extreme circumstances but less so in day to day society. Unfortunately, early-life adversity can shape the developing stress-response system toward a heightened state of reactivity, and there is evidence to suggest support the effect of early-life stress on the malleable HPA-axis in children (Joos, Wodzinski, Wadsworth, & Dorn, 2018) . When paired with early-life adversity such as a mother's hostile or withdrawn parenting behaviors, biological sensitivity can increase the risk for poor health and disease.

There is evidence to suggest that children are affected differently by maternal depression according to their genotypes. For example, Kennedy and colleagues found that prenatal maternal depression affected infant emotionality mediated by genetic variability (2017). Children with a biological sensitivity toward depression are likely at greater risk for heightened stress-reactivity in the context of maternal depression. This repeated activation of the child's HPA would

negatively affect the child's physical wellbeing, and this negative effect of maternal depression on the child's stress-reactivity could possibly be seen in the child's TL. Moreover, the child's genetic sensitivity might moderate the negative effects of maternal depression on the child's TL given the association between 5-HTT genotype and serotonin levels, but this has not been tested. The current study tested the effect of maternal depression on child TL and the effect of child TL on adolescent depression moderated by genetic variability.

1.4 Genotypic risk and moderation

Since a hallmark study by Caspi and colleagues (2003) found an interaction between stress, 5-HTT genotype, and depressive symptoms and suicidality, researchers have become increasingly focused on the role of the 5-HTT gene. The serotonin transporter gene (5-HTT) codes for proteins that transport serotonin between the synapses. This is especially salient to psychopharmacology given that psychiatric medications often act on the serotonin transporter to increase serotonin levels and decrease depressive symptoms (Lesch et al., 2016). Variations of 5-HTT genotype are associated with the serotonin transporter's efficiency and possibly a greater risk for depression in the context of stress (Caspi et al., 2003; Martin, Cleak, Willis-Owen, Flint, & Shifman, 2007; Pezawas et al., 2005). Specifically, the allelic expression of this gene is believed to moderate the serotonin transporter's efficiency in the context of stress.

In an extensive review, Klein-Gunnewiek and colleagues (2018) concluded that individuals with the short-short (SS) 5-HTT length polymorphism (5-HTTLPR) had a higher presence of atypical cortisol levels in the presence of stressful life events and were at greater risk for depressive outcomes (Klein-Gunnewiek, Homberg, & Kozicz, 2018). Briefly, length polymorphism refers to the variability of allele length. The allele is comprised of a repeated sequence of base-pair proteins, and the number of repeated base-pairs varies across individuals.

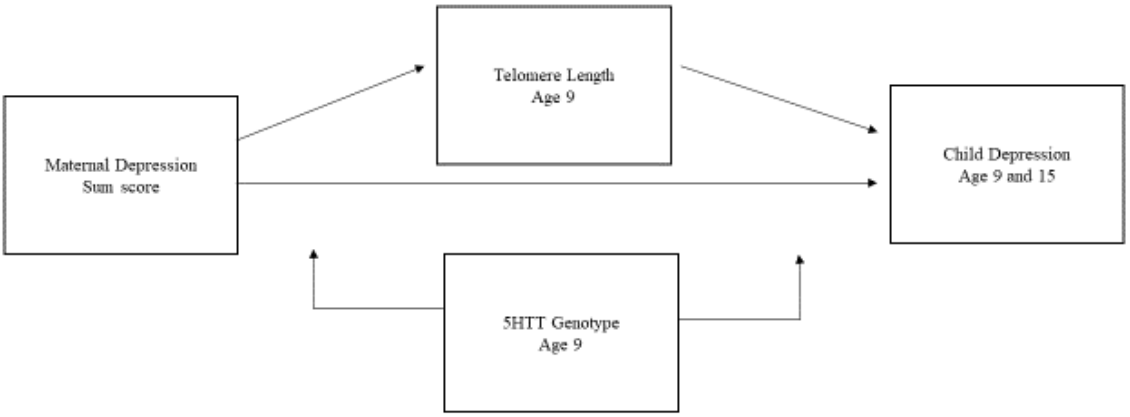
Each chromosome has two alleles located at the foci of the chromosome, one donated from each of the biological parents. Having one short allele, or two short alleles, is associated with decreased ability to maintain healthy levels of serotonin and increased risk for depression (Ancelin & Ryan, 2018; Ancelin et al., 2017). Thus the 5-HTT genotype could moderate the biological and environmental effects from the stress of maternal depression on adolescent depressive outcomes.

There is growing support for 5-HTTLPR as a moderator of stress on depression in both the child and adult literature (Klein-Gunnewiek et al., 2018), but the findings are inconsistent. For example, one meta-analysis found no evidence of moderation by 5-HTTLPR genotype for the effect of stress on major depression (Risch, Herrell, & Lehner, 2009), but in a later meta-analysis, Karg and colleagues (2011) found evidence of moderation by 5-HTTLPR. Evidence suggests moderation by 5-HTTLPR extends to the effect of maternal depression on child socioemotional outcomes. For example, research has found that the effect of postnatal (Araya et al., 2009) and prenatal depression (Green et al., 2017) on child emotionality was moderated by 5-HTTLPR. Moderation by child 5-HTTLPR has also been found for the effect of maternal history of depression on adolescent social information processing (Jacobs et al., 2011).

Research has tried to clarify the relation between genetics and depression, but findings remain inconsistent. For example, Clasen and colleagues (2011) found the effect of stress on rumination behaviors in young adults was moderated by 5-HTTLPR (Clasen, Wells, Knopik, Mcgeary, & Beevers, 2011). Conversely, Gibb and colleagues (2012) found that children of mothers experiencing MDD were at risk for ruminating behaviors, but found no support for moderation by 5-HTTLPR (Gibb, Grassia, Stone, Uhrlass, & McGeary, 2012). Further contributing to inconsistent findings, the SS allele is not consistently predictive of greater risk for

depressive symptoms across sex (Klein-Gunnewiek et al., 2018). For example, Hammen and colleagues (2010) found the effect of stress on depression was moderated by 5-HTTLPR among adolescent females only. Additionally, Eley and colleagues (2004) found an interaction between environmental stress, adolescent depression, and 5-HTTLPR in female adolescents only (Eley et al., 2004). Given these sex specific findings, it was hypothesized that the effects of maternal depression on adolescent depression would be moderated by child sex and genotypic risk.

Figure 1 The Theoretical Model



1.5 Connecting genetics, stress, and depression

The negative outcomes associated with depression are ubiquitous, including shorter TL (Verhoeven et al., 2016), atypical corticotropic stress-reactivity (Burke, Davis, Otte, & Mohr, 2005), and disease (Michel et al., 2012). Research suggests oxidative stress and HPA reactivity could be the pathway through which children of depressed mothers have shorter TL (Beijers et al., 2020; Gotlib et al., 2015; Nelson et al., 2018). The mediating role of child TL in the effect of maternal depression on adolescent depressive outcomes is unknown given the limited availability of studies. Currently, only one study has investigated the mediating role of child TL in the effect of maternal depression on child internalizing behavior (Beijers et al., 2020), but other studies

have found an associative relation between maternal depression and shorter child TL (Gotlib et al., 2015; Nelson et al., 2018). Given the increased risk for depression and poor health among adolescents whose mother was depressed, the biological mechanisms through which maternal depression leads to adolescent depression need to be explored.

The primary aim of this study was to test the mediation by TL hypothesis in the effect of maternal depression on adolescent depression. Secondly, the current study aimed to test the moderating role of 5-HTTLPR in the effect of maternal depression on adolescent depression mediated by child TL. Currently, the added genetic sensitivity toward depression in relation to maternal depression and child TL has not been explored. Lastly, the current study investigated possible child sex differences in the hypothesized effects. The 5-HTTLPR is frequently found to moderate the effect of maternal depression on child socioemotional outcomes, such as adolescent social information processing (Jacobs et al., 2011) and child emotionality (Araya et al., 2009; Green et al., 2017). The moderating effects of 5-HTTLPR for the effect of maternal depression on adolescent depression has not been tested, but the associative relations between these variables suggest that genetic sensitivity could importantly be a moderator.

