INFLAMMATION, MENTAL HEALTH, AND THE COVID-19 PANDEMIC: A PILOT STUDY WITH CHILD WELFARE SERVICE INVOLVED FAMILIES

by

SARAH R. HORN

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DISSERTATION APPROVAL PAGE

Student: Sarah R. Horn

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This dissertation has been accepted and approved in partial fulfillment of the requirements for the Doctor of Philosophy degree in the Department of Psychology by:

Dr. Philip Fisher	Chairperson/Advisor
Dr. Elliot Berkman	Core Member
Dr. Elizabeth Skowron	Core Member
Dr. Nicole Giuliani	Institutional Representative

and

Krista Chronister	Vice Provost for Graduate Studies

Original approval signatures are on file with the University of Oregon Division of Graduate Studies.

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DISSERTATION ABSTRACT

Sarah Rachel Horn

Doctor of Philosophy

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Title: Inflammation, Mental Health, and the COVID-19 Pandemic: A Pilot Study with Child Welfare Service Involved Families

The coronavirus (COVID-19) pandemic has posited unique challenges for families and significantly disrupted several aspects of children's environments. The pandemic is an ongoing risk experience, with young children being repeatedly exposed to multiple stressors, such as school closures, social isolation, material hardship, and worsening mental health. For child welfare service involved (CWS) families, these stressors may be amplified in both frequency and severity. For both caregivers and children, the pandemic-related cumulative environmental risk may also be reflected in parallel physiologic and neurobiological processes, such as the immune system. Alterations to immune level functioning may in turn correlate to children's current mental health and impact their future response to available support systems *and* life stressors. Using a longitudinal design, I evaluated the degree to which parental stressors, parent and child inflammation (C-reactive protein, assayed via dried blood spots), and parent and child outcomes changed from before the pandemic to during the pandemic. I investigated associations underlying these complex relationships. Pre-pandemic data was collected on 22 parent-child dyads between 2016-2019 and pandemic data was collected between August 2021- December 2021.

As predicted, household chaos significantly increased during the pandemic but was unexpectedly inversely associated with child's inflammation. Contrary to predictions, child's

mental health symptoms (i.e., behavioral problems and trauma symptoms) and parenting stress decreased from the pre-pandemic time point to the current study, though this was primarily accounted for by the child's age. Parent anxiety did not significantly change between timepoints. Parent depressive symptoms increased during the pandemic and parent inflammation significantly interacted with parent depression to predict the intensity of children's behavioral problems. Parent and child inflammation both increased between the pre-pandemic time point to the current study, though this change was not statistically significant. This initial pilot study identified important patterns among parent mental health, inflammation, and child well-being that should be evaluated in a larger sample. Further research will help to inform intervention efforts designed for parents and children most impacted by the pandemic.

CURRICULUM VITAE

NAME OF AUTHOR: Sarah R. Horn

GRADUATE AND UNDERGRADUATE SCHOOLS ATTENDED:

University of Oregon, Eugene

DEGREES AWARDED:

Doctor of Philosophy, Clinical Psychology, 2023, University of Oregon
Master of Science, Clinical Psychology, 2017, University of Oregon
Bachelor of Arts, Psychology, Spanish, 2013, University of Michigan (Ann Arbor)

AREAS OF SPECIAL INTEREST:

Clinical Psychology

GRANTS, AWARDS, AND HONORS:

Center for Study of Women in Society, Graduate Student Research Grant, University of Oregon, 2021

Center on Parenting and Opioids Training Grant, University of Oregon, 2021

Graduate Research Fellowship, National Science Foundation, University of Oregon, 2017

First Year Fellowship Award, University of Oregon, 2016

PUBLICATIONS:

Salisbury, MR, Roos, LE, **Horn, SR,** Peake, SJ, & Fisher, PA (2022). The effectiveness of KEEP for families of children with developmental delays: Integrating FIND video coaching into parent management training- Oregon Model, a randomized controlled trial. *Prevention Science*, 1-12.

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Book Chapters:

Blaisdell, K, **Horn, SR**, & Fisher PA (In press). Prevention strategies: Prevention and promotion in child mental health. *Handbook of Clinical Child Psychology: Theory to Practice.*

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I dedicate this Dissertation to my niece, Eliette Rose Horn, the “pandemic baby” with the most brilliant smile and spirit. May my research, and the work of dedicated scientists and psychologists, provide you with the better and safer world you deserve.

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Chapter 1: Introduction

The outbreak of the 2019 novel coronavirus (2019-nCoV) was officially declared the COVID-19 pandemic in March 2020 by the World Health Organization (WHO) (Cucinotta & Vanelli, 2020). As of July 3rd, 2022, the virus has spread to 221 countries and territories worldwide, with at least 549 million infections and over six million associated deaths (Dong, Du, & Gardner, 2020). At least 13.4 million children have tested positive for COVID-19 in the United States alone (American Academy of Pediatrics, 2022). While children are less susceptible to severe illness associated with the virus, the disease itself, and the measures implemented to reduce viral spread, have already exerted a significant impact on many school-aged children's psychological (e.g., mental health, e.g., Panchal et al., 2021) and physical health (e.g., activation of stress response systems, e.g., Cianfarani & Pampanini, 2021). The pandemic constitutes an ongoing form of adversity for children, which is amplified by the co-occurring pandemic-related adverse experiences that many children personally face, such as school closure and social isolation (Imran et al, 2020; Wong et al., 2020), as well as the problems encountered by the caregiver, including material hardship, financial stressors, and caregiver stress and mental health difficulties (Karpman & Zuckerman, 2021; Liu & Fisher, 2022, Memmott et al., 2021). Attention has been called to this "secondary pandemic," with concerns voiced on the degree to which pandemic responses are likely to contribute to deleterious outcomes for pediatric populations, including the potential for worsening mental health, increased risk of abuse or neglect, and widening gaps in school achievement (Wong et al., 2020). In short, for young children, the pandemic is a continuing cumulative risk experience, with many children being exposed

repeatedly to co-occurring stressors, all of which independently and collectively elevate the risk of socioemotional, behavioral, and physical health problems (Cianfarani & Pampanini, 2021).

Notably, for many children this cumulative environmental risk will also be reflected in parallel physiologic and neurobiological processes, in which children's stress response systems, such as immune systems, are likely to become frequently activated, overwhelmed, and eventually depleted (Wade et al, 2020). This is critical as alterations to stress response systems may in turn moderate how children respond to available supports in their lives as well as their response to present and future additional stressors (Wade et al., 2020). Further, not all children are at equal risk for experiencing pandemic-related adversities, perturbations to stress response systems, or corresponding negative behavioral or health consequences. Children from marginalized backgrounds, such as lower-income households, with child welfare service (CWS) involvement, and those from racial and ethnic minorities, are at greatest risk for experiencing these stressors and the subsequent short and long-term consequences stemming from the pandemic (Imran et al., 2020; Karpman & Zuckemran, 2021).

As the pandemic continues to unfold, there is a vital opportunity for innovative translational scientific progress to elucidate children's health trajectories and inform policy and practice. Translational neuroscience is a systematic, theory-driven approach that leverages basic and clinical neuroscientific knowledge to aid the development and optimization of clinical and public health policy and intervention (Horn et al., 2020a). In the context of the pandemic, bridging pre-pandemic data with new data collection will allow for a more nuanced understanding of the impact of the pandemic on children and their families. An advantage of translational neuroscience is the ability to integrate advanced neuroscientific measures, such as immune assays, with survey data on mental health and well-being (Horn et al., 2020a). This

approach, especially with the advantage of a rich pre-pandemic dataset, will connect basic and clinical findings to investigate children's functioning rigorously and holistically across multiple domains. In turn, the results gleaned from this study may inform prevention and intervention efforts to support children and families adversely impacted by the COVID-19 pandemic.

This dissertation is a follow-up study of parents and their school-aged children (6-10 years old) to assess the impact of pandemic-related stress on children's well-being relative to the last time the families were studied, in 2016-2019. Specifically, the current study includes a sample of parent-child dyads who, prior to the onset of the COVID-19 pandemic, had previously participated in a randomized controlled trial (RCT) of a parenting intervention (Nekkanti et al., 2020). In following up with these families, we can leverage pre-existing data to determine changes in types of parental stress pre-pandemic to mid-pandemic as well as subsequent and related changes to maternal and child inflammation and child well-being.

Chapter 1 includes an in-depth review of the complex relationships between parental stress and mental health, child mental health, and immunological pathways in the context of pandemics and epidemics. I will first review the extant literature on parent and children's stress and mental health during and following infectious disease epidemics, including the COVID-19 pandemic. I will then provide a concise review of children's developing immune systems, and link this to psychosocial risk to stress response systems during the COVID-19 pandemic. Lastly, I will present the conceptual model for this dissertation study and introduce the key hypotheses of this project.

Stress and Children's Mental Health during Infectious Disease Outbreaks and the COVID-19 Pandemic

An extensive scientific literature has examined the impact of large-scale disruptive events, such as natural disasters, terrorist attacks, and human conflict, on children's psychological well-being (e.g., Betancourt & Khan, 2008, Tang et al., 2014). Within this broader context of literature, there is a subset of studies specifically focused on children's mental health during and following infectious disease outbreaks.

Children are particularly susceptible to stress stemming from public health crises. Several factors moderate children's responses to the crisis: their own level of understanding about the crisis, the reaction of their caregivers, exposure to mass media coverage or social media, and their emotion regulation skills (Imran et al., 2020, Rao & Fisher, 2021), which translates to a broad range of coping mechanisms and functioning (Center for Disease Control, 2020, Rao & Fisher, 2020). While there are no exact modern parallels to the COVID-19 pandemic (especially in terms of scope of impact), studies on the mental health of young children conducted in the aftermath of other pandemics and epidemics yield important lessons.

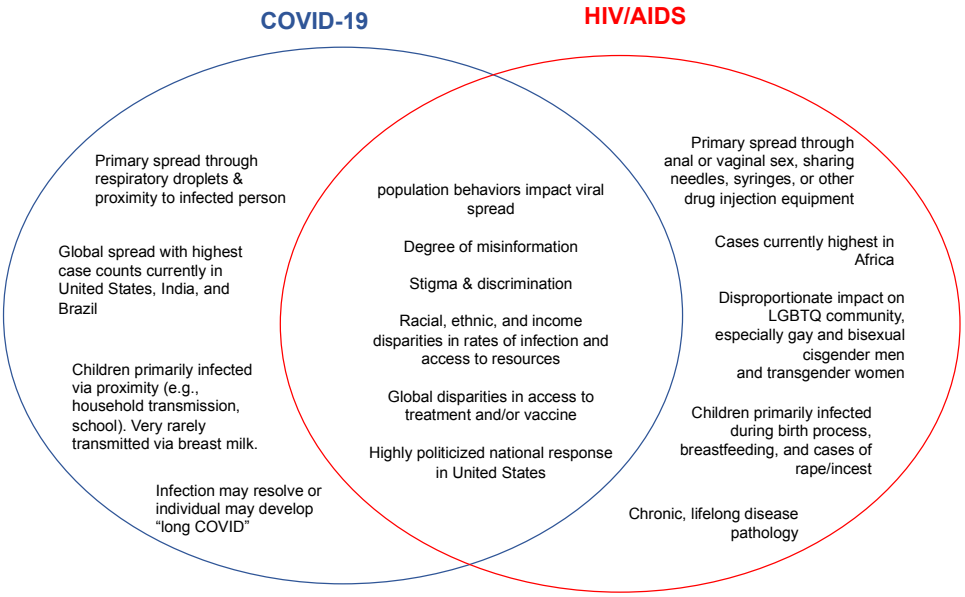
Parallels to the HIV/AIDS Epidemic

The human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) is a generalized epidemic that began in 1981 and remains an ongoing global public health issue, with a disproportionate impact in Africa. The transition of HIV/AIDS from pandemic to epidemic status, and the aftermath of the height of the crisis, offers insight into what we may anticipate for children's mental health during and after the active stages of the COVID-19 pandemic. There are several key similarities between the HIV/AIDS epidemic and the COVID-19 pandemic, including the role that population behaviors play in the spread of the viruses, as well as the negative influence of stigma, discrimination, and misinformation (Banati

& Idele, 2021) (see Figure 1). Comparable to the COVID-19 pandemic (Macias et al., 2020, Millett et al., 2020), a relationship also emerged between HIV/AIDS prevalence with income and race and ethnicity, with elevated rates of infection observed among more vulnerable populations, such as Black and Latinx demographics (Laurencin et al., 2018, Rose et al., 2008). However, a significant difference between HIV/AIDS and COVID-19 pandemic is the course of illness following an infection. Specifically, HIV/AIDS remains a chronic disease (Siegal & Lekas, 2002), though advances in treatments (i.e., anti-retroviral therapy) have rendered the illness more manageable (De Clercq, 1991). However, this is a key deviation from COVID-19, where illness typically resolves within six weeks (except for early death or "long COVID," a collective term referring to the persistence of symptoms in individuals who have otherwise recovered from SARS-CoV-2 infections (Raveendran et al., 2021)). Thus, the role of a short-term versus chronic illness must be considered when comparing studies during the HIV/AIDs epidemic to the COVID-19 pandemic.

Figure 1

Similarities and Differences between COVID-19 and HIV/AIDS Pandemics



HIV/AIDS and Parental Stress. As HIV infections increased, more families became impacted by the epidemic either via parental and/or child HIV+ status. Several studies have found that parents in HIV+ families report significantly elevated levels of parenting stress compared to the general population (Murphy et al., 2009, Rochat et al., 2017, Silver et al., 2003, Wiener et al., 2001). In turn, higher levels of parental stress can negatively impact parenting skills and children's well-being. One study of mothers with HIV+ status and their children found that maternal stress was negatively associated with a range of positive parenting skills (e.g., establishing routines, consistent discipline), which then predicted higher rates of child problem behaviors (Murphy et al., 2009). A separate study conducted in China demonstrated that caregiver distress negatively affected child well-being, a relationship that was mediated by parental stress, parental competence, and parental responsiveness (Chi et al., 2015). Further, poverty and caregiver mental health (e.g., depression/anxiety), experiences exponentially more prevalent in HIV/AIDS-affected families, have been identified as important moderating factors in the association between parental stress and child outcomes (e.g., behavior problems, child mental health) (Lachman et al., 2014). Significant lessons can be gleaned from the HIV/AIDS epidemic, including the importance of parental support and parenting programs to help caregivers navigate the deleterious mental and physical health impacts associated with COVID-19 (Banati & Idele, 2021). Supportive programs that target the reduction of parental stress, and fortify positive parent-child dynamics, may be particularly helpful in the wake of the COVID-19 pandemic.

HIV/AIDS and Children's Mental Health. Several key studies demonstrated worsening child mental health for children in HIV/AIDS affected families, as indicated by lower psychosocial, emotional, and school functioning relative to non-affected families (Xu et al.,

2010) and higher rates of stigma (Lin et al., 2010; Xu et al., 2009). A rapid review systematic review sought to synthesize the literature on child and adolescent mental health as related to the HIV/AIDS epidemic, with the goal of translating these findings to inform prevention efforts for children during and in the aftermath of the COVID-19 pandemic (Banati & Idele, 2021). Six key domains were identified that heavily influenced children's mental health following the HIV/AIDS epidemic: 1) poverty and related stressors, 2) living arrangements/ child neglect and abuse potential, 3) quality of health systems, 4) school-based platforms, 5) caregiving and family environment and social support systems, and 6) stigma and discrimination (Banati & Idele, 2021). Ultimately, the authors recommended that, to lessen the impact of COVID-19 on children's mental health, preventative initiatives could operate on the individual level (e.g., mitigating economic impacts), the community level (e.g., campaigns to combat stigma, mental health resources in schools), and the health system level (e.g., preparing frontline workers to screen for child mental health) (Banati & Idele, 2021).

These results emphasize the importance of contextualizing the multifaceted impact of a health crisis as it is embedded within a child's environment and support systems. From the HIV/AIDS crisis, a pattern emerged in which intersecting levers and barriers, especially parental stress and well-being, can both buffer children against poor mental health impacts and predispose them to even more elevated risk.

Other Infectious Disease Outbreaks

There are also documented mental health concerns in children who have survived other infectious disease epidemics, such as the West Africa Ebola virus and the H1N1 virus outbreaks. The West Africa Ebola virus outbreak has been linked to elevated rates of fear and stigma in children affected by the Ebola virus (Denis-Ramirez et al., 2017), and interventions were

designed to mitigate the trauma impact of the virus on affected youth (e.g., Cénat et al., 2020; Decosimo et al., 2019). For children quarantined during the H1N1 pandemic, one study found that up to 30% of the quarantined children experienced post-traumatic stress disorder relative to those who had not been in isolation during the pandemic (Sprang & Silman, 2013). A recent systematic review summarized 11 studies that focused specifically on child and adolescent mental health associated with respiratory infectious outbreaks (Berger et al., 2021). Children reported increased anxiety and fear, but the review also found that, across studies, children's psychological responses varied based on how parents communicate about the event (Berger et al., 2021). A separate systematic review that looked at child and adolescent mental health during COVID-19 and other past pandemics found that children were likely to suffer high rates of depression and anxiety during and after a pandemic (Meherali et al., 2021).

Altogether, while studies on children's mental health during other pandemics and epidemics remains relatively limited in scope and replication, there is strong emerging evidence that infectious disease pandemics, and the related management strategies (e.g., quarantines), can negatively impact children's mental health and that parenting factors influence this relationship. Further, the COVID-19 pandemic has led to more severe and long-lasting disruptions to children's lives relative to prior epidemics (e.g., longer quarantines, prolonged school closures). Thus, the influence of prior disease epidemics on child mental health may be "lower bound" estimates relative to the possible effect of the COVID-19 pandemic. A small, but growing number of studies have been conducted since the onset of the COVID-19 pandemic to ascertain impacts on families, including parental stress and children's well-being.

The COVID-19 Pandemic Stressors and Parental Stress

Worldwide studies have found consistent evidence for a substantial increase in parental stress levels since the onset of the COVID-19 pandemic (as reviewed by Rao & Fisher, 2021). As the pandemic spread, the home environment and family dynamics markedly changed for most families. Parents faced several challenges in adapting to the crisis and were tasked with balancing childcare, education, and health needs, and of their children with minimal support. As reviewed previously, pandemic disasters, and related disease-containment responses, contribute to traumatic stress responses in both parents and children (Sprang & Silman, 2013).

A growing body of research has been conducted to assess parental stress during the COVID-19 pandemic, with studies investigating several types of pandemic-related stressors on parents, such as depressive and anxiety symptoms, household chaos or changes to family dynamics, and self-rated stress levels. Parents in general were particularly vulnerable to increased stress levels, with one report indicating that non-parents were 70% less likely to endorse feelings of stress compared to parents during the COVID-19 pandemic (Alonzo et al., 2022). These studies have spanned the globe, with early reports emerging from countries who endured the initial wave of COVID-19. In China, a study from 2020 revealed mothers endorsing significantly elevated stress levels compared to before the pandemic, and stress levels were highest for single mothers and mothers in small households (Tchimtchoua Tamo, 2020). In Italy, another country impacted earlier during the pandemic, parents reported higher levels of stress, and this was highest in parents who rated quarantine as being very difficult for their children (Spinelli et al., 2020) or in parents who reported challenges with adapting to the pandemic (Moscardino et al., 2021). Compared to pre-pandemic data, parents reported high rates of depression, anxiety, stress, irritability, and higher alcohol consumption (Lamar et al., 2021, Westrupp et al., 2021). Separate studies all found compelling evidence for increases in parental

stress across the globe including in Canada (Roos et al., 2021), Norway (Skjerdingstad et al., 2021), India (Sahithya et al., 2020), Germany (Calvano et al., 2021, Li et al., 2021), Guatemala (Alonzo et al., 2022), Australia (Westrupp et al., 2021), and the United States (Adams et al., 2021, Brown et al., 2020, Kerr et al., 2021).

Additionally, studies began to investigate individual differences that may help identify parents most vulnerable to substantial increases in stress or mental health difficulties. These studies, conducted across the globe, identified several factors that enhanced vulnerability to elevated parental stress, including being a mother (Yue et al., 2020), younger age of parent (Westrupp et al., 2021, Yue et al., 2020), lower levels of income (Kerr et al., ,2021, Westrupp et al., 2021, Yue et al., 2020), lower social support (Wu et al., 2020), parental history of mental illness pre-pandemic (Wu et al., 2020), and experiencing greater COVID-19 related stressors (e.g., decline in physical health, stressors related to child's academics) (Brown et al., 2020, Westrupp et al., 2021). In contrast, greater parental control and enhanced perceived control were protective factors that buffered against parental stress (Brown et al., 2020).

Changes to the levels of household chaos have also been investigated in the context of the COVID-19 pandemic. Longitudinal studies that capitalize on pre-pandemic samples have helped to elucidate changes in household dynamics. An ongoing study of low-income children and their parents in Oklahoma leveraged pre-existing data (collected in 2018) and collected new data during the pandemic to assess changes to the children's home environments and routines following stay-at-home orders and school closures. Results indicated that household chaos increased during the pandemic and was associated with larger household size, food insecurity, parental depressive symptoms, and pre-pandemic household chaos (Johnson et al., 2022). A separate larger study investigated over 2000 participants across five Midwestern states, finding

increases in household chaos that were subsequently associated with increased parent-child conflict and strain among siblings (Cassinat et al., 2021). Household chaos has also been associated with increased challenges for caregivers to participate in children's learning (Zhang, 2021), while more school support has been associated with reduced household chaos levels (McGoron et al., 2022).

