BIOBEHAVIORAL AND SOCIAL PATHWAYS LINKING CHILDHOOD ADVERSITY AND HEALTH ACROSS THE LIFESPAN

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Editorial: Biobehavioral and social pathways linking childhood adversity and health across the lifespan

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Editorial on the Research Topic
Biobehavioral and social pathways linking childhood adversity and health across the lifespan

Adverse events in childhood are linked to mental and physical health well into old age. Beginning with the landmark study by Felitti et al. (1998), and with dozens of subsequent follow-up investigations in the decades since, we have ample evidence for a strong and graded association between adverse childhood experiences (ACEs) and multiple risk factors for several of the leading causes of death in adults. This pattern is especially worrisome, as we know that ACEs are common, affecting an estimated two thirds of the US population, with a potentially higher prevalence in middle- and low-income countries (Merrick et al., 2018; Kidman et al., 2020). The COVID-19 pandemic has exacerbated these trends, with evidence that children's exposure to adversity has increased as a consequence of the pandemic (Calvano et al., 2021).

Despite abundant evidence for the negative health effects of ACEs, less is known about the biobehavioral and social pathways through which ACEs impart these enduring negative effects. The purpose of this Research Topic was to collect articles that shed light on these potential pathways. With a better understanding of these pathways, it will be possible to identify promising points of focus for interventions seeking to reduce the negative consequences of childhood adversity for later health.

This Research Topic includes nine articles which collectively paint a picture of the complex and multifaceted relationship between ACEs and psychological, behavioral, social, and biological variables. For example, Novais et al. showed that ACEs affect a wide range of health-related problems. Relative to individuals who had not experienced

adversity in childhood, individuals with adversity exposures in childhood had higher total scores for more risk behaviors and health conditions, ranging from adverse mental health as well as adverse cardiometabolic outcomes. Similarly, Willemen et al. showed that a higher number of child maltreatment types, as well as distinct types of maltreatment such as emotional neglect, emotional abuse and sexual abuse were associated with a greater risk for current depressed mood. In this study, C-reactive protein (CRP), an index of low-grade inflammation, was evaluated as potential mediator between child maltreatment and comorbid depression and metabolic syndrome. However, contrary to expectations, CRP was not related to child maltreatment.

Chen et al. reviewed the evidence for immune and epigenetic pathways as promising candidates that may underlie the link between childhood adversity and subsequent adverse health outcomes. They conclude that childhood adversity, ranging from child abuse and neglect to poor parent-child relationships, to low socioeconomic status, can negatively shape immune and epigenetic pathways across the lifespan, with widespread implications for mental and physical health. Counts et al. studied acute cortisol reactivity to stress as a potential pathway linking childhood adversity and health. They found that blunted cortisol was related to childhood adversity, in part due to greater threat appraisals and lower challenge appraisals. Traces of having experienced childhood threat can also been found in resting state functioning of the brain as demonstrated by Banihashemi et al. who showed that greater childhood threat was associated with lower functional connectivity between several areas in the brain controlling stress responses. Evidence from a study by Iffland and Neuner suggests that it is likely that attentional biases in the aftermath of victimization put individuals at risk for the development of psychopathology. The work by Kogan et al. shows that, for young adults from disadvantaged backgrounds, high levels of planful self-control promote positive psychosocial outcomes but simultaneously confer vulnerabilities to chronic metabolic diseases. A final pathway from ACEs to adverse health outcomes may be through sleep. ACEs have been demonstrated to be associated with adult sleep disorders (Kajeepeta et al., 2015) and in this Research Topic Yang et al. show that sleep quality is associated with life satisfaction, and this association is mediated by perceived stress and depressive symptoms.

Sleep then may be a potential pathway to intervene on in trying to mitigate adverse health effects of ACEs. Another potential target for intervention has been studied by Bleil et al. who suggest that targeting parenting quality may reduce the negative effects of ACEs on health. They describe findings from a number of family-based intervention studies, which have provided promising evidence for the possibility that improving parenting quality for children who experience adversity may yield benefits for children's cardiometabolic health.

Collectively, the findings described in this Research Topic highlight a number of different pathways that help explain the negative health effects of ACEs as well as potential targets for behavioral and psychosocial interventions. While the work in this collection focuses primarily on pathways which may contribute to the poor health outcomes linked to childhood adversity, future work should elucidate sources of resilience for individuals who experienced adversity in childhood. Understanding protective factors is essential to inform intervention efforts aiming to offset the health risks associated with childhood adversity. Because children's exposure to adversity may shape health via many divergent pathways, successful interventions may require a multipronged approach that targets several vulnerabilities and enhances protective factors simultaneously. We are encouraged by the findings of Bleil et al. which suggests that interventions might be able to mitigate some of the sequelae associated with early life adversity.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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MINI REVIEW
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Targeting Parenting Quality to Reduce Early Life Adversity Impacts on Lifespan Cardiometabolic Risk

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Mounting evidence that early life adversity (ELA) exposures confer risk for cardiometabolic disease over the lifespan motivated this narrative review to examine parenting quality as a potential intervention target to reduce ELA exposures or mitigate their impact as a way of reducing or preventing cardiometabolic disease. We describe findings from the limited number of family-based intervention studies in ELA-exposed children that have tested parenting impacts on cardiometabolic health outcomes. We then describe the implications of this work and make recommendations for future research that will move this field forward.

Keywords: early life adversity, parenting, parenting quality, parental sensitivity, attachment, cardiometabolic health, cardiometabolic risk factors, early life intervention

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INTRODUCTION

Mounting evidence points to the toxic role of early life adversity (ELA) exposures such as family turmoil, stressful or traumatic events, and contextual stressors (i.e., poverty) in shaping cardiometabolic risk over the lifespan. In this context, it is imperative that we build our knowledge of potential interventions to either target the reduction of ELA exposures or to mitigate their impact as a means of reducing or preventing cardiometabolic disease. Given the large number of ELA exposures that have been identified as well as the intractable nature of their effects, much work remains to identify the type and delivery of interventions that would be most effective. In this narrative review, we examine the early emergence of cardiometabolic risk in childhood and the evidence relating ELA exposures to cardiometabolic health over the lifespan. We then provide a conceptual framework using attachment theory to highlight the potential role of parenting quality in mitigating ELA impacts on cardiometabolic health. Finally, we describe findings from the limited number of family-based intervention studies among ELA-exposed children that have tested parenting effects on cardiometabolic health outcomes and make recommendations for future research to move this field forward.

EARLY LIFE ADVERSITY AND THE ORIGINS OF ADULTHOOD CARDIOMETABOLIC DISEASE

Risk for adulthood cardiometabolic disease begins early in life (Olson et al., 2017). Elevated blood pressure and hypertension have been increasing in children (Din-Dzietham et al., 2007; Rosner et al., 2013; Flynn et al., 2017) as have overweight and obesity, with severe obesity in particular rising sharply in children ages 2–5 (Skinner et al., 2018). Type 2 diabetes increased 30% over an 8-year period in one study of almost 2 million children and by 7.1% annually in another study of 4.5 million children (Dabelea et al., 2014; Mayer-Davis et al., 2017). In a community sample, 5%

of children ages 7–9 years met criteria for metabolic syndrome and 45% exhibited 1–2 metabolic syndrome components (Dubose et al., 2006). Moreover, insulin resistance and cardiovascular risk factors, including hypertensive status, low HDL cholesterol, and high triglycerides, have been reported in overweight or obese children as young as ages 3–5 years (Bocca et al., 2013). Evidence also shows that children of minority race/ethnic backgrounds exhibit disproportionate risk across these health indicators, including higher rates of hypertension, obesity, and type 2 diabetes compared to their non-Hispanic, white counterparts (Dabelea et al., 2014; Kit et al., 2015; Mayer-Davis et al., 2017; Skinner et al., 2018).

Taken together, the early emergence of risk for adulthood cardiometabolic disease highlights the need to identify modifiable risk factors early in life. ELA exposures are a subset of risk factors or social determinants of health that may be targeted to this end. These exposures encompass a range of experiences that threaten a child's physical or emotional security, such as family dysfunction, stressful or traumatic events, and contextual factors such as socioeconomic disadvantage. ELA exposures are hypothesized to become biologically embedded, possibly through stress-related physiological disruptions in neuroendocrine, immune, and metabolic systems that predispose children to preclinical disease processes and resulting poor cardiometabolic health (Berens et al., 2017). The link between ELA exposures and health was revealed in early findings from The Adverse Childhood Experiences (ACE) Study in which a graded relationship between the number of ELA exposure categories (e.g., physical abuse) and the occurrence of adulthood diseases was observed (Felitti et al., 1998).

To date, a robust and growing literature has substantiated strong and often prospective links between ELA exposures and adulthood health (Galobardes et al., 2008; Shonkoff and Garner, 2012; Su et al., 2015a; Basu et al., 2017; Elsenburg et al., 2017; Suglia et al., 2018), including all-cause and disease-specific mortality (Claussen et al., 2003; Lawlor et al., 2006; Naess et al., 2007), clinical and subclinical cardiovascular disease (CVD) (Roy et al., 2010; Rich-Edwards et al., 2012; Campbell et al., 2016; Hakulinen et al., 2016), CVD risk factors (Danese et al., 2007; Rich-Edwards et al., 2010; Alastalo et al., 2013; Midei et al., 2013; Su et al., 2015b), a worsening of CVD risk over time (Su et al., 2015b; Hakulinen et al., 2016), and negative health behaviors (e.g., cigarette smoking, poor diet) (Anda et al., 1999; Gavrieli et al., 2015). ELA exposures are common in the population, with 60% of adults reporting having experienced at least one type of adversity (CDC, 2010; Bethell et al., 2014). ELA exposures also disproportionately affect vulnerable groups (Slopen et al., 2016; Turney and Wildeman, 2017), suggesting they may contribute to pronounced socioeconomic- and race/ethnicity-based disparities in cardiometabolic health (Chen et al., 2006; Shonkoff et al., 2009).

Abbreviations: ABC, Attachment and Biobehavioral Catch-up; BMI, body mass index; CVD, cardiovascular disease; ELA, early life adversity; MIECHV, Maternal, Infant, and Early Childhood Home Visiting; SAAF, Strong African American Families.

Although studies of ELA exposures have primarily focused on adulthood health, emerging evidence supports links between ELA exposures and parallel health outcomes in children and adolescents. ELA exposures have been associated with higher systolic blood pressure in children age 5–6 (Smarius et al., 2018) and more rapid increases in blood pressure in young adults (Su et al., 2015b). ELA exposures have also been associated with obesity (Suglia et al., 2012), insulin resistance (Goodman et al., 2007), arterial stiffness (Klassen et al., 2016), and inflammation (Miller and Chen, 2007, 2010; Ehrlich et al., 2016) in children and adolescents, as well as a range of caregiver-reported health problems, including global ratings of the child's health status and medical problems serious enough to require medical attention or impacting functional outcomes such as missing school (Flaherty et al., 2006, 2013; Luby et al., 2017). Findings across the developmental spectrum suggest there is continuity in the role ELA exposures may play in conferring risk for poor cardiometabolic health over periods of childhood, adolescence, and adulthood.

PARENTING QUALITY, CHILD SELF-REGULATION, AND CHILD CARDIOMETABOLIC HEALTH

The ELA-health literature is large in volume, but has several gaps outlined in recent publications, including a Scientific Statement from the American Heart Association and a report from an expert panel assembled as a part of an NHLBI workshop entitled "Social determinants of health: Early life adversity as a contributor to disparities in cardiovascular diseases" (Suglia et al., 2018, 2020). One gap concerns a lack of studies examining factors that modify ELA risk or that test interventions to lessen ELA impacts on cardiometabolic health. Recommendations for future research emphasize the need to test early life interventions which act on upstream ELA exposures, especially during vulnerable or sensitive developmental periods when intervention efforts may be most effective (Reynolds et al., 2011; Garner, 2013; McLaughlin et al., 2015; Michalopoulos et al., 2017). One potential target for intervention is parenting quality which is hypothesized to have protective effects on child cardiometabolic health by preventing or lessening the negative impacts of ELA exposures.

Attachment theory provides a potent conceptual framework for considering how parenting quality may "get into the body" to protect child health. Attachment theory posits that the ability of the primary caregiver to appropriately respond to the needs of the child, especially in times of distress, facilitates the development of self-regulatory processes in the child (Ainsworth et al., 1978; Coan, 2016). Self-regulatory processes represent key inter-related pathways through which parenting may operate to influence child health, including, but not limited to, self-regulation of socioemotional well-being (Cooke et al., 2019), stress responses systems (Gunnar, 2017), and emerging health behaviors (Bergmeier et al., 2020). In the context of ELA exposures, enhancing parenting quality may be especially important, potentially reducing the ELA exposures themselves,

due to the parent's heighted awareness of their impact, or buffering the harmful impacts of ELA exposures. Moreover, effects of parenting-focused approaches may be far-reaching by generalizing to a broad array of family situations over time and by protecting children against a variety of ELA exposures, many of which are unavoidable.

The role of parenting quality, parent-child relationships, and self-regulatory child behaviors have generally been understudied in relation to physical health outcomes in children. This gap was noted in a recent review in which Bergmeier et al. (2020) urged that the quality of early parent-child relationships, well-studied in relation to areas of child socioemotional development, be examined in relation to childhood weight gain and obesity risk. In longitudinal studies, insecure mother-child attachment as well as a composite of insecure mother-child attachment and reduced maternal sensitivity predicted greater obesity risk in childhood (age 4.5 years) (Anderson and Whitaker, 2011) and adolescence (age 15 years) (Anderson et al., 2012), respectively. Insecure mother-child attachment among preadolescents also predicted changes in maladaptive eating behaviors, including increases in dietary constraint and body image concerns as well as increases in BMI over a 1-year period (Goossens et al., 2012). In one of the few studies with a broader health focus, insecure mother-child attachment assessed in infancy predicted an increased likelihood of having a physical illness in adulthood 30 years later, albeit as assessed by self-reports of health conditions (Puig et al., 2013).

Children with insecure (vs. secure) attachment relationships exhibit poor self-regulation, including maladaptive coping strategies in response to feelings of distress that paradoxically result in unresolved or further distress (Aldao et al., 2010; Cooke et al., 2019). This cyclical process may explain how self-regulatory behaviors, shaped by early parenting practices, influence emerging health behaviors and associated health outcomes. For example, poor self-regulation has been related to problematic eating behaviors (Stoeckel et al., 2017) such as emotional eating, decreased sensitivity to satiety (vs. external) food cues, and binge eating (Frankel et al., 2012; Braden et al., 2014; Dingemans et al., 2017). Emotional eating refers to the use of food as a way to manage negative emotions, potentially serving as a substitute for a lack of support in other areas, including parental support (Haedt-Matt and Keel, 2011). A separate literature shows *adulthood* attachment insecurity is also related to unhealthy eating behaviors (Faber et al., 2018) and eating disorders (Ringer and Crittenden, 2007), as well as to cardiometabolic risk, indexed by metabolic syndrome (Davis et al., 2014; Farrell et al., 2019).

In future studies, more work is necessary to extend these findings to consider physical health outcomes in children beyond those related to eating behaviors and to bridge the child and adulthood attachment literatures in relation to health by examining types of insecure childhood attachment strategies (both minimizing negative emotional expression, Type A, and maximizing negative emotional expression, Type C) (Ringer and Crittenden, 2007; Kozlowska et al., 2011; Crittenden, 2016; Cooke et al., 2019) in relation to parameters of cardiometabolic health in adulthood. In addition, although a significant role for fathers, apart from mothers, is supported by studies relating paternal sensitivity and attachment to child socioemotional and behavioral outcomes (Lucassen et al., 2011; Bureau et al., 2017; Fernandes et al., 2020), father-child attachment has not been examined in relation to child health. Consideration should also be given to the role of grandmothers who play an important role in supporting the parenting behaviors of young mothers and who often contribute to co-parenting efforts, especially in racial/ethnic minority families in whom multigenerational households are more common (Oberlander et al., 2007; Sellers et al., 2011; Cohn and Passel, 2018).

CONCEPTUAL MODEL: ELA, PARENTING QUALITY, AND CHILD CARDIOMETABOLIC HEALTH

Based on the findings described above, a conceptual model is presented in **Figure 1**, depicting the hypothesized role of parenting quality as a protective factor in reducing ELA exposures or in mitigating their impact on child cardiometabolic health, in part, through child self-regulation in areas of socioemotional well-being, stress regulation, and the emergence of early feeding and sleep practices. In this framework, it is plausible that interventions to improve parenting quality among ELA-exposed children may reduce or even prevent cardiometabolic disease. Targeted areas for risk reduction may include chronic inflammation, individual cardiometabolic risk factors, and health behaviors. Although not an exhaustive list, these risk markers are important areas of focus as they are influenced by ELA exposures, show meaningful variation in children, and predict future clinical cardiometabolic disease.

Specifically, levels of chronic inflammation are elevated in individuals with disadvantaged backgrounds including histories of poverty, child abuse, and family stress (Taylor et al., 2006; Danese et al., 2007; Baumeister et al., 2016). Chronic inflammation is itself correlated with obesity in children (Shashaj et al., 2014) and predicts the development of cardiometabolic diseases (e.g., type 2 diabetes) (Ridker et al., 2000a,b; Pradhan et al., 2001; Pradhan and Ridker, 2002)—some emerging even in early childhood (Hernandez et al., 1998; Weiss, 2007; Messiah et al., 2012; Bocca et al., 2013; Shashaj et al., 2014; Bornhorst et al., 2016; Perng et al., 2016). Likewise, cardiometabolic risk factors, risk factor composites such as metabolic syndrome, and relevant health behaviors are all negatively impacted by ELA exposures (Berens et al., 2017). The early emergence of cardiometabolic risk factors, including, for example, patterns of weight gain in the first years of life, predict trajectories of obesity and cardiometabolic risk over time (Stettler et al., 2003). Thus, there is strong support for the proposed conceptual model describing directional associations between ELA, parenting, and child cardiometabolic health that may ultimately lead to better understanding adulthood risk for cardiometabolic disease.