2 METHOD

Given the paucity of research in children, the mediating role of child TL is unknown. Further, the current models do not evaluate how genotypic risk for depression might moderate the effects of maternal depression on child TL, leaving unanswered questions about which children are more sensitive to maternal depression. This research tested for moderation by child sex and genotypic risk to further clarify who is most vulnerable to the effects of maternal depression. The current study conducted secondary analyses using data from the Fragile Families and Child Wellbeing (FFCW) study. The FFCW study aimed to identify risk and protective

factors for youth born to families at high risk for dissolution and poverty by oversampling unwed mothers from large urban cities across the US. Through secondary analysis of this dataset, the following hypotheses were tested:

1.) There would be an effect of maternal MDE on child depressive symptoms (Fig. 2, Path C).
2.) This effect would be mediated through child TL (Paths A & B).
3.) The effect of maternal MDE on child TL would be moderated by 5-HTTLPR (Paths Xa)
4.) The effect of maternal MDE on child depressive symptoms would be moderated through 5-HTTLPR (Path Xc)
5.) The effect of child TL on child depressive behaviors would be moderated through 5-HTTLPR (Path Xb)

Additionally, possible sex differences in the models' paths were investigated.

2.1 Participants and procedures

The FFCW study sampled a cohort consisting of nearly 5,000 with children born between 1998-2000 across several large US cities. Recruitment targeted unwed mothers to oversample families at high risk for dissolution and poverty. The FFCW is funded largely in part by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) award number R01HD36916, R01HD39135, and R01HD40421 (Fragile Families and Child Wellbeing Study, 2019). The FFCW study includes data collected at birth and ages three, five, nine, and fifteen for each focal child. Mother, father, child and primary caregiver participated in the study across the various waves. Stratified random sampling was used to identify cities for the first cohort, limiting criteria to cities of 200,000 or more. Random sampling was used to identify cities for the second cohort. For this study, (N= 2,884) complete genetic

data was available for 2,859 children. Mothers were typically in their mid-twenties at the birth of the child (*M*= 25.0, *SD*=5.92) with at most a high school degree and on average living above the poverty line (Table 2). Most children identified as Black or African American (Black/ African American= 41.7%) and were reported to be in good health at one year of age. Additional demographic information is provided below.

Table 1 Descriptive Statistics

Variable	Mean	Min	Max	N
Child TL	8.06	3.15	19.71	2480
Mother MDE	0.73	0.00	4.00	2402
Child CBCL age 3	0.51	0.00	1.73	2276
Child CBCL age 9	0.19	0.00	2.00	2831
Poverty Ratio	2.27	0.00	14.90	2348
Mother Education	0.66	0.00	3.00	2878
Child Health age 1	1.51	0.00	5.00	2723
Mother age at birth	25.01	15.00	43.00	2881
Mother health age 1	2.23	1.00	5.00	2733
Child Race	0.48	0.00	1.00	2520
Mother TL	6.66	2.79	16.16	2397
Child CESD-SF age 15	2.31	1.00	9.60	2608
Child CBCL age 15	0.25	0.00	2.00	2712

Table 2 Race and Ethnicity

White only, Non-Hispanic	15.6%
Black/African American only, Non-Hispanic	41.7%
Hispanic/Latino	23.2%
Other only, Non-Hispanic	2.3%
Multi-racial, Non-Hispanic	4.6%
Missing	12.6%

3 MEASURES

Table 3 Measures Used Over Time

Construct	*Birth*	*Age 1*	*Age 3*	*Age 5*	*Age 9*	*Age 15*
1. Mother, CIDI-SF-SF	x	x	x	x		
2. Mother report, CBCL			x		x	x
3. Child report, CESD-SF						x
4. Child telomere length						
6. Mother telomere length					x	
7. Child gene candidate 5-HTT					x	
8. Poverty- ratio	x					
9. Demographics	x					
10. Child and maternal health		x				

3.1 Maternal depression

The major depressive episode subscale questions from the Composite International Diagnostic Interview Short Form were used to measure maternal major depressive episodes (MDE). These questions pertained to the severity and frequency of feelings of dysphoria and anhedonia within the past year. Portions of the CIDI regarding recency, persistence, and impairment were not included in the short form interview. Interviewers calculated a probability that represents the likelihood the respondent would have been diagnosed with a major depressive episode if having completed the entire questionnaire. The probability of having been diagnosed as a case has both a liberal and conservative probability cut point. According to Kessler, Andrews, and Mroczek (1998), the liberal cut point is met when a participant endorses the dysphoric stem question while endorsing frequency of at least half of the day. Participants endorsing all of the anhedonia questions can also meet the liberal cut point (Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998). According to Walters (2002), the more conservative cut point requires that participants report symptom frequency at least most of the day in addition to endorsing the dysphoric stem question. For the purposes of the current study, the liberal cut point was used.

The CIDI-SF is widely used and is accepted by the World Health Organization as a diagnostic tool for MDE. Further, the WHO accepts the abbreviated short form of the CIDI-SF as a diagnostic tool for MDE (Ghimire, Chardoul, Kessler, & William, 2013; Kessler et al., 1998). The FFCW scored this data as a case based on liberal clinical thresholds to increase variability (1=case, 0= not a case). Each MDE across child ages 0, 1, 3, and 5 years was then summed to create a total number of MDE (table 1) for a maximum score of four (0= no MDE, 4= 4 MDE). By using a sum score, the data are more likely to represent the child's exposure to the chronic emotional stress experienced through exposure to maternal MDE.

3.2 Child depression

The Center for Epidemiological Studies Depression scale Short Form (CESD-SF) was administered to the participating focal child at age 15 (wave 6). The CESD-SF-SF was used to calculate child depressive symptoms using five items (I feel I cannot shake off the blues even with help, I feel sad, I feel happy, I feel life is not worth living, I feel depressed). The five-item Likert scale was recoded such that higher values indicated higher levels of symptoms (1=strongly agree, 2= somewhat agree, 3=somewhat disagree, and 4= strongly disagree). These five items have been found to reliably measure symptoms associated with depression (Radloff, 1977). The five-item short form has even been found more reliable than the full scale across several ethnic-racial groups (Perreira, Deeb-Sossa, Harris, & Bollen, 2005). A recent publication using the FFCW data using the CESD-SF has been found to have a coefficient alpha of .76 (Mathew, Hale, & Chang, 2019).

Child depressive behavior prior to child TL measure was assessed at age three and then again at age nine and 15 years using maternal report of the Child Behavior Checklist (CBCL) depression subscale (Achenbach, 1991; Achenbach, Verhulst, Baron, & Althaus, 1987). The

CBCL contains eight subscales including anxious depressive behavior. Mothers were asked to answer questions regarding the child's behaviors on a Likert scale (0= not true, 1=sometimes or somewhat true, 2= very true or often true of her child). This scale contains 11 items and maintains reasonable reliability for the FFCW full sample at ages three (α=.62) and ages nine (α=.78) (Bendheim-Thoman Center for Research on Child Wellbeing & Columbia Population Research Center, 2018; Hall & Population, 2013). Separate models were created at age 15 for both the CBCL and the CESD-SF to compare outcomes with child reported and mother reported measures.

3.3 Genotype

When the focal child was nine years old, DNA were collected by salivary assay, using the Oragane-DNA Self-Collection kit, from mother (*N*=2760) and child (*N*=2882). This kit maintains and purifies the sample using ethanol-precipitation protocols used to produce DNA weights within the sample. Samples were then mailed to Westat for safe storage and then mailed to Princeton University's Molecular Biology Laboratory for analysis. Specimen vials had a barcode which corresponded to participant identification number. When data were extracted, researchers followed the Oragene Protocol Manual Purification of DNA. Data were then stored in DNA Genotek kits, from which the researchers used the DNA Genotek kits manufacturer's protocol to purify the DNA.