The impact of the COVID-19 pandemic on parenting also has downstream effects on children's well-being. Caregiver depression, along with multiple household and pandemic-related risk factors, has been associated with lower quality parenting during the COVID-19 pandemic (Roos et al., 2021), with other studies linking increased COVID-19 related parental stress to harsher parenting (Chung et al., 2020). Alarmingly, parental stress during COVID-19 has also been associated with increases in children's experience of adverse events, such as witnessing interpersonal violence (Calvano et al., 2021), and higher rates of anxiety and depressive symptoms in parents predicted higher child abuse potential in one sample (Brown et al., 2020). Protective factors have also been identified; in preschool-aged children, predictability in the home environment protected against mental health symptoms, an effect that persisted even after statistical control for income, maternal psychopathology, and food insecurity (Glynn et al., 2020) while greater parental support also buffers against child abuse potential (Brown et al., 2020).

The COVID-19 Pandemic and Children's Mental Health

Several studies have begun to track children during the COVID-19 pandemic and collect cross-sectional and longitudinal data on key outcomes, including children's mental health. Of note, many of these studies have been conducted in adolescent-aged children (as summarized in Meherali et al., 2021). However, the studies in younger, prepubescent children highlight similar

findings. A series of studies conducted in China have found elevated rates of anxiety and depressive symptoms in school-aged children (Duan et al., 2020; Tang et al., 2021; Xie et al., 2020). Comparable results have been observed in other countries as well, including India (Saurabh & Ranjan, 2020), Ireland (O'Sullivan et al., 2021), Canada (Cost et al., 2021), and Germany, in which a large study of 1865 children and adolescents documented that a stunning 2/3rd of the youth felt highly burdened by the pandemic (Ravens- Sieberer et al., 2021). A large survey study in the United States found a substantial proportion of parents reported that their children's mental health was worsening during the pandemic, especially if the parents' own mental health was also deteriorating (Patrick et al., 2020). Alarmingly, a separate study in the United States found a 24% increase in mental health-related emergency department visits among children aged 5-11 from March 2020- October 2020 (Leeb et al., 2020).

Many studies have also investigated the mechanisms underlying the pandemic-mental health relationship, such as factors that worsened children's mental health outcomes, including more time spent in quarantine (Saurabh & Ranjan, 2020), knowing a family member infected by the coronavirus (Duan et al., 2020), lower socioeconomic status (Ravens-Sieberer et al., 2021), and having limited living space (Ravens-Sieberer et al., 2021). A recent study of Chinese American families also highlights the role of stigma and discrimination on children's mental health. Researchers found that higher levels of parent- and youth-perceived racism and racial discrimination were associated with poorer mental health (Cheah et al., 2020). Protective factors have also been identified, such as a finding by Tang et al., (2021) showing that positive parent-child discussions about physical distancing measures buffered children against worsening mental health symptoms.

Taken together, there are significant patterns that emerge from research during and following major public health crises, such as the HIV/AIDS epidemic, the West Africa Ebola outbreak, the H1NI outbreak, and the current COVID-19 pandemic. Commonalities across these studies include the worsening of mental health symptoms for young children, while also emphasizing that the level of risk for mental health deterioration varies widely. Protective factors include a positive caregiving environment and predictability in the home, while common risk factors include elevated stress related to income insecurity, heightened exposure to the virus/knowing someone directly infected, access to healthcare, and the threat of racism, discrimination, and stigma. As the COVID-19 pandemic evolves, longitudinal research will help to cement the relative risk of mental health problems, elucidate longer-term trajectories, and further identify environmental factors that increase or decrease child's risk in both the short and long-term.

Direct and Indirect Influences of the COVID-19 Pandemic on Children's Immune Function

In the context of the COVID-19 pandemic, the role of the immune system is complex and evolving. There are both direct and indirect associations between the COVID-19 pandemic and the immune system, with corresponding and significant implications on children's mental health and psychological well-being. First, I will review normative immunological development in children, as well as the role of stress in child immune development. Then, I will discuss the intersection of the COVID-19 pandemic on child immune health as it pertains to psychological well-being.

Development of the Immune System

Throughout fetal, neonatal, and childhood, the immune system matures. As this continuous process unfolds naturally, impacts to the immune system at critical points in

development can carry significant consequences as the child ages (Ygberg & Nilsson, 2012). A human's immune response has two primary arms: innate immunity (which an organism is born with) and adaptive immunity (acquired following disease and pathogen exposure). Both the innate and adaptive immune systems develop gradually during the neonatal and infancy periods, as newborns are eventually exposed to various antigens, including infections, vaccinations, and microbes (Simon et al., 2015). As a child grows, their immune competence becomes subsequently shaped by further infections and vaccinations. Eventually, children develop an expanding "immune repertoire," of memory T and B cells, which have all been triggered by prior infections, and vaccinations, as well as shaped by food and inhaled antigens (Simon et al., 2015). During childhood and adolescence, child growth, hormonal fluctuations, and behavioral changes are also all relevant internal and external experiences to the child's ongoing immune system development (West, 2002). It is not until later in life that the immune system begins to decline, predisposing older adults to higher risk of acute viral and bacterial infections and mortality related to illness (Simon et al., 2015).

The Immune System and the Stress Response

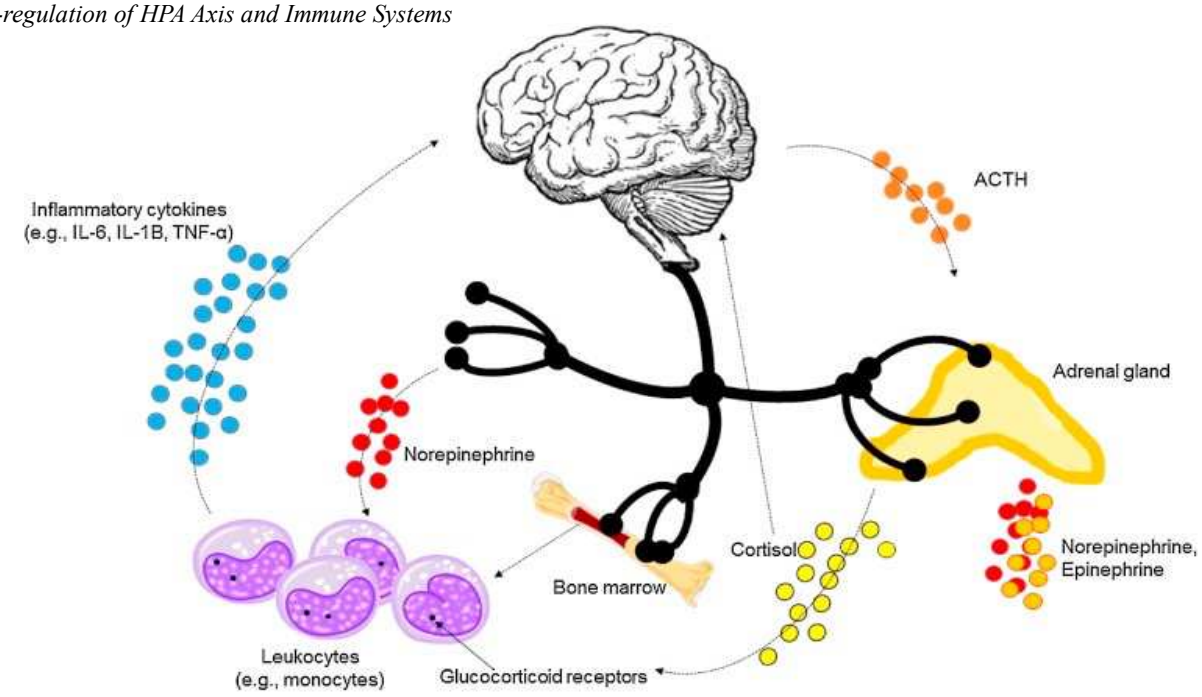
The immune system is also a central component within the broader stress response network, influencing brain development, gut microbiota, the neuroendocrine system, and general central nervous system functioning (Rook et al., 2016). Specifically, in response to stress, there is a synchronization of the sympathetic nervous system, hypothalamic-pituitary adrenal (HPA) axis, and the inflammatory arm of the immune system (Gunnar & Quevedo, 2007; Kuhlman et al., 2017). Under stress, the HPA-axis and immune system are both activated (see Figure 2).

The HPA-axis strives to maintain homeostasis via a complex hormonal cascade first via release of corticotropin release hormone (CRH) and vasopressin from hypothalamus to the

anterior pituitary gland which triggers adrenocorticotropin hormone (ACTH). In turn, ACTH stimulates the adrenal gland to increase production of glucocorticoids, known as cortisol in humans. Figure 2 illustrates the complex and multidirectional pathways between the HPA axis, inflammatory responses, and the brain.

Figure 2

Co-regulation of HPA Axis and Immune Systems



In the immune system, inflammation is the early response to pathogens or stress (Steptoe et al., 2007), which cause the release of pro-inflammatory cytokines (Black, 2002), or soluble proteins that serve as chemical cellular messengers. The most common measure of inflammation in humans is to measure concentrations of cytokines or systemic markers of inflammation, such as C-reactive protein (CRP). CRP is an acute phase protein synthesized in the liver in response to the pro-inflammatory cytokine interleukin-6; CRP is a gold-standard measure of inflammation, and concentrations greater than 3.0 mg/L in adults are considered reliable predictors of global disease risk (Ridker, 2003).

Notably, the HPA axis and immune system work in concert (see above, Figure 2). A critical role of the HPA-axis is to regulate inflammation, as glucocorticoid receptors are found in immune cells. The binding of glucocorticoids to glucocorticoid receptors downregulates cytokine production (Silverman et al., 2005). Thus, proper function of the HPA-axis is necessary to prevent chronic inflammation (Stark et al., 2001). In cases of chronic or prolonged stress, glucocorticoid receptor insensitivity develops, which leads to an inability of such receptors to "hear" inhibitory signals of glucocorticoids in immune cells, which then contributes to chronic inflammation (as reviewed in, Kuhlman et al., 2017).

Further, direct and indirect threats to the immune system in childhood may predispose the individual to later onset health consequences, spanning from physical (e.g., cancer) to psychological (e.g., depression) disorders. Outside of exposure to infection, vaccination, and antigens, several factors will activate a child's immune system. Social determinants of health, such as stress related to living in poverty, racism and discrimination, and reduced access to healthcare, have also all been linked to immune system perturbations in children (Miller & Chen, 2013; Pachter & Coll, 2009). Other important associations with inflammation include childhood adversity (Kuhlman et al., 2020) and maternal psychopathology (Plant et al., 2016; Ulmer-Yaniv et al., 2018). Lastly, it should be noted that the presence of immune-related ailments, such as asthma, can also lead to inflammation (Lemanske, 2003), thus making immune-compromised children uniquely vulnerable to immune system threats. Overall, immune system functioning will vary widely from person to person, depending on an individuals' "immune repertoire," which is influenced by factors ranging from vaccinations received, prior infections, bacterial exposure, and social and environmental factors.

Direct Impacts of SARS-CoV-2 on Child Immune Systems

The direct impact of a SARS-CoV-2 infection on child immunological functioning is not the primary purpose of this study; however, it is important to briefly delineate, as a subset of the study participants (caregiver and/or child) may have been exposed to and/or endured a COVID-19 infection. Directly, a SARS-CoV-2 infection leads to an aggressive release of inflammatory cytokines as the immune system responds to the virus. For a subset of individuals, this initial immune response can result in a "cytokine storm," a hyper-inflammatory response linked to more severe courses of illness and higher mortality rates (Tay et al., 2020). In children, COVID-19 infections are typically mild, which has largely been attributed to developmental differences in immune function (Zhu et al., 2020). Several theories have been posited regarding children's decreased susceptibility to the coronavirus, including typically elevated angiotensin-converting enzyme activity in childhood or decreases in CD4 cell concentrations in children (Zhu et al., 2020). In rare cases, children are severely affected by a SARS-CoV-2 infection, with an infrequent complication known as multisystem inflammatory syndrome (MIS-C) developing in children who have an abnormal immune response to the virus (Jiang et al., 2020). Notably, a study comparing 539 pediatric patients with MIS-C and 577 pediatric patients with severe COVID-19, found that MIS-C patients were more likely to be children aged 6-12 years old, non-Hispanic Black children, and to have illness with more extreme inflammation, further highlighting the importance of demographic factors in delineating risk (Feldstein et al., 2021).

Indirect Impacts of the COVID-19 Pandemic on Child Immune Systems

The pandemic, and related management strategies, increase the frequency and severity of cumulative and overlapping environmental challenges, including but not limited to social isolation, financial insecurity, increased family conflict, gaps in learning, and caregiver mental

health and stress. All these experiences, independently and collectively, steeply increase the demand on children's stress response networks, including their immune systems. Repeated stress is linked to over-activity of immune responses, and it has been theorized that psychological problems associated with quarantine and social isolation, and exacerbated by parent stress, may be driven by stress response dysregulation (Raony et al., 2020).

Inflammation is the immune system's initial defense against pathogens, tissue injury, and other threats, including social threats and prolonged stress. Psychosocial stress has been shown to induce inflammatory responses in the brain and peripheral systems by activating pathways usually activated by pathogens (Dantzer et al., 2008; Korn & Kallies, 2017). As reviewed above, the relationship between stress and the immune system is complex and bidirectional, as stressors activate immune responses, and alterations in immune function can further elicit stress response (Holzer et al., 2017). While initially protective, chronic inflammation has been linked to the pathogenesis of many diseases. For example, inflammation reorganizes human behavior to facilitate healing, leading to sickness behaviors in the long run (e.g., isolation, withdrawal, suppressed appetite, sleep disruptions), which mimic the behavioral phenotype of depression (Dantzer et al., 2008).

There is substantial literature linking inflammation in children to several of the known pandemic-related stressors. Prior studies have demonstrated that social isolation during childhood and adolescence is associated with high levels of CRP later in life (Danese et al., 2009; Lacey et al., 2014). Economic instability and household chaos have been linked to disruptions in stress response systems in children, including the neuroendocrine system (Brown et al., 2019) and the immune system (Schmeer & Yoon, 2016). Maternal psychopathology, especially depression, is also a potent risk factor for increased child inflammation (Plant et al.,

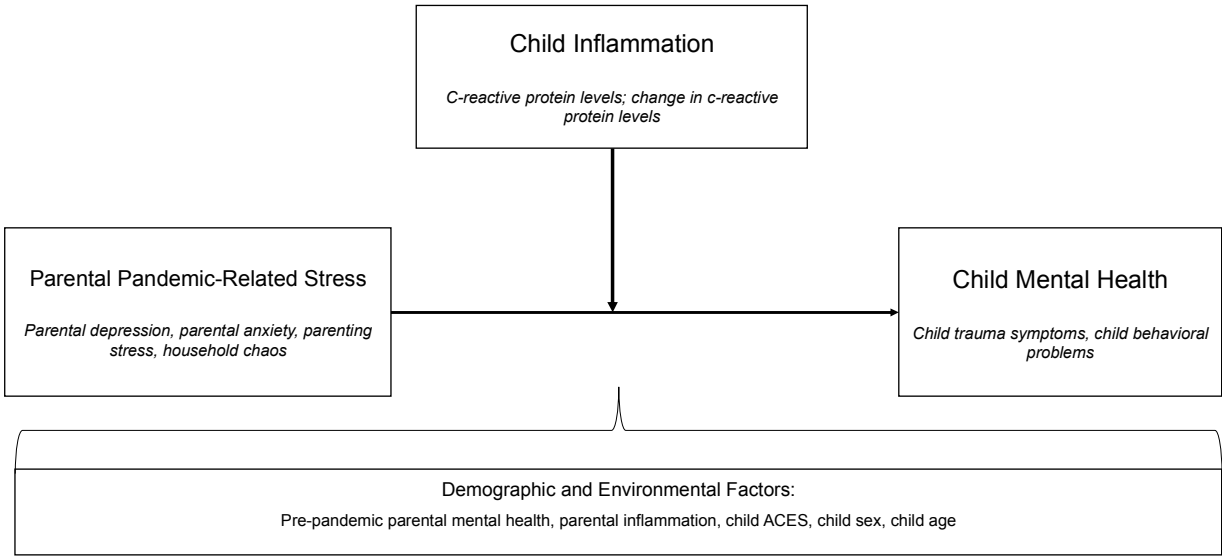
2016; Ulmer-Yaniv et al., 2018). Importantly, protective factors identified to buffer children against the negative impact of the pandemic stress on their mental health, such as a positive caregiving environment, have also been shown to protect children against inflammation (Bernard et al., 2019).

Conceptual Model

Overall, there emerges a complex set of pathways that link together pandemic-related stressors and the child's environment to inflammation and mental health symptomatology in children. As illustrated in Figure 3, pandemic-related stressors, specifically parental mental health (i.e., anxiety and depressive symptoms, parenting stress) and an unpredictable home environment (i.e., household chaos), directly influence child mental health (i.e., trauma symptoms; disruptive behaviors); this has been supported by a groundswell of evidence predating and during the COVID-19 pandemic (*Aim 1*). Child inflammation (i.e., CRP) is also positively correlated both with these stressful experiences (*Aim 1*) and change in child inflammation with child mental health symptoms *(Aim 2)*. *Aim 3* is examining the extent to which a higher degree of change in child inflammation moderates the relationship between pandemic stressors and child mental health. Lastly, the model highlights key demographic and environmental factors also likely to influence the core relationships within the model (*Aim 4*).

Figure 3

Dissertation Conceptual Model



Current Study and Hypotheses

This study leverages two time points. The first is referred to as the "pre-pandemic time point," which was data collected from the families at the end of a randomized controlled trial, 2-5 years prior to the onset of the COVID-19 pandemic (between 2016-2019) (Nekkanti et al., 2020). The second time point is referred to as "the current study" or "during the pandemic," in which data was collected between 17-21 months after the initial onset of the COVID-19 pandemic (August 2021-December 2021).

The central hypotheses are that (1) pandemic-related stress, and increases in pandemic-related stress from pre-pandemic to the current study, will be positively correlated with child inflammation and child mental health; (2) a positive correlation will be observed in change in child inflammation (pre-pandemic to the current study time point) and mental health problems in children; (3) change in child inflammation (from pre-pandemic to the current study) will

moderate the association between pandemic-related stress and child mental health, such that the positive relationship between pandemic-related stress and increased mental health will only be statistically significant in children demonstrating a greater increase in child inflammation; (4) demographic and environmental factors will further influence this relationship.

Chapter 2: Methods and Data Analytic Strategy

The Parent CAPS study

The parent study from which participants were recruited included 250 caregiver-child dyads, with children aged between 2-7 years old at study entry. Families with CWS-involvement were randomized to either the parent-child interaction therapy (PCIT) intervention (described below) or a comparison condition (i.e., services as usual in the community). The CAPS study included three waves of data collection (baseline, mid-intervention for PCIT families, and post-intervention), and utilized a multi-rater, multimethod assessment approach that spanned neural measures, physiological measures, immune measures (dried blood spots, urine collection), observations of parent-child interactions, and self-report measures of stress and caregiver and child mental health.

PCIT Intervention Description

PCIT is an intensive behavioral parent-training model grounded in social learning, attachment, and family systems theories (Funderburk & Eyberg, 2011). In approximately 16-20 sessions, the intervention is delivered via live coaching of parent-child interactions. The PCIT program is designed to enhance child functioning by interrupting patterns of harsh, coercive interactions, enhancing caregiver use of warm and positive behaviors, reducing instances of child maltreatment and neglect, and promoting child management skills (Funderburk & Eyberg, 2011). The intervention includes three sequential modules: 1) Motivational Enhancement (pre-training; support caregiver readiness for change), 2) Phase 1 of Child-Directed Interaction (CDI; includes the "PRIDE" skills of "praise, reflection, imitation, description, enthusiasm"), and 3) Phase 2 of Parent-Directed Interaction (PDI; coaching parents on effective commands, time-out protocols). In all, PCIT is an assessment-driven, evidence-based intervention (Funderburk & Eyberg, 2011).

Current Study

Participants

The sample consisted of 22 mother-child dyads for a single time point follow up visit. This project was approved by the University of Oregon Research Compliance Services Institutional Review Board (IRB) as an addendum to the ongoing CAP study (IRB Protocol Number: 07102014.013). Written consent for study participation was obtained from parents. For children aged 7 or older, a separate written consent for study participation was obtained from the child. The consent procedure was approved by the IRB. Of note, study recruitment was significantly impacted by the "Delta wave" of COVID-19 infections, leading to an underpowered study, limiting the ability to detect true effects and interpret the data fully. Further, we note that while the Results includes *p*-values, and reports statistical significance at $\alpha < 0.05$, this is an underpowered sample and thus effect sizes and directionality of findings are equally emphasized in discussing the findings. This limitation, and how the effect sizes indicate important future directions for study, is discussed in detail in the Discussion.

All caregivers for the current study were biological parents. Out of the 22 parents, 21 identified as cisgender female and one identified as non-binary and/or gender non-conforming. Thus, the term "parent" will be utilized. Children were aged between 5-10 years old. A full demographic breakdown is included in Results.

Recruitment

Subjects for the dissertation study were recruited from former CAPS participants who granted the team permission to be recontacted for future studies. A team of research assistants conducted a short phone screen describing the study, compensation, and to answer any questions. To enhance feasibility of the study, there were no major exclusion criteria to participate, with the exception that no family (parent, target child, or any household member) had current symptoms

of COVID-19 or a recent known COVID-19 exposure. Participants with a recent COVID-19 infection were eligible once they tested negative.