In future studies, important elaborations on this model will be necessary, including consideration of the developmental context of ELA exposures that might heighten risk for cardiometabolic disease. The Developmental Origins of Health and Disease Hypothesis, for example, focuses on exposures during the period

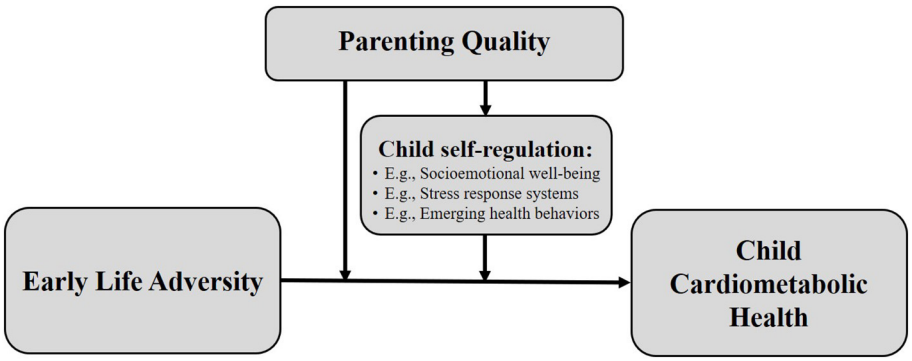

FIGURE 1 | Conceptual model depicting hypothesized role of parenting quality as a protective factor in reducing early life adversity exposures or in mitigating their impact on child cardiometabolic health, in part, through child self-regulation mechanisms.

of gestation in relation to adulthood cardiovascular risk (Barker et al., 1990; Barker, 1992). Another developmental period of interest is puberty during which time the occurrence of ELA exposures may also confer excess cardiovascular risk (Bleil et al., 2015). Furthermore, the pathway of pubertal development itself is of interest as ELA exposures appear to accelerate the onset of puberty (Belsky et al., 1991; Moffitt et al., 1992; Ellis, 2004; Bleil et al., 2013, 2021) and earlier pubertal timing, in turn, predicts post-pubertal weight gain, worsening CVD risk factor profiles, and incident cardiometabolic disease, and early mortality (Cooper et al., 1999; Frontini et al., 2003; Feng et al., 2008; Jacobsen et al., 2009; Lakshman et al., 2009).

PARENTING QUALITY: EVIDENCE FROM OBSERVATIONAL AND INTERVENTION STUDIES

Parenting as a Moderator

A growing number of observational studies have examined the potential moderating role of parenting quality. Findings show responsive caregiving buffers impacts of ELA exposures on a range of health outcomes in adults and children (Evans et al., 2007; Chen et al., 2011; Miller et al., 2011; Asok et al., 2013; Carroll et al., 2013; Farrell et al., 2017; Bernard et al., 2019a). In one study, adults who were socioeconomically disadvantaged as children, but experienced high levels of maternal warmth, displayed fewer pro-inflammatory risk markers compared to their adult counterparts in whom maternal warmth was low (Chen et al., 2011). In another study, consistency in the quality and timing of parent-child interactions was linked prospectively to healthier *in vitro* inflammatory responses in adolescence (Manczak et al., 2018). Findings extend beyond the examination of inflammatory outcomes as well, showing responsive caregiving also buffers impacts of ELA exposures on metabolic syndrome, allostatic load, and BMI, as well as self-reports of physical symptoms and self-ratings of health (Evans et al., 2007; Miller et al., 2011; Carroll et al., 2013; Farrell et al., 2017).

Parenting Focused Interventions

With respect to randomized controlled trials, few studies have tested family-based interventions among ELA-exposed children to determine whether improvements in parenting may attenuate ELA impacts on cardiometabolic health. Findings among these studies, however, warrant special attention to evaluate evidence for the role of parenting, the ways in which parenting may be leveraged in future studies of child cardiometabolic health, and the broader implications for action in clinical and policy-making settings.

In the Strong African American Families (SAAF) study of vulnerable, low-income families, mothers and their children (11 years old) were randomized to a multifaceted family-based intervention versus control condition in which only the study assessments were administered (Brody et al., 2004). In secondary analyses of a subset of the mother-child dyads, children who received the intervention were found to have lower levels of inflammation 8 years later, as reflected by a composite of markers (IFN-γ, IL-10, IL-1β, IL-6, IL-8, and TNF-α) (Miller et al., 2014). Parenting quality, one of the multiple targets of the intervention, mediated this effect; intervention-related improvements in parenting, including *both* increases in nurturant-involved parenting and decreases in harsh-inconsistent parenting were associated with the lowest levels of inflammation. Moreover, improvements in parenting were greatest, and levels of inflammation the lowest, among the most at-risk families, suggesting the most vulnerable families experienced the most intervention benefit.

Additional secondary analyses in the SAAF study showed intervention effects extended to other cardiometabolic risk indicators as well, including metabolic syndrome and pre-diabetes (Brody et al., 2017, 2019; Chen et al., 2017, 2018). Randomization to the family-based intervention (vs. control condition) mitigated impacts of unsupportive parenting on metabolic syndrome assessed at age 25 with mediational analyses showing effects were attributable to changes in the intervention targets pertaining to parenting quality and parent-child relationships (Chen et al., 2018). Similarly, the family-based intervention (vs. control condition) was found to lessen risk for higher fasting glucose, a marker of pre-diabetes, at age 25 and

to eliminate the association between the number of adversity exposures and pre-diabetes (Brody et al., 2017).

In another family-based intervention study, children and their parents who had a history of involvement with child protective services (CPS) due to an identified risk in the home (e.g., maltreatment, domestic violence) were randomized to receive the Attachment and Biobehavioral Catch-up (ABC) intervention vs. control condition in which educational materials about child development were delivered (Bernard et al., 2019a). The ABC intervention used parent coaching and feedback to promote parents' responsivity to child distress as a way of enhancing attachment security and child self-regulation. In the ABC intervention group, 52% of the children were classified as securely attached vs. 32% in the control condition, and attachment security predicted lower BMI at age 4 years and steeper declines in BMI between ages 2 and 4 years. While there was no direct effect of the ABC intervention on child BMI, the mediated or indirect effect of the intervention via attachment security reached marginal significance. In a separate analysis of a subset of children drawn from the same study, children with insecure (vs. secure) attachments exhibited higher levels of inflammation which predicted increases in BMI between ages 4 and 8 years, highlighting the potential mechanistic role of inflammation (Bernard et al., 2019b).

IMPLICATIONS AND FUTURE DIRECTIONS

The studies reviewed above, describing effects of family-based interventions on health outcomes, highlight the important role of parenting as the "key ingredient" in such interventions. Findings indicate that the influence of parenting on these outcomes may even be causal as suggested by randomized control trials involving families randomized to receive parenting-focused training vs. control conditions. In this context, the use of parenting support interventions as a tool to improve cardiometabolic health in children is an exciting and promising new direction. Importantly, evidence also shows that intervention effects are stronger in families in greatest need (Miller et al., 2014), raising the possibility that such interventions may attenuate pronounced ELA-related health burdens in the most vulnerable families.

As a next step, it is important to move this literature forward by focusing on parenting quality directly as well as the potential mechanisms of its effects (e.g., improved child self-regulation). There is immense untapped potential in existing evidence-based parenting interventions that have already been developed to enhance outcomes in areas of child socioemotional well-being and parent-child relationships. These same interventions should be re-examined in relation to child health outcomes. Some examples of established parenting interventions include the ABC intervention mentioned above (Bernard et al., 2019a) and the Promoting First Relationships program, an attachment theory based program which focuses on enhancing positive parent-child relationships (Kelly et al., 2008). Another intervention, the New Beginnings Program, is a parenting-focused program designed to prevent problems in children who experience adversity such as parental divorce (Sandler et al., 2020). Thus, an urgent research question concerns whether existing parenting interventions that are effective in improving child socioemotional well-being and parent-child relationship outcomes, are also effective in reducing ELA impacts on child cardiometabolic health.

Existing parenting interventions are also uniquely positioned for large-scale dissemination through mechanisms such as the federally funded Maternal, Infant, and Early Childhood Home Visiting (MIECHV) program or other established home-visiting programs. MIECHV, described here to illustrate this potential, started in 2010 as a provision within the Affordable Care Act to provide states with resources for home visiting. Seventy-five percent of funds to the states are required to go to evidence-based home visiting programs. Currently, there are 18 programs listed as evidence-based ("US Department of Health and Human Services, Home Visiting Evidence of Effectiveness[1],"). Although a few of these programs have reported at least some effects on "positive parenting" and "child health" defined broadly, none have tested the hypothesis presented here—that enhanced parenting quality may prevent or mitigate ELA impacts on child cardiometabolic health. It is plausible that if the benefits of one of these programs were found to extend to child health, there may be "shovel ready" treatment options available for dissemination on a large scale. Dissemination through a mechanism such as MIECHV would make it possible to reach thousands of mother-infant dyads during a sensitive developmental period that sets the stage for lifespan cardiometabolic risk.

CONCLUSIONS

In response to mounting evidence that ELA exposures confer risk for cardiometabolic disease, starting even in early childhood, we highlighted the role of parenting as a potential focus of intervention for the reduction of ELA exposures or their mitigation as a way of reducing or preventing cardiometabolic disease. Among the limited number of family-based intervention studies that examined cardiometabolic health outcomes in ELA-exposed children, significant intervention effects on health outcomes were mediated by improvements in parenting behaviors specifically, confirming the key role of parenting. These findings raise the profile of existing evidence-based parenting interventions that have primarily focused on child socioemotional and behavioral outcomes by identifying the opportunity to test these interventions in relation to child cardiometabolic health. Moreover, existing parenting interventions, if found to also benefit child health, have the potential for broad dissemination through home-visiting mechanisms such as the federally funded MIECHV program, making it plausible to reach the most vulnerable families in whom ELA exposures and cardiometabolic risk factors are disproportionately prevalent.

[1]US Department of Health and Human Services, Home Visiting Evidence of Effectiveness. *Evidence-Based Models Eligible to Maternal, Infant, and Early Childhood Home Visiting (MIECHV) Grantees*. Retrieved from: https://homvee.acf.hhs.gov/HRSA-Models-Eligible-MIECHV-Grantees.

AUTHOR CONTRIBUTIONS

MB developed the study concept and drafted the manuscript. SS and CB-L provided critical revisions. All authors read and approved the final version of the manuscript for submission.

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When Problems Only Get Bigger: The Impact of Adverse Childhood Experience on Adult Health

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Introduction: Previous studies have shown that adverse childhood experiences negatively impact child development, with consequences throughout the lifespan. Some of these consequences include the exacerbation or onset of several pathologies and risk behaviors.

Materials and Methods: A convenience sample of 398 individuals aged 20 years or older from the Porto metropolitan area, with quotas, was collected. The evaluation was conducted using an anonymous questionnaire that included sociodemographic questions about exposure to adverse childhood experiences, a list of current health conditions, questions about risk behaviors, the AUDIT-C test, the Fagerström test and the Childhood Trauma Questionnaire–brief form. Variables were quantified to measure adverse childhood experiences, pathologies, and risk behaviors in adult individuals for comparison purposes.

Results: Individuals with different forms of adverse childhood experiences present higher rates of smoking dependence, self-harm behaviors, victimization of/aggression toward intimate partners, early onset of sexual life, sexually transmitted infections, multiple sexual partners, abortions, anxiety, depression, diabetes, arthritis, high cholesterol, hypertension, and stroke. Different associations are analyzed and presented.

Discussion and Conclusions: The results show that individuals with adverse childhood experiences have higher total scores for more risk behaviors and health conditions than individuals without traumatic backgrounds. These results are relevant for health purposes and indicate the need for further research to promote preventive and protective measures.

Keywords: child abuse, trauma, adverse childhood experience, health, risk behavior

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INTRODUCTION

Child maltreatment (MT) or child abuse and neglect is a severe public health problem with a long-term impact on the victim's life and health (Felitti et al., 2019). Child maltreatment, along with other types of trauma, is currently considered an adverse childhood experience (ACE).

Felitti et al. (2019) took the first steps to designate MT categories as an ACE ["Centers for Disease Control and Prevention. Preventing adverse childhood experiences (ACEs): leveraging the best available evidence," 2019; Felitti et al., 2019]. Seven categories of ACEs were initially studied: three were related to child MT (physical, sexual, and psychological abuse), and four family dysfuncion (substance abuse, mental illness, MT of the mother, and criminal behavior) [Andersen and Blosnich, 2013; "Centers for Disease Control and Prevention. Preventing adverse childhood experiences (ACEs): leveraging the best available evidence," 2019; Felitti et al., 2019]. In addition to the MT itself, ACEs' cumulative effect has also been highlighted. A dose-effect relationship has been identified between the number of ACEs and the risk of a higher incidence of negative outcomes (Chapman et al., 2004; Felitti et al., 2019).

The consequences of MT can be immediate or can arise in the medium or long term (Flaherty et al., 2013; Chiang et al., 2015; Kalmakis and Chandler, 2015). The most frequent and immediate effects are traumatic injuries (e.g., bruises, abrasions, hematomas, fractures, traumatic brain injury) and psychosomatic disorders associated with stressful experiences (e.g., sleep or eating disorders, anxiety disorder). In the medium and long term (in youth and adulthood), health risk behaviors and physical and mental health disorders may arise (Larkin et al., 2012; King, 2020).

Regarding health risk behaviors, there is a trend on increased rates of substance abuse (Hillis et al., 2001; Dube et al., 2003; Andersen and Blosnich, 2013; Felitti et al., 2019) (e.g., abuse of anxiolytics, analgesics, tobacco, drugs, and alcohol), physical inactivity (Hillis et al., 2001; Felitti et al., 2019), risky sexual behaviors (Dube et al., 2003; Andersen and Blosnich, 2013; Felitti et al., 2019) (e.g., juvenile sexuality, multiple partners, unprotected intercourse), self-harming behaviors (Dube et al., 2003; Andersen and Blosnich, 2013) (e.g., self-aggression and attempted suicide or suicide), and deviant behaviors related to repeated violence (e.g., intimate partner aggression) (Hillis et al., 2001; Dube et al., 2003; Andersen and Blosnich, 2013).

These consequences are associated with the impact of traumatic stress on various systems linked to body homeostasis (namely, the neurological, immune, and endocrine systems), including the hypothalamic-pituitary-adrenal (HPA) axis. The hyperactivation of this axis favors the occurrence, in the long term, of dysfunctions at different levels: metabolic (Vargas et al., 2016; Felitti et al., 2019) (e.g., obesity, dyslipidaemia, diabetes); cardiocerebrovascular (Dong et al., 2004; Stein et al., 2010; Andersen and Blosnich, 2013) [e.g., atherosclerosis, high blood pressure (HBP), acute myocardial infarction, stroke]; respiratory (Anda et al., 2008; Bellis et al., 2015; Hughes et al., 2017; Felitti et al., 2019) (e.g., chronic obstructive pulmonary disease); inflammatory (Danese et al., 2007; Dube et al., 2009) (e.g., rheumatoid arthritis, lupus, asthma); oncological (Holman et al., 2016; Felitti et al., 2019) and sexual/reproductive [sexually transmitted infections (STI), unwanted pregnancy and abortions] (Hillis et al., 2001; Dube et al., 2003; Andersen and Blosnich, 2013; Felitti et al., 2019). Increased cortisol levels, decreased activity of cortisol receptors and increased corticotrophin-releasing factor (Dube et al., 2003; Anda et al., 2006) can trigger genetically programmed diseases that would be latent in the absence of traumatic stress (Dube et al., 2003; Anda et al., 2006). On the other hand, a change in the HPA axis may also contribute to a pro-inflammatory state and a consequent increase in morbidity such as depressive disorders (Heim et al., 2008), rheumatoid arthritis (Colebatch and Edwards, 2011), and metabolic diseases, such as hyperinsulinemia (Maniam et al., 2014).

It is, however, important to note that these outcomes have individual variability. They are influenced by age, resilience, personality characteristics, and developmental stage that the victim was at when MT occurred, type, frequency, duration, and severity of MT, and by the victim-abuser relationship/closeness (Leitch, 2017). Their occurrence also depends on the early detection of MT and the quality of professional intervention received. So, not all adult individuals who have suffered ACEs–specifically MT–will have negative health outcomes, yet, a great proportion is expected to be at increased risk for such (Monnat and Chandler, 2015). Thus, it is currently understood that traumatic experiences in childhood may lead to many disorders and pathologies that manifest in adulthood, many of which may have gone unnoticed in health contexts during childhood (Kalmakis and Chandler, 2015).

This study's general objective is to analyze the relationship of ACEs, namely, those related to MT, with the occurrence of adult health problems in a population in the Porto region, in Portugal.

MATERIALS AND METHODS

The present study was based on self-completed questionnaires administered to a convenience sample of participants collected according to quotas, stratified by gender and age and drawn from the Porto region's population (1,391,726 inhabitants). The total sample consisted of 398 healthcare users who met the following selection criteria: (a) residents of the Porto area and (b) older than 19 years old, taking into account the age group for which the childhood trauma questionnaire that we used [CTQ-SF] was validated. A member of the research team distributed paper versions of the questionnaire in five private healthcare services (medical centers and clinics) in the Porto area. In each center/clinic, an internal collaborator recruited participants and managed both delivery and reception of questionnaires, using a deposit box in order to guarantee the anonymity of participants. Responses were collected between July 2019 and January 2020. The questionnaire included information about the participants, reflecting the literature on the topic (Nabais, 2014; Alves et al., 2015): (a) sociodemographic data, (b) risk behaviors (alcohol consumption, tobacco use, drug abuse, onset of sexual activity before 16 years of age, three or more sexual partners in the last year, abortion before age 18 years, attempted suicide, self-harm behaviors, being aggressive to an intimate partner, being victimized by an intimate partner), and (c) current health conditions (hypercholesterolemia, HBP, anxiety disorder, diabetes, depression, asthma, rheumatoid arthritis, thyroid pathology, stroke sequelae, oncological disease, liver disease, renal pathology, acute myocardial infarction sequelae, chronic obstructive pulmonary disease, or bulimia).

Sociodemographic data included age, sex and level of education of the respondents. This last parameter was classified as (a) elementary school completion (b) high school attendance (c) high school completion and (d) higher education attendance or completion. The referred setting–private health services–is predominantly used by medium-high-income individuals (Nurses, 2011).