The 5-HTT gene candidate was then assessed for short and long allelic expression using quantitative polymerase chain reaction (qPCR) and electrophoresis. qPCR requires that DNA specimen undergo multiple temperature manipulations to produce several copies for a targeted portion of the DNA. DNA replication was manipulated by adding the Taq polymerase to the specimen. The primer corresponding to the gene candidate of interest was added to initiate

replication. Finally, data were visualized using the gel electrophoresis technique which sends the extracted DNA through a gel matrix using electrical currents. These visualizations were used to analyze short and long repeat alleles within the 5-HTT gene candidate.

Short alleles were considered indicative of risk and coding was modeled after previous research. In another study using the FFCW, Mitchell and colleagues summed short alleles to form a genetic sensitivity score (Mitchell et al., 2014). Recall that alleles are comprised of repeated base-pair proteins. According to the FFCW, 14 repeats or less was considered short (short=S), and 16 or more repeats was considered long (long=L). For the purpose of this research, the number of risk alleles (the short alleles) were summed for a maximum score of two (S= 1, Long=0). For example, a heterozygous individual would have one short and one long allele and a score of one (SL=1) while a homozygous individual would have two short alleles and a score of two (SS=2). This method of sum scores is recommended for individual level data (Choi, Mak, & O'Reilly, 2018) and has been used in prior research using the FFCW data (Mitchell et al., 2011).

3.4 Telomere length

Telomere length was derived from DNA sampling using qPCR method to determine absolute TL. From the qPCR technique, an average TL for the chromosome tested was produced and is described in detail in a review by Montpetit and colleagues (2014). FFCW states this average is the combination of three assays taken from the sample. Variation TL was normalized using the geometric mean of a reference DNA sample. The shortest and longest 1% of TL data were removed. A normal distribution of TL was then created using log transformation. According to Montpetit and colleagues' review of TL methodology, this method is limited by using an average as opposed to absolute TL (or aTL) (Montpetit et al., 2014). Montpetit and

colleagues (2014) concluded that qPCR is a widely accepted methodology and is often preferred for large studies. According to FFCW, incomplete genetic data included insufficient sample donation and cannot be analyzed (*n*=25).

4 COVARIATES

In the review by Klein-Gunnewiek and colleagues (2018) common differences in the interaction between 5-HTTLPR, stress, and depression emerged across sex, age, SES, and life experiences, warranting further investigation into group differences. This finding builds upon an earlier review by Uher and McGuffin (2010) which also found sex differences in the moderating effects of 5-HTTLPR. Given these findings and other findings of sociodemographic differences, the following variables were measured shortly after the child's birth and considered as covariates: income-to-needs ratio, health, and education.

4.1 Poverty and education

Rates of postpartum depressive symptoms can be eleven times higher among mothers experiencing multiple poverty-related risk factors such as unemployment or low income (Goyal, Gay, & Lee, 2010). To account for differences in depressive symptoms among mothers, economic hardship was treated as a covariate. FFCW provided a poverty ratio which was calculated by dividing total household income by the U.S. Census Bureau's official criteria for poverty threshold. There are also recent findings that suggest an interaction between economic hardship and biology. For example, male children from disadvantaged backgrounds were found to have shorter TL (Mitchell et al., 2014), and moderating effects of the 5-HTT gene were found on SES and postpartum depression (Mitchell et al., 2011). Educational attainment is also correlated with TL (Steptoe et al., 2011). Using self-reported data from the mother, education at

birth of child was treated as a covariate (1=at most a high school degree, 0=more than a high school degree).

4.2 Health and maternal age

Health outcomes such as Alzheimer disease, diabetes, and certain cancers are associated with shorter TL (Smith et al., 2019). Maternal self-report of overall perceived health at year one was considered as covariates. Mothers were asked “In general, how is your health?” and “In general, how is your child’s health?”. Data were coded such that lower numbers are associated with better health (1=excellent, 5=poor). This measure has been used in publications regarding both children and parents participating in the FFCW study (Huang & Lee, 2008; Zhang, De Luca, Oh, Liu, & Song, 2019; Zhang, Padilla, & Kim, 2017).

Lastly, several studies have found that TL is highly heritable and associated with parent health (Costa et al., 2015; Njajou et al., 2007; Nordfjäll, Larefalk, Lindgren, Holmberg, & Roos, 2005). Child TL is frequently associated with maternal TL, and this association is believed to be explained by both environmental and genetic factors (Hjort et al., 2018; Nguyen et al., 2019; Whiteman, Goswami, & Salihu, 2017). Maternal TL at age 9 was used as a covariate in the model. Building on these previous findings, maternal TL was treated as a covariate to better tease apart the effects of MDE on child TL.

Advanced maternal age at birth is associated with greater levels of maternal depressive symptoms (Muraca & Joseph, 2014) and higher rates of various depressive symptoms in adult daughters (Tearne,. et al., 2016). Further, research indicates that maternal age at birth of the child is associated with child TL (Eisenberg, Hayes, & Kuzawa, 2012; Martinez et al., 2019; Wulaningsih, Hardy, Wong, & Kuh, 2018). Educational attainment is also associated with

depressive symptomology and even has protective effects for some populations (Bauldry, 2015). Maternal age and educational attainment were treated as covariates.

4.3 Race and ethnicity

Lastly, racial and ethnic disparities in depression are ubiquitous (Abrams & Curran, 2009; Chae et al., 2016; Ertel, Rich-Edwards, & Koenen, 2011), and importantly, population stratification for genotype can contribute to spurious relationships within racial ethnic groups (Price, Zaitlen, Reich, & Patterson, 2010). Race was self-reported by children at age 15 years and then dummy coded (1=Black/ African American, 0=Not Black/ African American) as most children identified as Black or African American.

5 DATA ANALYSIS

All hypotheses were tested using Mplus V8. Of the original participating families (N=3,498), 2,884 children (Male=1,480) provided DNA samples for genetic testing. Given the large sample size, a conservative alpha was set to minimize type I error (α=.01). Initial group comparisons between those who did (n= 2,882) and did not submit (n=614,) DNA suggested there were no significant differences across racial groups for children at the conservative alpha level ($F(4)$=2.45, p<.04). Post-hoc comparison found that Hispanic children were more likely to provide DNA samples than African American children. No other differences on demographic variables or maternal MDE were found.

Of the children who did provide DNA, there were no significant difference in 5-HTTLPR across child sex. Children who provided DNA did differ significantly in 5-HTTLPR across race (F(4)=70.81, p<.00) (Table 5). A greater percentage of children identifying as Black or African American carried two long alleles. Similar population stratification has been found in other research; as typical in other research, genetic population stratification was accounted for by

including child race as a covariate (Price et al., 2010). Maximum likelihood methods with robust standard errors were used to construct the model as is appropriate for multigroup modeling (Graham, 2009). Full information maximum likelihood methods were used to address missing data. Further, covariates were brought into the model as endogenous variables and model-predicted imputations were used to prevent listwise deletion of participants with missing data.

Table 4 5-HTTLPR Frequencies within Racial Ethnic Groups

Racial ethnic group	LL	LS	SS
White only, Non-Hispanic	33.63%	46.64%	19.73%
Black/African American only, Non-Hispanic	57.33%	35.17%	7.50%
Hispanic/Latino	24.01%	49.24%	26.75%
Other only, Non-Hispanic	33.85%	44.62%	21.54%
Multi-racial, Non-Hispanic	43.41%	41.86%	14.73%
Total child sample	42.99%	41.51%	15.49%

Note: 5-HTTLPR risk score coding (LL=0, LS=1, SS=2)

5.1 Mediation hypotheses

Structural equation modeling was used to test the mediation by TL hypothesis using a single-group model for each outcome separately. The first model examined mediation of the effects of TL at age 9 on mother report of CBCL at age nine (Fig.2, path A). A second, longitudinal, structural equation model with a single group was used to test the mediation by child TL at age 9 hypothesis using mother report CBCL at age 15. A third, longitudinal, structural equation model with a single group was used to test the mediation by child TL hypothesis using child self-report CESD-SF at age 15 (Fig. 2, Path B). All parameters were freely estimated (Fig 2., Paths A, B, and C), leaving 0 df in the model. The three mediational models were then tested for moderation by genotypic risk and then by child sex.