Measures

The current study includes two major components: 1) survey questionnaire, and 2) dried blood spot (DBS) collection to index inflammation.

Survey Questionnaire

The survey questionnaire repeated several key measures from the parent study, and included new questions related to the COVID-19 pandemic. The survey took approximately 45 minutes to 1 hour to complete; parents were instructed to complete the survey prior to the in-person visit when possible. The survey was accessed via Qualtrics and could be completed on a smartphone, tablet, or computer with WiFi or cellular access. If the parent endorsed any barriers during the phone screen—including limited access to WiFi/cellular service or not owning a compatible device—they completed the survey during the in-person visit. Except for the COVID-19 specific questions, *all* below questionnaires were also administered at the pre-pandemic study time point.

Demographic Questions. Parents reported on demographic and identity characteristics of themselves and their child (e.g., gender/sex, race and ethnicity, income, marital status, education). Parents also reported on service utilization, including Women Infants and Children (WIC), food stamps, social security, Temporary Assistance for Needy Family (TANF), and use of Oregon Health Plan (OHP) or Medicaid.

Parent Physical Health. Parents reported their medications, dosage, and last time taken for themselves and child. Parents were asked if they have been diagnosed with or experience any of the following health conditions: allergies, problems with vision, problems with hearing,

frequent colds/flus, skin irritations, frequent infections, weight concerns, asthma/problems breathing, diabetes, seizures/epilepsy, high blood pressure, fine motor skill or hand problems, traumatic brain injury (TBI)/concussion/dizzy spells, loss of consciousness, headaches or migraines, encephalitis or polio, attention deficit hyperactivity disorder (ADHD), learning disability, substance or alcohol use related disorder, or any other medical, mental health, or stress-related condition (including a diagnosis of a depressive or anxiety disorder). If conditions were endorsed, the parent was asked follow-up questions regarding timing of diagnosis and medications prescribed. Parents are also asked to rank their physical health as "excellent," "good," "fair," or "poor" and how well they can resist illness. Parents were also asked if they are currently pregnant or have a pacemaker. Parents had a free-text option to list any known health diagnoses and medications. Parents' medical results were coded to create variables to indicate the presence of a mental health disorder and a medical health condition. Medical health conditions did not include seasonal health allergies or weight concerns, as neither are chronic illnesses nor formal health diagnoses.

Child Physical Health. Parents were asked the same set of questions regarding their child's health, except for current pregnancy or pacemaker. Parents were also asked how they pay when their child must go to the doctor, how often their child has been to the emergency room in the last year, and if the child has been treated or diagnosed by a therapist or other mental health professional. Responses were coded to create a yes/no variable for presence of a mental health disorder and presence of a medical disorder. For medical disorder, endorsement of seasonal allergies, TBI, and weight concerns were not coded as a medical disorder as they are not considered chronic illnesses.

COVID-19 Questions. Parents were asked a total of 68 questions regarding COVID-19, ranging from questions regarding vaccination status, infections, schooling stressors, and health stressors specific to COVID-19. Parents were asked if they or their child had a known exposure to COVID-19 at any point and to provide details on timing of exposure, testing, and symptoms developed. If endorsed, parents were also asked to report if they or their child was hospitalized due to COVID-19, and if the child developed MIC-S. Parents were also asked if they know anyone in their social circle diagnosed with COVID-19 or if they know anyone seriously ill/hospitalized/or died due to COVID-19. Parents were also asked if they chose to receive the vaccine; if yes, they were asked to report which vaccine and dates of dose(s). If not, they were asked to indicate reasons why they did not receive the vaccine. They are also asked if they are open to the COVID-19 vaccination in the future and if they plan to get their child vaccinated once the vaccine was approved for children under 12. Of note, the COVID-19 vaccine was approved for children above the age of 5 during the study; parents recruited after this were asked if the child had been or would be vaccinated. Parents were asked if they received federal stimulus checks during the pandemic and how that money was primarily utilized (e.g., saving, paying bills).

Parents were also asked if they discussed privileges or challenges related to the child's race and ethnicity status prior to and during the pandemic. There was an open-text option for parents to write about challenges, concerns, sources of support, thoughts on the community, and employment experiences during the pandemic.

Child Adversity. Parents also reported on the Adverse Childhood Experiences (ACE; Felitti et al., 1998) questionnaire for both themselves and their child. The ACE questionnaire assesses 10 possible adverse experiences occurring prior to the age 18, which include emotional

abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, witnessing intimate partner violence, household substance abuse, parental separation or divorce, criminal household member, and mental illness in the household. In the dissertation study survey, parents were also asked to indicate if the ACE was a new incident in the child's life since March 2020. The ACE screening tool demonstrates adequate internal consistency and good construct validity (Meinck et al., 2016). For each endorsed ACE, parents were also asked if this was a new event that had occurred since the start of the COVID-19 pandemic. Parents were instructed to select "Yes" even if the event had also occurred before the pandemic, if it was a new incidence since the start of the pandemic (e.g., if a parent had been divorced prior to the pandemic and got divorced a second time since the pandemic started, it would be endorsed as an ACE occurring since the pandemic started).

Child Behavior and Mental Health Symptoms. Parents completed the Trauma Symptom Checklist for Young Children (TSCYC), which includes 36 self-report items to assess for trauma-related symptoms in children aged 3-12 (Briere, 2005). The TSCYC scoring indicates subscales of trauma symptoms, including total trauma symptoms, anxiety trauma symptoms, arousal trauma symptoms, avoidance trauma symptoms, and intrusive trauma symptoms (Briere, 2005). The "total" trauma score is derived from the sum of the intrusive, arousal, and avoidance symptoms. A T-score was computed from the raw scores for the total TSCYC trauma symptoms and each subscale. For the TSCYC, T-scores above 65 are considered clinically significant (Briere, 2005). The value for Cronbach's Alpha for the TSCYC in the current study was $\alpha = 0.95$.

Parents also completed the Intensity subscale of the Eyberg Child Behavior Inventory (ECBI), a 36 item self-report measure that assesses the frequency and severity of disruptive child behaviors (Eyberg & Pincus, 1999). A subscale for Intensity of child behavior was calculated. Of

note, there is also an associated Problem subscale, which was not measured in this study (due to a study administration error). The ECBI intensity raw scores were converted to T-scores. The cut-off T-score for clinical significance is greater than or equal to 60 (Eyberg & Pincus, 1999). The value for Cronbach's Alpha for the ECBI in the current study was $\alpha = 0.95$.

Parent Mental Health. Parents completed a short form of the Brief Symptom Inventory (BSI), a 12-item self-report of depressive and anxiety symptoms (Derogatis & Spencer, 1993). Raw scores for the BSI are converted to T-scores based on gender-specific normative data from non-patient community dwelling U.S. adults. T-scores greater than or equal to 63 are considered clinically significant for both the depression and anxiety subscales (Derogatis, 2001). The value for Cronbach's Alpha for the BSI in the current study was $\alpha = 0.84$.

Parenting Stress. Parents completed the Parenting Stress Index (PSI) (Abidin, 1990), which evaluates the magnitude of stress in the parent-child system. The PSI includes 24 -items that parents rate on a scale of options from "strongly disagree," "disagree," "not sure," "agree," and "strongly agree." Two subscales were derived from the PSI: 1) Parent-Child Dysfunctional Interaction, or the extent to which parents feel satisfied with their child and their interactions with them, and 2) Difficult Child, or how a parent perceives their child to be, and whether they perceive it is easy or difficult to take care of their child. Raw scores are calculated directly from the questions and higher scores indicate higher levels of stress. The raw scores are converted into percentiles which describe the parents' relative standing within all the parents assessed during the development of the PSI (e.g., a percentile score of 88 indicates that 88% of parents reported lower levels of stress and 12% reported higher levels of stress). Percentile scores between 15-80 are considered normative. Higher stress scores range from 81-84 for the Parent Child Dysfunctional Interaction and above 89 for Difficult Child. A percentile score of 90 is

considered clinically significant across both subscales (Abidin, 1990). The value for Cronbach's Alpha for the PSI in the current study was $\alpha = 0.93$.

Household Chaos. Parents completed the CHAOS (Confusion, Hubbub, and Order Scale) in which they rated 15 items as True or False regarding level of confusion and disorganization in the child's home environment (Matheny Jr et al., 1995). Example items include "thre is very little commotion in the household" and "it's a real zoo in our home," and "first thing in the day, we have a regular routine at home." Higher scores are indicative of more household chaos (Matheny Jr et al., 1995). The value for Cronbach's Alpha for the CHAOS scale in the current study was $\alpha = 0.73$.

Immune Assays and Dried Blood Spot (DBS) Collection

Dried blood spots were collected for both caregiver and child, using the Tasso-M20 device (from Tasso Inc), which allows for ready collection of a single blood sample. The sample type is whole dried blood and collects 4 samples of 20µL ±5%.

Collection and Storage Procedure. The parent and child's upper arm was rubbed quickly and firmly below the shoulder. A gel heat pack was briefly used to enhance blood flow. The area was cleaned thoroughly with an alcohol pad. The Tasso device was then placed onto the arm, with an adhesive sticker. The assessor then pressed the button on the top of the device for under two seconds, which caused a vacuum to form, and a lancet pricked the surface of the skin. The vacuum draws blood from the capillaries and into a sample pod that is attached to the bottom of the Tasso button (Tasso Inc, n.d.). The device was removed once blood appeared on all four allotted spots; average time of completion was 1-2 minutes, and the device was always removed after five minutes. Full DBS samples were collected on $N = 21$ children, with one child refusing collection after the initial collection failed. Two children had incomplete collections;

however, there was a sufficient sample to analyze for CRP. Four children exhibited distress with the Tasso collection (e.g., crying, screaming), but were ultimately able to complete the DBS collection. The sample pod was then exposed to vent and allow drying of the spots. After 15-30 minutes, the device was stored in a foil bag with desiccants. The samples were moved to a -80°C freezer within one week of collection.

Assay Procedures. The DBS samples were shipped and assayed at the Human Immune Monitoring Center at Stanford University. Samples were shipped on dry ice, in sturdy, high quality boxes with desiccant packs to preserve samples. Samples were assayed for CRP using Magnetic Luminex Performance Assay (Bernard et al., 2015). The Luminex assay measures the amount of the target (CRP) bound between a matched antibody pair (Bio-Techne, n.d.). The target specific antibody for CRP is pre-coated in the walls of the microplate and samples. Then, standards and controls are added into the wells that bind to the immobilized antibody. After washing away unbound substances, a biotinylated antibody cocktail specific to CRP is added to each well. A wash removes any unbound biotinylated antibody and then Streptavidin-Phycoerythrin conjugate (Streptavidin-PE) is added to each well to bind to the biotinylated detection antibodies. Per the Luminex protocol, "a final wash removes the unbound Streptavidin-PE and the microparticles are resuspended in buffer and read using a Luminex analyzer" (Bio-Techne, n.d.). A bead-specific laser identifies which analyte is being detected and a magnet in the analyzer captures and holds the superparamagnetic microparticles in a monolayer. Two spectrally distinct Light Emitting Diodes (LEDs) illuminate the beads. One LED identifies the analyte that is being detected and the second LED determines the magnitude of the PE-derived signal, which is in direct proportion to the amount of analyte bound (in this case, CRP) (Bernard et al., 2015). All CRP readings were measured in duplicate and the average of the two readings

was utilized in analysis. The assays were highly reliable with all inter and intra-assay coefficient variables (CV) being under 13%, with an average CV of 4.02%.

Inflammation-Specific Confounders. Parents' height and weight was collected to calculate body mass index (BMI) via the formula BMI = kg/m^2 where kg is a person's weight in kilograms and m^2 is their height in meters squared. For children, height and weight was collected to calculate BMI. Children's BMI was then converted into the World Health Organization (WHO) percentiles normed by children's age and sex (WHO, 2007). This approach is preferable for children to assess how their measurements compare to others of the same sex and age. Parents were asked if they smoked nicotine or used any nicotine products within 24 hours. Their responses were then coded for Yes (use within the last 24 hours) and No (no use). All parents and children had their temperature checked. No participants had a temperature over 98.5 degrees Fahrenheit. All parents were asked about cold or COVID-like symptoms within the last 72 hours. No participants (parent or child) endorsed any cold or COVID-like symptoms during participation. Parents were also asked about their NSAID (e.g., Advil) use within the last 24 hours and this was coded as Yes (use within the last 48 hours) and No (no use within the last 48 hours). No participating children had taken NSAIDs within the 48 hours prior to the study visit.

Data Analysis Plan and Hypotheses

Clinical and demographic characteristics of the sample are summarized. A summary of changes in key measures from pre-pandemic data collection to current data collection is provided, including parent's stress via mental health symptoms (indexed via BSI) and household chaos (indexed via household CHAOS) and parent stress (indexed via PSI) and children's behavioral and mental health symptoms (indexed via ECBI, TSCYC). Zero-order correlations between variables of interest and demographic variables and potential confounders are presented

in Results. Multivariate linear regressions and/or multilevel modeling (MLM) were utilized to probe the hypotheses.

Analytic Plan for Aim 1

For Hypothesis 1, ordinary least squares regression models were run to probe 1) degree to which pandemic-related stress variables (i.e., parental anxiety, parental depression, parental stress, and household chaos), and change in pandemic-related stress variables, predict child CRP levels during the pandemic, 2) degree to which child CRP level during pandemic predicts child's mental health at pandemic timepoint (i.e., child trauma symptoms, child behavioral problems), and 3) degree to which pandemic-related stress variables predict child mental health during the pandemic.

Analytic Plan for Aim 2

For Hypothesis 2, MLM is an appropriate analytic strategy for nested data, where observations across time are nested within participants. In MLM, a statistical model describes the effects at each nesting level (e.g., within a person across time; between people) and cross-level interaction terms capture the effects of variables at one level in relation to lower levels (e.g., effects of individual differences on temporal change). For Hypothesis 2, MLM were run to determine the extent to which *change* in child CRP from pre-pandemic to pandemic predicts child's mental health problems. Change in child CRP was calculated by taking the difference of the pre-pandemic child CRP concentrations and the current study child CRP concentration. These models were run to predict all mental health outcomes (i.e., trauma symptoms/types of trauma symptoms and child behavior problems).

Analytic Plan for Aim 3

For Hypothesis 3, I investigated the extent to which change in child CRP moderates the Hypothesis 1 association between pandemic-related parent stress and children's mental health. To test the moderating effects of child CRP change score on the association between parental anxiety and child trauma, an interaction analysis was conducted where the interaction term of child CRP change score and each predicting variable was calculated and added to the regression model. For significant interactions, graphs were plotted to visualize the interaction and the Johnson-Neyman technique was utilized.

Analytic Strategy for Aim 4

For Hypothesis 4, the same approach was utilized to analyze the potential moderating impact of relevant demographic and health variables on the pandemic stress- child mental health relationship (i.e., pre-pandemic parental anxiety and depression, parental CRP levels and change in parental CRP, age and sex of the child, and child's current CRP levels). For significant interactions, graphs were plotted to visualize the interaction and the Johnson-Neyman technique was utilized.

Covariates

For all models, relevant covariates were included if statistically indicated (i.e., body mass index, tobacco use, age, NSAID use, etc); to preserve statistical power, potential covariates that are not significantly correlated with any relevant measures were omitted from statistical models. Further, CRP levels are typically non-normally distributed and positively skewed. Thus, normality testing was conducted for skewness and kurtosis along with data visualization (e.g., histograms). If skewness is above or below 0.5 and kurtosis is above or below 3, log-transformation was applied to normalize the data. Outliers are also identified, but in order to maintain full sample size, outliers were not removed if normality statistics are within expected

range (Curran-Everett, 2018). Further, novel research has recently highlighted that excluding CRP values over 10 mg/L (a common criterion for an acute infection) may inadvertently minimize important variability and unintentionally exclude individuals of interest (Mac Giollabhui et al., 2020).

Missing Data

Six children did not have existing CRP data from prior to the pandemic and one child had missing CRP data from the current study time point. Two children were missing the ECBI-Total Intensity T-score for the pre-pandemic time point. One household chaos score was missing for the current study. One Parent Child Dysfunction Index scores and one Difficult Child index scores were missing from the current study. Data was missing completely at random based on Little's test ($\chi 2(23) = 21.97$, $p = .52$). The missing data was imputed with the median value for each corresponding variable (Rubin, 1996).

Chapter 3: Results

Clinical and Demographic Sample Characteristics

Clinical and demographic characteristics of the sample are described in Table 1 and briefly summarized below. In this section, the means and SD for key variables at the pre-pandemic and current study time point will also be summarized. These results will be further presented in the Hypothesis testing.

Table 1

Clinical and demographic characteristics of the sample

Variable	Parent	Child
Age in years; mean (SD)	35.5 (4.25)	8.23 (1.34)
Gender		
Cisgender female	21 (95.0%)	11 (50%)
Cisgender male	0 (0%)	11 (50%)
Non-binary and/or gender non-conforming	1 (4.5%)	0 (0%)
Race (*N*, %)		
European American/White	20 (90.9%)	22 (100%)
Black or African American	2 (9.09%)	4 (18.2%)
Native American	4 (18.2%)	5 (22.7%)
Asian American/Pacific Islander	0 (0%)	2 (9.09%)
Ethnicity (*N*, %)		
Non-Hispanic White	19 (86.4%)	19 (86.4%)
Hispanic or Latinx	3 (13.6%)	3 (13.6%)
Marital Status		
Married	6 (27.3%)	
Engaged/living with partner	5 (22.7%)	
Separated/divorced	4 (18.2%)	
Widowed	1 (4.5%)	
Single	6 (27.3%)	

Table 1 Continued	Parent	Child
Parent Education		
No schooling	1 (4.5%)	
Partial high school	1 (4.5%)	
Graduated high school/GED	8 (36.4%)	
Technical/Vocational degree	3 (13.6%)	
Associate degree/Junior college	3 (13.6%)	
Bachelor's degree	3 (13.6%)	
Graduate degree	3 (13.6%)	
Parent employment status		
No employment	12 (54.5%)	
Full time/stable employment	6 (27.3%)	
Parttime/stable employment	2 (9.1%)	
Parttime temporary/seasonal work	1 (4.5%)	
Household Income		
Yearly (mean; SD)	$34, 908 (28, 714)	
Number of people income supports (M; SD)	4.15 (1.79)	
Pre-pandemic C-reactive protein (mg/L) (M; SD)	2.86 (2.94)	0.64 (1.16)
Pandemic C-reactive protein (mg/L) (M; SD)	4.27 (4.66)	0.80 (1.75)

Sociodemographic Variables

The mean age for parents was 35.5 years old (SD = 4.25, range = 27- 43 years) and child participants had a mean age of 8.23 years old (SD = 1.34, range = 6-11 years old). Out of 22 parents, 21 identified as cisgender female (95.5%) while one parent identified as non-binary/ gender non-conforming (4.5%). Half of the children were cisgender male (N = 11) and half were cisgender female (N = 11). There was a near-even split of families who had been in the intervention arm (PCIT) (N = 10, 45.5%) versus families in the control arm of the parent study (N = 12, 54.5%). The racial and ethnic breakdown of the sample reflects the local community. Some participants identified as multiracial; thus, the percentage breakdown for certain groups is

over 100%. For the parents, the racial and ethnic breakdown was 90.9% European American/White, 9.09% Black or African-American, and 18.2% Native American. For the children, 100% were European American/White. Within the sample, 64% of the children were biracial or multiracial with 18.2% Black or African-American, 22.7% Native American, and 9.09% Asian American/Pacific Islander. Within the sample, 13.6% of parents and children identified as Hispanic-American or Latin(x).

The mean household income was $34,908; however, we note that there was a very wide range of incomes reported ($0-$140,000) with one significant outlier on the higher end ($140,000). The average number of people supported on the household income was 4.15 (SD = 1.79, range = 2-9 people). Out of the sample, 19 parents reported utilizing food stamps (86.4%) and Oregon Health Plan (OHP) or Medicaid (86.4%). Over half of the families also utilized the free lunch service for children (54.5%). Over half of the parents reported that they were unemployed (*N* = 12, 54.5%). Of those with employment, six reported full-time/stable employment (27.3%) while 9.1% reported part-time stable employment and 4.5% reported part-time temporary or seasonal employment.

Child Adversity Exposures

Parents also reported on child's prior adverse experience exposure as well as new adverse experience exposures during the pandemic. The average number of ACEs reported was 2.05 (SD = 1.6). Five children experienced four or more ACES (22.7%). During the pandemic specifically, the average number of new ACEs experienced was 0.55 (SD = .67). In total, 8 children experienced a new ACE during the pandemic (36.4%) and two children experienced 2 ACEs during the pandemic (9.1%); over half the sample did not experience a new ACE during the pandemic (54.5%).

The most common ACE exposures, in general, were parental separation/divorce (*n* = 12, 54.5%), the child living with someone depressed (*n* = 11, 50%), the child living with a "problem drinker" (*n* = 9, 40.9%), the child witnessing violence at home (*n* = 4, 18.2%), the child living with someone who went to prison (*n* = 2, 9.1%), a parent in the home swearing at the child (*n* = 2, 9.1%), a parent in home hurting the child (*n* = 1, 4.5%), the child not having enough to eat (*n* = 1, 4.5%), parents too drunk or high to care for the child (*n* = 1, 4.5%), and child wearing dirty clothes (*n* = 1, 4.5%).