The AUDIT-C test, adapted for the Portuguese population (Cunha, 2002) from the work of Bush et al. (1998), was used for alcohol consumption screening. This tool is used to reliably identify people with hazardous drinking habits (i.e., binge drinking) or with active alcohol-related disorders (i.e., dependence).

The Fagerström test evaluated nicotine dependence using the validated version for the Portuguese population (Ferreira et al., 2009) from the scale by Heatherton et al. (1991), which showed satisfactory total internal consistency ($\alpha = 0.66$) (Heatherton et al., 1991; Ferreira et al., 2009).

The CTQ-SF, in the validated version for the Portuguese population (Pennebaker and Susman, 1988; Dias et al., 2013) was employed to assess the individual's ACEs. This version is based on the short-form scale tested by Thombs et al. (2009) and its original version (Bernstein et al., 1998). The CTQ-SF includes 28 items rated on a 5-point Likert scale and has 5 main factors: *emotional* ($\alpha = 0.71$), *physical* ($\alpha = 0.77$) and *sexual* ($\alpha = 0.71$) *abuse* and *emotional* ($\alpha = 0.79$) and *physical* ($\alpha = 0.47$) *neglect*. The total scale shows high internal consistency ($\alpha = 0.84$). The reliability observed for the *physical neglect* subscale does not affect the total consistency of the scale, and its removal was not considered beneficial according to the confirmatory factor analysis performed by the authors in a non-clinical population (test-retest reliability) (Dias et al., 2013). Responses ranged from 1–never to 5–always and each of the five factors of the scale encompassed 4 to 7 items. Each of the 5 factors of the scale ranges from 5 to 25 points.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 26. We performed a descriptive analysis of the variables, and the categorical variables are described as absolute frequencies and their respective percentages. Chi-square tests were used to assess relationships between categorical variables. We first verified the distributions' normality for continuous variables, by observing the histogram; when normality was not observed, the continuous variables are described as medians and their respective interquartile ranges. Associations between the different ACE factors (*emotional abuse, physical abuse, sexual abuse, emotional neglect,* and *physical neglect*) were evaluated using Spearman's correlation. We used the Mann-Whitney and Kruskal-Wallis tests to compare the various ACE factors and different groups of risk behaviors and pathologies. The mean imputation technique was applied to the missing data in the CTQ-SF questions. A statistical significance level of 0.05 was considered.

The study was approved by the Ethics Committee for Health of the *Centro Hospitalar Universitário de São João* (University Hospital Center of São João) and the Medical School of the University of Porto.

RESULTS

Respondent Characteristics

Of the respondents, 53.5% were female ($n = 213$). The mean age was 50.6 years (median = 50; min = 20; max = 97). Regarding education level, 14.8% ($n = 59$) completed elementary school, 15.8% (n = 63) attended high school without completing, 33.4% ($n = 133$) completed high school, and 35.7% ($n = 142$) had a higher education degree or were currently attending college.

At the time of the study, the respondents reported the following:

a) Regarding health risk behaviors: excessive alcohol consumption ($n = 68$; 24.0%); moderate and high consumption of tobacco ($n = 86$; 21.6%); drug abuse ($n = 14$; 3.5%); onset of sexual activity before 16 years of age ($n = 72$; 18.8% of 383 sexually active individuals); STI ($n = 15$; 3.9%); three or more partners in the last year ($n = 14$; 3.7%); abortion before age 18 years ($n = 18$; 4.7%); attempted suicide ($n = 24$; 6%); self-harm behaviors ($n = 20$; 5%); being aggressive to an intimate partner ($n = 25$; 6.3%); being victimized by an intimate partner ($n = 15$; 3.8%).
b) Regarding diseases: at the time of the study, 61.8% of the participants had at least one of the following diseases: hypercholesterolemia ($n = 109$; 27.4%), HBP ($n = 93$; 23.4%), anxiety disorder ($n = 73$; 18.3%), diabetes ($n = 61$; 15.3%), depression ($n = 59$; 14.6%), asthma ($n = 36$; 9.0%), rheumatoid arthritis ($n = 23$; 5.8%), thyroid pathology ($n = 21$; 5.3%), stroke sequelae ($n = 20$; 5.0%), oncological disease ($n = 17$; 4.3%), liver disease ($n = 7$; 1.8%), renal pathology ($n = 7$; 1.8%), acute myocardial infarction sequelae ($n = 7$; 1.8%), chronic obstructive pulmonary disease ($n = 3$; 0.8%) or bulimia ($n = 1$; 0.3%).

ACE Factors and Their Correlations

Table 1 presents the median and interquartile ranges for the individual ACE factors and the general score (CTQ-SF) by gender and their correlations with the respondents' age. Bearing in mind the reliability previously found for the *physical neglect* subscale, the results obtained with this subscale in the present study were interpreted with due reserve. The *emotional neglect* factor had the highest values, meaning that a high percentage of respondents scored in this subscale, while *sexual abuse* and *physical abuse* had lower values and showed less variation among responses. Considering the sex of participants, *emotional abuse* and *sexual abuse* had higher scores among female respondents, although differences were moderate ($p = 0.04$). A significant negative association was found between age and emotional abuse in childhood, which means younger individuals report higher emotional abuse values. Also, a significant positive association was found between age and physical neglect, which means higher physical neglect values were more frequently reported by older respondents.

There were three major associations among the different ACE factors. The strongest was between *emotional abuse* and *physical abuse* ($r = 0.452$), followed by the associations between *emotional abuse* and *emotional neglect* ($r = 0.441$) and between *emotional neglect* and *physical neglect* ($r = 0.422$) (**Table 2**).

TABLE 1 | ACE factors–median and interquartile range; median and interquartile range by gender; correlation with age.

	Total ($n = 398$) Med[c] (Q1[d], Q3[e])	Male ($n = 185$) Med[c] (Q1[d], Q3[e])	Female ($n = 213$) Med[c] (Q1[d], Q3[e])	Spearman's coefficient for age
Emotional abuse	6 (5, 9)	**6 (5, 8)**	**7 (5, 9)**	**−0.143**[a]
Emotional neglect	8 (6, 11)	8 (6, 11)	8 (6, 11)	0.01
Sexual abuse	5 (5, 5)	**5 (5, 5)**	**5 (5, 5)**	−0.018
Physical abuse	5 (5, 6)	5 (5, 6)	5 (5, 6)	0.079
Physical neglect	6 (5, 9)	6 (5, 8)	6 (5, 9)	**0.300**[b]
CTQ-SF	32 (28, 38)	32 (28, 37)	32 (29, 38)	0.064

[a]$p < 0.005$; [b]$p < 0.001$; [c]Med–median; [d]Q1–first quartile; [e]Q3–third quartile. *Values in bold indicate statistically significant results ($p < 0.05$).*

Since the Spearman correlations found between all of the CTQ-SF subscales are statistically significant ($p < 0.01$), this explains the shared variance. The *sexual abuse* subscale has the lowest correlation with the other subscales, as in the validation study. It was also found that the sum of the subscales' scores may be used as a general indicator of child maltreatment.

Health Risk Behaviors and Correlations With ACE Factors

No differences in alcohol and drug consumption were found among the various factors. Individuals with partial scores (higher scores for *emotional abuse, emotional neglect,* and *physical neglect*) and higher total scores had a higher dependence on tobacco (**Table 3**).

Regarding high risk of sexual behaviors (**Table 4**): (a) individuals with early onset of sexual intercourse present higher scores on the *emotional abuse* factor and a significantly higher ACE total score; (b) individuals reporting prior STI reveal higher physical abuse scores; (c) individuals who reported not having a sexual partner in the last year or having had three or more, presented a higher score on the *physical neglect* factor; (d) individuals who reported having had at least one abortion before completing 18 years of age had higher scores on the *physical abuse* and *physical neglect* factors.

Nearly all ACE scores (partial and total) were significantly higher in subjects who (**Table 5**): (a) attempted suicide; (b) committed self-harm; (c) reported being aggressive with an intimate partner. All ACE scores except *emotional neglect* were significantly higher in individuals who reported suffering violence from an intimate partner. Other correlations were found: of the 20 individuals who committed self-harm, 35% ($n = 7$) reported being violent with their intimate partners, while 26% ($n = 5$) reportedly were victims of intimate partner violence; and, of the 25 individuals who reported intimate partner violence perpetration, 40% ($n = 10$) also reported having suffered from violence from an intimate partner.

Physical and Psychological Health and Correlations With ACE Factors

Table 6 illustrates the higher ACEs values for the considered pathologies in individuals who had the following pathologies: (a) individuals with hypercholesterolemia, HBP, or who had a stroke presented with higher partial *physical neglect* and total scores; (b) individuals with diabetes had significantly higher partial (emotional and physical neglect and physical abuse) and total ACE score; (c) individuals with rheumatoid arthritis exhibited higher partial (*emotional* and *physical neglect* and *sexual abuse*) and total ACE score; (d) individuals with an anxiety disorder had higher partial and total ACE score; (e) individuals with depression had higher partial (all except *emotional* and *sexual abuse*) and total ACE score.

Positive moderated correlations were also found: (a) between depression/anxiety disorder and smoking dependence and (b) between depression/anxiety disorder and suicide attempts and/or self-harm behaviors.

DISCUSSION

In this study, we evaluated the impact of ACE/MT on adult individuals' health risk behaviors and their overall health. This is an original study, and no publications related to this impact on adult individuals or populations in the Porto region have been identified.

Correlations Between ACE Factors and Respondent Characteristics

Regarding the respondents' age, we found a significant positive association with the *physical neglect* factor (**Table 1**). The explanation may lie in the fact that older individuals are more likely to have experienced physical neglect because it was socially acceptable and common when these respondents were children, given that the social condemnation and criminalization of such practices occurred only recently (Magalhães, 2020). We also found a significant but negative association between age and the *emotional abuse* factor (**Table 1**), which may reflect a greater awareness among younger individuals of what constitutes abuse; additionally, for temporal reasons, their self-reports may have greater reliability (Colman et al., 2016).

Regarding gender, we found that emotional and sexual abuse were more frequently reported by female respondents (**Table 1**), which is consistent with the literature that reports a higher frequency of females exposed to these types of abuse (Magalhães et al., 2010; Pinto et al., 2014).

TABLE 2 | Correlations between ACE factors.

	Emotional neglect	Sexual abuse	Physical abuse	Physical neglect	CTQ-SF
Emotional abuse	0.441[a]	0.372[a]	0.452[a]	0.235[a]	0.690[a]
Emotional neglect		0.204[a]	0.382[a]	0.422[a]	0.831[a]
Sexual abuse			0.296[a]	0.183[a]	0.367[a]
Physical abuse				0.382[a]	0.580[a]
Physical neglect					0.660[a]
CTQ-SF					

[a]$p < 0.001$.

TABLE 3 | Median, interquartile range, and *p*-value for the relationship between the different ACE factors and tobacco consumption.

			Emotional abuse	Emotional neglect	Sexual abuse	Physical abuse	Physical neglect	CTQ-SF
Tobacco consumption	NO ($n = 250$; 62.8%)	Med[a] (Q1[b],Q3[c])	6 (5, 8)	9 (6, 11)	5 (5, 5)	5 (5, 6)	6 (5, 9)	33 (28, 38)
	YES ($n = 86$; 21.6%)	Med[a] (Q1[b],Q3[c])	6 (5, 9)	8 (7, 11)	5 (5, 5)	5 (5, 6)	6 (5, 8)	31 (29, 37)
	No longer consumes ($n = 62$; 15.6%)	Med[a] (Q1[b],Q3[c])	6 (5, 8)	7 (5, 10)	5 (5, 5)	5 (5, 7)	6 (5, 9)	32 (28, 38)
	KRUSKAL-WALLIS	*P*-value	0.459	0.129	0.193	**0.029**	0.404	0.729
Tobacco dependence	LOW ($n = 62$; 72.1%)	Med[a] (Q1[b],Q3[c])	6 (5, 9)	7 (6, 10)	5 (5, 5)	5 (5, 6)	5 (5, 7)	30 (28, 34)
	MODERATE ($n = 19$; 22.1%)	Med[a] (Q1[b],Q3[c])	7 (6, 9)	9 (7, 11)	5 (5, 5)	5 (5, 6)	6 (5, 9)	35 (30, 39)
	HIGH ($n = 62$; 5.8%)	Med[a] (Q1[b],Q3[c])	14 (14, 19)	19 (15, 21)	5 (5, 9)	6 (5, 11)	16 (14, 17)	59 (56, 75)
	KRUSKAL-WALLIS	*P*-value	**0.013**	**0.008**	0.4	0.115	**<0.001**	**0.002**

[a]*Med–median;* [b]*Q1–first quartile;* [c]*Q3–third quartile. Values in bold indicate statistically significant results ($p < 0.05$).*

Health Risk Behaviors and Correlations With ACE

Adopting risk behaviors such as substance abuse as coping mechanisms by individuals with ACEs is widely described in the literature. A study by Anda et al. (2006) analyzed the relationship between the number of ACEs and 18 outcomes (including somatic disorders; consumption of tobacco, alcohol, and drugs; early onset of sexual activity; and multiple sexual partners). The relationship between the number of ACEs score and each of the outcomes under study, as well as with the total number of these outcomes, revealed a dose-response relationship, i.e., the higher the number of ACEs, the greater rate of the observed comorbidity. Similarly, the ACE Study (Felitti et al., 2019) concluded that individuals exposed to four or more ACEs' have an increased risk of alcoholism, drug abuse, depression, suicide attempts, tobacco use, multiple sexual partners, STI, physical inactivity, and severe obesity. The authors confirm the existence of a relationship between exposure to ACEs and the presence of several risk factors associated with the main causes of death in adults, i.e., early death. Additionally, a systematic review and meta-analysis by Hughes et al. (2017) defend that exposure to multiple ACEs is the greatest risk factor for various clinical conditions and risk behaviors, including a strong relationship between ACEs and alcohol abuse, substance use, risky sexual behavior, and mental illness.

The present study showed that individuals who have higher number ACEs have greater smoking dependence, similar to the findings of other studies (Dube et al., 2003; Anda et al., 2006; Mersky et al., 2013; Hughes et al., 2017). The explanation may be that nicotine has psychoactive properties (acting on the dopaminergic pathways) that promote increased pleasure sensation and decreased anxiety and lead to improved mood (Benowitz, 2010; Crouch et al., 2018).

No associations were found with other substance abuse, as would be expected (Cole et al., 2011; Mersky et al., 2013). This is probably due to the following: (1) it may be hypothesized that the sample was generally of medium-high-income population since it was collected in private health settings, and people with higher income are usually those with access to it (Nurses, 2011) and there are studies linking poverty or unemployment to alcohol use (Khan et al., 2002; Henkel, 2011) and low-income to lower illicit drug use (Sunder et al., 2007; Kuo et al., 2011), although other authors find access to drugs positively correlated to higher income (Long et al., 2014); (2)

TABLE 4 | Median and correlation between the different ACE factors and sexual risk behaviors.

			Emotional abuse	Emotional neglect	Sexual abuse	Physical abuse	Physical neglect	CTQ-SF
Age at onset of sexual intercourse, years	<16 ($n = 72$,18.8%)	Med[a] (Q1[b],Q3[c])	7 (5, 10)	9 (7, 13)	5 (5, 5)	5 (5, 7)	7 (5, 9)	34 (30, 42)
	16–18 ($n = 133$, 34.7%)	Med[a] (Q1[b],Q3[c])	6 (5, 8)	9 (6, 11)	5 (5, 5)	5 (5, 6)	6 (5, 8)	33 (28, 38)
	>18 ($n = 171$, 44.6%)	Med[a] (Q1[b],Q3[c])	6 (5, 8)	8 (6, 10)	5 (5, 5)	5 (5, 5)	5 (5, 9)	31 (28, 35)
	KRUSKAL-WALLIS	*P*-value	**0.007**	**0.023**	0.148	**<0.001**	0.145	**0.013**
Sexually transmitted infections	NO ($n = 361$, 94.3%)	Med[a] (Q1[b],Q3[c])	6 (5, 9)	8 (6, 11)	5 (5, 5)	5 (5, 6)	6 (5, 9)	32 (28, 38)
	YES ($n = 15$, 3.9%)	Med[a] (Q1[b],Q3[c])	8 (6, 9)	10 (5, 12)	5 (5, 7)	6 (5, 7)	8 (6, 9)	36 (31, 41)
	MANN-WHITNEY	*P*-value	0.113	0.495	0.375	**0.042**	0.054	0.05
Number of sexual partners in the last year	0 ($n = 64$, 16.7%)	Med[a] (Q1[b],Q3[c])	6 (5, 7)	9 (7, 11)	5 (5, 5)	5 (5, 6)	7 (5, 9)	33 (30, 40)
	1 ($n = 271$, 70.8%)	Med[a] (Q1[b],Q3[c])	6 (5, 8)	8 (6, 10)	5 (5, 5)	5 (5, 6)	5 (5, 8)	31 (28, 36)
	2 ($n = 27$, 7.0%)	Med[a] (Q1[b],Q3[c])	7 (5, 9)	9 (7, 11)	5 (5, 7)	5 (5, 6)	6 (5, 9)	33 (29, 44)
	3+ ($n = 14$, 3.7%)	Med[a] (Q1[b],Q3[c])	7 (5, 10)	9 (7, 15)	5 (5, 6)	5 (5, 7)	7 (5, 11)	32 (29, 48)
	KRUSKAL-WALLIS	*P*-value	0.526	0.197	**0.037**	0.206	**0.001**	0.088
Abortion	NO ($n = 294$, 76.8%)	Med[a] (Q1[b],Q3[c])	6 (5, 9)	8 (6, 11)	5 (5, 5)	5 (5, 6)	6 (5, 9)	31 (28, 38)
	YES ($n = 18$, 4.7%)	Med[a] (Q1[b],Q3[c])	7 (5, 9)	9 (7, 12)	5 (5, 5)	6 (5, 8)	8 (5, 10)	36 (30, 46)
	MANN-WHITNEY	*P*-value	0.531	0.534	0.854	**0.032**	**0.031**	0.077

[a]*Med–median;* [b]*Q1–first quartile;* [c]*Q3–third quartile. Values in bold indicate statistically significant results ($p < 0.05$).*

employment, a source of economic empowerment, is positively correlated to access to health services, especially private (Liu et al., 2013). (3) Substance abuse has been found to be more prevalent in lower social strata (Cole et al., 2011; Mersky et al., 2013). It is possible to hypothesize that accounting for family disfunction measures might allow to refine this correlation study.