5.2 Moderation hypotheses

5.2.1 CBCL Age 9

A multigroup model was created from the mediational model using CBCL at age nine to test for moderation by genotypic risk with all paths freely estimated. Given the large gap in time between measurement of TL and depressive outcomes available in the FFCW dataset, concurrent outcomes at age nine were also tested for moderation. Groups of genotypic risk were created according to 5-HTTLPR. Equality constraints were then imposed to test for group differences across genotype on the parameters of interest. Specifically, the hypothesized paths (Fig. 2, Paths A and B) and the path from CBCL at age three to child TL were constrained to be equal across groups, leaving 4 df in the model. The constrained model was then compared to the freely estimated model using fit indices (CFI and TLI) to see if the constrained model fit significantly worse. This same mediational model was then tested for moderation by child sex with all paths freely estimated, leaving 0 df in the model. Equality constraints were then imposed to test for group differences across child sex on the parameters of interest. Specifically, the hypothesized paths (Fig. 2, Paths A and B) and the path from CBCL at age three to child TL were constrained to be equal across child sex, leaving 8 df in the model. The constrained model was then compared to the freely estimated model using fit indices (CFI and TLI) to see if the constrained model fit significantly worse.

5.2.2 CBCL Age 15

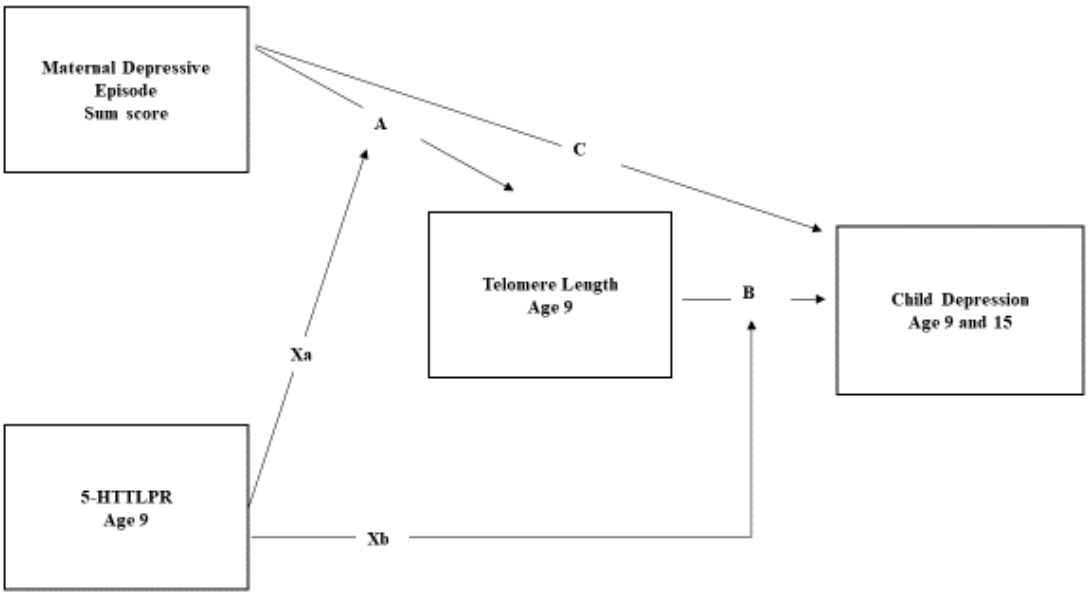
The longitudinal mediational model using CBCL at age 15 was then tested for moderation by genotypic risk with all paths freely estimated. Equality constraints were then imposed to test for group differences across genotype on the parameters of interest. The constrained model was then compared to the freely estimated model using fit indices to see if the

constrained model fit significantly worse. Similarly, the longitudinal mediational model was tested for moderation by child sex using the same constraints. The constrained model and then compared to the freely estimated model using fit indices.

5.2.3 CESD-SF Age 15

The longitudinal mediational model using child report of CESD-SF at age 15 was then tested for moderation by genotypic risk with all paths freely estimated. Equality constraints were then imposed to test for group differences across genotype on the parameters of interest. The hypothesized paths (Fig. 2, Paths A, B, and C) and the path from CBCL at age three to child TL were constrained to be equal across groups, and the constrained model was then compared to the freely estimated model. Similarly, the longitudinal mediational model was tested for moderation by child sex using the same constraints, and the constrained model was then compared to the freely estimated model.

Figure 2 The Analytic Model



6 RESULTS

6.1 Descriptive statistics

Initial inferential statistics revealed a nearly significant negative correlation between mother report of child depressive behaviors at age three with child TL at age nine, r= -.051, p<.05. As expected, maternal report of child CBCL depressive behaviors was significantly correlated across ages three, nine, and fifteen. Maternal MDE was also significantly correlated with maternal report of child depressive behavior at ages three, nine, and fifteen (Table 5). Interestingly, maternal MDE was not significantly correlated with child report of depressive symptoms at age 15 using the CESD-SF, or with child TL at age nine.

Table 5 Correlations

		1	2	3	4	5	6	7	8	9	10	11	12	13
1	Child TL	1												
2	Mother MDE	-0.01	1											
3	Child CBCL age 3	-0.04	0.18*	1										
4	Child CBCL age 9	0.03	0.20*	0.20*	1									
5	Poverty Ratio	0.05*	-0.10*	-0.17*	-0.01	1								
6	Mother Education	-0.05	0.05*	0.24*	0.02	-0.40*	1							
7	Child Health age 1	0.03	0.09*	0.15*	0.11*	-0.11*	0.10*	1						
8	Mother age at birth	0.06*	-0.05*	-0.11*	0.03	0.30*	-0.32*	-0.01	1					
9	Mother health age 1	0.01	0.26*	0.11*	0.11*	-0.15*	0.10*	0.23*	0.02	1				
10	Child Race	-0.03*	0.05*	0.06*	-0.10*	-0.17*	0.13	0.01	-0.12*	0.00	1			
11	Mother TL	0.32	0.01	0.03	0.01	-0.01	0.01	0.05*	-0.05	-0.01	0.02	1		
12	Child CESD-SF age 15	0.01	0.01	0.03	0.02	-0.02	0.03	-0.02	-0.02	0.02	0.01	0.04	1	
13	Child CBCL age 15	0.02	0.17*	0.16*	0.33*	0.00	0.05	0.08*	-0.03	0.13*	-0.12*	0.00	0.05	1

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

6.2 CBCL Age 9

From the single group model, results did not support an effect of MDE on child depressive behaviors at age 9 mediated by child TL. We found no significant direct effect of maternal MDE on child TL (Table 7). Maternal MDE had a direct effect on child depressive

behaviors at age nine (β= .03, p<.00) as expected. Additionally, the direct effect of child behaviors at age three on child TL trended toward significance (p = .06). Of the other covariates, only a mother's age (β= .03, p<.00) and TL (β= .42, p<.00) had an effect on child TL. Of the covariates, only a child's health at age one (β= .02, p=.01) and a child's race (β= -.05, p<.00) had a significant effect on child CBCL at age nine. That is, children with older mothers at birth were likely to have longer TL, and children with poorer health or who identified as Black or African American had higher levels of depressive behavior.