The most common ACEs during the pandemic were the child living with someone depressed (*n* = 6, 27.3%), parental separation or divorce (*n* = 2, 9.1%), the child living with a problem drinker (*n* = 1, 4.5%), the child witnessing violence at home (*n* = 1, 4.5%), parent in home swearing or making the child afraid (*n* = 1, 4.5%), and a parent being too drunk or high to care for the child (*n* = 1, 4.5%).

Parent Physical Health

In total, 21 of the 22 parents (95.5%) indicated the presence of a medical disorder diagnosis (even when excluding intermittent conditions, such as allergies). Further, 14 parents (63.6%) indicated the presence of a psychological disorder diagnosis. For medical disorders, the following diagnoses were indicated via the questionnaire and free-text option in order of frequency: chronic headaches/migraines (*n* = 8, 36.4%), skin irritations (*n* = 7, 31.8%), asthma or breathing concerns (*n* = 6, 27.3%), hypothyroidism (*n* = 5, 22.7%), frequent colds/flues (*n* = 3, 13.6%), seizures/epilepsy (*n* = 2, 9.1%), Type 2 diabetes (*n* = 1, 4.5%), high blood pressure/hypertension (*n* = 1, 4.5%), fibromyalgia (*n* = 1, 4.5%), and a prior brain aneurysm (*n* = 1, 4.5%). Parents also ranked their own physical health on a scale of 1 (poor), 2 (fair), 3 (good), and 4 (excellent). Most parents rated their health as Good (59.1%) or better, Excellent (9.1%),

while 27.3% of parents rated their health as fair and one parent rated their health as poor (4.5%). Parents also rated their ability to resist illness on a scale of 1 (not good), 2 (OK), 3 (Good), and 4 (Excellent); similarly, most rated their ability to resist illness as good (50%) or better, excellent (18.2%) while 27.3% rated as OK and one parent rated their ability to resist illnesses as not good (4.5%).

Parent Psychological Health

For psychological or mental health disorders, over half of parents endorsed having a current psychological disorder diagnosis (*n* = 14, 63.6%). The most common psychological disorder endorsed was substance use disorder (*n* = 9, 40.9%), followed by anxiety disorder (*n* = 7, 31.8%), PTSD (*n* = 27.3%), depressive disorder (*n* = 4, 18.2%), ADHD (*n* = 6, 27.3%), bipolar disorder (*n* = 1, 4.5%), and personality disorder diagnosis (*n* = 1, 4.5%).

Child Physical Health

For children, a total of nine children had a known medical diagnosis (40.9%). Out of the entire sample, parents endorsed that 40.9% experienced allergies to foods or insects (*n* = 9), 22.7% had skin irritations (such as eczema or rashes) (*n* = 5), 13.6% had frequent headaches or migraines (*n* = 3), 9.1% had asthma or breathing concerns (*n* = 2), and 4.5% had seizures or epilepsy (*n* = 1). Parents also reported on weight and digestive problems (*n* = 6, 27.3%), speech and language problems (*n* = 4, 18.2%), vision problems (*n* = 2, 9.1%), toileting concerns (*n* = 2, 9.1%), fine motor skill problems (*n* = 2, 9.1%), and frequent ear infections (*n* = 1, 4.5%). All parents rated their children's physical health as good (*n* = 10, 45.5%) or excellent (*n* = 12, 54.5%) and their ability to resist illness as OK (*n* = 5, 22.7%), good (*n* = 13, 59.1%), or excellent (*n* = 4, 18.2%). Over 75% of the children had not been to the emergency room in the last year (77.3%), while five children having emergency room visits between 1-2 times (22.7%).

Child Psychological Health

A total of five children (22.7%) had a psychological disorder diagnosis. All five children had ADHD (*n* = 5, 22.7%). A subset of these children had comorbid psychological conditions, including learning disorder (*n* = 3, 13.6%), anxiety disorder (*n* = 2, 9.1%), and depression (*n* = 1, 4.5%).

Experiences of COVID-19 Pandemic

SARS-CoV-2 Infections

Five parents reported having a known exposure to COVID-19 (22.7%), with one parent reporting testing positive for COVID-19 (prior to the study). This parent endorsed experiencing a fever, shortness of breath, body aches, loss of smell, and a sore throat. One parent noted experiencing symptoms of COVID-19, including loss of smell and body aches, but denied testing positive for the virus. Three parents reported that their child was directly exposed to COVID-19 (13.6%). One child tested positive for COVID-19 and experienced headaches, a cough, nausea, and a fever. No children developed MIC-S or were hospitalized due to COVID-19.

COVID-19 Vaccinations

For the COVID-19 vaccination, 14 parents reported receiving at least one dose of a vaccine (63.6%) while seven parents did not receive the vaccine (31.8%). Out of the 14 vaccinated parents, half received the Pfizer vaccine and half received the Moderna vaccine. For the parents who declined a vaccination, the following reasons were provided for the decision against vaccination: side effects (22.7%), rapid development of vaccine (18.2%), consideration of self as "low-risk" for COVID-19 (13.6%), and general disapproval or mistrust of vaccines (9.1%). Two of these parents endorsed being open to receiving the vaccine in the future. The COVID-19 vaccine became available for children over 5 and 12 participants were queried about

if their child got the vaccine. Of these 12 parents, 10 reported that their child received the vaccine and two reported that their child did not receive the COVID-19 vaccine.

Financial Support During the Pandemic

Out of 22 parents, 17 (77.3%) endorsed that they received the first stimulus check, with 47% of these parents using the first stimulus to pay off debt, 41.2% of parents mostly spending it, and the remaining 11.8% of parents mostly saving the stimulus check. A similar pattern was observed for the second and third stimulus checks. For the second stimulus check, 72.3% (n = 16) parents received the check, with most parents spending the money to pay off debt (43.8%), followed by spending the check (31.3%) and saving it (23.5%). For the third check, 59% of parents received the check, with four parents noting it had not come yet in the mail, but they were eligible. For the third check, half of the parents used the check to pay off debt (50%).

Pandemic-Related Employment Changes

A summary of parent's endorsed employment challenges is presented in Table 2. The primary endorsed employment challenge was balancing work with childcare and homeschooling, with 81.8% of parents reporting that this was a significant challenge during the pandemic specific to their employment. Employment burnout (45%), mental health challenges as an employee (59%), and financial insecurity (40.9%) were also significant challenges. A subset of parents identified that reducing hours, anxiety over layoffs, and switching from a full-time to part-time job or taking a leave of absence were also significant challenges. Notably, 86.4% of the parents reported they were responsible for most or all the household labor.

Table 2

Summary of COVID-19 Impact on Parent's Employment

	Frequency (*n*, %)
Reducing Hours	7 (31.2%)
Switch to less demanding job	4 (18.2%)
Taking a leave of absence	5 (22.7%)
Moving from full-time to part-time	6 (27.2%)
Leaving workplace all-together	3 (13.6%)
Anxiety over layoffs/furloughs	5 (22.7%)
Employment burnout	10 (45.5%)
Mental health (as employee) challenges	13 (59%)
Childcare/homeschooling challenges	18 (81.8%)
Financial insecurity	9 (40.9%)

Parents also provided free-text answers for the primary challenges their family faced during the pandemic. Sixteen parents opted to include a free-text answer. Of these 16, six indicated that financial difficulties were the primary challenge, providing reports such as "... it is hard on us financially to survive," and "keeping a steady income." Other common themes included burnout, desiring a return to normalcy, employment issues, and health concerns. Parents also provided answers on what had been the most helpful; for this question, 21 parents provided responses. The most common theme was assistance, such as the stimulus checks, food stamps, and subsidized housing. Other common themes were help from relatives on childcare, increased flexibility in working from home, and being together as a family.

Discussions of Privileges and Challenges Related to Race and Ethnicity

Prior to the pandemic, seven parents discussed with their child about the challenges they may face due to their race or ethnicity. Since the pandemic, eight parents endorsed discussing challenges their child may face due to their race or ethnicity. Prior to the pandemic, eight parents reported that they talked to their child about the advantages they may face because of their race or ethnicity. Since the pandemic, ten parents endorsed that they talked to their child about advantages related to their race or ethnicity.

Comparison of Key Variables Between Pre-Pandemic and Current Study

Summary of Parent and Child CRP

Parent CRP Concentrations. For the pre-pandemic timepoint, the raw mean CRP level for parents was 2.87 mg/L (SD = 2.94, Skewness = 1.96, kurtosis = 4.66). For the current time point, the raw mean CRP level for parents was 4.27 mg/L (SD = 4.67, skewness = 1.64, kurtosis = 2.70). Due to the skewed distribution of parent's CRP levels, a natural log transformation was applied, which successfully normalized the data to allow for parametric testing. The mean log-transformed CRP data for pre-pandemic for parents is 0.23 (SD = -0.50), and for the current time point, the mean log-transformed CRP levels were 0.32 (SD = 0.61). The skewness was < -.05 and kurtosis was < 3. A paired sample t-test (with the log-transformed data) was run to determine if the increase in mean parent CRP levels was significant. Results indicated that the increase in parent's CRP levels from pre-pandemic to the study time point was not statistically significant ($t(21) = 0.73$, $p = 0.24$).

Child CRP Concentrations. For the pre-pandemic timepoint, the raw mean CRP level for children was 0.64 mg/L (SD = 1.16, Skewness = 2.75, kurtosis = 7.40). For the pre-pandemic time point, one child had a CRP value below the detection limit, which was coded as the assay's

lower detection limit (CRP = 0.03 mg/L). For the current time point, the raw mean CRP level for children was 0.80 mg/L (SD = 1.75, skewness = 3.07, kurtosis = 9.87). Due to the skewed distribution of children's CRP levels, a natural log transformation was applied, which successfully normalized the data to allow for parametric testing. The mean log-transformed CRP data for pre-pandemic for children was -0.66 (SD = 0.69), and for the current time point, the mean log-transformed CRP levels were -0.83 (SD = 0.80). The skewness was < -0.5 and kurtosis was < 3. A paired sample t-test (with the log-transformed data) was run to determine if the increase in mean children CRP levels was significant. Results indicated that the slight increase in children's CRP levels from pre-pandemic to the study time point was not statistically significant ($t(21) = 0.02$, $p = 0.49$).

Parent and Child Outcome Measures. Table 3, below, summarizes all major changes. In summary, household chaos levels significantly increased from the pre-pandemic time point to the current study ($p < 0.001$). Mean parent depressive symptoms, child's intrusive trauma symptoms, child's anxiety symptoms, parent's CRP levels, and child's CRP levels did increase from pre-pandemic to the current time point, but these changes were not statistically significant ($p > 0.05$).

The average scores for intensity of children's behavioral problems, Parent Child Dysfunctional Index, and Difficult Child index all significantly decreased from the pre-pandemic (2016-2019) to the current study time point (August-December 2021) ($p < 0.03$). When controlling for child age, the decrease in intensity of child behavior problems became non-significant ($\beta = -0.25$, B = -4.18, SE = 2.50, $R^2 = 0.05$, $p = 0.10$, 95% CI = [-9.23, -0.87]). When controlling for child age, the decrease in parent child dysfunctional interaction index also became non-significant ($\beta = -0.22, 7$, B = -12.86, SE = 8.94, $R^2 = 0.02$, $p = 0.16$, 95% CI = [-30.91,

5.82]). When controlling for child age, the decrease in the difficult child score remained significant (β = -0.31, 7, B = -19.41, SE = 9.37, R^2 = 0.07, p = 0.04, 95% CI = [-38.33, -0.49]). The mean of children's total trauma symptoms, avoidance trauma symptoms, and arousal trauma symptoms also decreased between the pre-pandemic time point and the current study, though this change was not statistically significant ($p > 0.1$). Table 3 summarizes the mean, SD, and paired sample t-tests for pre-pandemic and current study values for key variables.

Zero-Order Bivariate Correlation Analyses

Zero-order correlations between all variables of interest and potential confounders, including parent and child age, household income, parent education, child sex, parent BMI, child BMI (WHO percentile rank), household chaos level (i.e., CHAOS score, pre-pandemic and current), parent anxiety symptoms (i.e., BSI T-score pre-pandemic and current levels), parent depression symptoms (i.e., BSI T-score, pre-pandemic and current levels), parenting stress (i.e., PSI score, pre-pandemic and current levels), child behavior problems (i.e., ECBI- Total Intensity score, pre-pandemic and current levels), child trauma symptoms (i.e., TSCYC total score pre-pandemic and current), parent CRP levels (pre-pandemic and current), and child CRP levels (pre-pandemic and current), parent NSAID use, and parent smoking status. Independent *t*-tests were examined for dichotomous variables (i.e., child sex, parent smoking status at time of study (yes or no)). Table 4 shows the zero-order bivariate correlation for the primary demographic variables (parent age, child age, child gender, etc) and the current study outcome variables (i.e., parent anxiety, parent depression, household chaos, parent stress, child behavior, child trauma, and parent and child CRP). All other results are summarized in text. Several variables had statistically significant ($p < 0.05$) associations and are summarized below.

Table 3

Means and SD of Key Variables Pre-Pandemic (2016-2019) and Current Study (2021)

Variable	Pre-Pandemic Mean (SD)	Current Mean (SD)	*t*	*p*
Parent Anxiety Symptoms	54.05 (11.35)	52.73 (11.91)	-0.06	0.58
Parent Depressive Symptoms	53.13 (8.48)	56.14 (8.11)	1.30	0.21
Child Behavior Problems Intensity	53.90 (5.41)	49.59 (10.52)	-1.98	0.03
Child Trauma Symptoms (Total)	59.91 (11.22)	58.36 (15.07)	-0.50	0.31
Child Trauma Symptoms (Intrusive)	54.64 (10.31)	58.82 (16.06)	1.30	0.11
Child Trauma Symptoms (Avoidance)	59.78 (18.48)	58.36 (17.35)	-0.38	0.10
Child Trauma Symptoms (Arousal)	59.50 (13.30)	55.27 (11.90)	-1.36	0.10
Child Trauma Symptoms (Anxiety)	56.32 (10.72)	60.73 (18.01)	1.16	0.13
Parent Child Dysfunction (Percentile)	59.45 (25.90)	46.43 (33.58)	-3.16	0.002
Difficult Child (Percentile)	63.00 (27.77)	42.90 (34.89)	-2.66	0.01
Household Chaos	4.86 (2.45)	9.05 (2.48)	5.07	<0.001
Parent CRP Levels (Raw; mg/L)$^{+}$	2.87 (2.94)	4.27 (4.67)	0.73	0.24
Child CRP Levels (Raw; mg/L)$^{+}$	0.64 (1.16)	0.80 (1.75)	0.02	0.49

+ the t and p values were calculated with log-transformed means and SD due to non-normal distribution of raw CRP data

Table 4

Zero-Order Bivariate Correlation Table

Variables	Parent Age	Child Age	Child Sex	Parent BMI	Child BMI	Child ACEs	Group Condition	Income	Parent Anxiety	Parent Depression	Household Chaos	Parent-Child Dysfunction	Difficult Child Rating	Child Behavior	Child Trauma	Parent CRP	Child CRP
Parent Age	x	0.32	-0.30	0.23	0.08	0.29	0.02	-0.27	0.11	0.42+	-0.09	0.36	0.29	0.28	0.25	0.08	0.09
Child Age	x	x	-0.51*	0.13	0.3	0.36	0.05	0.15	0.53*	0.56*	-0.07	0.18	0.14	0.17	0.29	-0.26	0.44*
Child Sex	x	x	x	0.06	-0.04	-0.38+	0	0.03	-0.09	-0.33	0.15	-0.14	-0.11	-0.15	-0.15	-0.05	-0.36+
Parent BMI	x	x	x	x	0.48*	0.11	0.36*	-0.19	-0.05	-0.06	-0.27	-0.03	-0.09	0.18	0.25	0.49	0.28+
Child BMI	x	x	x	x	x	0.14	0.27	0.13	-0.05	0.32	-0.16	0.08	0.11	0.36	0.28	-0.02	0.41+
Child ACEs	x	x	x	x	x	x	0.09	-0.21	0.21	0.23	0.07	-0.03	0.23	-0.06	0.48*	-0.24	-0.15
Group Condition	x	x	x	x	x	x	x	0.24	0.01	-0.004	-0.12	0.42+	0.15	0.09	0.45*	0.4	0.36*
Income	x	x	x	x	x	x	x	x	0.15	0.12	0.06	0.12	-0.02	0.44*	0.28	-0.05	0.1
Parent Anxiety	x	x	x	x	x	x	x	x	x	0.64**	0.3	0.12	0.32	0.13	0.48*	-0.16	0.27
Parent Depression	x	x	x	x	x	x	x	x	x	x	-0.01	0.37+	0.37+	0.33	0.38+	-0.18	0.29
Household Chaos	x	x	x	x	x	x	x	x	x	x	x	-0.15	0.09	0.01	-0.12	-0.37+	-0.08
Parent-Child Dysfunction	x	x	x	x	x	x	x	x	x	x	x	x	0.76**	0.14	0.14	0.23	0.30
Difficult Child Rating	x	x	x	x	x	x	x	x	x	x	x	x	x	0.26	0.26	-0.03	0.14
Child Behavior	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.42+	0.13	0.2
Child Trauma	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.27	0.06
Parent CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.25
Child CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

+p<0.09, * p<0.05, ** p<0.001

Parental age was positively associated with the intensity of child's level of behavioral problems pre-pandemic ($r = 0.55$, $p = 0.01$); however, parent age was not significantly associated with the intensity of child behavioral problems at the current study time point ($r = 0.28$, $p = 0.22$). Parent age was marginally associated with parent's depressive symptoms ($r = 0.42$, $p = 0.052$). Parent age at time of study was not significantly associated or trending significantly with any other variable of interest ($p > 0.20$).

Child's age was significantly associated with child sex ($t(20) = 2.63$, $p = .008$), such that, on average, the cisgender male child participants were older ($M = 8.90$, SD = 1.30) compared to the cisgender female child participants ($M = 7.55$, SD = 1.12). Child's age was also positively significantly correlated with parent's anxiety score at the time of the study ($r = 0.53$, $p = .012$) and parent's depression score at the time of the study ($r = .056$, $p = 0.01$). Lastly, child age was significantly and positively correlated with child's current CRP levels ($r = 0.44$, $p = 0.04$).

Child sex was associated with recent ACES occurring since the COVID-19 pandemic began. Specifically, the mean of new ACES occurring since the COVID-19 pandemic was higher in cisgender male children ($M = 0.82$, SD = 0.75) than cisgender female children ($M = 0.27$, SD = .47) ($t(20) = 2.05$, $p = 0.03$). Child sex was marginally associated with total ACES ($p = 0.09$). Child sex was marginally associated with child CRP, such that on average, cisgender male children had higher CRP values (M(raw CRP) = 1.41 mg/L, SD = 2.34) compared to cisgender female children's CRP values (M(raw CRP) = 0.18, SD = 0.31), $t(20) = 1.71$, $p = 0.05$). Child trauma symptoms were also positively correlated with child ACES ($r = 0.48$, $p = 0.02$).

Higher parent BMI was associated with higher child BMI by WHO percentile ($r = 0.48$, $p = 0.02$). Parent's BMI was also positively associated with pre-pandemic CRP levels ($r = 0.74$, $p < .001$) and current CRP levels ($r = 0.49$, $p = 0.02$). Child BMI (by WHO percentile rank) was

marginally associated with child's CRP levels at the study time point ($r = 0.41$, $p = 0.06$). Parent smoking was also significantly associated with parent's CRP levels at the time of the current study ($t(20) = -2.02$, $p = 0.03$), with mean CRP values on average lower in parents who smoked ($n = 6$) (M(raw) = 2.05, SD = 3.25) versus those who did not smoke ($n = 16$) (M(raw) = 5.11, SD = 4.91). Parent's use of NSAIDs was also significantly associated with parent's CRP values at the time of the study, such that parents who had taken an NSAID within the last 24 hours prior to the study had lower CRP values ($n = 5$, M(raw) = 1.92, SD = 3.30) compared to those who had not taken an NSAID ($n = 17$, M(raw) = 4.97, SD = 4.84) ($t(20) = -2.32$, $p = 0.02$). Very few parents endorsed prior COVID-19 infections and no relationship was found between prior COVID-19 infection and parent CRP levels ($p = 0.90$).

Parent's anxiety and depression were also significantly associated at both pre-pandemic time point ($r = 0.63$, $p = 0.002$) and the current study time point ($r = 0.64$, $p = 0.001$). Parent anxiety was positively associated with child's current trauma symptoms ($r = 0.48$, $p = 0.03$). Parent depression was marginally associated with child's current trauma symptoms ($r = 0.38$, $p = 0.08$). Current household chaos was marginally inversely associated with parent's CRP ($r = -0.37$, $p = 0.09$).

Yearly household income was only significantly correlated with child's current behavioral problems ($r = 0.44$, $p = 0.04$). Intensity of child's behavior was marginally associated with child's trauma scores ($r = 0.42$, $p = 0.06$). Parent and child race and ethnicity were not statistically associated with any other variables of interest ($p > 0.10$).

Summary of Group Differences

Independent sample *t*-tests were run to compare differences in key outcome or predictors variables by intervention versus control groups and to identify any demographic differences

between the intervention and control groups. No demographic variables were statistically different between the two groups ($p > .10$), except for parent BMI, which was, on average, higher in the intervention group relative to the control group ($p = 0.049$). For variables of interest, in summary, the following variables had statistically significant differences between the Control and Intervention group: TSCYC- Total Trauma and all trauma subscale scores (except Arousal) at the current study time point and parent CRP levels at the pre-pandemic and current study time point. Thus, group condition was considered a covariate for analyses containing these variables.