Regarding the risky sexual behaviors that were analyzed, we found that some individuals who reported these behaviors had higher partial and total number of ACE. Additionally, a cohort found that each type of ACE was associated with an increased risk of early onset of sexual activity, multiple sexual partners, and HIV (Hillis et al., 2001). Regarding abortion in adolescence, another study evaluated its relationship with ACEs and concluded that, in addition to other factors, a history of ACEs (namely, physical and sexual abuse) is associated with repeated abortions (Fisher et al., 2005). Associations with sexual abuse were not found, which may be related to the low values (less respondents scoring in this type of abuse) and variability of responses found in the sexual abuse score. These values may occur due to the sample's social characteristics, as mentioned (Hillis et al., 2000), or due to stigmas in reporting sexual abuse.

Individuals who reported self-harm behavior had higher partial (except for sexual abuse) and total ACE scores. This relationship between self-harm behaviors and exposure to ACEs is consistent with the results of other authors who show that individuals exposed to ACEs have a higher risk of suicide attempts (Dube et al., 2003, 2005; Hughes et al., 2017). A cohort study by Dube et al. (2001) confirms that individuals exposed to ACE have an increased risk of suicide throughout their lives. This relationship is partially mediated by alcoholism, depressed mood, and substance abuse. These results suggest that ACEs are related to certain mental health outcomes (such as low self-esteem, emotional dysregulation, or inadequate attachment) that favor the development of depression and suicide attempts (Whiffen et al., 2000; Dube et al., 2001). However, it should be noted that the present study was conducted with a sample of adults who reported their childhood experiences, which, due to the elapsed time and the possible existence of other competing factors, hinders the establishment of a cause-effect relationship.

Results show that individuals who revealed that they had perpetrated or suffered violence in intimate relationships had higher ACE scores (except for sexual abuse in perpetrators) than those who did not commit or experience violence, pointing in the

TABLE 5 | Median, interquartile range, and p-value between the different ACE factors, self-harm behaviors, and perpetuation of violence.

			Emotional abuse	Emotional neglect	Sexual abuse	Physical abuse	Physical neglect	CTQ-SF	
Attempted suicide	NO ($n = 360$, 90.5%)	Med[a] (Q1[b],Q3[c])	6 (5, 8)	8 (6, 10)	5 (5, 5)	5 (5, 6)	6 (5, 8)	31 (28, 37)
	YES ($n = 24$, 6.0%)	Med[a] (Q1[b],Q3[c])	9 (7, 14)	11 (8, 17)	5 (5, 8)	6 (5, 8)	8 (5, 13)	43 (35, 56)
	MANN-WHITNEY	*P*-value	**<0.001**	**0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Self-harm	NO ($n = 308$, 77.4%)	Med[a] (Q1[b],Q3[c])	6 (5, 8)	8 (6, 11)	5 (5, 5)	5 (5, 6)	6 (5, 9)	31 (28, 37)
	YES ($n = 20$, 5.0%)	Med[a] (Q1[b],Q3[c])	8 (7, 13)	11 (7, 17)	5 (5, 9)	7 (5, 8)	9 (5, 12)	41 (35, 56)
	MANN-WHITNEY	*P*-value	**0.001**	**0.029**	**<0.001**	**<0.001**	**0.006**	**<0.001**
Aggression against an intimate partner	NO ($n = 295$, 74.1%)	Med[a] (Q1[b],Q3[c])	6 (5, 8)	8 (6, 11)	5 (5, 5)	5 (5, 6)	5 (5, 9)	31 (28, 36)
	YES ($n = 25$, 6.3%)	Med[a] (Q1[b],Q3[c])	8 (7, 11)	10 (7, 17)	5 (5, 9)	7 (5, 8)	7 (6, 10)	41 (35, 54)
	MANN-WHITNEY	*P*-value	**<0.001**	**0.004**	**0.001**	**<0.001**	**0.002**	**<0.001**
Aggression by an intimate partner	NO ($n = 306$, 76.9%)	Med[a] (Q1[b],Q3[c])	6 (5, 8)	8 (6, 11)	5 (5, 5)	5 (5, 6)	5 (5, 8)	31 (28, 37)
	YES ($n = 15$, 3.8%)	Med[a] (Q1[b],Q3[c])	9 (5, 18)	10 (7, 15)	6 (5, 11)	6 (5, 8)	9 (7, 12)	47 (35, 61)
	MANN-WHITNEY	*P*-value	**0.007**	0.082	**<0.001**	**0.008**	**<0.001**	**<0.001**

[a]*Med–median;* [b]*Q1–first quartile;* [c]*Q3–third quartile. Values in bold indicate statistically significant results ($p < 0.05$).*

same direction as: (a) Heyman and Slep (2002), who found higher probability of experiencing and perpetrating partner abuse in those who had been exposed to adverse childhood experiences related to violence; (b) Anda et al. (2006) who found greater difficulty in anger control, and risk of perpetrating IPV, increased 4.0-,and 5.5-fold, respectively, for individuals with ≥4 ACEs and (3) Hughes et al. (2017), who found higher odds of both violence victimization and perpetration in individuals who had different ACEs.

There are significant associations between all factors except emotional neglect in victims. These results are in line with the systematic review and meta-analysis by Hughes et al. (2017), who argue that exposure to multiple ACEs is a risk factor for violence. It also considers that the outcomes most strongly associated with ACE represent an increased risk of these ACEs being transmitted to the next generation via generational transmission of violence, as it is referred to in the literature (Dodge et al., 1990; Pears and Capaldi, 2001; Heyman and Slep, 2002; Duke et al., 2010; Roberts et al., 2011).

Given these results, we can say that ACEs, as a source of stress, greatly impact the adoption of risk behaviors with harmful long-term consequences for the health of individuals who have experienced them.

Physical and Psychological Health and Correlations With ACE

The most prevalent pathologies in the study sample were metabolic diseases (hypercholesterolemia and diabetes), cardiocerebrovascular diseases (HBP and stroke) and inflammatory diseases (rheumatoid arthritis) (**Table 6**).

The factor *physical neglect* had a statistically significant association with all of the diseases studied (**Table 6**), possibly because this factor is related to older age, as mentioned above (**Table 1**). Conversely, the negative correlation found between the *emotional abuse* factor and age (**Table 6**) may mask possible associations between this factor and certain health problems, as it is known that, as a rule, morbidity is higher at older ages. We did not find other associations, particularly with respiratory diseases and neoplasia; based on the literature, this may be expected due to the size of the sample (Dube et al., 2003; Anda et al., 2008; Holman et al., 2016; Felitti et al., 2019).

We found a hypercholesterolemia prevalence of 27.4%. When compared to a Portuguese population-based study that obtained a high low-density lipoprotein (LDL) cholesterol in of 63.3% (INSA, 2016), it may be hypothesized, since the latter considered not only self-reports (prevalence of 11%) but also biochemical analysis (prevalence of 52.3%). The laboratory confirmation detected hypercholesterolemia in individuals who did not know that they had it or did not report it.

The current study met a prevalence of 23.4% of HBP. Comparing to values previously found for the general Portuguese population aged 25 to 74 years (36%) this is much lower. Similarly to hypercholesterolemia, this discrepancy may be due to the fact that we based our research on self-reports alone, without a medical check. According to Stein et al. (2010), who analyzed the relationship between ACEs and early adult HBP, anxiety

TABLE 6 | Absolute and relative frequency, median, and interquartile range of the scores of the different ACEs factors for each clinical condition and their respective *p*-values (Mann-Whitney test).

	Emotional abuse Med[a] (Q1[b],Q3[c])	Emotional neglect Med[a] (Q1[b],Q3[c])	Sexual abuse Med[a] (Q1[b],Q3[c])	Physical abuse Med[a] (Q1[b],Q3[c])	Physical neglect Med[a] (Q1[b],Q3[c])	CTQ-SF Med[a] (Q1[b],Q3[c])
Cholesterol, *n* = 109 (27.4%)						
Absent	6 (5, 9)	8 (6, 10)	5 (5, 5)	5 (5, 6)	6 (5, 8)	31 (28,36)
Present	7 (5, 9)	9 (6, 12)	5 (5, 5)	5 (5, 6)	7 (5, 9)	34 (29,40)
p-value	0.718	0.157	0.45	0.416	**0.008**	**0.028**
High blood pressure, *n* = 93 (23.4%)						
Absent	6 (5, 9)	8 (6, 11)	5 (5, 5)	5 (5, 6)	5 (5, 8)	32 (28,37)
Present	6 (5, 8)	9 (7, 11)	5 (5, 5)	5 (5, 6)	7 (5, 9)	35 (30,40)
p-value	0.748	0.13	0.678	0.1	**<0.001**	**0.044**
Anxiety disorder, *n* = 73 (18.3%)						
Absent	6 (5, 8)	8 (6, 10)	5 (5, 5)	5 (5, 6)	6 (5, 8)	31 (28,26)
Present	7 (6,10)	9 (7, 14)	5 (5, 6)	5 (5, 7)	7 (5, 9)	35 (30,42)
p-value	**0.002**	**0.002**	**0.013**	**0.003**	**0.039**	**<0.001**
Diabetes, *n* = 61 (15.3%)						
Absent	6 (5, 9)	8 (6, 10)	5 (5, 5)	5 (5, 6)	5 (5, 8)	31 (28,36)
Present	7 (5, 9)	9 (7, 12)	5 (5, 5)	5 (5, 7)	9 (6, 9)	35 (30,42)
p-value	0.928	**0.008**	0.741	**0.014**	**<0.001**	**0.001**
Depression, *n* = 59 (14.6%)						
Absent	6 (5, 9)	8 (6, 10)	5 (5, 5)	5 (5, 6)	6 (5, 8)	31 (28,36)
Present	7 (5, 8)	9 (7, 13)	5 (5, 6)	5 (5, 7)	7 (5, 11)	36 (31,43)
p-value	0.383	**0.003**	0.07	**0.046**	**<0.001**	**<0.001**
Rheumatoid arthritis, *n* = 23 (5.8%)						
Absent	6 (5, 9)	8 (6, 11)	5 (5, 5)	5 (5, 6)	6 (5, 8)	32 (28,38)
Present	8 (5, 9)	9 (8, 14)	5 (5, 6)	6 (5, 6)	9 (7, 11)	35 (33,46)
p-value	0.337	**0.04**	**0.009**	0.09	**<0.001**	**0.017**
Stroke, *n* = 20 (5.0%)						
Absent	6 (5, 9)	8 (6, 11)	5 (5, 5)	5 (5, 6)	6 (5, 8)	32 (28,27)
Present	7 (6, 7)	9 (7, 13)	5 (5, 6)	5 (5, 6)	9 (6, 13)	35 (31,44)
P-value	0.481	0.138	0.301	0.067	**<0.001**	**0.029**
Neoplasia, *n* = 17 (4.3%)						
Absent	6 (5, 8)	8 (6, 11)	5 (5, 5)	5 (5, 6)	6 (5, 8)	32 (28,38)
Present	6 (5, 9)	7 (6, 11)	5 (5, 5)	5 (5, 6)	9 (7, 11)	35 (29,40)
p-value	0.94	0.695	0.134	0.885	**0.01**	0.382

[a]*Med–Median;* [b]*Q1–first quartile;* [c]*Q3–third quartile. Values in bold indicate statistically significant results (p < 0.05).*

disorder and early-onset depression may be mediators of this relationship; moreover, they demonstrated that being exposed to one adverse event does not increase the risk of HBP in adulthood, while exposure to two or more ACEs increases this risk, and the reiteration and duration of events (dose-response effect) are relevant to the development of HBP.

In diabetes, a rate of 15.3% was found, which was higher than that found in the general Portuguese population (9.8%) (INSA, 2016). This rate agrees with the literature that predicts a higher risk of diabetes in individuals with ACEs (Huang et al., 2015; Huffhines et al., 2016).

The same trend was observed for rheumatoid arthritis, the 5.8% prevalence of which in the present study was also higher than that found in the Portuguese population (0.7%) (ReumaCensus, 2015). This finding is in line with the results from other studies, especially concerning women (Rubinstein et al., 2020). There are, however, studies that do not identify this relationship (Carette et al., 2000).

Anxiety disorder had a prevalence of 18.3%, slightly higher than a recent estimation made for the general Portuguese population (16.5%) (CNS, 2019). However, the possibility that current mental health problems influence how adversity experienced in childhood is manifested cannot be excluded (Colman et al., 2016). In this particular case, assessing the possible mediating role of household dysfunction might allow a more thorough approach. For depression, the prevalence was 15.3%, higher than the Portuguese prevalence rate (10%) (CNS, 2019), also suggesting higher rates in individuals reporting ACEs as in other studies (Poole et al., 2017; Von Cheong et al., 2017).

Suicidal attempts are known to be higher among those who report ACEs (Thompson et al., 2019), especially physical abuse

(Fuller-Thomson et al., 2016; Thompson et al., 2019) which is confirmed by the present study.

There are findings supporting smoking-related DNA methylation changes due to toxic stress in early years suggesting greater nicotine consumption and dependence in individuals reporting ACEs (Sugden et al., 2019). In the present study, tobacco consumption was significantly related with reports of physical abuse while tobacco dependence is significantly associated with the global scale of trauma, with a highly significant association with neglect (emotional and physical) and emotional abuse.

Other findings of the current study are to be noted, although not depicted in the tables: (a) depression and anxiety disorder are have positive correlation with smoking dependence, which is aligned with other results (McKenzie et al., 2010). This dependence risk was found to be higher also in individuals who reported suicide attempts or self-harm behaviors, suggesting that it may be important to assess nicotine use in cases of suicide or self-harm related events (Yaworski et al., 2011).

The fact that no relationship was found between ACEs and other negative *outcomes* identified in the literature (Hillis et al., 2000; Dong et al., 2004; Mersky et al., 2013; Chiang et al., 2015; Holman et al., 2016; Felitti et al., 2019) may be related to some of the study's limitations discussed below.

Study Limitations and Future Perspectives

We identified the following limitations in this study: (a) the limited number of cases for a population-based study; (b) the analysis of only five ACE factors, although the literature identifies additional factors of interest such as household ACEs (Felitti et al., 2019), considering that the focus of our study is MT; and, for that reason, experiences related to the death of a close relative, parental divorce, abuse of any family member and domestic violence were not analyzed, which might allow a more refined statistical analysis of findings; (c) specific ACEs such as household ACEs experienced by each participant were not evaluated, which might help understand the enduring effects of ACEs (Chapman et al., 2004; Anda et al., 2006; Hughes et al., 2017; Felitti et al., 2019), also limiting the extent of our interpretations; (d) possible bias related to some missing data (lack of answers), difficulty remembering or identifying certain ACEs (especially when they occurred at very early ages) and subjectivity/individual differences in the valuation of these experiences and the eventual incorrect classification of ACEs. A large number of these biases could be overcome with the use of an other-administered questionnaire, although this could create new biases, particularly those related to feelings of shame and difficulties with disclosure to others (Wojcik et al., 2019); (e) the fact that the sample was limited to the Porto region, and to a population that could afford private healthcare, which does not allow the generalization of the results to the entire country.

However, this study is the first consideration of this subject in the Porto region, and it should be considered a preliminary analysis.

Future studies should consider the limitations mentioned above, including increasing the sample size, analyzing and quantifying all of the identified ACEs, validating the I-CAST and its application to the Portuguese population, and possibly extending the studied geographic region.

CONCLUSION

The results show significant associations between some (or all) ACE factors related to MT and specific adulthood characteristics. In particular, associations were found with health risk behaviors, including: smoking, early onset of sexual activity, STI, having multiple sexual partners in the last year, abortion, suicide attempts, self-harming behavior, victimization, and perpetration abuse in intimate relationships. Moreover, the ACE factors are related to pathologies, namely, hypercholesterolemia, stroke, HBP, diabetes, rheumatoid arthritis, neoplasia, depression, and anxiety disorder.

Physical neglect appears in this study as the ACE type that is most commonly found in individuals with the most prevalent health problems in the Portuguese population. All ACEs related to MT in this study are strongly related to violent experiences in adulthood, particularly violence in intimate relationships and self-directed violence.

Therefore, we identified the need to continue these studies in the various regions in Portugal to understand this phenomenon more broadly, given that it is essential for guiding prevention actions at various levels.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Hospital Centre of São João, Porto Portugal. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TM and MN: conceptualization. MN and TH: methodology. MN, MV-A, and TH: formal analysis and investigation. MN, TM, and MV-A: writing—original draft preparation. TM, MV-A, and TH: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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REVIEW
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Immune and Epigenetic Pathways Linking Childhood Adversity and Health Across the Lifespan

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Childhood adversity is associated with a host of mental and physical health problems across the lifespan. Individuals who have experienced childhood adversity (e.g., child abuse and neglect, family conflict, poor parent/child relationships, low socioeconomic status or extreme poverty) are at a greater risk for morbidity and premature mortality than those not exposed to childhood adversity. Several mechanisms likely contribute to the relationship between childhood adversity and health across the lifespan (e.g., health behaviors, cardiovascular reactivity). In this paper, we review a large body of research within the field of psychoneuroimmunology, demonstrating the relationship between early life stress and alterations of the immune system. We first review the literature demonstrating that childhood adversity is associated with immune dysregulation across different indices, including proinflammatory cytokine production (and its impact on telomere length), illness and infection susceptibility, latent herpesvirus reactivation, and immune response to a tumor. We then summarize the growing literature on how childhood adversity may alter epigenetic processes. Finally, we propose future directions related to this work that have basic and applied implications.

Keywords: childhood adversity, early life stress, immune pathways, epigenetic pathways, inflammation

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INTRODUCTION

There is ample research demonstrating a link between childhood adversity and a host of mental and physical health problems across the lifespan. Childhood adversity refers to experiences of early life stress, including child abuse and neglect, family conflict, poor parent/child relationships, low socioeconomic status or extreme poverty, and other challenges that place undue stress on an individual during their sensitive developmental periods (i.e., during childhood and adolescence when developmental systems are forming). Individuals who have experienced toxic childhood stress (e.g., childhood abuse, neglect, poverty) are at a greater risk for morbidity, and premature mortality than those not exposed to significant adverse childhood experiences (Dong et al., 2004; Anda et al., 2009; Dube et al., 2009; Miller et al., 2011). The health implications of this data are vast. Multiple mechanisms likely contribute to the link between early-life stress and adult health, repeatedly reported in the epidemiological literature (e.g., health behaviors, cardiovascular reactivity). In this paper, we focus on the immune system. We review a large body of research within

the field of psychoneuroimmunology, showing that early life stress is associated with immune system alterations that impact disease risk.