From the multigroup genotypic risk model, we found no support for the moderation hypothesis by 5-HTTLPR. The constrained model did not fit significantly worse than the freely estimated model (X^2(8)=8.63, *CFI*=.99, p=.38) meaning there was no moderation by genotype, and hypothesized paths did not differ between genetic risk groups. Lastly, we found no support for moderation by child sex. The model that constrained paths to be equal between boys and girls did not fit significantly worse than the freely estimated by sex model (X^2(4)=7.670, *CFI*=.991, p=.105), thus we found no support for moderation of the hypothesized paths by child sex. Paths for the unconstrained multigroup models are included in Appendix B.

6.3 CBCL Age 15

From our single group, we found no support for mediation by child TL (Table 8). We found no significant direct effects of maternal MDE on child TL (Table 8). We found no effects of child TL on adolescent depressive behaviors. Like the age nine single-group model, the direct effect of child depressive behaviors at age three on child TL was trending toward significance (β =-.04, p=.06). As expected, there were direct effects of MDE on adolescent depressive behaviors at age 15 (β =.13, p<.00). Meaning, adolescents were more likely to experience higher levels of depressive behaviors as the number of maternal MDE increased. Of the covariates, only maternal

TL (β =.32, p<.00) and age (β =.06, p<.00) had a significant effect on child TL, with maternal TL have a much greater effect than age. Child race (β =-.14, p<.00) and maternal health (β =.08, p<.00) had a significant effect on adolescent depressive behaviors at age 15. This suggests that children who identified as African American or Black reported higher levels of adolescent depressive behaviors like findings in the age nine CBCL model. There was a significant effect of previous child depressive behaviors at age three on adolescent depressive behaviors (β =.13, p<.00) that was equal to the effect of maternal MDE.

In our multigroup model testing the moderation hypothesis of genetic sensitivity, there was no support for moderation by 5-HTTLPR. The constrained model did not fit significantly worse than the freely estimated model (X^2(8)= 6.64, p=.58, CFI= 1.0). In our multigroup model testing the hypothesis of moderation by child sex, there was no support for moderation. The constrained model did not fit significantly worse than the freely estimated model (X^2(4)= 6.36, p=.17, CFI= .99). Paths for the unconstrained multigroup models are included in Appendix B.

6.4 CESD-SF Age 15

From our single-group model, we found no support for the mediation by TL hypothesis (Table 9). There was no effect of child TL on adolescent depressive behaviors. There was no direct effect of MDE on child TL or adolescent depressive symptoms at age 15. Like the previous models, depressive child behaviors at age 3 had an effect on child TL that was trending toward significance (β = -.04, p=.05). Of the covariates, a mother's health, education, and TL all had a significant effect on child TL with maternal TL having the largest effect (β =.48, p<.00). Surprisingly, there were no significant effects of covariates on child depressive symptoms.

From the multigroup model, we found no support for the genetic sensitivity hypothesis. The constrained model did not fit significantly worse than the freely estimated model

($X^2(8)=9.76$, *CFI*=.99, $p=.28$) suggesting there was no moderation by genotype. In our multigroup model testing the hypothesis of moderation by child sex, there was no support for moderation. The constrained model did not fit significantly worse than the freely estimated model at a conservative alpha level ($X^2(4)=11.382$, *CFI*=.967, $p=.023$). Even though the p-value did not meet the conservative alpha level of .01, there were slight differences of interest that emerged between the child sex groups (Appendix A, Appendix B Table 13).

Table 6 Model Fit

Model	*N*	X^2	*df*	*p*	*CFI*
CBCL age 9, LPR Constrained	2857	8.63	8.00	0.38	1.00
CBCL age 15, LPR Constrained	2857	6.64	8.00	0.58	1.00
CESD-SF age 15, LPR Constrained	2857	9.76	8.00	0.28	0.99
CBCL age 9, Sex Constrained	2884	7.67	4.00	0.11	0.99
CBCL age 15, Sex Constrained	2882	6.36	4.00	0.17	0.99
CESD-SF age 15, Sex Constrained	2882	11.38	4.00	0.02	0.97

Table 7 Single Group Child CBCL Age 9

		β	S.E.	*p*
Child TL age 9	Maternal MDE	-0.02	-0.32	0.75
	Poverty-ratio	0.02	0.86	0.39
	Mother education	-0.08	-0.58	0.56
	Child health age 1	0.07	0.95	0.34
	Mother age	0.03	2.96	0.00
	Mother health	0.05	0.92	0.36
	Child Race	-0.11	-0.99	0.32
	CBCL age 3	-0.38	-1.91	0.06
	Mother TL	0.42	13.22	0.00
CBCL age 9	Child TL	0.00	1.50	0.13
	Maternal MDE	0.03	6.48	0.00
	Poverty-ratio	0.00	0.88	0.38
	Mother education	0.00	-0.44	0.66
	Child health age 1	0.02	2.68	0.01
	Mother age	0.00	1.76	0.08
	Mother health	0.01	1.85	0.06

Child Race	-0.05	-5.91	0.00
CBCL age 3	0.13	7.53	0.00
Mother TL	0.00	-0.47	0.64

Note. S.E. = standard error. Std. = fully standardized estimate.

Table 8 Single Group Child CBCL Age 15

		β	S.E.	*p*
Child TL age 9	Mother MDE	-0.01	0.02	0.75
	Poverty-ratio	0.02	0.02	0.39
	Mother education	-0.01	0.02	0.57
	Child health age 1	0.02	0.02	0.36
	Mother age at birth	0.06	0.02	0.00
	Mother health	0.02	0.02	0.35
	Child race	-0.02	0.02	0.34
	Mother TL	0.32	0.02	0.00
	Child CBCL age 3	-0.04	0.02	0.06
Child CBCL age 15	Child TL	0.02	0.02	0.30
	Mother MDE	0.13	0.02	0.00
	Poverty-ratio	0.04	0.02	0.08
	Mother education	0.02	0.02	0.29
	Child health age 1	0.03	0.02	0.18
	Mother age at birth	-0.03	0.02	0.15
	Mother health	0.08	0.02	0.00
	Child race	-0.14	0.02	0.00
	Mother TL	-0.02	0.02	0.51
	Child CBCL age 3	0.13	0.02	0.00

Note. S.E. = standard error. Std. = fully standardized estimate.

Table 9 Single Group Child CESD-SF Age 15

		β	S.E.	*p*
Child TL	Maternal MDE	-0.01	0.02	0.69
	Poverty-ratio	0.02	0.02	0.41
	Mother education	-0.01	0.02	0.55
	Child health age 1	0.02	0.02	0.35
	Mother age	0.06	0.02	0.00
	Mother health	0.02	0.02	0.33
	Child Race	-0.02	0.02	0.34
	Mother TL	0.32	0.02	0.00
	CBCL age 3	-0.04	0.02	0.05
Child CESD-SF age 15	Child TL	0.00	0.02	0.98
	Maternal MDE	0.00	0.02	0.86

Poverty-ratio	-0.01	0.03	0.69
Mother education	0.02	0.03	0.50
Child health age 1	-0.04	0.02	0.09
Mother age	0.00	0.02	0.93
Mother health	0.03	0.02	0.26
Child Race	0.00	0.02	0.96
Mother TL	0.04	0.02	0.06
CBCL age 3	0.02	0.02	0.44

Note. S.E. = standard error. Std. = fully standardized estimate.

7 DISCUSSION

This investigation is the first test of whether the effect of maternal depression on child and adolescent depressive outcomes is mediated by child telomere length (TL). This research adds to our current understanding of the biological mechanisms that maternal depression may act on and why some children may be at more at risk by way of genetic sensitivity and child sex. The results of this study provide additional support that maternal depression in early childhood is associated with both child and adolescent depressive outcomes (Goodman et al., 2011; Sanger et al., 2015). The results of the current study, however, did not support the mediation or moderation hypotheses. These results leave the explanatory mechanisms for the effect of maternal MDE on child depressive outcomes largely unexplained. This research adds critical information to the mediation by TL hypothesis and adds evidence that TL may not predict depression in children. Other studies have found that children of mothers who experienced depression have shorter TL (Beijers et al., 2020; Gotlib et al., 2015; Nelson et al., 2018), but the current study is the first longitudinal test of direct effects of maternal MDE on child TL.