Results for Hypotheses 1a- 1m

Aim 1 examines the extent to which parent stress variables during the pandemic and *change* in parent's stress variables (i.e., parental anxiety, parental depression, household chaos, and parent stress) are associated with child's CRP levels during the pandemic. Aim 1 also examines the extent to which child CRP at the pandemic study point is associated with child trauma symptoms and intensity of child behavioral problems. Table 5 summarizes the results of associations between parent pandemic stress variables, change in parent stress variables, and child CRP levels (Hypothesis 1a- Hypothesis 1d).

Hypothesis 1b Results (Parent Depression and Child CRP)

Parental depression levels during the pandemic were not statistically associated with child's CRP levels during the pandemic ($\beta = 0.29$, B = 0.03, SE = 0.02, $R^2 = 0.04$, p = 0.20, 95% CI = [-0.02, -0.07]). There was no significant difference in mean child CRP concentration between parent depression scores below ($n = 17$) or above ($n = 5$) the clinical cut off ($t(20) = 1.08$, $p = 0.15$).

Table 5

Hypothesis 1: Results of Parental Pandemic Stress Associations with Child CRP during the COVID-19 pandemic

Variable	β	B	SE	R^2	p	95%CI
Parent Anxiety	0.27	0.02	0.01	0.02	0.22	[-0.02, 0.05]
Change in Parent Anxiety	-0.05	-0.003	0.03	-0.05	0.81	[-0.04, 0.03]
Parent Depression	0.29	0.03	0.02	0.04	0.20	[-0.00, 0.07]
Change in Parent Depression	0.06	0.004	0.02	-0.05	0.79	[-0.03, 0.03]
Household Chaos	-0.07	-0.02	0.08	-0.05	0.76	[-0.18, 0.13]
Change in Household Chaos*	-0.49	-0.11	0.04	0.20	**0.02**	[-0.20, -0.02]
Parent-Child Dysfunction	0.30	0.01	0.01	0.04	0.82	[-0.003, 0.02]
Change in Parent-Child Dysfunction	0.19	0.01	0.01	-0.01	0.41	[-0.01, 0.03]
Difficult Child Rating	0.14	0.003	0.01	0.04	0.54	[-0.01, 0.01]
Change in Difficult Child Rating	0.19	0.01	0.01	-0.01	0.41	[-0.01, 0.03]

**Model became marginally significant when accounting for child WHO percentile and child age (p=0.09)*

Hypothesis 1c Results (Household Chaos and Child CRP)

Household chaos level during the pandemic was not statistically associated with child's CRP levels during the pandemic (β = -0.07, B = -0.02, SE = 0.08, R^2 = -0.05, p = 0.76, 95% CI = [-0.18, -0.13]). Change in household chaos levels from pre-pandemic to the current time point was significantly associated with child CRP levels at the current study. Contrary to the *a priori* hypothesis, results show that increases in household chaos were associated with lower levels of child CRP during the pandemic (β = -0.49, B = -0.11, SE = 0.04, R^2 = 0.20, p = 0.02, 95% CI = [-0.20, -0.02]). After adding child WHO BMI percentile and child age, the model explained 28% of the total variance (R^2 = 0.28). In this model, the association between change in household chaos levels and child CRP attenuated to become marginally significant (β = -0.36, B = -0.08, SE = 0.04, p = 0.09, 95% CI = [-0.17, -0.01]). Child WHO BMI percentile was not significantly associated with child CRP in this model (β = 0.21, B = 0.004, SE = 0.005, p = 0.33, 95% CI = [-0.005, 0.02]) nor was child age significantly associated with child CRP in this model (β = 0.29, B = 0.17, SE = 0.12, p = 0.17, 95% CI = [-0.08, 0.41]).

Hypothesis 1d Results (Parent Stress and Child CRP)

Parent-Child Dysfunction percentile score at the pandemic time point was not significantly associated with child CRP at the pandemic (β = 0.30, B = 0.01, SE = 0.01, R^2 = 0.04, p = 0.82, 95% CI = [-0.003, 0.02]). There was a marginally significant difference in mean child CRP concentrations for parents who endorsed dysfunctional interactions at a clinically significant level (n = 4) and parents with scores below the 90th percentile (n = 17), in that child CRP in the group above the 90th percentile on the Parent-Child Dysfunction scale had higher CRP levels (t(20) = 1.67, p = 0.06). Difficult Child percentile score at the pandemic time point was also not significantly associated with child CRP at the pandemic (β = 0.14, B = 0.003, SE =

0.01, R^2 = 0.04, p = 0.54, 95% CI = [-0.01, 0.01]). There was no significant difference in mean child CRP concentration between the Difficult Child below 90th percentile scores (n = 17) and those above the 90th percentile (n = 4) (t(20) = 1.29, p = 0.11).

Change in Parent-Child Dysfunction scores was not significantly associated with child's current CRP (β = 0.19, B = 0.01, SE = 0.01, R^2 = -0.01, p = 0.41, 95% CI = [-0.01, 0.03]). Change in Difficult Child score was also not significantly associated with child's current CRP (β = 0.19, B = 0.01, SE = 0.01, R^2 = -0.01, p = 0.41, 95% CI = [-0.01, 0.03]).

Hypothesis 1e Results (Child CRP and Child Trauma)

Child CRP levels were not significantly associated with the child's total trauma symptoms (β = 0.06, B = 1.07, SE = 4.21, R^2 = -0.05, p = .80, 95% CI = [-7.72, 9.86]). Child CRP levels were also not significantly associated with any of the TSCYC trauma subscales (p > 0.40). There was no difference in mean CRP concentrations between children with clinically significant trauma scores (n=4) and those below the clinical cut-off of 65 (n = 18) (t(20) = 0.57, p = 0.29).

Hypothesis 1f Results (Child CRP and Child Behavioral Problems)

Child CRP levels were not significantly associated with intensity of child's problem behaviors (β = 0.20, B = -0.11, SE = 2.64, R^2 = -0.01, p = 0.37, 95% CI = [-3.38, 8.66]). For children with a clinically significant ECBI Intensity T-score of ≥ 60 (n = 5), the mean CRP level was significantly higher than children whose T-scores fell below 60 (n = 17); (t(20) = 1.88, p = 0.04).

Hypothesis 1g Results (Parent Anxiety and Child Trauma)

Parental anxiety (at the pandemic time point) was significantly associated with child's total trauma symptoms (at the pandemic (β = 0.48, B = 0.60, SE = 0.25, R^2 = 0.19, p = 0.03, 95%

CI = [.08, 1.12]). After controlling for both child age and group condition (intervention versus control), parental anxiety remained significantly associated with child's total trauma symptoms (β = 0.46, B = 0.58, SE = 0.27, R^2 = 0.33, p = 0.43, 95% CI = [0.02, 1.14]). In this model, group condition was significantly associated with child's trauma symptoms (p = 0.02), but child age was not associated with child's trauma symptoms (p = 0.89). Parental anxiety was also significantly associated with all trauma subscales ($p < 0.03$), except for child's trauma arousal symptoms ($p > 0.05$). The average of total child trauma symptoms was higher in parents (M = 65.17, SD = 19.93, n = 6) who had clinically significant anxiety scores compared to those below the clinical cut off (M = 55.81, SD = 12.64, n = 16); however, this difference in mean trauma symptoms scores was not statistically significant ($t(20) = 1.32$, p = 0.10).

Hypothesis 1h Results (Parent Anxiety and Child Behavioral Problems)

Parental anxiety was not significantly associated with intensity of child's behavioral problems (β = 0.12, B = 0.11, SE = 0.20, R^2 = -0.03, p = 0.57, 95% CI = [-0.30, 0.52]). The average child behavioral intensity score was lower in parents who had anxiety scores above the clinical cut off (M = 45.83, SD = 7.25, n = 6) than in those parents who had anxiety scores below the clinical cut off (M = 51.13, SD = 11.37, n = 16); however, this difference in means was not significant between groups ($t(20) = -1.05$, p = 0.15).

Hypothesis 1i Results (Parent Depression and Child Trauma)

Parental depression was marginally associated with child's total trauma symptoms (β = 0.38, B = 0.70, SE = 0.38, R^2 = 0.10, p = 0.08, 95% CI = [-0.10, 1.51]). Parental depression was only significantly associated with child's trauma arousal symptoms (β = 0.51, B = 0.75, SE = 0.28, R^2 = 0.22, p = 0.02, 95% CI = [0.16, 1.34]). This association between parental depression and child arousal trauma symptoms remained significant even when controlling for child age,

parent age, and group condition ($\beta = 0.59$, B = 0.86, SE = 0.36, $p = 0.03$, 95% CI = [0.11, 1.61]). There were no other significant associations observed between parental depression scores and the other trauma subscale ($p > 0.05$). The average of total child trauma symptoms was higher in parents ($M = 64.40$, SD = 20.72, $n = 5$) who had clinically significant depression scores compared to those below the clinical cut-off (M = 55.59, SD = 13.26, $n = 17$); however, this difference in mean trauma symptoms scores was not statistically significant ($t(20) = 1.02$, $p = 0.16$).

Hypothesis 1j Results (Parent Depression and Child Behavioral Problems)

Parental depression was not significantly associated with intensity of child's behavioral problems ($\beta = 0.33$, B = 0.43, SE = 0.27, $R^2 = 0.07$, $p = 0.13$, 95% CI = [-0.13, 1.00]). The average child behavioral intensity score was higher in parents who had depression scores above the clinical cut off ($M = 53.40$, SD = 14.67, $n = 5$) than in those parents who had depression scores below the clinical cut off ($M = 48.59$, SD = 9.26, $n = 17$); however, this difference in means was not significant between groups ($t(20) = 0.90$, $p = 0.19$).

Hypothesis 1k Results (Household Chaos and Child Trauma, Child Behavioral Problems)

Household chaos was not associated with child's total trauma ($\beta = 0.38$, B = 0.70, SE = 0.38, $R^2 = 0.10$, $p = 0.08$, 95% CI = [-0.10, 1.51]). Household chaos was not significantly associated with any of the trauma subscales ($p > 0.05$). Household chaos was not significantly associated with intensity of child behavioral problems ($\beta = 0.18$, B = 0.65, SE = 0.83, $R^2 = -0.02$, $p = 0.44$, 95% CI = [-1.09, 2.38]).

Hypothesis 1l Results (Parent Stress and Child Trauma)

Parent Child Dysfunction Index percentile was not associated with child's total trauma ($\beta = 0.15$, B = 0.06, SE = 0.09, $R^2 = -0.03$, $p = 0.51$, 95% CI = [-0.12, 0.25]). Parent Child

Dysfunction percentile was not significantly associated with any of the trauma subscales ($p > 0.05$). The Difficult Child percentile was not significantly associated with child trauma ($\beta = 0.32$, B = 0.12, SE = 0.08, $R^2 = 0.06$, $p = 0.15$, 95% CI = [-0.05, 0.30]) or any subscales except for a marginal significant association with child's trauma arousal symptoms ($\beta = 0.43$, B = 0.12, SE = 0.06, $R^2 = 0.14$, $p = 0.05$, 95% CI = [-0.002, 0.24]). The average child trauma score was not significantly different between parents who endorsed a percentile over the 90th percentile and those below the 90th percentile for Parent Child Dysfunctional Interactions ($t(20) = -0.21$, $p = 0.42$). The mean child trauma score was not significantly different in parents endorsing Difficult Child at or above the 90th percentile or below the 90th percentile ($t(20) = 0.28$, $p = 0.39$).

Hypothesis 1m Results (Parent Stress and Child Behavioral Problems)

Parent Child Dysfunctional Interactions percentile was not significantly associated with intensity of child behavioral problems ($\beta = 0.15$, B = 0.04, SE = 0.06, $R^2 = -0.03$, $p = 0.51$, 95% CI = [-0.09, 1.7]) nor was the Difficult Child Index percentile significantly associated with intensity of child behavioral problems ($\beta = 0.34$, B = 0.09, SE = 0.06, $R^2 = 0.07$, $p = 0.14$, 95% CI = [-0.03, 0.21]). The average child behavior intensity score was not significantly different between parents who endorsed a percentile over the 90th percentile and those below the 90th percentile for Parent Child Dysfunctional Interactions ($t(20) = 0.39$, $p = 0.76$). The mean child behavior intensity score was significantly higher in parents endorsing Difficult Child at or above the 90th percentile ($M = 56.75$, SD = 7.85, $n = 4$) compared to those below the 90th percentile ($M = 46.53$, SD = 8.40, $n = 17$) ($t(20) = 2.12$, $p = 0.02$).

Results Hypotheses 2a-2f

Aim 2 examines the extent to which change in child CRP from pre-pandemic (2016-2019) and the current study (2021) predicts children's mental health symptoms at the current study time point. Table 6 summarizes Aim 2 results.

Hypothesis 2a (Change in Child CRP and Total Trauma)

At the first level (Time), time was not significantly associated with child's total trauma symptoms (B = -1.52, SE = 3.22, p = 0.64, 95% CI = [-7.80, 4.77]). At the second level (Between Child), CRP change score was not significantly associated with the child's total trauma symptoms (B =1.55, SE = 3.76, p = 0.68, 95% CI = [-5.66, 8.76]). The effect of the interaction of time x child CRP change term on child trauma symptoms was not significant (B = 0.17, SE = 4.10, p = 0.97, 95% CI = [-7.84, 8.18].

Hypothesis 2b (Change in Child CRP and Anxiety Trauma)

At the first level (Time), time was not significantly associated with child's anxiety trauma symptoms (B = 4.76, SE = 3.96, p = 0.24, 95% CI = [-2.97, 12.50]). At the second level (Between Child), CRP change score was not significantly associated with the child's anxiety trauma symptoms (B = 3.31, SE = 4.09, p = 0.42, 95% CI = [-4.52, 11.14]). The effect of the time x child CRP change term on child anxiety trauma symptoms was not significant (B = 2.17, SE = 5.04, p = 0.67, 95% CI = [-7.68, 12.02].

Hypothesis 2c (Change in Child CRP and Intrusive Trauma)

At the first level (Time), time was not significantly associated with child's intrusive trauma symptoms (B = 3.97, SE = 3.38, p = 0.25, 95% CI = [-2.63, 10.56]). At the second level (Between Child), CRP change score was not significantly associated with the child's intrusive trauma symptoms (B = 3.22, SE = 4.79, p = 0.40, 95% CI = [-4.04, 10.49]). The effect of the

time x child CRP change term on child intrusive trauma symptoms was not significant (B = -1.33, SE = 4.30, p = 0.76, 95% CI = [-9.72, 7.07].

Hypothesis 2d (Change in Child CRP and Avoidance Trauma)

At the first level (Time), time was not significantly associated with child's avoidance trauma symptoms (B = -0.72, SE = 3.85, p = 0.85, 95% CI = [-8.25, 6.80]). At the second level (Between Child), CRP change score was not significantly associated with the child's avoidance trauma symptoms (B = -2.43, SE = 5.08, p = 0.64, 95% CI = [-12.19, 7.34]). The effect of the time x child CRP change term on child avoidance trauma symptoms was not significant (B = 4.21, SE = 4.91, p = 0.40, 95% CI = [-5.37, 13.79].

Hypothesis 2e (Change in Child CRP and Arousal Trauma)

At the first level (Time), time was not significantly associated with child's arousal trauma symptoms (B = -4.41, SE = 3.26, p = 0.19, 95% CI = [-10.78, 1.96]). At the second level (Between Child), CRP change score was not significantly associated with the child's arousal trauma symptoms (B = 3.03, SE = 3.54, p= 0.40, 95% CI = [-3.76, 9.81]). The effect of the time x child CRP change term on child arousal trauma symptoms was not significant (B = -1.12, SE = 4.15, p = 0.79, 95% CI = [-9.23, 6.99].

Hypothesis 2f (Change in Child CRP and Child Behavioral Problems)

At the first level (Time), time was marginally associated with child's behavior problems (B = -3.86, SE= 2.18, p = 0.09, 95% CI = [-8.13, 0.41]). At the second level (Between Child), CRP change score was not significantly associated with the child's behavior problems (B = 1.19, SE = 2.32, p = 0.61, 95% CI = [-3.24, 5.63]). The effect of the time x child CRP change term on intensity of child behavior problems was not significant (B = 1.96, SE = 2.78, p = 0.49, 95% CI = [-3.47, 7.40].

Table 6

Hypothesis 2: Results of Multi-Level Models of Change in Child CRP Predicting Child Mental Health Outcomes

	Trauma (Total)		**Trauma (Anxiety)**		**Trauma (Intrusive)**		**Trauma (Avoidance)**		**Trauma (Arousal)**		**Child Behavior (Intensity)**	
Level One												
	B (SE)	**95% CI**	**B (SE)**	**95%CI**	**B (SE)**	**95%CI**	**B (SE)**	**95%CI**	**B (SE)**	**95% CI**	**B (SE)**	**95%CI**
Time	-1.52 (3.75)	-7.80 4.77	4.76 (3.96)	-2.97 12.50	3.97 (3.38)	-2.63 10.56	-0.72 (3.85)	-2.63 10.56	-4.41 (3.26)	-10.78 1.96	-3.86 (2.18)	-10.78 1.96
Level Two												
Between Child	1.55 (3.76)	-5.66 8.76	3.31 (4.09)	-4.52 11.14	3.22 (4.79)	-4.04 10.49	-2.43 (5.09)	-4.04 10.49	3.03 (3.54)	3.76 9.81	1.19 (2.32)	-3.76 9.81
Time x Child CRP	0.17 (4.10)	-7.84 8.18	2.17 (5.04)	-7.68 12.02	-1.33 (4.30)	-9.72 7.07	4.21 (4.91)	-9.72 7.07	-1.12 (4.15)	-9.23 6.9	1.96 (2.78)	-9.23 6.99

Note: No results were statistically significant ($p > 0.10$).

Results Hypotheses 3a-3d

Aim 3 examined the extent to which change in child CRP moderates the hypothesized association between pandemic-related stress and children's mental health.

Hypothesis 3a (Change in Child CRP, Parent Anxiety, and Child Mental Health)

The association between the interaction term (change in child CRP x parental anxiety) and child's total trauma symptoms was not significant (β = -0.02, B = -0.01, SE = 0.35, R^2 = .10, p = .99, 95% CI = [-0.75- 0.73]). Child CRP change score was not significantly associated with child's total trauma symptoms (β = -0.02, B = -0.38, SE = 18.46, p = .98, 95% CI = [-39.16, 38.40]). No significant results were found for change in child CRP moderating the association between parental anxiety and child trauma subtypes ($p > 0.10$).

The association between the interaction term (change in child CRP x parental anxiety) and intensity of child's behavioral problems was not significant (β = -0.31, B = -0.08, SE = 0.27, R^2 = -0.09, p = .78, 95% CI = [-0.65, 0.49]). Child CRP change score was not significantly associated with child's behavior problems (β = 0.53, B = 7.04, SE = 14.18, p = .63, 95% CI = [-22.75, 36.83]).

Hypothesis 3b (Change in Child CRP, Parent Depression, and Child Mental Health)

The association between the interaction term (change in child CRP x parental depression) and child's total trauma symptoms was not significant (β = 2.01, B = 1.00, SE = 0.70, R^2 = .03, p = .49, 95% CI = [-1.41, 2.80]). Child CRP change score was not significantly associated with child's total trauma symptoms (β = -2.03, B = -38.85, SE = 57.66 p = .52, 95% CI = [-160.00, 82.30]). No significant results were found for change in child CRP moderating the association between parental depression and child trauma subtypes ($p > 0.10$).

The association between the interaction term (change in child CRP x parental depression) and intensity of child's behavioral problems was not significant (β = -0.94, B = -0.22, SE = 0.70, R^2 = 0.02, p = .76, 95% CI = [-1.70, 1.26]). Child CRP change score was not significantly associated with child's behavior problems in this model (β = 1.15 B = 15.34, SE = 40.44, p = 0.71, 95% CI = [-69.60, 100.30]).

Hypothesis 3c (Change in Child CRP, Household Chaos, and Child Mental Health)

The association between the interaction term (change in child CRP x household chaos) and child's total trauma symptoms was marginally significant (β = -1.81, B = -3.49, SE = 1.78, R^2 = .06, p = .07, 95% CI = [-7.22, 0.25]). Child CRP change score was marginally significantly associated with child's total trauma symptoms (β = 1.86, B = 35.69, SE = 17.55, p = .06, 95% CI = [-1.19, 72.56]). In this model, household chaos was not significantly associated with child's trauma symptoms (β = -0.05, B = -0.30, SE = 1.37, p = .83, 95% CI = [-3.17, 2.57]). When controlling for child WHO BMI percentile, group condition, and child age, the association between the interaction term (change in child CRP x household chaos) and child's total trauma symptoms was marginally significant (β = -1.69, B = -3.20, SE = 1.60, R^2 = 0.25, p = 0.06, 95% CI = [-6.63, 0.21]). Child CRP change score was not significantly associated with child's total trauma symptoms (β = 1.38, B = 36.48, SE = 16.12, p = 0.12, 95% CI = [-7.87, 60.83]). In this model, household chaos was not significantly associated with child's trauma symptoms (β = 0.11, B = 0.68, SE = 1.29, p = 0.60, 95% CI = [-2.06, 3.42]). In this model, group condition was significantly associated with child trauma symptoms (β = 0.49, B = 14.50, SE = 6.47, p = 0.04, 95% CI = [0.72, 28.30]), while child age and child WHO BMI percentile were not significantly associated with child trauma (p > 0.25).