Several models contribute to our understanding of childhood adversity and health. For example, biological embedding models of childhood adversity imply that stressors that occur during sensitive periods of development impact the proper development of immune and other physiological systems and, in turn, make individuals more vulnerable to disease in adulthood (Miller et al., 2011). Mechanistically, childhood adversity affects health, in part, by disrupting the body's ability to regulate itself. Childhood adversity disrupts the development of the body's regulatory system, which can lead to immune dysregulation, particularly when facing a stressor later in life (Gunnar et al., 2001, 2003; Ellis et al., 2005). Furthermore, early life stress promotes increased stress sensitivity across the lifespan, leading to further adverse health outcomes later in life. For instance, people who have experienced early life stress have significantly more emotional reactivity (measured by negative affect) to daily-life stress than people who have not experienced early life stress (Glaser et al., 2006). Greater emotional reactivity to daily-life stressors is associated with an exaggerated inflammatory response in those who reported childhood trauma than those who did not report childhood trauma (Carpenter et al., 2010). Early adversity and increased psychological vulnerability in adulthood can also been seen in those with a history of childhood abuse or low SES as they perceive ambiguous situations as more threatening compared to those without a history of childhood abuse or low SES (Chen and Matthews, 2003; Miller et al., 2011). Those who experienced early adversities may find certain events more stressful than others and show greater vulnerability to immune dysregulation during stressful events in adulthood, supporting the notion that severe chronic stressors have long-term consequences on one's physiology (Miller et al., 2011).

Overview

We first summarize data showing that adverse childhood experiences are associated with immune dysregulation across many indices, including proinflammatory cytokine production (and its impact on telomere length), illness and infection susceptibility, latent herpesvirus reactivation, and immune response to a tumor. We then review the growing literature concerning how early life stress may alter epigenetic processes. Finally, we propose directions for future work that have basic and applied implications.

CHILDHOOD ADVERSITY AND IMMUNE PATHWAYS

Inflammation

Early life stress negatively affects health by elevating levels of inflammation across the lifespan (Miller et al., 2011; Fagundes et al., 2013a; Schwaiger et al., 2016). Under normal conditions, the local inflammatory response helps the body maintain physical health by killing invaders when the immune system identifies a foreign bacteria or virus. However, conditions of chronic stress lead to elevated systemic, chronic inflammation, which is associated with fatigue, disability, and disease including cardiovascular disease, type II diabetes, Alzheimer's disease, osteoporosis, periodontal disease, rheumatoid arthritis, and some cancers (Ershler and Keller, 2000; Libby, 2007; Carpenter et al., 2010; Fioranelli et al., 2018; Agorastos et al., 2019). Higher levels of inflammatory markers such as proinflammatory cytokines [e.g., interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α)], C-reactive protein (CRP), and fibrinogen, reliably predict increased morbidity and mortality and decreased quality of life in older adults (Ershler and Keller, 2000; Mills et al., 2005; Kiecolt-Glaser et al., 2010; Proctor et al., 2015; Puzianowska-Kuźnicka et al., 2016; Li et al., 2017). Thus, the measurement of inflammatory biomarkers is important in understanding the pathways by which early life stress affects physical health.

Early life stress increases the risk of elevated inflammation through many mechanisms, including psychological and physiological hypersensitivity to stress. Hypersensitivity to physiological stress disrupts neurobiological development and alters the brain's autonomic stress response, increasing sympathetic activity and decreasing parasympathetic activity (Heim et al., 2000). This response is consistent with increases in inflammation as norepinephrine promotes the production of proinflammatory cytokines while parasympathetic activity is associated with the cholinergic anti-inflammatory pathway (Bierhaus et al., 2003; Tracey, 2009). In line with this notion, those experiencing childhood maltreatment have been found to have lower parasympathetic activity by measurement of heart-rate variability (Dale et al., 2009; Oosterman et al., 2010). Additionally, children raised in low-SES families showed greater levels of sympathetic activity, as measured by increases in the catecholamine epinephrine (Evans and English, 2002). These autonomic processes have linked early life stress to more pronounced stress-induced HPA axis activity in adulthood, increasing cortisol levels to the point of glucocorticoid insensitivity, which in turn dysregulates the production of proinflammatory cytokines (Heim et al., 2000; Miller et al., 2011).

Early life stress affects the body's response to stress by signaling proinflammatory pathways that promote inflammation (Schwaiger et al., 2016). Early life stress increases the risk of elevated inflammation through several mechanisms. One model regarding early adversity and heightened inflammation states that early life stress triggers monocytes and macrophages to activate an excessive inflammatory response to microbial stimulation (Miller et al., 2011). Early life stress also triggers immune cell insensitivity to the anti-inflammatory effects of cortisol, causing resistance to inhibitory mechanisms of inflammation (Miller et al., 2011). Another mechanism through which early life stress can elevate systemic inflammation is through increased transcription of nuclear factor kappa B cells (NF-κB), an intracellular signaling molecule that regulates proinflammatory-cytokine gene expression (Straub and Härle, 2005). One possible mechanism explaining the increased transcription of NF-κB is through epigenetic processes that favor the production of inflammatory cytokines (Gillespie et al., 2019).

Childhood Socioeconomic Status

There is evidence to show that low socioeconomic status in childhood has an impact on inflammation in adulthood. Lawlor et al. (2005) found that older adults raised in low SES homes in childhood had higher CRP levels than those raised in higher SES homes. Another study showed that adults who grew up in lower SES neighborhoods or whose parents had less education had higher serum levels of CRP and fibrinogen than those who grew up in higher SES neighborhoods or whose parents were more educated (Pollitt et al., 2007). Taylor et al. (2006) also found an association between low childhood SES and elevated CRP levels in adulthood and an association between harsh family environments and elevated CRP levels in adulthood; furthermore, they found that these relationships were mediated by psychosocial functioning and BMI. In another study, Chen et al. (2003) studied how low SES affected adolescents with persistent asthma and found that those in lower SES neighborhoods had higher IL-5 and IFN-γ. Furthermore, several other studies also found associations between low SES in childhood and increased inflammatory markers, such as IL-6, NF-κB, and CRP, in adulthood (Danese et al., 2007; Tabassum et al., 2008; Miller et al., 2009; Phillips et al., 2009). Expanding upon this line of research, Chen et al. (2011) found that in adults who experienced low childhood SES, maternal warmth buffered the association between low childhood SES and pro-inflammatory signaling. Specifically, individuals with low childhood SES who had mothers who expressed high warmth toward them exhibited less IL-6 production and reduced NF-κB activity than individuals with low childhood SES who experienced low maternal warmth. These findings imply that the family environment could have an impact on the relationship between childhood SES and inflammation.

Harsh Family Environments and Adverse Childhood Experiences

Researchers have examined the relationship between the family environment (e.g., whether the individual felt cared for, was shown physical affection, was verbally or physically abused, lived with a substance abuser, lived in a well-managed household) and inflammation. For instance, Miller and Chen (2010) found that adolescents who grew up in harsher family environments showed greater IL-6 production in response to a microbial challenge; they also found that they had increased glucocorticoid resistance over time, which prevented cortisol from inhibiting inflammatory marker production. In another study, Chiang et al. (2017) found that in adolescents, there was a significant interaction between abdominal adiposity, IL-6 reactivity, and early adversity (i.e., frequency of conflict, violence, harsh discipline, affectionate behaviors, neglect, and chaos/disorganization in their family environment), where early adversity was associated with higher IL-6 reactivity only among adolescents with higher abdominal adiposity. Using a composite scoring system that incorporated elements of stressful life events, quality of relationships with parents, and presence of verbal abuse, Slopen et al. (2010) found early life adversity was associated with CRP, IL-6, fibrinogen, E-selectin, and sICAM-1, the soluble form of intracellular adhesion molecule-1 (ICAM-1) which facilitates leukocyte migration into tissues, among African Americans, while early life adversity was not associated with CRP, IL-6, fibrinogen, E-selectin, and sICAM-1 among White Americans.

Researchers have similarly investigated the role of adverse childhood experiences, including child abuse and neglect, parental separation or divorce, and living in a violent household on inflammation (Felitti et al., 1998). For instance, Rasmussen et al. (2020) found that 18-year-olds who had been exposed to more adverse childhood experiences showed higher levels of suPAR (a biomarker of immune activity and chronic inflammation) compared to those with less exposure to adverse childhood experiences. Recent work has also demonstrated a significant association between adverse childhood experiences and CRP in adolescents (Kliewer and Robins, 2021) and an association between childhood victimization and CRP in 18-year-old females, but not males (Baldwin et al., 2018). In another study, Lacey et al. (2020) studied how specific adverse childhood experiences affected inflammation and found that 9-year-olds who had experienced parental separation had statistically elevated IL-6 compared to those who had experienced other types of adverse childhood experiences. Other research examining specific types of adverse childhood experiences includes work examining the impact of childhood maltreatment, defined as physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse (Bernstein et al., 2003; Mauritz et al., 2013). For instance, Carpenter et al. (2010) found that in adults without psychiatric disorders, those who self-reported a history of childhood maltreatment showed higher levels of IL-6 and higher increases of IL-6 in response to a lab social stress test compared to those without a history of childhood maltreatment. Kiecolt-Glaser et al. (2011) studied the interaction between caregiver status and childhood maltreatment in older adults and found that childhood maltreatment was independently associated with increased IL-6 and TNF-α levels; however, there was an interaction between caregiver status, childhood maltreatment, and inflammation where the association between childhood maltreatment and TNF-α was augmented in caregivers. In Baumeister et al. (2016) conducted a meta-analysis that showed a relationship between childhood maltreatment and inflammation markers such as IL-6, TNF-α, and CRP. Recently, Ehrlich et al. (2021) found an association between maltreatment and inflammation in 8–12-year-old girls, but there was no association present in boys. In another study, Entringer et al. (2020) reported similar findings; among 3–5-year-olds who were studied prospectively immediately after experiencing maltreatment, they found an association between maltreatment and CRP only in girls but not boys. Most recently, Renna et al. (2021) assessed the relationship between childhood abuse and inflammation trajectories over time and found that those who had experienced abuse in childhood exhibited steeper rises in inflammation across time than those who did not experience any type of abuse.

Early Life Stress, Inflammation, and Depression

Early life stress can contribute to a proinflammatory phenotype evident in a subset of individuals with depression. For example, Danese et al. (2008) found that adults with a current diagnosis of major depression and a history of childhood maltreatment

were 1.48 times more likely to exhibit elevated CRP levels than depressed patients with no history of maltreatment. In another study, MDD patients with a history of childhood adversity, but not MDD patients without childhood adversity, had higher levels of IL-6 compared to healthy controls (De Punder et al., 2018). Furthermore, Pace et al. (2006) showed that individuals with current major depression and increased early life stress exhibited elevated baseline levels of inflammation coupled with a larger inflammatory response to an experimental stressor compared to healthy controls, suggesting a history of major depression and childhood adversity can sensitize the inflammatory response to psychological stressors. Finally, in a longitudinal study among female adolescents, developing a recent major depressive episode (i.e., over the past 6 months) in those with higher levels of childhood adversity was associated with larger increases in CRP and IL-6 levels compared to when participants were euthymic (Miller and Cole, 2012). Importantly, elevated CRP levels in these individuals persisted 6 months later in the absence of depressive episodes. In this context, Danese et al. (2011) raised an important question of when the effect of exposure to childhood adversity on inflammation emerges. To answer this question, Danese et al. (2011) studied a sample of children at age 12 and found that children with depression who had a history of physical maltreatment exhibited elevated levels of CRP compared to control children (i.e., no depression at age 12 and no history of physical maltreatment). This difference was not evident in depressed-only or maltreated-only children. The findings from this study suggest that the effect of childhood adversity on inflammation among individuals with depression can emerge during the childhood years.

In general, these findings are in line with the concept of neuro-inflammatory sensitization, which links stress, inflammation, and depression (Slavich and Irwin, 2014). The notion of neuro-inflammatory sensitization posits that exposure to early life stress can potentiate the stress response *via* the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis, such that the threshold or magnitude of psychological distress evoking inflammation may be lowered over time (Slavich and Irwin, 2014). Inflammation, in turn, can signal the central nervous system and promote depressive symptoms *via* behavioral and neurobiological alterations. One of these neurobiological alterations include the breakdown of the blood-brain barrier, which filters the connection between the brain and the body. This alteration results from increased levels of intracellular adhesion molecule-1 (ICAM-1), which sits in the endothelium of blood vessels and facilitates the recruitment and entrance of leukocytes into tissues, such as the brain. ICAM-1 can be released from the endothelium as soluble intracellular adhesion molecule-1 (sICAM-1), which then circulates in the blood, which can act as a biomarker for neural-inflammation. Indeed, higher sICAM-1 levels in the blood are associated with the clinical severity of depressive symptoms (Müller, 2019). As a result, the neural-inflammatory pathway may become more robust in depressed individuals with early life stress, such that less stress is required to promote inflammation and inflammation could persist in the absence of actual or perceived stressor (Miller and Cole, 2012; Slavich and Irwin, 2014).

Susceptibility to Infectious Disease and Response to Vaccines

Several studies have indicated the role of childhood adversity on the immune system's susceptibility to infection and illness. For instance, Wyman et al. (2007) found that more parental psychiatric symptoms occurring with family stressors were associated with a greater frequency of illnesses in children. Furthermore, greater chronic stress in parents was associated with children's enhanced natural killer cell function, which functions to recognize cells in the body that have become compromised (i.e., through infection of a virus or conversion to a tumor cell) and kill them to eliminate the threat against the body (Wyman et al., 2007). Caserta et al. (2008) expanded on these findings and similarly found that among children ages 5–10, parental psychiatric symptoms were associated with a higher frequency and rate of illnesses and enhanced natural killer cell function. Clover et al. (1989) found that individuals who perceived their families as dysfunctional had greater rates of influenza B infection than individuals who perceived their families as balanced (as measured by adaptability and cohesion). In another study, Boyce et al. (1995) found that stress was associated with higher respiratory illness rates among children who reported high levels of reactivity to a laboratory or naturalistic stressor, while children with lower levels of reactivity did not exhibit a relationship between stress and illness rates. Wright et al. (2002) examined a potential mechanism between parental stress and respiratory illness and found that higher parental stress prospectively predicted wheezing among infants. Specifically, they hypothesized that parental stress could cause wheezing in infants by impacting the immune system. However, they found that parental stress predicted infant wheezing even after controlling for potential mediators such as maternal smoking, allergen exposure, and increased susceptibility to lower respiratory infections.

Low socioeconomic status during childhood and adolescence has also been associated with greater susceptibility to infectious diseases, such as the common cold in adulthood (Cohen et al., 2004, 2013; Miller et al., 2009; Ziol-Guest et al., 2012). Cohen et al. (2004, 2013) found that childhood socioeconomic status, measured by the number of years during childhood that an individual's parents owned their homes, was inversely related to an individual's cold susceptibility in adulthood. However, recent work has shown that high relationship quality with one's parents, measured by parental care, love and support, lack of conflict with parents, and family cohesiveness, buffered the relationship between low childhood socioeconomic status and susceptibility to the common cold (Cohen et al., 2020).

Stress and other psychosocial factors can blunt the body's response to vaccines (Madison et al., 2021), yet few studies have explicitly looked at the role of early life stress on vaccine responses. One review by Hayward et al. (2020) postulated that early life stress could modify vaccine response through its effect on mental health. Additionally, O'Connor et al. (2015) showed that negative and hostile interactions observed in a laboratory task between a parent and child predicted a weaker response to the meningococcal vaccine up to 6 months later. During the COVID-19 pandemic, the interaction between early life stress

and vaccination immune response will be an important future direction to pursue.

Latent Herpesvirus Reactivation

Research has also demonstrated an important relationship between childhood adversity and partial latent virus reactivation, and more broadly, the role of early life stress and cellular immune function. Herpes simplex virus (HSV), Epstein–Barr virus (EBV), and cytomegalovirus (CMV) are prevalent herpesviruses that can enter a latent state after infection and then reactivate when the immune system is dysregulated. In other words, after individuals are infected with one of these viruses, the virus remains latent in their body, but if their cellular immune response is compromised, for instance, due to stress, the virus can be reactivated, as reflected by increased antibody titers to the virus (Glaser et al., 1991; Stowe et al., 2010). Thus, early life stress can promote vulnerability to herpesvirus reactivation, reflecting poorer cellular immune system control over the latent virus (Stowe et al., 2010).

Several studies have implicated the relationship between early childhood stress and herpes virus reactivation. Shirtcliff et al. (2009) examined two different types of adverse childhood experiences, institutionalization, and physical abuse, and found higher antibody titers to herpes simplex type-1 (HSV-1) among both adolescents who had been institutionalized and adolescents who had been abused compared to control participants, highlighting a worse cellular immune response over the latent virus among individuals who had experienced an adverse childhood experience. Furthermore, McDade et al. (2000) found that adolescent girls who had experienced trauma had higher EBV antibody titers than girls who had not experienced trauma. Another study showed that individuals who experienced separation from their parents followed by adoption had higher CMV titers than control participants who were not adopted (Elwenspoek et al., 2017). Similarly, among prior EBV-infected adolescents, those who moved into a new parent/caregiver household in early childhood displayed an estimated 100% increase in EBV DNA shedding (Schmeer et al., 2019). In another study, parental psychiatric symptoms were associated with increased CMV-specific T cell activity among CMV seropositive children (Caserta et al., 2008).