Further, this is the first study to test for moderation by 5-HTTLPR for the effect of maternal MDE on child TL and depressive outcomes. While other research supports moderation by 5-HTTLPR for the effect of maternal depression on child socioemotional outcomes (Eley et

al., 2004; Hammen, Brennan, Keenan-Miller, Hazel, & Najman, 2010; Jacobs et al., 2011), the current study did not find evidence of moderation. Some researchers believe that the 5-HTTLPR may not be a moderator for the effect of stress on depression, but it may interact with environmental stress and the HPA axis increasing the risk for depression (Ancelin & Ryan, 2018; Ancelin et al., 2017). Ancelin and colleagues (2017) found that older adults with the SS 5-HTTLPR had unhealthy cortisol levels and an increased risk for depression. Ancelin and Ryan (2018) proposed using 5-HTTLPR and neuroendocrine measures to inform treatment plans as some depression may be more resistant to treatment without appropriate pharmacological intervention. Currently, it remains unclear if this interaction between 5-HTTLPR and HPA stress reactivity can be generalized to the development of depression in children.

In addition to the primary aims of this study, several findings emerged regarding the effect of covariates on child TL. Similar to previous findings, in each of our three models, a mother's TL (Costa et al., 2015; Nordfjäll et al., 2005) and her age (Eisenberg et al., 2012; Martinez et al., 2019; Wulaningsih et al., 2018) had a significant effect on child TL. Contrary to previous findings, child health had no effect on child TL, but this could have been a limitation of the time intervals between measurements. Child health was measured at age one year while TL was measured at age nine years. The poverty-ratio also had no effect on child TL, in contrast to previous findings (Belsky & Shalev, 2016; Chae et al., 2016; Mitchell et al., 2014). The income used to calculate the poverty-ratio was provided by the mother at birth of the child, and this self-reported income data could be inaccurate. Alternatively, the poverty ratio could fail to adequately capture additional means of support or hardships.

Interestingly, the effect of child depressive behavior at age three on child TL at age nine trended toward significance in each of the models. The strongest effects emerged from the child

CESD-SF outcome model (β=-.04, p=.05). Much of the adult literature finds various forms of depression are predictive of shorter TL (Darrow et al., 2016), but currently, research has not tested this among children in a prospective study. Our hypothesis that maternal MDE would affect child TL while accounting for previous child depressive symptoms was not supported; however, the trending effect of child CBCL at age three on child TL at age 9 mirror the effects found in adult populations.

Other interesting effects emerged regarding the effect of covariates on child depressive outcomes. Maternal health and child race had significant effects on child CBCL at ages nine and fifteen but not on child CESD-SF at age fifteen. This could be due to differences in maternal versus child report or differences in measurement properties between the CBCL and the CESD-SF. The CBCL anxious depressive scale measures depressive behaviors while the CESD-SF measures depressive symptoms. It was expected that the covariates would affect these outcomes similarly, but there were no effects of any covariates on child CESD-SF at age fifteen.

7.1 Limitations and future directions

While the current study adds information to the mediation and moderation hypotheses, there are limitations to consider. Despite the strengths of the current study, it is limited by having only one measure of TL. Additional measures of TL over time could test the importance of recent compared to distal exposure to maternal MDE. Further, there is evidence to support an associative relation between depression and TL, but longitudinal research can account for additional stressors such as health or previous depression. The current study cannot account for naturally occurring individual differences in TL; however, the current study does account for the effect of previous child depressive behaviors on child TL. Lastly regarding TL, it has been debated whether salivary TL and leukocyte TL are equivalent. Research has demonstrated that

salivary TL can serve as an accurate measure, while other research finds that leukocyte TL is the most accurate measure (Montpetit et al., 2014). While leukocyte TL might be the superior measure, with such a large sample spanning across the US, leukocyte TL would prove extremely difficult to collect and costly to analyze.

Further, there are limitations to the measurement of maternal depression. There are large gaps in time between measurements in the Fragile Families and Child Wellbeing study could fail to capture recent effects of maternal MDE on child depressive outcomes and TL. These gaps in measurement also limit our ability to detect periods when maternal MDE might be more likely to interact with a child's genetic sensitivity. In addition to large gaps in time, maternal depression is measured using only a binary score from the CIDI-SF, which limits our ability to identify depressive symptomology that could be more harmful to children. The original FFCW dataset provided a binary outcome of caseness from the CIDI-SF only. This binary outcome prevents analyses using symptom severity, type, or duration on child outcomes. Regarding maternal depression, the current study also fails to capture the effect of maternal depression on parenting behaviors and the child's home. Likely, the effects of maternal depression affect children through these additional variables that are not captured in the present study.

The current study also focused on only the 5-HTT genotype. A polygenic approach might better capture the moderating effects of genotype, and this approach has been used successfully to test for moderation of behavioral traits in other research (Assary, Vincent, Keers, & Pluess, 2018). For example, genes associated with dopamine transmission (DRD2) and HPA reactivity (SLC6A3) have been found to moderate the effects of maternal depressive symptoms on infant cortisol (Kennedy et al., 2015). Other research has found genes related to dopamine (DRD2) and the 5-HTT gene moderated the effect of social disadvantage on TL in male children (Mitchell et

al., 2014).

Lastly, future research might aim to include the additional measure of HPA reactivity to address questions of other explanatory mechanisms not addressed by the current study. Several studies have found that 5-HTTLPR moderates the effect of maternal depression on child HPA reactivity, and dysregulated HPA reactivity can lead to shorter TL through increased levels of oxidative stress. For example, Dougherty and colleagues (2010) found that 5-HTTLPR moderated the effect of stress on cortisol levels in children ages 3-4 years. Gotlib and colleagues (2008) found that 5-HTTLPR moderated the effect of stress on cortisol levels in adolescent girls. Importantly, research has found evidence that HPA reactivity may be the link between maternal depression and child TL (Gotlib et al., 2015; Nelson et al., 2018), but to date, the effect of HPA reactivity on child TL and depressive outcomes moderated by 5-HTTLPR has not been tested.

7.2 Implications and conclusions

This research is the first to test the mediational hypothesis of child TL for the effect of maternal MDE on adolescent depressive outcomes with multigroup structural equation modeling in a large longitudinal dataset of diverse families. There are currently no studies which test the mediating effect of child TL at age nine for the effect of maternal depression on adolescent depression while also accounting for previous child depression. There remain large gaps in information regarding the effect of maternal depression on child TL and child socioemotional outcomes at varied stages in development. The current investigation uses TL at age nine which could add important information about the effects of maternal depression on child telomere biology prior to puberty. The current study is also only the second to date to test the mediating role of TL in the effect of maternal depression on child depression (Beijers et al., 2020), and it is

the only one with a sample of older children and adolescents who are ethnically, racially, and socially diverse.

While several studies have found support for moderation by 5-HTTLPR in the effect of maternal depression on child socioemotional outcomes, we did not find support for the moderation by 5-HTTLPR hypothesis. Given the growing evidence suggesting that children whose mothers experienced depression have shorter TL and altered corticotropic stress reactivity, future research endeavors might test the effect of maternal depression on child TL through other mechanisms not accounted for in this study. The exact pathways through which maternal depression affects children are unclear, but the present study aligns with previous research which finds that maternal depression places children are at greater risk for depressive outcomes. Future research should continue investigating the mechanisms through which maternal depression is associated to negative child outcomes, in order to develop effective prevention strategies to lessen the risk for transmission from mothers to their children.

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9 APPENDICES

9.1 Appendix A

There was not significant support at a conservative level for direct effects of child depressive behaviors at age three on child TL for male (β =-.045, p=.05) or female (β =-.044, p=.05) children. Of the covariates, only maternal TL had a significant effect on both male and female child TL. Interestingly, a mother's age had a significant effect on child TL for female children only (β =.108, p<.00). No covariates had a significant effect on adolescent depressive symptoms.