Household Chaos and Avoidance Trauma. The association between the interaction term (change in child CRP x household chaos) and child's avoidance trauma symptoms was statistically significant (β = -2.17, B = -4.80, SE = 1.97, R^2 = 0.14, p = 0.03, 95% CI = [-8.93, -0.67]). Child CRP change score was significantly associated with child's avoidance trauma symptoms (β = 2.19, B = 48.29, SE = 19.40, p = .02, 95% CI = [7.54, 89.04]). In this model, household chaos was not significantly associated with child's avoidance trauma symptoms (β = 0.01, B = 0.04, SE = 1.51, p = .98, 95% CI = [-3.14, 3.21]). The model remained significant when controlling for child WHO BMI percentile, child age, and group condition (β = -1.99, B = -4.42, SE = 1.59, R^2 = 0.44, p = 0.01, 95% CI = [-7.81, -1.03]). In this model, child CRP change score was significantly associated with child's avoidance trauma symptoms (β = 1.64, B = 36.14, SE = 15.90, p = 0.04, 95% CI = [2.08, 70.20]). For covariates, group condition was significantly associated with child's avoidance trauma symptoms (p = 0.01); however, child age and WHO BMI percentile were not associated with child avoidance trauma symptoms (p > 0.13).

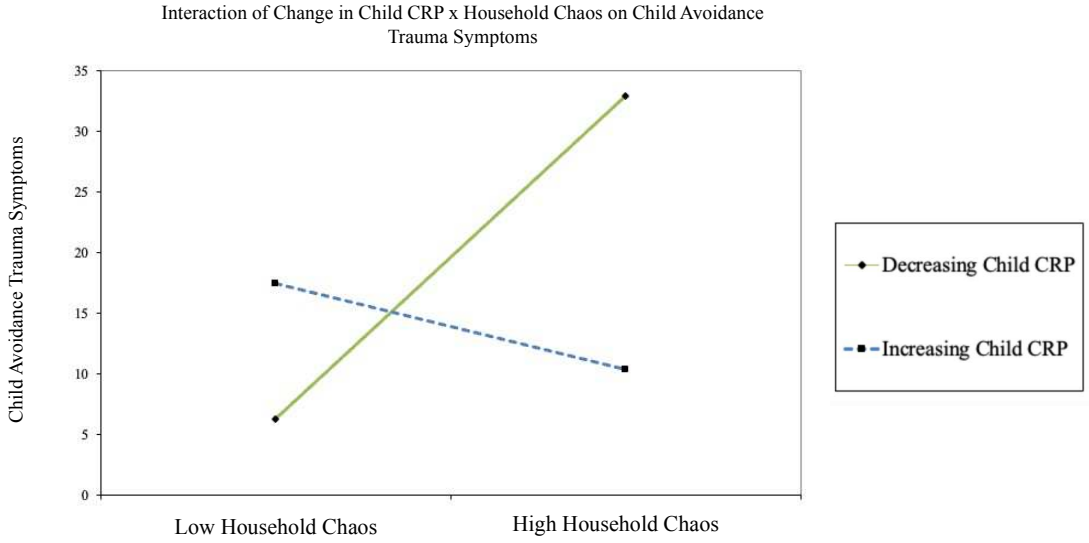
The interaction was probed by testing the conditional effects of household chaos during the pandemic at two levels: one SD below the mean (6.57) and one SD above the mean (score = 11.43). Figure 4.1, below, was created to visualize the interaction.

Johnson-Neyman Test for Hypothesis 3c- Avoidance Trauma. The moderation effect of household chaos x change in child CRP is probed using the Johnson-Neyman technique (as shown in Figure 4.2). According to this Figure, when CRP decreased from pre-pandemic to the current study, household chaos was positively associated with child avoidance trauma symptoms. When child CRP increased from pre-pandemic to now, household chaos was negatively associated with child avoidance trauma symptoms. The slope of household chaos on child avoidance trauma was only significantly related when child CRP decreased by 0.016 mg/L or

increased by 8.5 mg/L or more. There were two observations of child CRP decreasing by 0.016 mg/L. However, there were no observations of child CRP increasing by a magnitude of 8.5 mg/L, so the high end of this significant region does not apply to this sample.

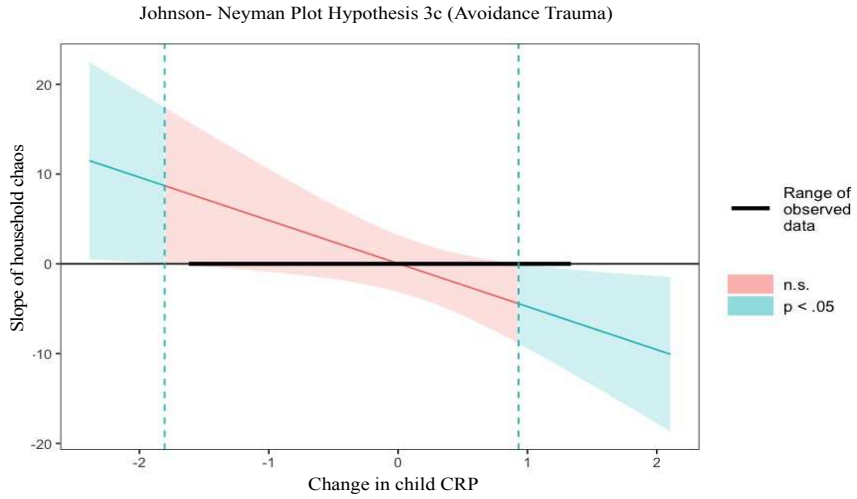
Figure 4.1

First Interaction Plot for Hypothesis 3C



Note. In this model predictor is household chaos, moderator is change in child CRP, and outcome is child avoidance trauma symptoms.

Figure 4.2 *First Johnson-Neyman Plot for Hypothesis 3c*

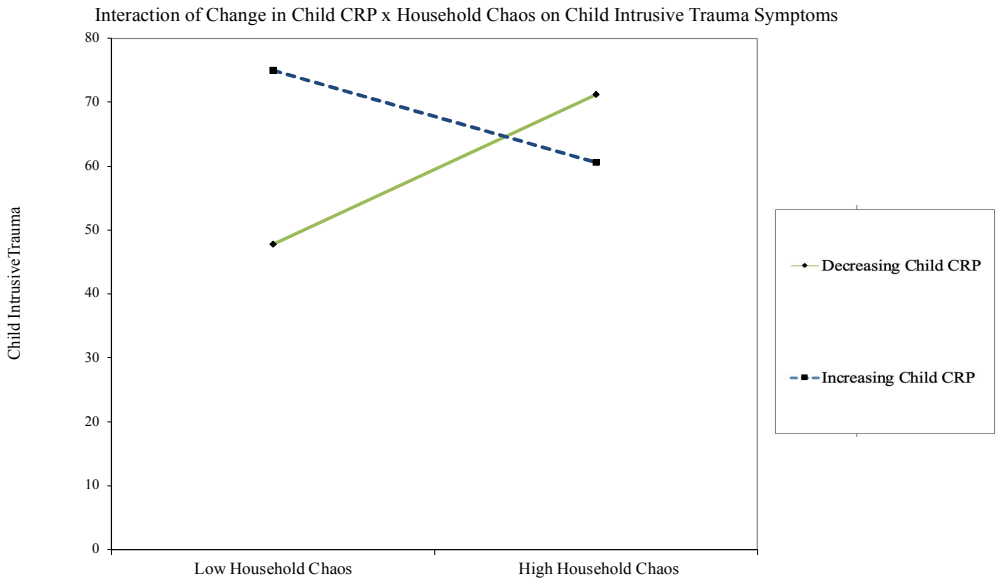


Note. In the Johnson-Neyman plot, the moderator (change in child CRP) is plotted along the X-axis. The main effect of the slope of household chaos (independent variable) on child's avoidance trauma symptoms (dependent variable) is plotted on the Y-axis.

Household Chaos and Intrusive Trauma. The association between the interaction term (change in child CRP x household chaos) and child's intrusive trauma symptoms was statistically significant (β = -2.42, B = -4.95, SE = 1.74, R^2 = .21, p = 0.01, 95% CI = [-8.61, -1.29]). Child CRP change score was significantly associated with child's avoidance trauma symptoms (β = 2.44, B = 49.80, SE = 17.19, p = 0.01, 95% CI = [13.68, 85.93]). In this model, household chaos was not significantly associated with child's intrusive trauma symptoms (β = 0.02, B = 0.12, SE = 1.34, p = 0.93, 95% CI = [-2.69, 2.94]). The interaction remained significant even when controlling for child WHO BMI percentile, group, and child age (β = -2.26, B = -4.63, SE = 1.59, p = 0.01, 95% CI = [-8.03, -1.25]). In this model, change in child CRP and group condition were both significantly associated with child's intrusive trauma symptoms (p < 0.04) (see Figure 5.1).

Figure 5.1

Second Interaction Plot for Hypothesis 3c

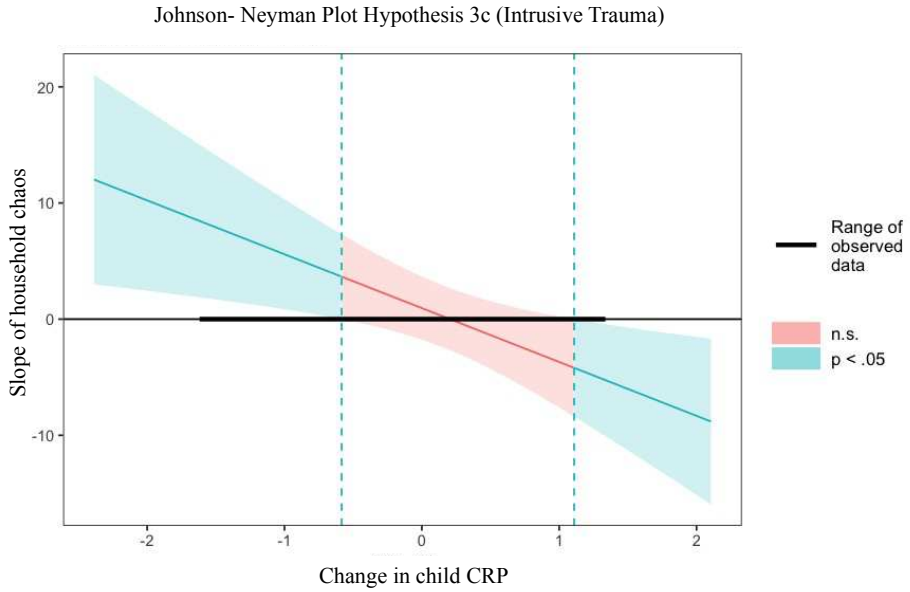


Note. In this model predictor is household chaos rating, moderator is change in child CRP, and outcome is child intrusive trauma symptoms.

Johnson-Neyman Test for Hypothesis 3c- Intrusive Trauma. The moderation effect of household chaos x change in child CRP is probed using the Johnson-Neyman technique (see Figure 4.2). Results indicate that when CRP decreased from pre-pandemic to the current study, household chaos was positively associated with child intrusive trauma symptoms. When child CRP increased from pre-pandemic to now, household chaos was negatively associated with child intrusive trauma symptoms. The slope of household chaos on child intrusive trauma was only significantly related when child CRP decreased by 0.03 mg/L or increased by 12.88 mg/L or more. Child CRP decreased by 0.03 mg/L or more in 4 children. However, there were no observations of child CRP increasing by a magnitude of 12.88 mg/L or more, so the higher end of this significant region does not apply to this sample (see Figure 5.2).

Figure 5.2.

Second Johnson-Neyman Plot for Hypothesis 3c



Note. In the Johnson-Neyman plot, the moderator (change in child CRP) is plotted along the X-axis. The main effect of the slope of household chaos (independent variable) on child's intrusive trauma symptoms (dependent variable) is plotted on the Y-axis.

Household Chaos and Anxiety Trauma. The association between the interaction term (change in child CRP x household chaos) and child's anxious trauma symptoms was marginally significant (β = -1.64, B = -3.78, SE = 2.10, R^2 = 0.09, p = 0.09, 95% CI = [-8.19, 0.64]). Child CRP change score was marginally associated with child's anxious trauma symptoms (β = 1.85, B = 42.34, SE = 20.71, p = 0.06, 95% CI = [-1.18, 85.86]). In this model, household chaos was not significantly associated with child's anxious trauma symptoms (β = -0.06, B = -0.46, SE = 1.61, p = 0.78, 95% CI = [-3.85, 2.93]). No significant results were found for change in child CRP moderating the association between household chaos and child arousal trauma symptoms (p > 0.10).

Household Chaos and Child Behavior. The association between the interaction term (change in child CRP x household chaos) and intensity of child's behavioral problems was not significant (β = -0.28, B = -0.37, SE = 1.34, R^2 = -0.09, p = .78, 95% CI = [-3.20, 2.45]). Child CRP change score was not significantly associated with child's behavior problems in this model (β = 0.49, B = 6.60, SE = 13.25, p = 0.62, 95% CI = [-21.23, 34.44]) nor was household chaos significantly associated with child behavior problems in this model (β = 0.07, B = 0.29, SE = 1.03, p = 0.78, 95% CI = [-1.87, 2.46]).

Hypothesis 3d (Change in Child CRP, Parent Stress, and Child Mental Health)

Parent-Child Dysfunction and Trauma. The association between the interaction term (change in child CRP x Parent Child Dysfunctional Interaction percentile) and child's total trauma symptoms was not statistically significant (β = -0.43, B = -0.14, SE = 0.15, R^2 = -0.08, p = 0.35, 95% CI = [-0.46, 0.17]). Child CRP change score was not significantly associated with child's total trauma symptoms in this model (β = 0.41, B = 7.86, SE = 8.51, p = 0.37, 95% CI = [-10.01, 25.74]). In this model, Parent Child Dysfunctional Interaction percentile rank was not

significantly associated with child's trauma symptoms (β = 0.13, B = 0.06, SE = 0.11, p = 0.59, 95% CI = [-0.17, 0.29]). There were no significant associations found in the subsequent models for intrusive, arousal, avoidance, or anxious trauma symptoms ($p > 0.10$).

Parent Child Dysfunction and Child Behavior. The association between the interaction term (change in child CRP x Parent Child Dysfunctional Interaction percentile) and intensity of child's behavior problems was not statistically significant (β = -0.16, B = -0.03, SE = 0.19, R^2 = -0.09, p = 0.72, 95% CI = [-0.26, 0.18]). Child CRP change score was not significantly associated with intensity of child's behavior problems in this model (β = 0.35, B = 4.69, SE = 5.95, p = 0.44, 95% CI = [-7.82, 17.19]). In this model, Parent Child Dysfunctional Interaction percentile rank was not significantly associated with intensity of child's behavioral problems (β = 0.07, B = 0.02, SE = 0.08, p = 0.76, 95% CI = [-0.14, 0.19]).

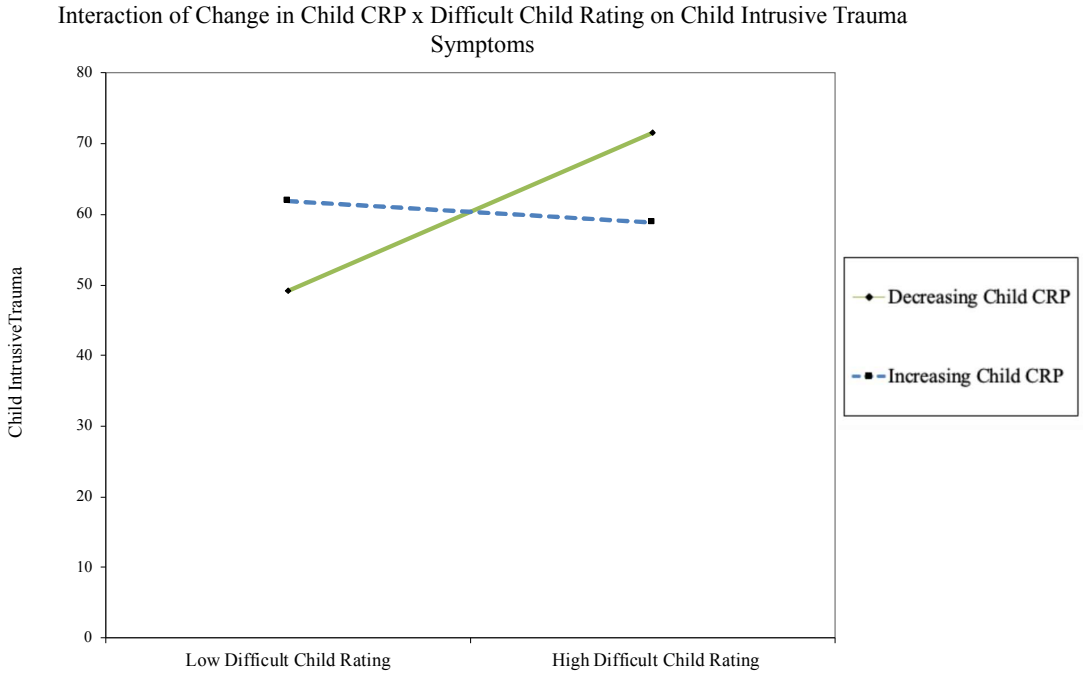
Difficult Child and Total Trauma. The association between the interaction term (change in child CRP x Difficult Child percentile) and child's total trauma symptoms was marginally statistically significant (β = -0.66, B = -0.24, SE = 0.11, R^2 = 0.12, p = 0.05, 95% CI = [-0.47, 0.003]). Child CRP change score was not significantly associated with child's total trauma symptoms in this model (β = 0.52, B = 10.03, SE = 6.31, p = 0.13, 95% CI = [-3.24, 23.29]). In this model, Difficult Child percentile rank was not significantly associated with child's trauma symptoms (β = 0.23, B = 0.19, SE = 0.10, p = 0.29, 95% CI = [-0.10, 0.30]). The interaction remained marginally significant when controlling for child WHO BMI percentile, Group condition, and child age (β = -0.20, B = -0.58, SE = 0.10, R^2 = 0.30, p = 0.06, 95% CI = [-0.43, 0.013]).

Difficult Child and Intrusive Trauma. The association between the interaction term (change in child CRP x Difficult Child percentile) and child's intrusive trauma symptoms was

statistically significant (β = -0.87, B = -0.33, SE = 0.11, R^2 = 0.21, p = 0.01, 95% CI = [-0.57, -0.09]). Child CRP change score was significantly associated with child's intrusive trauma symptoms in this model (β = 0.75, B = 10.39, SE = 6.38, p = 0.03, 95% CI = [1.99, 28.79]). In this model, Difficult Child percentile rank was not significantly associated with child's intrusive trauma symptoms (β = 0.03, B = 0.01, SE = 0.10, p = 0.90, 95% CI = [-0.19, 0.22]). The interaction remained significant when controlling for child BMI WHO percentile, child age, and group condition (β = -0.80, B = -0.31, SE = 0.11, R^2 = 0.34, p = 0.02, 95% CI = [-0.53, -0.08]). In this model, no covariates were significantly associated with child's intrusive trauma symptoms (p > 0.08) (see Figure 6.1).

Figure 6.1

First Interaction Plot for Hypothesis 3d

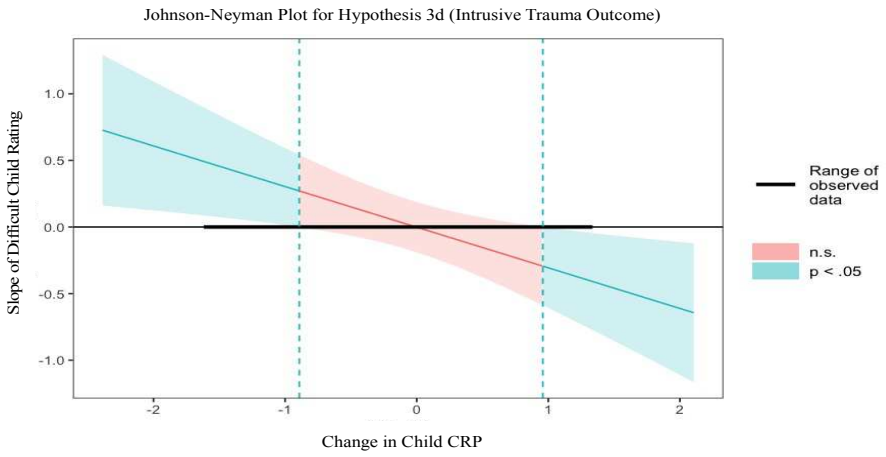


Note. In this model predictor is Difficult Child rating, moderator is change in child CRP, and outcome is child intrusive trauma symptoms.

Johnson-Neyman Test for Hypothesis 3d- Intrusive Trauma. The moderation effect of the Difficult Child rating percentile x change in child CRP is probed using the Johnson-Neyman technique (see Figure 6.2). Results indicate that when CRP decreased from pre-pandemic to the current study, the Difficult Child percentile rank was positively associated with child intrusive trauma symptoms. When child CRP increased from pre-pandemic to now, Difficult Child percentile was negatively associated with child intrusive trauma symptoms. The slope of the Difficult Child percentile rank on child intrusive trauma was only significantly related when child CRP decreased by 0.13 mg/L or more or increased by 20.89 mg/L or more. There was one case of a child's CRP decreasing by 0.13 mg/L or more; however, there were no observations of child CRP increasing by a magnitude of 20.89 mg/L, so the high end of the significant region does not apply to this sample.