Researchers have also examined the role of childhood socioeconomic status and herpesvirus latent reactivation. For instance, living in poverty was associated with elevated CMV antibody titers among children and adolescents ages 11–16 (Dowd et al., 2012). Furthermore, Slopen et al. (2013) examined both the role of childhood socioeconomic status and abuse and found that among adolescents, lower parental occupational status and some categories of lower education were associated with higher levels of EBV antibody titers and that adolescents who had experienced sexual abuse more than ten times had more EBV antibody titers compared to adolescents who had not reported sexual abuse. Furthermore, among individuals who had experienced physical abuse, those who initially experienced physical abuse at ages 3–5 had higher EBV antibodies than those who experienced physical abuse during adolescence (Slopen et al., 2013).

Other studies have examined the relationship between childhood adversity and latent herpesvirus reactivation among adults, demonstrating the role of early experiences on cellular immune responses to the latent virus across the lifespan. For instance, Janicki-Deverts et al. (2014) found that poorer childhood environments, reflected by childhood socioeconomic status, the physical environment, and family relationships, were associated with greater odds of infection with CMV and higher CMV antibody levels among CMV positive participants. Specifically, fewer years of parental homeownership, having a parent who smoked and living in a poorly maintained or unsafe neighborhood were independently associated with greater odds of infection with CMV. Furthermore, among CMV-positive participants, less family warmth, less harmony, more significant dysfunction, and poorer parental bonding were independently associated with higher CMV antibody levels (Janicki-Deverts et al., 2014). In another study, Fagundes et al., 2013b found that experiences of childhood adversities were associated with higher EBV and CMV titers among breast cancer survivors.

Tumor Environment

In addition to increasing susceptibility to illness, infection, and viruses, early life stress can also affect the immune response to some tumor types. Certain cancers, such as basal cell carcinoma (the most common form of skin cancer), are classified as immunogenic, as the immune system plays an important role in the progression of the tumors (Fagundes et al., 2012). Research on basal cell carcinoma patients who had experienced a severe life stressor in the past year showed that patients who had experienced emotional childhood maltreatment by their mothers or fathers were more likely to have a poorer immune response to the basal cell carcinoma tumor, as reflected by lower levels of messenger RNA (mRNA) coding for immune markers associated with basal cell carcinoma tumor progression and regression, i.e., CD25 (a component of the interleukin (IL)-2 receptor on lymphocytes), CD3ε (a component of the T-cell receptor), ICAM-1 (a cell membrane glycoprotein expressed in both endothelial cells and leukocytes), and CD68 (a cell membrane glycoprotein found in monocytes and macrophages) (Fagundes et al., 2012). However, these findings did not hold among individuals who had not experienced a severe life stressor in the last year, implicating that early adversity may particularly impact those who have recently experienced severe stress, potentially due to a hypersensitivity to stress among individuals who have faced early adversity.

There is work highlighting the relationship between childhood adversity and inflammation among breast cancer survivors. Although the clinical relevance of findings such as this is ambiguous, elevated inflammation is associated with breast cancer recurrence and post-treatment cancer-related fatigue (Bower, 2007; Tabassum and Polyak, 2015; Fagundes et al., 2017). Childhood adversity, measured by abuse, neglect, and a chaotic home environment, was associated with inflammatory markers

among breast cancer survivors, with a positive association between maltreatment and IL-6, chaotic home environment and IL-6, and a chaotic home environment and soluble TNF receptor type II (sTNF-RII; Crosswell et al., 2014). Furthermore, Janusek et al. (2013) found that experiences of childhood emotional abuse/neglect among women with breast cancer were associated with more significant behavioral symptoms and greater immune dysregulation, as measured by elevated IL-6 over time. Although findings such as these are intriguing, future work is needed to determine if they are clinically relevant.

Telomere Shortening

There has been mounting interest in examining the role between childhood adversity and telomere length. Telomeres, or the protective cap at the tips of chromosomes play an important role in facilitating cell aging. Chromosomes are structures made up of linear double-stranded DNA, containing genetic information that programs cells with the necessary characteristics for their specific functions. In humans, due to the mechanism of replication of DNA in chromosomes, the cell cannot copy the entirety of the chromosome. With each replication, the cell loses more and more genetic data, which can be fatal for the cell over time. To compensate for the innate loss of genetic data in replication, chromosomes have telomeres on their ends, which are made up of repeating segments of DNA that will not affect the cell if they are lost with each replication cycle. However, eventually, telomeres will shorten over time, which can indicate the cell's life span (see Calado and Young, 2009 for more background on telomeres). Shorter telomeres are associated with greater risk for earlier mortality (Epel et al., 2004; Mons et al., 2017; Wang et al., 2018) and psychiatric diseases, including depression (Lindqvist et al., 2015). Mechanistically, elevated inflammation can activate T-cell proliferation, leading to the shortening of telomeres (Aviv, 2004; Kiecolt-Glaser and Glaser, 2010). Importantly, a meta-analysis found a significant association between the level of childhood psychosocial stressors and telomere length across 27 samples, including 16,238 participants (Hanssen et al., 2017).

Tyrka et al. (2010) first examined the relationship between early-life stress and shortened telomeres among young adults, such that those who were maltreated as children had shorter telomeres in cells than those who reported no maltreatment. Kananen et al. (2010) further confirmed an association between childhood adversity and shorter telomere length, such that adults who reported more childhood adverse life events had shorter telomeres than those who reported fewer childhood adversities. However, there was no evidence that current psychological distress impacted telomere length. Recent studies and meta-analyses have continued to demonstrate the relationship between childhood adversity and telomere shortening (Tyrka et al., 2016; Ridout et al., 2018; Bürgin et al., 2019). Furthermore, this relationship between childhood adversity and telomere length existed among individuals with anxiety disorders and controls. O'Donovan et al. (2011) found that exposure to childhood trauma was associated with shorter leukocyte telomere length and that experiences of childhood trauma accounted for differences in leukocyte telomere length between individuals with PTSD and controls. Another study examined individuals at baseline (between 6 and 30 months old) and at a 54-month follow up and found that among individuals who had been institutionalized (e.g., in foster care) as young children, those who had been institutionalized for a greater length of time had significantly shorter telomeres than those who were institutionalized for less time (Drury et al., 2012). Drury et al. (2014) found that children with higher exposure to family violence and disruption had significantly shorter telomere length. Longitudinally, Shalev et al. (2013) found that children exposed to more than two forms of violence had shorter telomeres than children who were unexposed or less exposed to violence. Together, Drury et al. (2012, 2014) and Shalev et al. (2013) suggested that the relationship between early adversity and telomere shortening may also depend on the extent to which an individual faces adversity.

Researchers have also demonstrated that the relationship between early adversity and telomere length in older adults (Osler et al., 2016; Puterman et al., 2016). Ämmälä et al. (2021) recently found that adults with three or more childhood adversities had shorter leukocyte telomere length than individuals with 0, 1, or 2 childhood adversities; this effect remained significant after adjusting for known leukocyte telomere length-associated lifestyle and sociodemographic factors. Similarly, Surtees et al. (2011) found that among women ages 41–80, greater exposure to adverse childhood experiences was correlated with shorter telomeres, while current social adversity or emotional health did not have a relationship with telomere length. Furthermore, in a study of older adult family dementia caregivers and non-caregivers, those who experienced childhood adversity had shorter telomeres than those who were not abused, which potentially translates into a 7–15-year difference in lifespan (Kiecolt-Glaser et al., 2011).

Other studies have examined the role of childhood socioeconomic status and telomere length across the lifespan. For instance, among newborns, boys whose parents had a higher socioeconomic status had a longer cord blood telomere length and placental telomere length (Martens et al., 2020). In another study, Needham et al. (2012) measured childhood socioeconomic status by assessing parental education and found that children ages 7–13 with at least one parent who had completed college had longer telomeres than children whose parents did not attend college; this difference was roughly equivalent to 6 years of aging. In a similar study examining a sample of African American participants, Khan et al. (2021) found that participants whose mothers had more education had longer average telomere length. This study also found that 19% of this effect was mediated through the participant's education level. The relationship between childhood socioeconomic status and telomere length has also been examined among adults. Cohen et al. (2013) found that lower childhood SES, measured by fewer years of parental homeownership, was associated with shorter CD8+CD28- telomere length in adulthood. Thus, research has indicated that childhood socioeconomic status plays a role on telomere length across the lifespan.

CHILDHOOD ADVERSITY AND EPIGENETIC PATHWAYS

Researchers have aimed to understand how epigenetic mechanisms modulate the long-lasting adverse health effects of early adversity for the last decade. The stress associated with early adversity disrupts the regulation of fundamental biological systems during sensitive periods of development, which puts people at risk for a wide range of health problems (Miller et al., 2011). Further, the reprogramming of stress-sensitive gene pathways sensitizes the developing brain to the effects of early stress exposure throughout the lifespan (Bondar and Merkulova, 2016). Environmental programming of life-long phenotypes begins very early in life (Vaiserman, 2015); thus, epigenetic alterations may embed adverse early life experiences in the genome.

Epigenetics is the study of phenomena and mechanisms that cause chromosome-bound, heritable changes to gene expression, independent of DNA sequence changes (Deans and Maggert, 2015). These "phenomena" refer to behavioral and environmental impacts on gene functioning. Human development is controlled by epigenetic mechanisms, which help differentiate and record environmental information and shape cellular and physiological functions across the lifespan, with particularly pronounced effects during fetal development that decrease as age increases. One such mechanism is DNA methylation, or the addition of a methyl group to DNA that typically impairs the expression of a gene (Jones and Takai, 2001; McGowan et al., 2009; Crews, 2010). Higher DNA methylation levels are typically associated with lower rates of gene transcription and, therefore, functioning (Allis and Jenuwein, 2016). These modifications in DNA may underlie the associations between early life stress and physical health problems (McGowan et al., 2009; Crews, 2010).

Substantial evidence derived from research with animal models suggest that environmental programming of life-long phenotypes begins very early in life (e.g., maternal diet; Waterland and Jirtle, 2003). For instance, in animal models, maternal behavior can alter gene expression *via* DNA methylation changes in the offspring. For example, maternal care in rats can affect hippocampal glucocorticoid receptor expression and subsequent HPA function for the offspring (Weaver et al., 2004). Additionally, the maternal effect on glucocorticoid receptor expression and HPA response to stress was mediated by changes in chromatin structure (Weaver et al., 2004). Thus, both changes in methylation and chromatin structure are implicated.

Studies investigating epigenetic markers across the entire human genome, indicating that epigenetic impacts are both long-lasting and transgenerational. For example, Appleton et al. (2013) found that infants whose mothers experienced the greatest levels of socioeconomic adversity during pregnancy had the lowest extent of methylation of the placental 11b-HSD2 gene, indicating lower gene functioning. During prenatal development (pregnancy), environmental cues transmitted from mother to fetus may program an epigenetic response to the infant's post-natal environment through less cortisol exposure (O'Donnell et al., 2012). Further, experiences of maternal depression and anxiety were associated with poor newborn neurobehavior. Poor neurodevelopmental outcomes are associated with increased methylation of placental genes [i.e., NR3C1 and 11bhydroxysteroid dehydrogenase type 2 (11b-HSD-2)] involved in HPA axis functioning (Conradt et al., 2013). In this way, exposure to environmental stress *in utero* may program an infant's neurological functioning.

Far beyond fetal development, epigenetics plays an important role in determining the long-term impact of early life adversity. For example, epigenetic and environmental mechanisms are linked to the etiology and pathology of depression and serious negative mental health consequences, such as suicide (for a review, see Lin and Tsai, 2019). For instance, adolescents raised in lower SES environments as children had higher Toll-like receptor 4 (TLR4) mRNA levels than their higher SES counterparts, indicating that early adversity may alter the genes linked to adult immune dysregulation (Miller and Chen, 2007). In a post-mortem sample of people who had died by suicide, McGowan et al. (2009) examined differences in epigenetic regulation of hippocampal glucocorticoid receptor expression by comparing the brains of those with a child abuse history, those with no child abuse history, and those who were victims of sudden, accidental death with no history of abuse (controls). The researchers found decreased hippocampal NR3C1 gene expression in those who died by suicide and had a history of childhood abuse, compared to accidental death victims with no history of abuse. Furthermore, there were no differences in gene expression between suicide victims and accidental death victims *without* a history of childhood abuse, suggesting that changes in glucocorticoid receptor expression may be more closely associated with a history of childhood abuse than with suicide completion. McGowan et al. (2009) cautiously speculate that epigenetic processes might mediate the effects of a stressful early-life environment on hippocampal gene expression. DNA methylation, a stable epigenetic marker, could persist into adulthood and make people vulnerable for psychopathology, potentially *via* HPA activity (McGowan et al., 2009). While more research is still needed, these findings may have important clinical implications. For instance, Bower et al. (2020) utilized genome-wide transcriptional profiling of isolated monocytes and found greater NF-κB-binding motifs within the promoters of up-regulated vs. down-regulated genes in women with breast cancer who experienced childhood maltreatment, compared to women with breast cancer who did not experience childhood maltreatment. These findings held when controlling for depression and indicated greater inflammatory signaling among women with breast cancer who had experienced childhood maltreatment.

Epigenetic regulation may also mediate the relationship between broader environmental influences in early life than just those that tend to occur inside the home (e.g., childhood abuse, parental attentiveness). Recently, Reuben et al. (2020) provided evidence from a large longitudinal cohort study that neighborhood disadvantage is associated with DNA methylation differences in genes involved in inflammation. Continued research on the epigenetic influence of broader early life environments could provide vital information to inform

neighborhood-level policy interventions, impacting long-term health among those raised in disadvantaged neighborhoods.

The study of early life adversity and epigenetics is a growing field (Krause et al., 2020). One of the many major challenges of future investigation will be to uncover how specific factors interact with epigenetic mechanisms to promote susceptibility or resilience to the negative effects of early life adversity. For example, individual differences in sex, genetic background, age, and stressor type, timing, and duration may influence the extent to which early life adversity impacts the genome and behavioral outcomes. Furthermore, most studies studied DNA methylation, which is but one specific epigenetic mechanism. Epigenetic mechanisms other than DNA methylation may also contribute to the regulation of stress pathways. Future research should elucidate how different adverse childhood experiences result in epigenetic markers, and whether certain treatments may reverse these markers. For a complete review of epigenetics and early life adversity, see Burns et al. (2018).

DISCUSSION

In sum, childhood adversity, ranging from child abuse and neglect to poor parent/child relationships, to low socioeconomic status, can negatively impact immune and epigenetic pathways across the lifespan. There are several mechanisms and pathways in which immune and epigenetic dysregulation can emerge, including increased inflammation, susceptibility to illness, latent herpesvirus reactivation, shortened telomeres, DNA methylation, and histone modification. Importantly, these immune and epigenetic dysregulation as a result of childhood adversity can have severe clinical implications including poorer mental health, including increased risk of depression, as well as poorer physical health, including increased risk for cardiovascular, type II diabetes, and cancer in adulthood (Heim et al., 2008; Miller et al., 2011).

Future research should expand upon the work examining early life stress and health outcomes to identify racial disparities that underlie this relationship. It is important to note that early life adversity, including experiences of childhood maltreatment, exposure to crime, and other forms of external stressors, disproportionately affect racial/ethnic minorities (Suglia et al., 2020). For instance, African American and Hispanic youth have exhibited an increased risk of low-grade inflammation compared to White youth (Schmeer and Tarrence, 2018). Additionally, Ford and Stowe (2013) found that Black/African American youth had significantly higher EBV antibody levels than White youth. These disparities are increasingly understood as related to the chronic stress experienced by racial/ethnic minorities (Suglia et al., 2020). Future work should continue to examine how racial disparities can underlie the relationship between early adversity and poor health outcomes throughout the lifespan.

The contribution of early-life food insecurity to health across the lifespan is an important area for future research. Food insecurity generally may promote inflammation in several ways: (1) by promoting central adiposity (Salinas et al., 2016), (2) through psychosocial stress (Bermúdez-Millán et al., 2016), and (3) from a diet that directly promotes inflammation (Bergmans et al., 2018). Salinas et al. (2016) found that food insecurity, especially when food insecurity was assessed through a question focused on not having money to buy balanced meals, was associated with waist circumference for 554 Mexican-American women, which indicates that food insecurity promotes central adiposity. In a sample of 121 low-income Latino adults with type 2 diabetes mellitus, Bermúdez-Millán et al. (2016) identified that food insecurity was associated with suboptimal sleep quality and that this effect was mediated by several measures of psychological distress (i.e., depressive symptoms, anxiety symptoms, and diabetes distress); thus, food insecurity can be a significant source of distress and this distress is associated with worse sleep. In a sample of nearly 11,000 lower-income adults in the United States, Bergmans et al. (2018) identified that higher levels of food insecurity were associated with a higher Dietary Inflammatory Index (i.e., a diet that potential induces inflammatory pathways).

Despite the strong evidence of the relation between food insecurity and adult health, there is less research that examines the consequences of food insecurity in childhood on health across the lifespan. In addition to the previously addressed pathways from food insecurity to inflammation, early-life food insecurity may also affect neurodevelopment in a manner that has proven difficult to disentangle from poverty generally (Rosales et al., 2009; Johnson et al., 2016). However, in a study of approximately 11,500 children under 36 months of age, those who were food insecure were nearly 3× as likely to have been hospitalized since birth (Cook et al., 2004). Importantly, food stamps attenuated the relationship between increased food insecurity and caregiver reports of worse child health (Cook et al., 2004), which emphasizes both the importance and feasibility of using policy to reduce the impact of food insecurity on child health.

Given the ample research on immune and epigenetic pathways linking childhood adversity to health outcomes across the lifespan, future directions in this field should seek to develop, test, and implement interventions for those who have experienced early life stress. To develop interventions targeting the impact of early life stress and immune and epigenetic dysregulation, understanding the implications of attachment theory on these pathways can help develop targeted interventions with a theoretical basis. Attachment theory suggests that an individual's troubled relationships with their parents can lead to a developed sense of emotional insecurity that has lasting consequences on how an individual copes with relational stress and navigates close relationships across the lifespan (Thompson, 2008; Mikulincer and Shaver, 2009). An individual's attachment orientation can serve as an indirect pathway to adverse health outcomes following early-life adversity (Maunder et al., 2017; Widom et al., 2018). For example, in a sample of hospital workers and paramedics, researchers found a significant indirect effect of early life adversity on physical symptoms through attachment anxiety, a type of attachment insecurity (Maunder et al., 2017). Thus, individuals who experience childhood adversity, such as child abuse or neglect, may develop insecure attachment, contributing to poor health outcomes across the lifespan. Furthermore, there has been work examining the relationship between attachment insecurity

and immune dysregulation, including increased inflammation (Ehrlich et al., 2019; Gouin and MacNeil, 2019), shortened telomere length (Murdock et al., 2018a,b), and latent herpesvirus reactivation (Fagundes et al., 2014). For example, Fagundes et al. (2014) found that individuals with higher attachment anxiety also had higher EBV VCA IgG antibody titers than those with less attachment anxiety.