9.2 Appendix B

Table 10 Child CBCL age 9 Moderated by 5-HTTLPR

Group			β	S.E.	p
Low risk (LL)	Child TL	Maternal MDE	-0.04	0.04	0.32
		Poverty-Ratio	0.02	0.04	0.61
		Mother education	0.04	0.03	0.21
		Child health, age 1	0.01	0.03	0.84
		Mother age	0.06	0.03	0.05
		Mother health	-0.04	0.03	0.22
		Child race	-0.04	0.03	0.20
		CBCL age3	-0.05	0.03	0.11
		Mother TL	0.32	0.04	0.00
	CBCL age 9	Child TL	0.05	0.03	0.10
		Maternal MDE	0.16	0.04	0.00
		Poverty-Ratio	-0.02	0.03	0.53
		Mother education	-0.02	0.03	0.56
		Child health, age 1	0.07	0.04	0.06
		Mother age	0.02	0.03	0.54
		Mother health	0.05	0.03	0.14
		Child race	-0.09	0.03	0.00
		CBCL age3	0.14	0.04	0.00
		Mother TL	0.00	0.04	0.96
Medium risk (LS)	Child TL	Maternal MDE	0.05	0.04	0.15
		Poverty-Ratio	0.05	0.04	0.18
		Mother education	-0.02	0.04	0.54
		Child health, age 1	0.04	0.03	0.18
		Mother age	0.03	0.03	0.36
		Mother health	0.03	0.03	0.36
		Child race	0.00	0.03	0.95
		CBCL age3	-0.01	0.03	0.71
		Mother TL	0.25	0.04	0.00
	CBCL age 9	Child TL	0.00	0.03	0.95
		Maternal MDE	0.17	0.04	0.00
		Poverty-Ratio	0.02	0.04	0.55
		Mother education	-0.02	0.03	0.45
		Child health, age 1	0.05	0.03	0.14
		Mother age	0.06	0.03	0.02
		Mother health	0.03	0.04	0.33

		Child race	-0.14	0.03	0.00
		CBCL age3	0.21	0.03	0.00
		Mother TL	0.01	0.03	0.66
High risk (SS)	Child TL	Maternal MDE	-0.06	0.05	0.20
		Poverty-Ratio	-0.05	0.05	0.31
		Mother education	-0.14	0.06	0.02
		Child health, age 1	-0.01	0.05	0.78
		Mother age	0.10	0.05	0.05
		Mother health	0.14	0.05	0.01
		Child race	-0.03	0.05	0.57
		CBCL age3	-0.09	0.06	0.11
		Mother TL	0.49	0.05	0.00
	Child CBCL age 9	Child TL	0.04	0.06	0.52
		Maternal MDE	0.20	0.06	0.00
		Poverty-Ratio	0.10	0.06	0.07
		Mother education	0.05	0.05	0.37
		Child health, age 1	0.04	0.06	0.49
		Mother age	0.01	0.05	0.85
		Mother health	0.04	0.06	0.42
		Child race	-0.06	0.05	0.22
		CBCL age3	0.22	0.05	0.00
		Mother TL	-0.08	0.05	0.14

Note. S.E. = standard error. Std. = fully standardized estimate.

Table 11 Child CBCL age 9 Moderated by Child Sex

Group			*β*	S.E.	*p*
Male	Child TL	Mother MDE	-0.01	0.02	0.73
		CBCL age 3	-0.04	0.02	0.05
		Mother TL	0.30	0.03	0.00
		Poverty-ratio	0.01	0.03	0.77
		Mother education	-0.04	0.03	0.26
		Mother health	0.04	0.03	0.16
		Mother age	0.01	0.03	0.84
		Child health	0.05	0.03	0.10
		Child race	-0.03	0.03	0.37
	Child CBCL age 9	Child TL	0.03	0.02	0.12
		Mother MDE	0.16	0.03	0.00
		CBCL age 3	0.17	0.03	0.00
		Mother TL	-0.01	0.03	0.76

		Poverty-ratio	-0.01	0.03	0.86
		Mother education	0.01	0.03	0.87
		Mother health	0.05	0.03	0.12
		Mother age	0.06	0.03	0.03
		Child health	0.04	0.03	0.19
		Child race	-0.15	0.03	0.00
Female	Child TL	Mother MDE	-0.01	0.02	0.73
		CBCL age 3	-0.04	0.02	0.05
		Mother TL	0.34	0.03	0.00
		Poverty-ratio	0.03	0.03	0.33
		Mother education	0.01	0.03	0.87
		Mother health	0.00	0.03	0.94
		Mother age	0.11	0.03	0.00
		Child health	-0.01	0.03	0.73
		Child race	-0.02	0.03	0.56
	Child CBCL age 9	Child TL	0.03	0.02	0.12
		Mother MDE	0.16	0.03	0.00
		CBCL age 3	0.19	0.04	0.00
		Mother TL	-0.02	0.03	0.61
		Poverty-ratio	0.05	0.03	0.15
		Mother education	-0.02	0.03	0.42
		Mother health	0.08	0.03	0.02
		Mother age	0.00	0.03	0.93
		Child health	0.05	0.03	0.11
		Child race	-0.07	0.03	0.01

Note. S.E. = standard error. Std. = fully standardized estimate.

Table 12 Child CBCL Age 15 Moderated by 5-HTTLPR

Group			*β*	S.E.	*p*
Low risk (LL)	Child TL	Maternal MDE	-0.01	0.02	0.83
		Poverty-ratio	0.02	0.04	0.58
		Mother education	0.04	0.03	0.20
		Child health age 1	0.01	0.03	0.85
		Mother age	0.06	0.03	0.05
		Mother health	-0.05	0.03	0.14
		Child Race	-0.04	0.03	0.19
		Mother TL	0.32	0.04	0.00
		CBCL age 3	-0.05	0.02	0.04

	CBCL age 15	Child TL	0.02	0.02	0.39
		Maternal MDE	0.13	0.02	0.00
		Poverty-ratio	-0.01	0.03	0.68
		Mother education	0.04	0.03	0.25
		Child health age 1	0.03	0.03	0.32
		Mother age	-0.05	0.03	0.08
		Mother health	0.05	0.03	0.14
		Child Race	-0.17	0.03	0.00
		Mother TL	0.03	0.04	0.50
		CBCL age 3	0.13	0.03	0.00
Medium Risk (LS)	Child TL	Maternal MDE	-0.01	0.02	0.83
		Poverty-ratio	0.05	0.04	0.22
		Mother education	-0.02	0.04	0.63
		Child health age 1	0.05	0.03	0.14
		Mother age	0.03	0.03	0.42
		Mother health	0.04	0.03	0.17
		Child Race	0.00	0.03	0.93
		Mother TL	0.25	0.04	0.00
		CBCL age 3	-0.05	0.02	0.03
	CBCL age 15	Child TL	0.02	0.02	0.39
		Maternal MDE	0.13	0.02	0.00
		Poverty-ratio	0.06	0.04	0.09
		Mother education	0.02	0.03	0.58
		Child health age 1	0.05	0.03	0.15
		Mother age	0.00	0.03	0.99
		Mother health	0.11	0.03	0.00
		Child Race	-0.11	0.03	0.00
		Mother TL	-0.04	0.03	0.15
		CBCL age 3	0.15	0.04	0.00
High Risk (SS)	Child TL	Maternal MDE	0.00	0.02	0.83
		Poverty-ratio	-0.05	0.05	0.36
		Mother education	-0.15	0.06	0.01
		Child health age 1	-0.02	0.05	0.63
		Mother age	0.11	0.05	0.04
		Mother health	0.13	0.05	0.01
		Child Race	-0.03	0.05	0.55
		Mother TL	0.48	0.05	0.00
		CBCL age 3	-0.04	0.02	0.04

	CBCL age 15	Child TL	0.02	0.02	0.39
		Maternal MDE	0.12	0.02	0.00
		Poverty-ratio	0.14	0.07	0.03
		Mother education	0.02	0.09	0.84
		Child health age 1	-0.05	0.06	0.43
		Mother age	-0.06	0.06	0.32
		Mother health	0.11	0.05	0.05
		Child Race	-0.15	0.04	0.00
		Mother TL	-0.01	0.05	0.89
		CBCL age 3	0.08	0.06	0.18

Note. S.E. = standard error. Std. = fully standardized estimate.