Figure 6.2

First Johnson-Neyman Plot for Hypothesis 3d

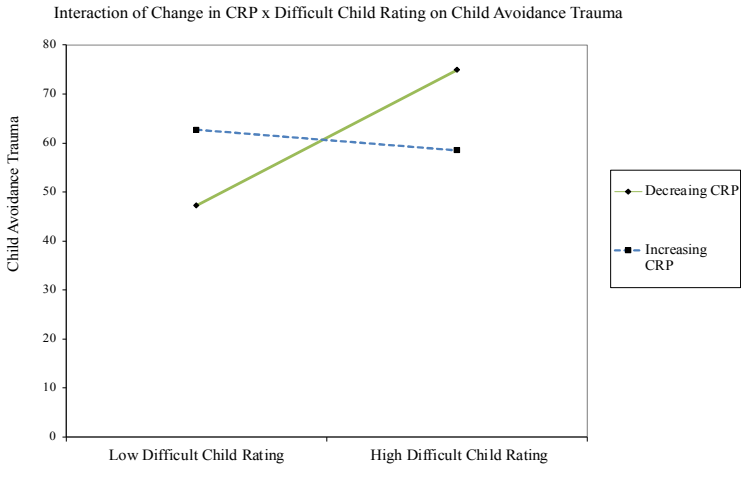


Note. In the Johnson-Neyman plot, the moderator (change in child CRP) is plotted along the X-axis. The main effect of the slope of Difficult Child rating (independent variable) on child's intrusive trauma symptoms (dependent variable) is plotted on the Y-axis.

Difficult Child and Avoidance Trauma. The association between the interaction term (change in child CRP x Difficult Child percentile) and child's avoidance trauma symptoms was statistically significant (β = -0.73, B = -0.30, SE = 0.13, R^2 = 0.17, p = 0.03, 95% CI = [-0.57, -0.03]). Child CRP change score was marginally associated with child's avoidance trauma symptoms in this model (β = 0.56, B = 12.34, SE = 7.08, p = 0.098, 95% CI = [-2.54, 27.21]). In this model, Difficult Child percentile rank was not significantly associated with child's intrusive trauma symptoms (β = 0.24, B = 0.12, SE = 0.11, p = 0.26, 95% CI = [-0.10, 0.35]). The interaction remained significant when controlling for child BMI WHO percentile, child age, and group condition (β = -0.64, B = -0.26, SE = 0.11, R^2 = 0.44, p = 0.03, 95% CI = [-0.49, -0.03]). In this model, group condition was significantly associated with child's avoidance trauma symptoms (p = 0.02); however, child BMI percentile and age were not significantly associated with child avoidance trauma symptoms (p > 0.08) (see Figure 7.1)

Figure 7.1

Second Interaction plot for Hypothesis 3d

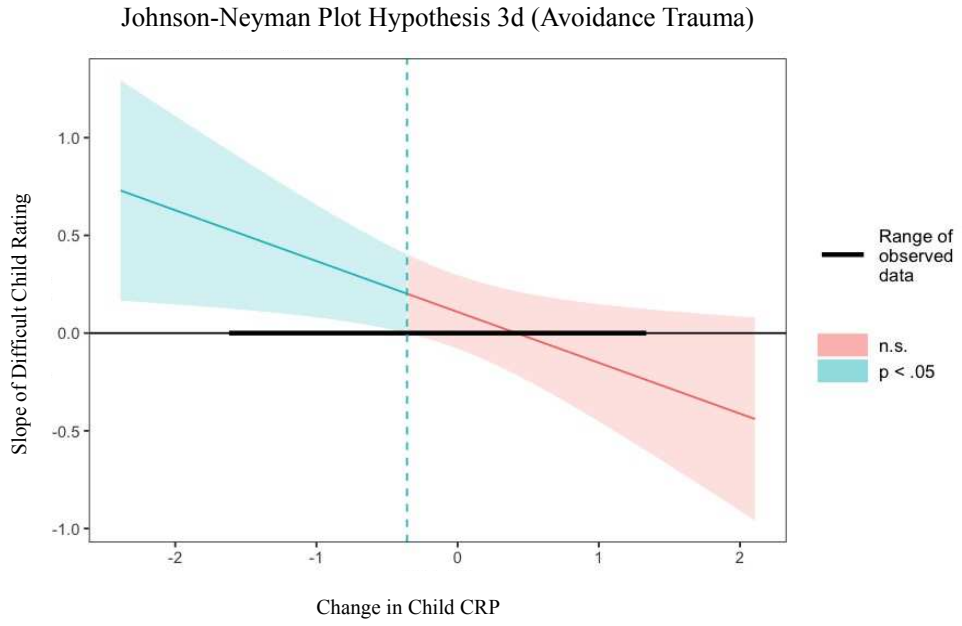


Note. In this model predictor is Difficult Child rating, moderator is change in child CRP, and outcome is child avoidance trauma symptoms.

Johnson-Neyman Test for Hypothesis 3d- Avoidance Trauma. The moderation effect of the Difficult Child rating percentile x change in child CRP is probed using the Johnson-Neyman technique (see Figure 7.2). Results indicate that when CRP decreased from pre-pandemic to the current study, the Difficult Child percentile rank was positively associated with child avoidance trauma symptoms. When child CRP increased from pre-pandemic to now, Difficult Child percentile was negatively associated with child avoidance trauma symptoms. The slope of the Difficult Child percentile rank on child avoidance trauma was only significantly related when child CRP increased by 20.89 mg/L or more; however, there were no observations of child CRP increasing by the magnitude, so the significant region does not apply to this sample.

Figure 7.2

Second Johnson-Neyman plot for Hypothesis 3d



Note. In the Johnson-Neyman plot, the moderator (change in child CRP) is plotted along the X-axis. The main effect of the slope of Difficult Child rating (independent variable) on child's avoidance trauma symptoms (dependent variable) is plotted on the Y-axis.

Difficult Child and Arousal and Anxiety Trauma. There were no significant main associations found in the subsequent models for arousal or anxious trauma symptoms. For anxious trauma symptoms, the change in CRP score was marginally associated with child's anxious trauma symptoms (β = 0.62, B = 14.18, SE = 7.91, p = 0.09, 95% CI = [-2.44, 30.79]).

Difficult Child and Child Behavior The association between the interaction term (change in child CRP x Difficult Child percentile) and intensity of child's behavior problems was not statistically significant (β = -0.29, B = -0.07, SE = 0.09, R^2 = -0.02, p = 0.40, 95% CI = [-0.25, 0.11]). Child CRP change score was not significantly associated with intensity of child's behavior problems in this model (β = 0.40, B = 5.34, SE = 4.74, p = 0.27, 95% CI = [-4.51, 15.30]). In this model, the Difficult Child percentile rank was not significantly associated with intensity of child's behavioral problems (β = 0.06, B = 0.19, SE = 0.07, p = 0.42, 95% CI = [-0.09, 0.21]).

Results for Hypotheses 4a- 4d

Hypothesis 4a (Interactions in Parent Anxiety-Child Mental Health Relationship)

For models examining the associations between parental anxiety and child mental health (i.e., child trauma symptoms, child behavior), no significant interactions were found with parental pre-pandemic anxiety, child ACEs, child's current CRP levels, parent's CRP levels or change in parent CRP, child sex, and child age ($p > 0.10$).

Hypothesis 4b (Interactions in Parent Depression-Child Mental Health Relationship)

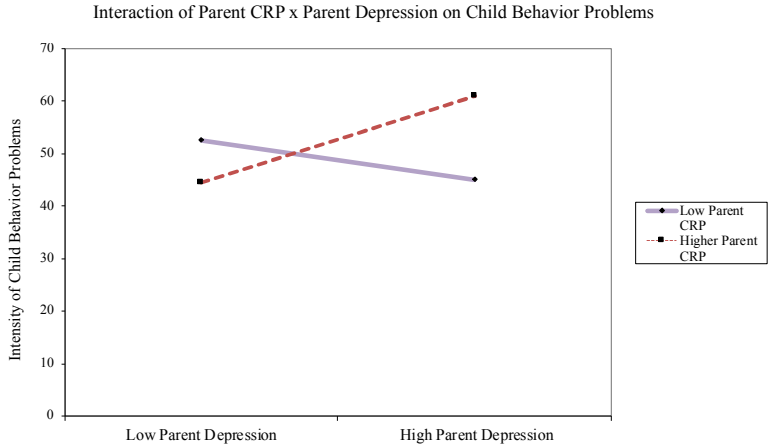
For models examining the associations between parental depression and child mental health (i.e., child trauma symptoms, child behavior), no significant interactions were found with pre-pandemic depressive symptoms, child ACEs, child's current CRP levels, child sex, and child age ($p > 0.10$).

Parent Depression x Parent CRP. There were significant findings for the moderating effect of parent CRP on the association between parental depression and intensity of child behavior, such that there was a significant association between the interaction term (parent CRP x parent depression) and intensity of child's behavior problems (β = 3.95, B = 1.22, SE = 0.49, R^2 = 0.26, p = 0.02, 95% CI = [0.20, 2.24]). Parent CRP levels were associated with intensity of child's behavior problems in this model (β = -3.78, B =-65.42, SE = 27.58, p = 0.03, 95% CI = [-123.36, -7.48]). In this model, parent depression was not significantly associated with intensity of child's behavioral problems (β = -0.08, B = -0.11, SE = 0.34, p = 0.75, 95% CI = [-0.83, 0.61]). The interaction remains significant when controlling for parent BMI, parent cigarette use, parent NSAID use, income, child age, and parent age (β = 3.74, B = 1.16, SE = 0.42, R^2 = 0.59, p = 0.02, 95% CI = [0.2, 89.50]). In this model, parent CRP, parent cigarette use, and income were all significantly associated with intensity of child's behavior problems ($p < 0.03$). The interaction was probed by testing the conditional effects of parent depression at two levels: one SD below the mean (score = 48.03) and one SD above the mean (score = 64.24) (Figure 8.1).

Johnson-Neyman Test for Hypothesis 4b- Moderator Parent CRP. The moderation effect of parent depression x parent CRP is probed using the Johnson-Neyman technique (as shown in Figure 8.2). According to this Figure, parent depression was significantly and positively associated with child behavior when parent CRP was above 8.51 mg/L (n = 4). Parent depression was negatively and significantly associated with child behavior when parent CRP was below 0.25 mg/L (n = 1). When parent CRP is between 0.25 and 8.51 mg/L, there was no significant association between parent depression and intensity of child behavior.

Figure 8.1

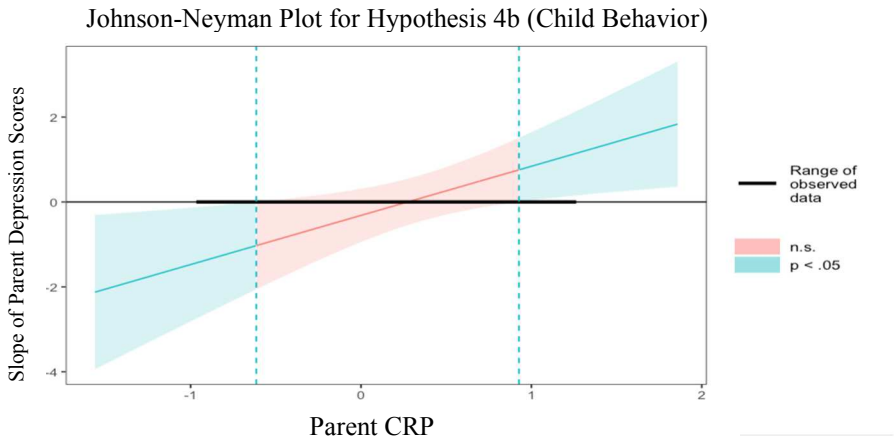
First Interaction plot for Hypothesis 4b



Note. In this model predictor is parent's depressive symptoms, moderator is parent CRP, and outcome is intensity of child's behavioral problems.

Figure 8.2

Second Johnson-Neyman Plot Hypothesis 4b

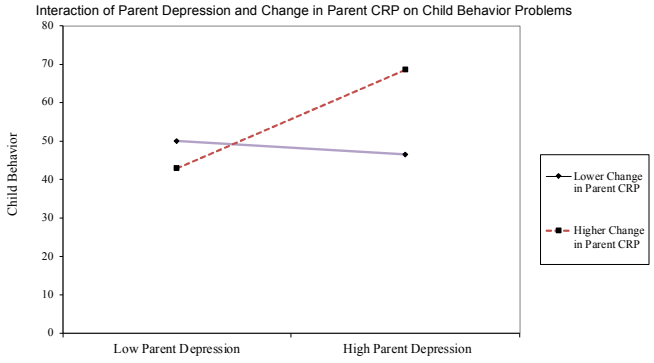


Note. In the Johnson-Neyman plot, the moderator (parent CRP) is plotted along the X-axis. The main effect of the slope of parent's depression scores (independent variable) on intensity of child behavioral problems (dependent variable) is plotted on the Y-axis.

Parent Depression x Change in Parent CRP. Similar results were found with change in parent CRP as a moderator. There was a significant association between the interaction term (change in parent CRP x parent depression) and intensity of child's behavior problems (β = 4.55, B = 1.54, SE = 0.53, R^2 = 0.30, p = 0.01, 95% CI = [0.44, 2.65]). Change in parent CRP levels was associated with intensity of child's behavior problems in this model (β = -4.45, B = -80.26, SE = 27.78, p = 0.01, 95% CI = [-138.62, -21.89]). In this model, parent depression was significantly associated with intensity of child's behavioral problems (β = 0.42, B = 0.54, SE = 0.25, p = 0.046, 95% CI = [0.01, 1.08]). The interaction remains significant when controlling for parent BMI, parent cigarette use, parent NSAID use, income, child age, and parent age (β = 4.55, B = 1.54, SE = 0.31, R^2 = 0.80, p = 0.0003, 95% CI = [0.87, 2.22]). In this model, change in parental CRP, parent depression, parent BMI, parent cigarette use, and income were significantly associated with intensity of child behavioral problems (p < 0.02). Figure 9.1 plots the interaction models.

Figure 9.1

Second Interaction Plot for Hypothesis 4b

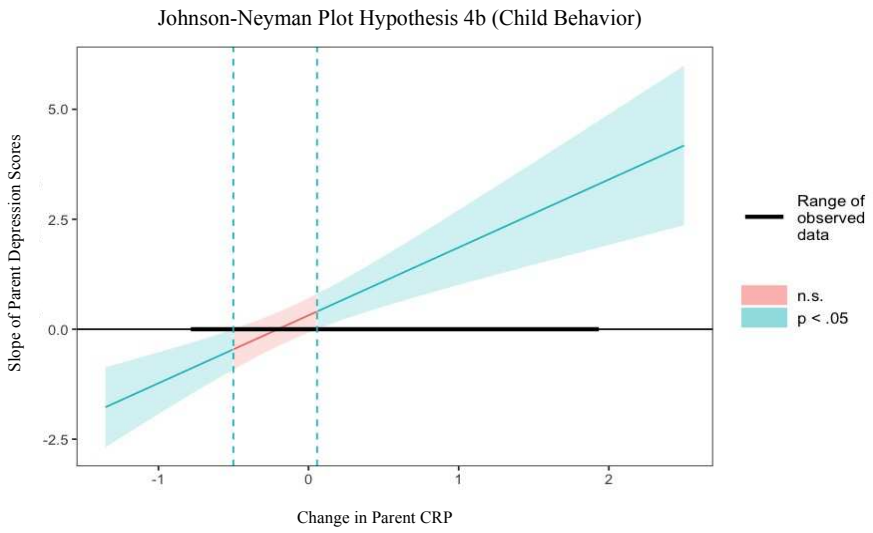


Note. In this model predictor is parent's depressive symptoms, moderator is change in parent CRP, and outcome is intensity of child's behavioral problems.

Johnson-Neyman Test for Hypothesis 4b- Moderator Change in Parent CRP. The moderation effect of parent depression x change parent CRP is probed using the Johnson-Neyman technique (as shown in Figure 6.2). According to this Figure, parent depression was significantly and positively associated with child behavior when parent CRP was increased by 83.18 mg/L. No parent had an increase in CRP of this magnitude. Parent depression was negatively and significantly associated with child behavior when parent CRP decreased by 0.17 mg/L (n = 9).

Figure 9.2

Second Johnson-Neyman Plot for Hypothesis 4b



Note. In the Johnson-Neyman plot, the moderator (change in parent CRP) is plotted along the X-axis. The main effect of the slope of parent's depression scores (independent variable) on intensity of child behavioral problems (dependent variable) is plotted on the Y-axis.

Hypothesis 4c (Interactions in Household Chaos-Child Mental Health Relationship)

For models examining the associations between household chaos and child mental health (i.e., child trauma symptoms, child behavior), no significant interactions were found with pre-

pandemic parental anxiety or depressive symptoms, child ACEs, child sex, and child age (p > 0.10).

For the moderating effect of child's current CRP levels, there was a marginally significant association between the interaction term (child CRP x household chaos) and child trauma symptoms (β = -1.95, B = -3.80, SE = 1.90, R^2 = 0.06, p = 0.06, 95% CI = [-7.79, 0.18]). In this model, child CRP at pandemic (p = 0.06) and household chaos (p = 0.09) were both marginally associated with child trauma symptoms.

Hypothesis 4d (Interactions for Parent Stress-Child Mental Health Relationship)

Parent Child Dysfunction Percentile. For models examining the associations between the Parent Child Dysfunction percentile and child mental health (i.e., child trauma symptoms, child behavior), no significant interactions were found with pre-pandemic parental anxiety or depressive symptoms, parent CRP, change in parent CRP, child ACEs, child's current CRP levels, child sex, and child age (p > 0.10).

Difficult Child Rating. For models examining the associations between the Difficult Child percentile and child mental health (i.e., child trauma symptoms, child behavior), no significant interactions were found with pre-pandemic parental anxiety or depressive symptoms, parent CRP, change in parent CRP, child ACEs, child's current CRP levels, child sex, and child age (p > 0.10).

Chapter 4: Discussion

In the two years since the WHO declared COVID-19 a worldwide pandemic (Cucinotta & Vanelli, 2020), the scientific field has conducted countless research studies in a remarkable effort to document and delineate the wide-spreading and multidimensional impact of this unparalleled global health crisis. This dissertation study sought to characterize the neurobiological and psychological impact of pandemic-related stress on parents and children by leveraging a longitudinal, multi-method study.

The current study had several core findings. As a general summary, the only significant finding from Aim 1 was that, contrary to prediction, change in household chaos was inversely associated with child CRP levels. For Aim 2, no significant results were found to support that change in child CRP predicted any key child outcomes. For Aim 3, there were significant interactions found that demonstrated an interaction between change in child CRP and household chaos as well as change in child CRP and Difficult Child ratings that influenced child's trauma symptoms, in the opposite expected direction. Lastly, for Aim 4, parent depression and parent CRP interacted significantly to predict child behavior in the expected direction. Below, I will review changes in key variables from pre-pandemic to now, and the findings from the above Aims, in detail below and interpret these findings in the context of the study and prior literature.

There were several changes in primary measures from the pre-pandemic study point to the current study collection point. First, it was hypothesized that parent CRP would substantially increase from the pre-pandemic time point to now. For the parents in the study, the raw CRP values, on average, increased from 2.87 mg/L to 4.27 mg/L. While this result was statistically non-significant, it may still allude to a concerning trend that could be elucidated in a larger, well-powered study. For example, the American Heart Association/Centers for Disease Control and

Prevention have implemented guidelines to stratify risk of heart disease for individuals; the current prevailing guideline is that CRP levels ≥3 mg/L indicates elevated risk for heart disease (Pearson et al., 2003). In the pre-pandemic time point, eight of the parents had CRP levels ≥3 mg/L, while in the current study, 12 parents presented with CRP levels above the clinical cutoff of ≥3 mg/L. Notably, parent's depressive symptoms also increased from the pre-pandemic time point to the current study. Similarly, while the change in symptoms was not statistically significant, this pattern aligns with research that has documented substantial increases in parental depression during the COVID-19 pandemic (Brown et al., 2020, Lamar et al., 2021, Westrupp et al., 2021). It is possible that parent's depressive symptoms were higher at the onset of the pandemic. At the pre-pandemic time point, zero parents had depressive symptoms above the clinical cut-off score while in this study, five parents endorsed clinically severe symptoms.

To date, there is a limited but growing number of studies investigating trajectories of chronic inflammatory markers starting from pre-pandemic timepoints. Such studies have begun to highlight that chronic and increasing inflammation is a key mechanism underlying pandemic-related outcomes. For example, one group leveraged a longitudinal study (the English Longitudinal Study of Ageing (ELSA)) and showed that adult participants who had higher baseline CRP concentrations before the pandemic had 40% higher odds of developing depressive symptoms during the pandemic, even after adjusting for several covariates (e.g., smoking) (Hamilton et al., 2021). Research from prior infectious disease outbreaks, such as the SARS epidemic, provide insight into how the relationship between depressive symptoms and inflammation may unfold in the context of a pandemic. A study by Wang and colleagues (2021) documented that Chinese adults living in communities exposed to SARS were more likely to

have elevated CRP compared to those in non-exposed communities; further, community SARS exposure was associated with greater risks in depression (Wang et al., 2021).

The current study's preliminary data shows an increase in parental CRP and in parental depression; however, it does not support a statistically significant association between parent CRP and parent depression. One interpretation is that the small sample size is fundamentally underpowered to identify a statistical relationship and there is a higher likelihood of Type II errors in small sample sizes. Further, the relationship between inflammation and depression is multifaceted, as both are highly influenced by environmental factors (Horn et al., 2018). In the context of the COVID-19 pandemic, there is an urgent need for researchers to thoroughly and rigorously investigate the putative mechanistic role of chronic and increasing inflammation not just in parent's psychological symptoms, but in the other indicators of health and well-being for both the parent and child.