Indeed, individuals who are insecurely attached are more physiologically sensitive to stress (reflected by greater cortisol increases in response to stress) than those with secure attachment (Diamond, 2001; Laurent and Powers, 2007; Diamond et al., 2008; Rifkin-Graboi, 2008; Diamond and Fagundes, 2010; Fagundes et al., 2011). Increased cortisol in response to stress is in accord with research linking poor early parental experience and more pronounced stress-induced glucocorticoid production (Heim et al., 2000, 2008; Sanchez, 2006). Importantly, increased cortisol sustained over time can lead to glucocorticoid insensitivity, which can, in turn, increase inflammation *via* the production of proinflammatory cytokines (Miller et al., 2002). Accordingly, the relationship between childhood adversity (e.g., child abuse and neglect, poor parent-child relationships, and family conflict) and inflammation may also be related to the association between attachment style and inflammation.

Based on findings that arose using animal models of maternal care in rats, there has been an experimental shift in human attachment research to focus on gene-by-environment interaction by epigenetic mechanisms (Champagne, 2008; Ein-Dor et al., 2018). Over many decades of attachment research, researchers documented a "transmission gap" of "maternal responsiveness" that can partly explain the intergenerational transmission of attachment (Van Ijzendoorn and Bakermans-Kranenburg, 1997). For example, epigenetic modification of the oxytocin and glucocorticoid receptor genes is linked to attachment avoidance in young adults (Ein-Dor et al., 2018). Indeed, studies show a direct link between attachment and DNA methylation (Van Ijzendoorn et al., 2010; Mulder et al., 2017; Bosmans et al., 2018). For instance, more stressed children with less maternal support report more significant attachment anxiety when their NR3C1 gene is highly methylated (Bosmans et al., 2018). Given the role that attachment insecurity can have on immune and epigenetic pathways (Maunder et al., 2017; Widom et al., 2018), understanding the implications of attachment theory on immune and epigenetic pathways can be useful in understanding the broader relationship of childhood adversity and health across the lifespan.

While there have been intervention programs targeting the impact of childhood adversity broadly, including programs for foster care parents and general therapies for parents and children (Shonkoff, 2016; Turner et al., 2016; Boparai et al., 2018), it is worth noting the utility of interventions that can address the impacts of childhood adversity across the lifespan. Furthermore, when developing interventions, it is efficacious to utilize a known theoretical framework to best target and operationalize specific points of intervention. Targeted interventions using attachment theory are especially effective in both adolescents facing adversity (e.g., incarceration; Keiley, 2002) and can continue to be useful even among adults (Bifulco and Thomas, 2012). Importantly, attachment theory has also been utilized among individuals who have experienced trauma (Muller, 2009), further providing evidence on the utility of using attachment theory as a framework that can be used to develop targeted interventions to those who have experienced childhood adversity, including child abuse and neglect, family conflict, and poor parent/child relationships. The field has come a long way in demonstrating the relationship between childhood adversity and health and immune and epigenetic pathways across the lifespan that contribute to this relationship. Thus, future directions in the field of childhood adversity and health should focus on developing targeted interventions for individuals across the lifespan that can mitigate adverse health outcomes in young children and older populations who continue to be impacted by the long shadow of childhood adversity.

AUTHOR CONTRIBUTIONS

MC wrote the introduction and discussion section and reviewed the majority of the childhood adversity and immune section. AL wrote the epigenetic pathways section. MM wrote the Early Life Stress, Inflammation, and Depression section. JC contributed to the writing of the inflammation section and telomere section. RB contributed to the conceptualization of early-life stress related to attachment theory/parental experiences and racial disparities. LC contributed to the vaccine portion of the manuscript and the overall conceptualization of the manuscript. CF contributed to the writing of all sections, giving thorough feedback at each level and playing a heavy role in the conceptualization of the manuscript and writing portions of each section. All authors have read and approved the final manuscript and contributed to the writing of this review.

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Serial Mediation Roles of Perceived Stress and Depressive Symptoms in the Association Between Sleep Quality and Life Satisfaction Among Middle-Aged American Adults

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In this study, we used data from the second wave of Midlife in the United States (MIDUS) Study, MIDUS Biomarkers and MIDUS 3. We applied the serial mediation model to explore the serial mediating effects of perceived stress and depressive symptoms on the relationship between sleep quality and life satisfaction. A total of 945 participants were included in our study. The total indirect effect of sleep quality on life satisfaction through perceived stress, depressive symptoms and the combination of perceived stress and depressive symptoms accounted for within the overall model was 45.5%. At the intervention level, programs designed to improve the level of life satisfaction among adults should focus on perceived stress and depressive symptoms. The prevention of perceived stress and depression contributes to improving life satisfaction and wellbeing. The serial mediation results should be confirmed by further longitudinal study.

Keywords: sleep quality, perceived stress, depressive symptom, life satisfaction, serial mediation

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INTRODUCTION

Sleep is an important component of every individual's overall health and wellbeing. Sleep quality is a critical indicator that measures how well people sleep. Studies from different countries around the world showed that the prevalence of sleep problems, including insomnia, sleep apnea, restless legs syndrome, and narcolepsy, ranges from 5 to 56% (Ohayon, 2011; Stickley et al., 2019). Life satisfaction is defined as cognitive assessment of subjective wellbeing. Previous studies demonstrated that good sleep quality predicted higher life satisfaction (Kim and Ko, 2018; Shin and Kim, 2018). According to a nationwide cohort study in Finland, poor sleep quality was associated with a higher risk of life dissatisfaction, compared with good sleep quality [odds ratio (OR) = 2.1, 95% confidence interval (CI): 1.7–2.7] (Paunio et al., 2008). Lemola et al. using MIDUS study also reported that subjective sleep quality is related to lower subjective wellbeing among middle-aged American adults (Lemola et al., 2013). In addition, previous studies demonstrated that perceived stress and depression were related to sleep problems and life dissatisfaction (Friedman, 2016; Seo et al., 2018). A study among 307 urban African American adults suggested that anxiety and depression are independently linked to life satisfaction (Dunne et al., 2018). A prospective cohort

study with 351 community-dwelling older American adults revealed that sleep disturbance acts as an independent risk factor for depression recurrence (Cho et al., 2008). A community longitudinal study of 3,636 young and middle-aged Australian adults demonstrated that self-reported sleep disturbance was significantly associated with an onset of major depressive disorder ($p = 0.006$; Batterham et al., 2012). A longitudinal study with 302 midlife women from the Study of Women's Health Across the Nation revealed that poorer sleep health is associated with higher depressive symptoms ($p < 0.001$; Bowman et al., 2021). A review conducted by Smagula et al. demonstrated that perceived stress is a major risk factor of sleep disturbance among American older adults (Smagula et al., 2016).

Overall, there is existing evidence establishing a link between sleep and life satisfaction, while depression and perceived stress are associated with a higher risk of poor sleep quality and life dissatisfaction (Glei et al., 2013; Chirinos et al., 2017). Although the associations among sleep quality, life satisfaction, depressive symptoms and perceived stress were shown in previous studies, it is still unclear how these psychosocial factors, like depressive symptoms and perceived stress, mediate the pathway through which sleep quality impacts on life satisfaction. Thus, our study used a serial mediation model to explore the serial multiple mediation effects of perceived stress and depressive symptoms on the association.

The present study examined the potential mediating effects of perceived stress and depressive symptoms on the association between sleep quality and life satisfaction. We hypothesized that poor sleep quality, perceived stress and depressive symptoms would be associated with a lower level of life satisfaction. A serial mediation model hypothesizes a causal chain linking of the mediators (perceived stress and depressive symptoms) with a specified direction flow (sleep quality → perceived stress → depressive symptoms → life satisfaction).

MATERIALS AND METHODS

Study Data and Participants

This study used data from the Midlife in the United States (MIDUS) Study which is the first national survey of midlife development. The aims of MIDUS are to investigate the role of behavioral, psychological, and social factors in accounting for age-related variations in health and wellbeing in a national sample of Americans (National Institue on Aging., 2020). As was previously reported (Dienberg Love et al., 2010; Chen et al., 2012), participants in MIDUS 2 were at age 35–84 in 2004–2006 (MIDUS 2, $n = 4{,}963$), and at age 43–94 in 2013–2014 (MIDUS 3, $n = 3{,}294$). We used MIDUS 2, MIDUS biomarker ($n = 1{,}255$), and MIDUS 3 to analyze longitudinal data and examined if perceived stress and depressive symptoms mediated the association between sleep quality and life satisfaction. Study participants only were included in the present study if they were MIDUS 2 and MIDUS 3 participants and they completed the Biomarker Project (Project 4) of MIDUS 2. Participants with missing data in all relevant measurements and covariates were excluded in our study. Data for the MIDUS study was approved by the UW-Madison Education and Social/Behavioral Science Institutional Review Board.

Measurements

Sleep Quality

Sleep quality was obtained from MIDUS biomarker project. A global measure of sleep quality was derived by using the Pittsburgh Sleep Quality Index (PSQI) across seven domains (Buysse et al., 1989). The PSQI is a retrospective, self-reported questionnaire containing 19-items that assess seven components of sleep and yield one global score of overall sleep quality. For this measure, participants are asked to respond to questions based on their sleep experiences over the past month. Scores are coded and summed into a global score with a possible range of 0–21. Lower global PSQI scores indicate better sleep quality. A global PSQI score >5 was defined as a poor sleep quality (Buysse et al., 1989). Several papers with MIDUS data used PSQI to report sleep quality (Owens et al., 2017; Brindle et al., 2019; Li et al., 2019).

Life Satisfaction

Life satisfaction as an outcome variable was obtained from MIDUS 3. Life satisfaction was measured using a five-item Self-Administered Questionnaire. Participants are asked to assess five dimensions of their lives on a scale from 0 (the worst possible) to 10 (the best possible), including life overall, work, health, relationship with spouse/partner, and relationship with children (Prenda and Lachman, 2001). The scores for the relationship with spouse/partner and the relationship with children are averaged to create one item. Then, this score is used along with the remaining three items to calculate an overall mean score. Higher scores indicate higher levels of life satisfaction and wellbeing.

Depressive Symptoms

Depressive symptoms were obtained from MIDUS biomarker project. Depressive symptoms were assessed using the Mood and Anxiety Symptom Questionnaire (MASQ), which is an instrument designed to measure a range of symptoms relevant to depression and anxiety, using a 5-point Likert scale (1 = not at all, 2 = little bit, 3 = moderately, 4 = quite a bit, 5 = extremely) (Buckby et al., 2007). General Distress-Depression assesses depressed/sad mood and other non-specific depressive symptoms (12 items; e.g., "felt sad," "felt like a failure"). All 12 items on a scale range from 12 to 60. Higher scores on General Distress-Depression were reflective of higher depressive symptoms.

Perceived Stress

Perceived stress were obtained from MIDUS biomarker project. Subjective perceived stress was evaluated using a well-validated perceived stress scale (PSS) (Cohen et al., 1983). Ten questions are included in the PSS, which is designed to measure the extent to which participants perceive their lives as unpredictable, uncontrollable, and overloaded. Each response is coded on a five-point scale (0–4), and all 10 items range from 0 to 40 (Chaaya et al., 2010). Higher scores reflect greater perceived stress (Vigoureux et al., 2020).

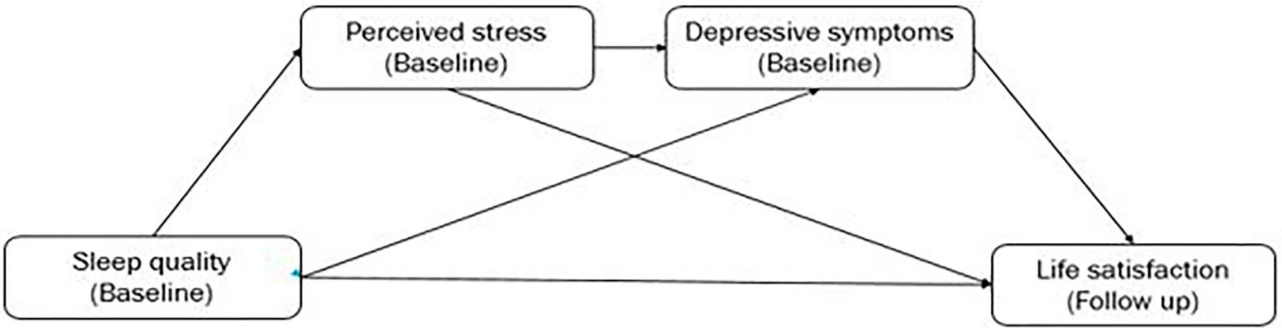

FIGURE 1 | The conceptual model of serial mediation with half-longitudinal study.

Covariates

Several confounding variables that are linked to life satisfaction at follow-up were included as covariates in this study: age, gender, race, and life satisfaction at baseline. All of these covariates were obtained from MIDUS 2. All statistical models were multivariable-adjusted for relevant covariates.

Statistical Analyses

The demographic variables, sleep quality, depressive symptoms, perceived stress scale and life satisfaction were described with mean, standard deviation (SD), and range, number (N), and percentage (%) as appropriate. To test the hypotheses that sleep quality, perceived stress, and depressive symptoms are associated with life satisfaction, we ran hierarchical multiple regression models with the control variables of age, gender, race and life satisfaction at baseline. All of the covariates were entered into model 1, sleep quality was added in model 2, and depressive symptoms and perceived stress entered together in model 3. Participants with missing values of sleep quality and life satisfaction were excluded in our study.

After association between sleep quality and life satisfaction was observed, a serial mediation model with four factors was applied to examine whether the association between sleep quality and life satisfaction was mediated by perceived stress and depressive symptoms. Three mediation tests were performed simultaneously. They were the triangle pathways: sleep quality → perceived stress → life satisfaction, sleep quality → depressive symptoms → life satisfaction, and the quadrangle pathway: sleep quality → perceived stress → depressive symptoms → life satisfaction. Sensitivity analysis was also conducted to detect the effects of the opposing relationship between perceived stress and depressive symptoms. The serial mediation model was analyzed using the PROCESS macro for SAS as proposed by Preacher and Hayes (Bolin, 2014; Blair, 2020).

Mediation analyses aim to explain how an exposure causes its putative effect on the outcome (Hayes, 2017). Ideally, all measurements should be separated in different-wave studies. However, Cole and Maxwell argue that half-longitudinal mediation may be studied in two-wave studies (Cole and Maxwell, 2003). Previous studies successfully have revealed that this statistical approach is applicable to demonstrate the role of mediators (Corlier et al., 2018; Li et al., 2018). Thus, our study applied a half-longitudinal study design to explore the effects of perceived stress (baseline) and depressive symptoms (baseline) on the association between sleep quality (baseline) and life satisfaction (follow-up). Serial multiple mediation analyses were based on 10,000 bootstrapped samples using Hayes' PROCESS. The conceptual model of a half-longitudinal study is shown in **Figure 1**. All of the analyses were conducted using SAS 9.4 and all statistical tests were two-sided, with $P < 0.05$ used to indicate statistical significance.

TABLE 1 | Descriptive statistics for sample (*N* =945).

Variable	M (SD)	Range	*N* (%)
Age	54.33 (11.06)	34–83	
Gender (% male)			420 (44.44)
Race (% white)			877 (92.80)
Life satisfaction at baseline	7.80 (1.15)	3.2–10	
Sleep quality	5.79 (3.40)	0–18	
Depressive symptoms	18.10 (6.15)	12–60	
Perceived stress scale	21.42 (6.10)	10–48	
Life satisfaction	7.90 (1.28)	1–10	

RESULTS

Descriptive Statistics

The descriptive characteristics of participants are presented in **Table 1**. A total of 945 participants with mean age of 54.33 were included in our study. Among them, 420 (44.44%) were males and 877 (92.8%) were whites. Most participants at baseline reported a higher level of life satisfaction (mean = 7.88), which almost equals the level of life satisfaction at follow-up (mean = 7.9). Participants in our study yielded the following descriptive statistics: sleep global score (mean = 5.79); depressive symptom (mean = 18.1); and perceived stress scale (mean = 21.42).

In the hierarchical regression models, demographic variables (including age, gender, and race) and life satisfaction at baseline were entered into model 1. Sleep quality was added in model 2 and depressive symptoms and perceived stress were added in

TABLE 2 | Summary of hierarchical regression analyses for life satisfaction.

Variable	Model 1			Model 2			Model 3		
	t	*p*	β	*t*	*p*	β	*t*	*p*	β
Age	1.19	0.2333	0.0355	1.73	0.0839	0.0485	1.06	0.2877	0.0295
Gender	0.11	0.9152	0.0046	1.01	0.3147	0.0274	1.38	0.1667	0.0371
Race	−0.37	0.7084	−0.0117	−1.02	0.3101	−0.0274	−1.26	0.2068	−0.0335
Life satisfaction at baseline	21.94	< 0.0001	0.6030	19.20	< 0.0001	0.5632	15.81	< 0.0001	0.4851
Sleep quality				−4.50	< 0.0001	−0.1288	−2.35	0.0189	−0.0689
Perceived stress scale							−2.16	0.0311	−0.0810
Depressive symptoms							−3.89	0.0001	−0.1473
Adjusted R^2			0.3755			0.3895			0.4098
F for change in R^2				135.85	< 0.0001		85.50	< 0.0001	

model 3. As shown in **Table 2**, after adjusting for age, gender, race, and life satisfaction at baseline, poor sleep quality was negatively associated with a higher level of life satisfaction. In addition, depressive symptoms and perceived stress were significantly associated with life satisfaction (adjusted $R^2 = 0.4098$, $F_{\text{change}} = 85.5$, $P < 0.01$).