Table 13 Child CBCL Age 15 Moderated by Child Sex

Group			*β*	S.E.	*p*
Male	Child TL age 9	Maternal MDE	0.04	0.03	0.18
		Poverty-ratio	0.01	0.03	0.73
		Mother education	-0.03	0.03	0.33
		Child health age 1	0.04	0.03	0.19
		Mother age	0.01	0.03	0.80
		Mother health	0.04	0.03	0.21
		Child Race	-0.03	0.03	0.38
		Mother TL	0.30	0.03	0.00
		CBCL age 3	-0.06	0.03	0.06
	CBCL age 15	Child TL	0.02	0.03	0.55
		Maternal MDE	0.12	0.03	0.00
		Poverty-ratio	0.05	0.03	0.11
		Mother education	0.02	0.03	0.62
		Child health age 1	0.04	0.03	0.19
		Mother age	-0.05	0.03	0.08
		Mother health	0.06	0.03	0.07
		Child Race	-0.12	0.03	0.00
		Mother TL	-0.01	0.03	0.66
		CBCL age 3	0.17	0.03	0.00
Female	Child TL age 9	Maternal MDE	-0.01	0.02	0.72
		Poverty-ratio	0.03	0.03	0.32
		Mother education	0.01	0.03	0.88
		Child health age 1	0.00	0.03	0.94
		Mother age	0.11	0.03	0.00
		Mother health	-0.01	0.03	0.76
		Child Race	-0.02	0.03	0.58
		Mother TL	0.34	0.03	0.00

	CBCL age 3	-0.04	0.02	0.05
CBCL age 15	Child TL	0.02	0.02	0.34
	Maternal MDE	0.12	0.02	0.00
	Poverty-ratio	0.03	0.03	0.32
	Mother education	0.03	0.03	0.35
	Child health age 1	0.03	0.03	0.30
	Mother age	-0.01	0.03	0.68
	Mother health	0.11	0.03	0.00
	Child Race	-0.15	0.03	0.00
	Mother TL	-0.02	0.04	0.63
	CBCL age 3	0.09	0.03	0.01

Note. S.E. = standard error. Std. = fully standardized estimate.

Table 14 Child CESD-SF Age 15 Moderated by 5-HTTLPR

Group			*β*	S.E.	*p*
Low risk (LL)	Child TL	Maternal MDE	-0.01	0.02	0.77
		Poverty-ratio	0.02	0.04	0.59
		Mother education	0.04	0.03	0.20
		Child health age 1	0.01	0.03	0.86
		Mother age	0.06	0.03	0.05
		Mother health	-0.05	0.03	0.15
		Child Race	-0.04	0.03	0.19
		Mother TL	0.32	0.04	0.00
		CBCL age 3	-0.05	0.02	0.03
	Child CESD-SF age 15	Child TL	0.00	0.02	0.94
		Maternal MDE	0.00	0.02	0.94
		Poverty-ratio	-0.02	0.04	0.56
		Mother education	0.00	0.04	0.91
		Child health age 1	-0.05	0.03	0.07
		Mother age	0.05	0.03	0.13
		Mother health	0.00	0.03	0.97
		Child Race	0.04	0.03	0.19
		Mother TL	0.06	0.03	0.07
		CBCL age 3	-0.01	0.04	0.89
Medium risk (LS)	Child TL	Maternal MDE	-0.01	0.02	0.77
		Poverty-ratio	0.04	0.04	0.24
		Mother education	-0.02	0.04	0.62

		Child health age 1	0.05	0.03	0.14
		Mother age	0.03	0.03	0.42
		Mother health	0.05	0.03	0.15
		Child Race	0.00	0.03	0.96
		Mother TL	0.25	0.04	0.00
		CBCL age 3	-0.05	0.02	0.03
	Child CESD-SF age 15	Child TL	0.00	0.02	0.94
		Maternal MDE	0.00	0.02	0.94
		Poverty-ratio	-0.01	0.04	0.71
		Mother education	-0.03	0.03	0.42
		Child health age 1	0.01	0.03	0.81
		Mother age	-0.07	0.03	0.04
		Mother health	0.02	0.03	0.61
		Child Race	-0.02	0.03	0.52
		Mother TL	0.01	0.03	0.67
		CBCL age 3	0.04	0.04	0.32
High risk (SS)	Child TL	Maternal MDE	-0.01	0.02	0.77
		Poverty-ratio	-0.05	0.05	0.36
		Mother education	-0.15	0.06	0.01
		Child health age 1	-0.02	0.05	0.66
		Mother age	0.11	0.05	0.04
		Mother health	0.13	0.05	0.01
		Child Race	-0.03	0.05	0.54
		Mother TL	0.48	0.05	0.00
		CBCL age 3	-0.05	0.02	0.04
	Child CESD-SF age 15	Child TL	0.00	0.02	0.94
		Maternal MDE	0.00	0.02	0.94
		Poverty-ratio	0.05	0.07	0.49
		Mother education	0.23	0.12	0.07
		Child health age 1	-0.11	0.07	0.08
		Mother age	0.04	0.06	0.54
		Mother health	0.10	0.06	0.08
		Child Race	-0.04	0.05	0.43
		Mother TL	0.07	0.06	0.21
		CBCL age 3	0.03	0.06	0.60

Note. S.E. = standard error. Std. = fully standardized estimate.

Table 15 Mediation of TL on Child CESD-SF Age 15 Moderated by Child Sex

Group			*β*	S.E.	*p*
Male	Child TL age 9	Maternal MDE	-0.01	0.02	0.66
		Poverty-ratio	0.01	0.03	0.78
		Mother education	-0.04	0.03	0.27
		Child health age 1	0.04	0.03	0.17
		Mother age	0.01	0.03	0.83
		Mother health	0.05	0.03	0.10
		Child Race	-0.03	0.03	0.40
		Mother TL	0.30	0.03	0.00
		CBCL age 3	-0.05	0.02	0.05
	Child CESD-SF age 15	Child TL	0.01	0.02	0.80
		Maternal MDE	0.00	0.02	0.89
		Poverty-ratio	0.01	0.03	0.79
		Mother education	0.01	0.03	0.80
		Child health age 1	-0.06	0.03	0.04
		Mother age	0.01	0.03	0.81
		Mother health	-0.01	0.03	0.72
		Child Race	0.05	0.03	0.08
		Mother TL	0.05	0.03	0.09
		CBCL age 3	0.01	0.03	0.74
Female	Child TL age 9	Maternal MDE	-0.01	0.02	0.67
		Poverty-ratio	0.03	0.03	0.34
		Mother education	0.00	0.03	0.89
		Child health age 1	0.00	0.03	0.95
		Mother age	0.11	0.03	0.00
		Mother health	-0.01	0.03	0.78
		Child Race	-0.02	0.03	0.57
		Mother TL	0.34	0.03	0.00
		CBCL age 3	-0.04	0.02	0.05
	Child CESD-SF age 15	Child TL	0.01	0.02	0.80
		Maternal MDE	0.00	0.02	0.89
		Poverty-ratio	-0.03	0.04	0.47
		Mother education	0.04	0.06	0.53
		Child health age 1	-0.01	0.04	0.77
		Mother age	-0.01	0.03	0.68
		Mother health	0.06	0.03	0.06
		Child Race	-0.05	0.03	0.08
		Mother TL	0.03	0.03	0.32

CBCL age 3	0.03	0.04	0.44

Note. S.E. = standard error. Std. = fully standardized