In this study, there was a marginally significant positive relationship between parent's depressive symptoms and child trauma symptoms and a positive, though non-significant relationship between parent CRP and child trauma symptoms. Given the small sample size, non-significant findings may still be useful signals for possible true effects that could be detected in a larger sample. There were no findings that supported any moderating factors in this relationship in this sample. However, while parent depression was not associated with child behavior problems overall, there were significant findings for the interaction of parent CRP on the association between parent depression and intensity of child behavior, a moderation model that remained significant even after controlling for several covariates (Hypothesis 4b). Results indicated that parent depression was significantly and positively associated with intensity of child behavior only when parent CRP was above 8.51 mg/L, which was true for a small subset of

four parents. Parent depression was negatively and significantly associated with child behavior when parent CRP was below 0.25 mg/L, though this was only true for one parent. Nonetheless, such results demonstrate that degree of parent inflammation may serve as both protective and risk factors in children's psychological health.

A very similar finding was documented for change in parent CRP, although interpretation is limited by the sample size, as the results demonstrated that parent CRP needed to increase by an extremely high amount in order to be associated with child behavior, with zero observations of that substantial of an increase in parent CRP. However, it also showed that parent depression was negatively and significantly associated with lower child behavior problems if the parent's CRP decreased by 0.17 mg/L or more, which was true for nine parents in this study. As more studies begin to investigate children's well-being before and during the pandemic, and link these outcomes to parent's health and well-being, the field will gain clarity on the complex associations and work to identify driving mechanisms of negative shifts in parent and child health as well as factors promoting positive outcomes.

Contrary to the study hypotheses, children's CRP did not substantially increase from the pre-pandemic time point to now. As such, the multilevel models probing the predictive value of change in child CRP on key outcomes were all non-significant (Hypothesis 2). This was unsurprising given that child CRP did not markedly change between time points. There are several important considerations in contextualizing this unexpected finding. First, the role of child age and the corresponding relative dearth of well-established normative values for pediatric CRP limits clinical interpretation. In pediatric medicine, child CRP values are often used to guide clinical decision making *within* an individual child; in other words, CRP values are often interpreted within the context of the child themselves, rather than compared to a range of

normative values and are used to track a child's inflammation throughout the course of an illness (e.g., Hofer et al., 2012). Compared to adults, children, on average, have substantially lower CRP values, which increase with age, and thus it would not be useful to apply adult normative values (i.e., the 3 mg/L cut off) to children (Schlenz et al., 2014). One study of pre-adolescent children in Europe sought to establish pediatric CRP norms and found that nearly half of children were below or equal to the detection limit of 0.2 mg/L and median child values range from 0.2 - 0.3 mg/L (Schlenz et al., 2014). It is expected that average CRP values vary only slightly in young children, and begin to rise in adolescence (Schlenz et al., 2014). In our study, at the pre-pandemic time point, raw child CRP values ranged from 0.003 to 4.63 (median = 0.21) and from 0.01-7.35 mg/L for the current study (median = 0.01). The restricted and low range of child CRP values found in this study is aligned with prior research in non-patient child samples (Schlenz et al., 2014). Further, child CRP was significantly and positively correlated with age, with older children in the study having higher elevations of CRP. As child CRP increases typically across the developmental lifespan, with major increases observed in adolescence, we may not be able to detect pandemic-related impacts on child inflammation in children this young, particularly in a small sample.

Similarly, there is only mixed evidence for positive associations between child inflammation and child health outcomes, such as child depression (Colasanto et al., 2020, Mitchell & Goldstein, 2014), and it is thus, while contrary to hypothesis, it is perhaps unsurprising that our results did not support a current association between child CRP and child trauma or child behavioral problems. As previously stated, the study is very small and lacks sufficient power to detect these statistical associations. For example, in this study, five children had child behavior scores above the clinical cutoff, and these five children did have statistically

significant higher mean CRP values compared to the 17 children whose behavioral intensity scores were below the cut-off. The pilot data points to the potential that in a larger, more diverse sample, with higher variability of child behavior problems and CRP, there may indeed be a detectable and positive relationship between child CRP and child behavior.

However, the lack of change in child CRP in the study, and lack of significant associations between child CRP and child outcomes, does not necessarily indicate that the cumulative risk of the COVID-19 pandemic has not influenced children's stress response network. Children's stress response symptoms have likely been more frequently activated in the context of the COVID-19 pandemic (Wade et al., 2020), but these perturbations may lead to so-called "sleeper effects," in which the downstream impact of prolonged stress on child neurobiological functioning will not fully present until later in development. A notable corollary in the literature can be observed in the established link between childhood adversity and health conditions (such as cancer, heart disease, and depression), which usually are onset in adulthood (Danese et al., 2009, Felitti, 2009, Taylor et al., 2011). It has been hypothesized that disruptions to stress response networks are one mechanistic pathway underlying not only the association between childhood adversity and health, but also the lag in onset of these poor health outcomes (Danese et al., 2009, Shonkoff et al., 2009). The *timing* of when stress "gets under the skin" and shifts stress response networks to increase risk has not been completely established. In the example of early life adversity and relationships to inflammation, a meta-analysis found a small relationship between early life adversity child inflammation; however, this association was stronger in adolescence compared to middle childhood, highlighting the importance of critical windows in understanding children's physiology and relationships of the environment to the developing immune system (Kuhlman et al., 2017). If we contextualize the COVID-19 pandemic

as a cumulative and ongoing form of adversity for children, then longitudinal research is desperately needed to track children's stress response networks *over time,* with a goal of identifying precisely when and how stress response networks begin to register the environmental impact. Equipped with that knowledge, the field would then be in an optimal position to link these putative changes in stress neurobiology to hypothesized related outcomes, such as child well-being and health.

Relatedly, the complexity of the developmental course of the innate immune system, and how and when stress has downstream influences on inflammation is highly relevant in interpreting any studies conducted during and about the COVID-19 pandemic (Horn et al., 2020b, Szcześniak et a l., 2021). For example, if children's stress response networks have indeed been "working overtime" since the beginning of the pandemic, the HPA axis would be highly activated, and there would be an expected and related increase in child basal cortisol levels. One study demonstrated that COVID-19 related stressors, such as family job loss and social isolation, were associated with child hair cortisol (Perry et al., 2022), indicating emerging evidence that COVID-19 related environmental stress may be reflected in a parallel impact on the child's HPA axis as measured via child cortisol. Cortisol exerts anti-inflammatory influences (Stark et al., 2011), and it is not until glucocorticoid receptor insensitivity develops, that the co-regulatory relationship between the HPA axis and the inflammatory arm of the immune system becomes extremely disrupted, leading to chronic inflammation (as reviewed in Kuhlman et al., 2017).

Thus, in theory, it is possible that children's stress response network has not reached this stage of disruption. In other words, we may expect to see elevated rates of basal cortisol now, which in turn, will eventually lead to downregulation of the HPA axis, then appearing as elevated chronic inflammation later in development. The orchestration of the stress response

network following chronic stress is undoubtedly extremely complex. Multimethod assessments are necessary in disentangling how these systems work in concert as well as how stress influences the timing of neurobiological disruption. In this study, a measure of cortisol and changes in cortisol would have helped to elucidate the degree to which pandemic-related stress is or is not currently influencing child's stress response networks.

This lens may also help to understand another significant set of findings from the pilot study. It was hypothesized that household chaos would, on average, increase from the pre-pandemic time point to now. In fact, in our study, this was the only pandemic-related stress variable to substantially and significantly increase from the pre-pandemic time point to the pandemic study time point (Hypothesis 1). Our study aligns with other researchers' findings that household chaos has increased during the pandemic (Cassinat et al., 2021, Johnson et al., 2022, Glynn et al., 2021, McGoron et al., 2022, Liu & Fisher, 2022). Further, our *a priori* hypothesis predicted that a change in household chaos would predict increased child CRP levels at the pandemic time point (Hypothesis 3). However, results showed just the opposite– a significant, inverse relationship between change in household chaos and child CRP, such that higher degree of household chaos change was associated with lower levels of child inflammation. While this relationship was attenuated by child BMI and child age, it remained marginally significant even with these control variables in a small sample. Relatedly, contrary to hypotheses, we found a moderation effect of household chaos x change in child CRP on children's trauma symptoms. Specifically, when child CRP increased between time points, household chaos was negatively associated with child's trauma symptoms. However, we note that the slope of household chaos on child trauma was only significant when child CRP increased by a degree that was not

observed in this sample. The small sample size, and restricted range of child CRP, limits interpretation of these unexpected findings.

However, there is the possibility that more household chaos would be reflected in an increase in child basal cortisol and that children's HPA axes have yet to downregulate, thus leading to an anti-inflammatory effect in the short-term, and lower CRP levels for children living in households with more chaos. Like the findings of the moderation of household chaos x change in child CRP, comparable results were found with the Difficult Child measure (Hypothesis 3), such that when CRP decreased from the pre-pandemic to the current study, the Difficult Child percentile rank was positively associated with child trauma symptoms. We note that this interpretation is grounded in theory but is not reflected in empirical data in this study and well-powered studies with multimethod, longitudinal assessments would be needed to rigorously examine this theory.

Unexpected findings were also found with the general changes in ratings parent stress, parent anxiety, and child behavioral symptoms. Unlike household chaos, ratings of parent stress and parent anxiety decreased from the pre-pandemic time point to the current study, though this was only a statistically significant decrease for parent stress. This finding was unexpected given the growing literature suggesting opposite trends, in which parents are endorsing substantially higher levels of anxiety and parent stress (e.g., Brown et al., 2020, Lamar et al., 2021, Spinelli et al., 2020, Tchimtchoua Tamo, 2020, Westrupp et al., 2021). For parent stress, the current study specifically investigated Parent-Child Dysfunctional interactions and Difficult Child ratings. Intensity of child behavior problems and child trauma symptoms also decreased, another unexpected finding given the growing body of research indicating substantial increases in school-aged children's behavioral problems and internalizing symptoms across different

countries (Cost et al., 2021, Duan et al., 2020, Leeb et al., 2020, O'Sullivan et al., 2021, Ravens-Sieberer et al., 2021, Saurabh & Ranjan, 2020, Tang et al., 2021, Xie et al., 2020). Notably, unlike household chaos, the changes in parent anxiety, depression, or parent stress were not associated with child CRP.

In this study, children were between 3-7 years old at the pre-pandemic time point, and are now between 6-11 years old; thus, it is possible that the significant decrease in parent stress and child symptoms is more related to the developmental age change from preschool/early school age to school age/pre-adolescence, as other studies have documented (Smith et al., 2004). Statistically, the decrease in Parent-Child dysfunctional ratings was no longer significant after controlling for age. Similarly, the decrease in intensity of child's behavioral problems and child's trauma symptoms was also rendered non-significant when controlling for age. However, the decrease in Difficult Child ratings remained significant even with statistical control, suggesting that, in this sample, the age of the child was not the only factor influencing unexpected decreases in parent stress. Notably, the parent stress ratings were not significantly correlated with any other variables of interest, including intensity of child behavior problems.

In addition to considering the role of the children aging, we must all consider the context of when the data was collected in the current study. The COVID-19 pandemic has been a rapidly evolving and dynamic process, leading to shifts in expectations and adjustments from parents and children. The current study data collection occurred at a very particular point in the pandemic, when vaccines had become readily available, stay-at-home guidelines were being lifted, and children were starting to return to in-person schooling. Further, during the study, the Delta variant wave contributed to further community shifts and increases in infections. Towards the very end of the study, child vaccinations became available. A single collection throughout

this turbulent time is inherently limited, particularly in interpreting the concept of change from the pre-pandemic time point to now. For example, we cannot know if household chaos levels and parental anxiety were possibly higher initially at the start of the pandemic and had begun to wane by the current study time point as families adjusted to the "new normal." Trajectories of data, with several time points, would fill in these important gaps and aid in interpreting results that appear counterintuitive.

Altogether, a complex set of findings emerged in this pilot study. These findings can help inform important next steps for researchers invested in studying parents and children during the COVID-19 pandemic. One of the more striking findings was the interaction between parent depression and parent CRP on child behavior. Parent depression and parent CRP both increased from pre-pandemic to the current study. In such a small sample, the fact that these increases did not reach the threshold of statistical significance does not exclude their importance and the need for larger, well-powered studies to more rigorously investigate these trends. The statistically significant interaction between these variables helped to elucidate how parent depression relates to child behavior problems. Similarly, research in a larger, more diverse sample would help determine the strength of this moderation model and examine if other factors influence these relationships, such as but not limited to, other forms of child adversity, material hardship, parent and child experiences of racism, and parent and child physical health. The unexpected findings related to household chaos also warrant more attention, with a particular focus on multi-method and longitudinal, multi-time point assessments, which will deeply enhance the interpretability of neurobiological mechanisms in the stress-health relationship. For example, collecting both markers of inflammation and HPA axis function could help to foment the timing of how and when an individuals' stress networks become dysregulated and, subsequently, offer insight into

the related impacts on child and parent well-being. By collecting data at various time points within the pandemic, we can help to flesh out patterns of change during this rapidly shifting public health crisis. The study also highlights the importance of studying children at various stages of development and following children from younger ages throughout adolescence to determine the trajectory of neurobiological and psychological changes during the pandemic. Researchers who can follow cohorts with data available pre-pandemic have a particular advantage in isolating the unique influence of the COVID-19 pandemic, and related stressors, as well as document changes in health over time.

Future Directions

Assuredly, there are endless routes that scientists can take in investigating the unparalleled and multifaceted impacts of the COVID-19 pandemic on parents and children. The results of this study advocate for a truly translational neuroscience approach to pandemic-related research. In the context of an immunomodulated viral pandemic, there is an urgent need to integrate neuroscientific measures into pandemic-related studies in our conceptual frameworks. There has long been clear evidence for the intersection of the psychological and physical stress domains (Segerstrom & Miller, 2004); now more than ever, to understand stress, and study its impact, stress response systems cannot be ignored in the equation (Horn et al., 2020b). Cross-disciplinary collaboration will be essential, such as work that bridges medical and psychological science to establish normative values and ranges of key stress biomarkers in pediatric samples.

To translate these basic findings in a meaningful way to clinical progress, such as interventions, requires a diverse set of skills, collaboration across the translational neuroscience spectrum, and funding models that support iterative and rapid clinical trials (Horn et al., 2020a). For clinical interventions in the psychological domain, most have begun to focus on reducing

mental health problems during and related to the pandemic. A systematic review examined 11 study protocols on interventions targeting children and caregivers to reduce psychosocial problems during the COVID-19 pandemic (Boldt et al., 2021). These studies are nascent, but primarily target bolstering positive parent-child relationships, and reducing anxiety and depressive symptoms. In comparison, studies that target inflammation have been conceptualized from a medical or physical lens and directly linked to COVID-19 infections, such as calls for dietary interventions that may reduce inflammation and thus lessen the severity of COVID-19 infections (Messina et al., 2020) and therapeutic agents to target immunoregulation in COVID-19 patients (Tay et al., 2020).

Few studies have sought, thus far, to bridge these psychological and physical domains. One example is a paper that called for interventions focused on targeting physical activity, with the hypothesis that this would improve both metabolic health (e.g., reduced inflammation) and mental health (e.g., depression) in COVID-19 patients (Clemente-Suárez et al., 2020). An intervention study looked at the effect of an aerobic training protocol for breast cancer survivors during the COVID-19 lockdown in Italy, with results suggesting improved cardiometabolic health (Natalucci et al., 2021).

While these studies may feel removed from the demographic of parents and children, a similar premise could be extended to this population. Intervention protocols should be developed that target putative mechanisms related to the well-being of parents and children in the context of the COVID-19 pandemic and focused on where families are headed now as stay-at-home guidelines have largely faded and children have returned to school. Results from this study, for example, would highlight the importance of targeting parent depressive symptoms and parent inflammation. An intervention aiming to influence those domains may include a focus on

physical activity, as well as other important modifiable factors, such as bolstering social support. Our study advocates for a translational and collaborative approach to intervention design that would include input from medical physicians, child psychologists, parenting experts, schooling officials, and families themselves. Programs that are co-designed with the community and the target population can help to overcome common barriers, promote inclusivity and cultural sensitivity, and design more effective protocols that speak to the needs of the individuals they aim to serve (Allen et al., 2014, Madison et al., 2000).

A successful example can be found in the HIV/AIDs research field, where a family-based, longitudinal HIV prevention program was developed based on prior research and was guided by a collaborative partnership with community members, including parents and school staff (Madison et al., 2000). In this intervention, researchers first identified maternal factors, family process factors, adolescent factors, contextual factors, and other moderators that exerted influence on HIV risk exposure (Madison et al., 2000). The intervention was then developed collaboratively with community members and included several iterative pilot trials that led to modifications made based on parent feedback. The final product, the CHAMP Family Program, became a 12-weekly 2-hour meeting intervention that included parent support and training, improving parent-child communication, setting boundaries on parental monitoring, and establishing family rules. The program was co-facilitated by community members and trained mental health professionals. The intervention program was successful in the recruitment and retention of families and found significant increases in knowledge about HIV/AIDs and improved parent-child communication. They also found increased social support following participation (Madison et al., 2000). The CHAMP program is an excellent model that highlights the importance of leveraging scientific research to inform the intervention's theory of change and

community collaboration to promote a successful, inclusive, and positive environment. Particularly at the onset of the COVID-19 pandemic, groups strove to collaborate with communities to prevent the spread of COVID-19 (Cepiku et al., 2020). Similar efforts must be made to continue to support parents and families even as COVID-19 infections wax and wane. For children, especially as they re-enter schooling, catch up on education, and adjust to the "new normal," support to the child and the parent-child relationship is key.

Strengths and Limitations of the Current Study

There are several strengths of the current study. The study benefited from a longitudinal design and was able to leverage a multimethod study that had recruited the parent-child dyads before the start of the pandemic. The collection of both parent and child measures allowed for a more nuanced conceptual model and permitted more rigorous examination of the factors influencing child well-being. The use of the Tasso M-20 device to collect DBS to assay for inflammation was highly innovative and presents several advantages over other DBS collection methods. The Tasso M-20 collection was quicker, less painful, and minimizes error in collection as there is no need to distribute the blood onto separate blotting paper. All but one child was able to successfully donate a sample. The Tasso M-20 device could also be utilized in remote data collection paradigms, allowing for a more diverse sample to be recruited across the United States (Tasso Inc, n.d.). Future research will benefit from this scalable and approachable mode of data collection of DBS.

There were also several notable limitations. The most significant limitation was the small and homogenous sample, which was truly underpowered to address the conceptual model at hand. Small sample sizes are linked to increased possibility of Type II error, reducing the chances of detecting a true effect (Button et al., 2013). Small sample size can also reduce the

likelihood that a statistically significant result reflects a true effect by overestimating effect size and leading to low reproducibility of results (Button et al., 2013). Thus, results from this study should be viewed with an absolute abundance of caution and through a lens of pilot data, with the hopes that it informs next steps rather than dictates current knowledge. Improving reproducibility in neuroscientific research is essential to the goals of translational neuroscience (Horn et al., 2020a) and critical to rigorously studying the stress-health relationship in the context of the COVID-19 pandemic. Researchers have begun to build off early, small sample, and cross-sectional findings from the onset of the pandemic to leverage rich, well-powered, and longitudinal cohort studies.

An additional limitation of the study is the lack of data collection or measure from the beginning of the pandemic, or data that could have been collected between the pre-pandemic time point and the current collection. Without this information, we are fundamentally limited in understanding what might have been changing concurrently with pandemic events at the parent and child biological and behavioral levels. We did find changes in household chaos and parent depression; however, we cannot know if these were gradual rises in levels, decreases from the beginning of the pandemic, or stable patterns.

Another major limitation is the lack of diversity of the sample, which reflected the geographic area of the Pacific Northwest. Without doubt, there are meaningful differences in pandemic experiences across racial, ethnic, class, and sexual minority lines (Gauthier et al., 2021). This study was predominantly cisgender female, white, and able-bodied from a specific geographic area. Thus, the results likely do not fully extend to other demographic groups, and we were unable to consider the complex roles or intersections of race, sex, disability, geography, and class in this study. We also note that several variables in the study and conceptual model were

highly related, particularly in the domain of pandemic-related stress. A more precise and honed theoretical model would reduce issues of multicollinearity and promote a more conceptually driven framework. As more research emerges following the start of the COVID-19 pandemic, there is a need to further strengthen and sharpen conceptual models.

Conclusion

In conclusion, this study examined the manifold and interconnected relationships between stress, health, child well-being, and neurobiology in the context of the COVID-19 pandemic. These are not easy or clear associations to disentangle, and more research is urgently needed to not only fully elucidate these relationships but bridge that knowledge to inform intervention and prevention efforts. Prior to 2020, most of the research was not conducted with the lens of a global health crisis, apart from dedicated scientists who continue to study the impact of the HIV/AIDs epidemic and other infectious disease outbreaks. Now, we must incorporate this lens, to not only understand the influence on health, but help support families as society rebounds and moves forward. The intersection of physical and mental health is on full display. As researchers, scientists, and clinicians it is now our opportunity, privilege, and duty to step up to the enormous challenge ahead and to utilize our skills to build collaborations intent on improving the well-being of parents and children across the world.

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