Mediation Analysis

Serial mediation analysis was applied to test whether the association between sleep quality and life satisfaction was mediated by perceived stress and depressive symptoms, after adjusting for all covariates. The serial models simultaneously tested three mediation pathways (see **Supplementary Table 1**). **Figure 2** depicts the effects of the paths linking sleep quality to each mediator and life satisfaction. The positive signs of the effects indicate that higher sleep scores (poor sleep quality) are related to increased perceived stress and depressive symptoms. All indirect paths from sleep quality to life satisfaction were negative, showing the reduction in life satisfaction levels through the increase in the levels of the mediators. From the values given in **Table 3** and **Supplementary Table 2**, perceived stress and depressive symptoms significantly mediated the relationship between sleep quality and life satisfaction, while controlling for demographic variables and life satisfaction at baseline. The direct effect of sleep quality on life satisfaction was significant (coefficient β = −0.0253, 95% CI = −0.0464–−0.0042). Meanwhile, the coefficient estimates—based on the use of 95% CI as evidence of the mediation of total indirect and indirect effects for perceived stress, depressive symptoms and the combination of perceived stress and life depressive symptoms—were calculated as follows: total indirect β = −0.0211, CI = −0.0332–−0.0118; indirect effect coefficient β (sleep quality → perceived stress → life satisfaction) = −0.0062, CI = −0.0125–−0.0008; indirect effect coefficient β (sleep quality → depressive symptoms → life satisfaction) = −0.0082, CI = −0.0154–−0.0029; indirect effect coefficient β (sleep quality → perceived stress → depressive symptoms → life satisfaction) = −0.0067, CI = −0.0123–−0.0026, respectively. The total indirect effect of sleep quality on life satisfaction accounted for in the overall model was 45.5%.

Sensitivity Analysis

The sensitivity analysis of serial mediation analysis is shown in **Supplementary Table 2**. The opposing direction effects of perceived stress and depressive symptoms on the association between sleep quality and life satisfaction were presented in the sensitivity analysis (sleep quality → depressive symptoms → perceived stress → life satisfaction). The variable of depressive symptoms was included as the first mediator, while perceived stress was considered as the second mediator. According to the sensitivity analysis, we found that sleep quality was not associated with perceived stress (coefficient β = 0.0712, $P = 0.138$) and perceived stress, as the second mediator, did not mediate the association between sleep quality and life satisfaction.

DISCUSSION

To our knowledge, this is the first study using serial mediation to test the effects of psychosocial factors on the association between sleep and life satisfaction within a middle-aged population in the United States. In the present study, the mean score of sleep quality was 5.79 ± 3.4. Our study results showed that 55.13% of American adults experienced poor sleep quality, which is higher than the prevalence reported from The Sleep Foundation (SleepFoundation., 2014). According to the report from The Sleep Foundation, it is estimated that 35% of Americans have poor sleep quality, although they obtain sufficient sleep hours (SleepFoundation., 2014). The findings of our study also indicated that poor sleep quality, depressive symptoms and perceived stress were negatively associated with life satisfaction, adjusted for age, gender, race and educational level, which are consistent with previous studies. A 10-year longitudinal study from the National Survey of Midlife Development in the United States revealed that insomnia symptoms had a significant relationship with wellbeing (Karlson et al., 2013). A Nationwide Cohort study of Twins has shown that poor sleep may have direct effects on the brain, emotions, and mood, which decreases the level of life satisfaction (Paunio et al., 2008). Another population-based cross-sectional study among American adults demonstrated that good sleep quality was found to predict greater quality of wellbeing and life satisfaction (Jean-Louis et al., 2000).

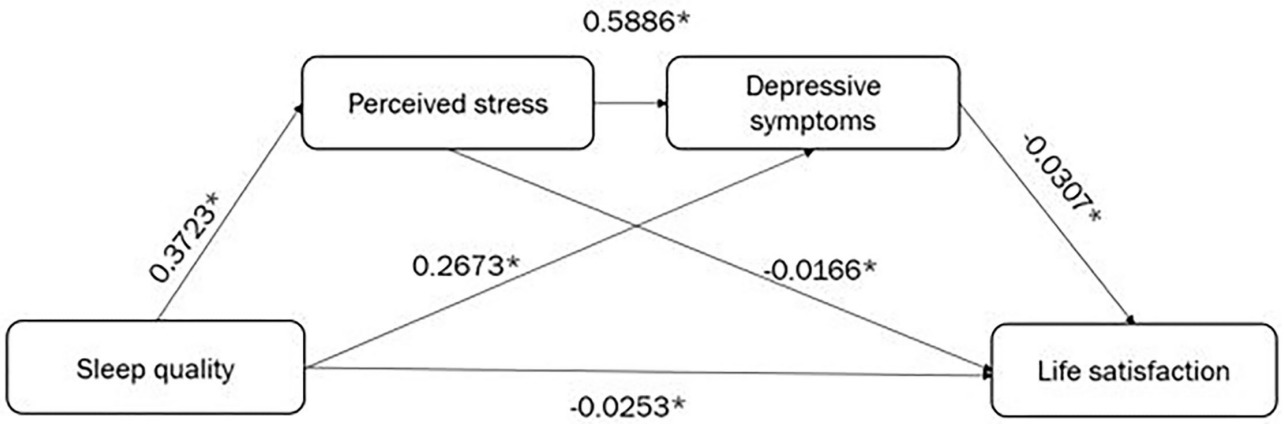

FIGURE 2 | The serial mediation of perceived stress and depressive symptoms. *$P < 0.05$, all results are statistically significant.

TABLE 3 | Direct and indirect effects of sleep quality on life satisfaction.

Outcome	β	BootSE	BootLLCI	BootULCI
Direct effect				
Sleep quality—life satisfaction	−0.0253	0.0107	−0.0464	−0.0042
Indirect effect				
Sleep quality—perceived stress scale—life satisfaction	−0.0062	0.003	−0.0125	−0.0008
Sleep quality—depressive symptoms—life satisfaction	−0.0082	0.0032	−0.0154	−0.0029
Sleep quality—perceived stress scale—depressive symptoms—life satisfaction	−0.0067	0.0025	−0.0123	−0.0026

Controlling for age, gender, race, life satisfaction at baseline.

Serial mediation analyses showed that perceived stress and depressive symptoms mediate the association between sleep quality and life satisfaction. The total indirect effect of sleep quality on life satisfaction through perceived stress, depressive symptoms and the combination of perceived stress and depressive symptoms accounted for the overall model was 45.5%, which indicates that mediation effects of perceived stress and depressive symptoms play important roles in the association between sleep quality and life satisfaction. Sensitivity analysis revealed that perceived stress, as the second mediator, was not associated with sleep quality directly and did not mediate the association between sleep quality and life satisfaction. Thus, poor sleep quality may lead to increased depressive symptoms, partially through increased perceived stress, which related to decreased life satisfaction. A study in China with elderly Chinese demonstrated depression plays partially mediated role on the associations of sleep duration and sleep quality with life satisfaction (Zhi et al., 2016). A cross-sectional study in Korea reported that depression was associated with sleep quality life (OR = 1.259, 95% CI 1.196–1.324, $p < 0.001$) and life satisfaction (OR = 0.881, 95% CI 0.837–0.891, $p < 0.001$) (Seo et al., 2018). A study in Nepal with mediation analysis demonstrated that depression had a significant direct effect on life satisfaction (β = −0.87, 95% CI: −1.01, −0.74) (Ghimire et al., 2018). Although few studies examine the mediating role of perceived stress on the association between sleep quality and life satisfaction, previous studies revealed the associations of sleep quality and life satisfaction with perceived stress. It is well-documented that sleep disruption can have an influence on levels of neurotransmitters and stress hormones, impairing thinking and emotional regulation (Chirinos et al., 2017; Harvardhealth., 2019; Huang and Zhu, 2020). A daily diary project from MIDUS study also revealed that daily stressor exposure predict daily wellbeing and higher daily stressor severity has been shown to be associated with lower levels of daily wellbeing (Surachman et al., 2019). Thus, perceived stress and depressive symptoms can be considered as mediators that impact the association between sleep quality and life satisfaction. At the intervention level, programs designed to improve the level of life satisfaction among adults should focus on perceived stress, depressive symptoms among middle-aged American adults.

Results and interpretations of the present study should be considered in light of several limitations. First, the study invoked a half—longitudinal study design in that the measures of sleep quality (exposure), perceived stress, and depressive symptoms (mediators) were obtained concurrently. The effects of sleep quality on perceived stress and depressive symptoms might be biased. However, several previous studies also applied mediation models, based on half-longitudinal study designs (Lyu and Agrigoroaei, 2016; Posick et al., 2019; Grossman and Gruenewald, 2020). A review on mediation models suggests that there still is progress to be made both in terms of the use of cross-sectional data, as well as the proper application

of longitudinal models of mediation (O'Laughlin et al., 2018). Second, the psychosocial variables and sleep quality variables were measured by self-reported questionnaires. Therefore, there might be some self-reported bias which affects our results. Third, most participants included in our study were whites and we included all participants with complete data. The results cannot be generalized for all populations and our results may present selection bias. Forth, potential confounding factors, like marital status, may not be considered as additional covariates. Despite these limitations, this study has numerous strengths. We used longitudinal data to explore the causal relationships of sleep quality, perceived stress and depressive symptoms with life satisfaction. In addition, this is the first study that examined the serial mediation effects of perceived stress and depressive symptoms on the association between sleep quality and life satisfaction among American adults.

CONCLUSION

The present study was the first to examine perceived stress and depressive symptoms as serial mediators of the relationship between sleep quality and life satisfaction. The results of the present study indicate that perceived stress followed by depressive symptoms may be important mechanisms that contribute to the positive relationship between sleep quality and life satisfaction. However, our findings do not support the contention that perceived stress and depressive symptoms operate in opposing directions in the relationship between sleep quality and life satisfaction. This causal chain should be confirmed by further longitudinal study. The findings from our study also indicated the prevention of perceived stress and depression may contribute to improving life satisfaction and wellbeing.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YY developed the research project, with the contribution of YC and VC. BA, KS, and DA reviewed the article. YY prepared the dataset and carried out the data analysis. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.822564/full#supplementary-material

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Childhood Threat Is Associated With Lower Resting-State Connectivity Within a Central Visceral Network

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Childhood adversity is associated with altered or dysregulated stress reactivity; these altered patterns of physiological functioning persist into adulthood. Evidence from both preclinical animal models and human neuroimaging studies indicates that early life experience differentially influences stressor-evoked activity within central visceral neural circuits proximally involved in the control of stress responses, including the subgenual anterior cingulate cortex (sgACC), paraventricular nucleus of the hypothalamus (PVN), bed nucleus of the stria terminalis (BNST) and amygdala. However, the relationship between childhood adversity and the resting-state connectivity of this central visceral network remains unclear. To this end, we examined relationships between childhood threat and childhood socioeconomic deprivation, the resting-state connectivity between our regions of interest (ROIs), and affective symptom severity and diagnoses. We recruited a transdiagnostic sample of young adult males and females ($n = 100$; mean age = 27.28, $SD = 3.99$; 59 females) with a full distribution of maltreatment history and symptom severity across multiple affective disorders. Resting-state data were acquired using a 7.2-min functional magnetic resonance imaging (fMRI) sequence; noted ROIs were applied as masks to determine ROI-to-ROI connectivity. Threat was determined by measures of childhood traumatic events and abuse. Socioeconomic deprivation (SED) was determined by a measure of childhood socioeconomic status (parental education level). Covarying for age, race and sex, greater childhood threat was significantly associated with lower BNST-PVN, amygdala-sgACC and PVN-sgACC connectivity. No significant relationships were found between SED and resting-state connectivity. BNST-PVN connectivity was associated with the number of lifetime affective diagnoses. Exposure to threat during early development may entrain altered patterns of resting-state connectivity between these stress-related ROIs in ways that contribute to dysregulated neural and physiological responses to stress and subsequent affective psychopathology.

Keywords: childhood trauma, subgenual anterior cingulate cortex, amygdala, bed nucleus of stria terminalis, extended amygdala, hypothalamus, affective disorders

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INTRODUCTION

Due to its high prevalence (Hillis et al., 2016; Merrick et al., 2018; Cuartas et al., 2019) and importance as a predictor of affective risk, childhood adversity is at the forefront of psychiatry's public health burden (Sara and Lappin, 2017). One sensitivity analysis of global past year violence against children found that a minimum of 1.4 out of 2 billion children aged 2–17 experienced physical, sexual or emotional violence (Hillis et al., 2016). Further, the COVID-19 pandemic has exacerbated systemic challenges, increasing children's risk of violence exposure (M'jid, 2020; Pereda and Díaz-Faes, 2020). Childhood adversity is a risk factor for and prospective predictor of greater affective symptoms and disorders (Danese et al., 2009; Nanni et al., 2012; Baldwin et al., 2021; Mayer et al., 2021; Russotti et al., 2021). Thus, greater mechanistic understanding of childhood adversity-related neural and physiological differences is necessary to mitigate these risks and guide treatment efforts.

Childhood adversity is associated with dysregulated (heightened or diminished) stress reactivity in childhood and later in life (Al'Absi et al., 2021), with alterations in both neuroendocrine and autonomic physiology and stress reactivity (Heim et al., 2000, 2001; Chen et al., 2004; Koopman et al., 2004; Carpenter et al., 2007, 2011; Gunnar et al., 2009; Lovallo et al., 2011; Hackman et al., 2012). There is evidence to suggest that there may be differential influences of childhood adversity dimensions, threat (e.g., abuse, traumatic events) and deprivation (e.g., neglect, socioeconomic deprivation, institutional rearing) (McLaughlin et al., 2014; Sheridan and McLaughlin, 2014) on stress reactivity, with threat blunting (Carpenter et al., 2007, 2011; Doom et al., 2014; Peckins et al., 2015; Bernard et al., 2017) and deprivation (i.e., low socioeconomic status, SES) heightening reactivity (Lupien et al., 2001; Cohen et al., 2006; Chen et al., 2009; Lê-Scherban et al., 2018). Despite evidence linking childhood threat and deprivation to altered physiological stress systems, how childhood adversity shapes specific, proximally stress-responsive neural circuits remains unclear.

The subgenual anterior cingulate cortex (sgACC), paraventricular nucleus of the hypothalamus (PVN), bed nucleus of the stria terminalis (BNST) and amygdala form a stress-responsive, central visceral network. These limbic forebrain and hypothalamic regions are central to reciprocal descending preautonomic/visceromotor and ascending viscerosensory (i.e., central visceral) pathways (see **Figure 1**) that control and modulate autonomic outflow and neuroendocrine function (Banihashemi and Rinaman, 2006; Card and Sved, 2011; Rinaman et al., 2011). Further, connections between these regions are important for stress regulation; the PVN, a gateway of hypothalamic-pituitary-adrenal (HPA)/neuroendocrine and autonomic regulation (Luiten et al., 1985; Herman et al., 2002), is directly innervated and influenced by the BNST (Dong et al., 2001b; Povysheva et al., 2021). With little to no innervation of the PVN (Freedman et al., 2000), the sgACC/Brodmann area 25 may access the PVN via direct connections to the BNST (Freedman et al., 2000; Vertes, 2004). The amygdala also has reciprocal connections to the sgACC (Heilbronner and Haber, 2014; Oler and Fudge, 2019; Sharma et al., 2019) and BNST (Dong et al., 2001a; Bienkowski et al., 2013; deCampo and Fudge, 2013; Oler et al., 2017; **Figure 1**). Further, the intrinsic functional connectivity of the extended amygdala (BNST/amygdala) appears to align with known anatomical connectivity; Tillman et al. (2018) showed that compared to the central nucleus of the amygdala, the BNST displayed stronger coupling with anterior cortical areas, including ventromedial prefrontal cortex/sgACC and brainstem/dorsal periaqueductal gray. This network (along with its central visceral connections) is involved in affective processes (e.g., emotional memory, threat responses, fear and anxiety) (Fendt et al., 2005; Schweimer et al., 2005; Somerville et al., 2010; Avery et al., 2014, 2016; Herrmann et al., 2016), implicated in psychopathology (e.g., depression, anxiety, trauma-related disorders) (Thayer and Lane, 2000; Gotlib et al., 2005; Drevets et al., 2008b; Lebow and Chen, 2016; Clauss, 2019; Clauss et al., 2019), and targeted for affective disorder treatments (e.g., deep brain stimulation for depression and obsessive compulsive disorder) (Johansen-Berg et al., 2008; Gutman et al., 2009; Drobisz and Damborská, 2018; Fitzgerald et al., 2018; Mosley et al., 2021).

Previous research in preclinical animal models (Banihashemi and Rinaman, 2010; Banihashemi et al., 2011) and human neuroimaging (Banihashemi et al., 2015) indicates that early life experience differentially influences stressor-evoked activity within this visceral, stress-responsive network. In physically and mentally healthy adults, childhood threat (i.e., physical abuse) is significantly associated with greater stressor-evoked activity across this central visceral, limbic forebrain-hypothalamic network (Banihashemi et al., 2015). Yet, how childhood adversity may influence resting-state connectivity of this central visceral network is virtually unknown.

Studies focused on childhood adversity and resting-state connectivity have spanned development and have primarily focused on amygdala-related or large-scale network connectivity (Teicher et al., 2020). In youth, findings tend to indicate that greater childhood maltreatment or trauma exposure is associated with greater amygdala-related connectivity (amygdala-sgACC cortex, amygdala-hippocampus, amygdala-salience network) (Marusak et al., 2015; Thomason et al., 2015; Rakesh et al., 2021b), while late adolescents/adults tend to display an opposing trend with greater maltreatment associated with less amygdala-related connectivity (amygdala-sgACC, amygdala-ventromedial prefrontal cortex, amygdala-orbitofrontal cortex/insula/hippocampus, amygdala-cuneus/precuneus) (Werff et al., 2012; Herringa et al., 2013; Souza-Queiroz et al., 2016). Rabellino et al. (2018) investigated BNST resting-state connectivity in PTSD and its dissociative subtype; however, they found no significant relationship between childhood maltreatment and BNST resting-state connectivity in subsequent analyses. To our knowledge, no studies of childhood adversity have focused exclusively on the resting-state connectivity of the central visceral network described. Thus, the current study is unique in examining this network in a transdiagnostic sample recruited specifically to represent a spectrum of severity across self-reported childhood physical abuse.

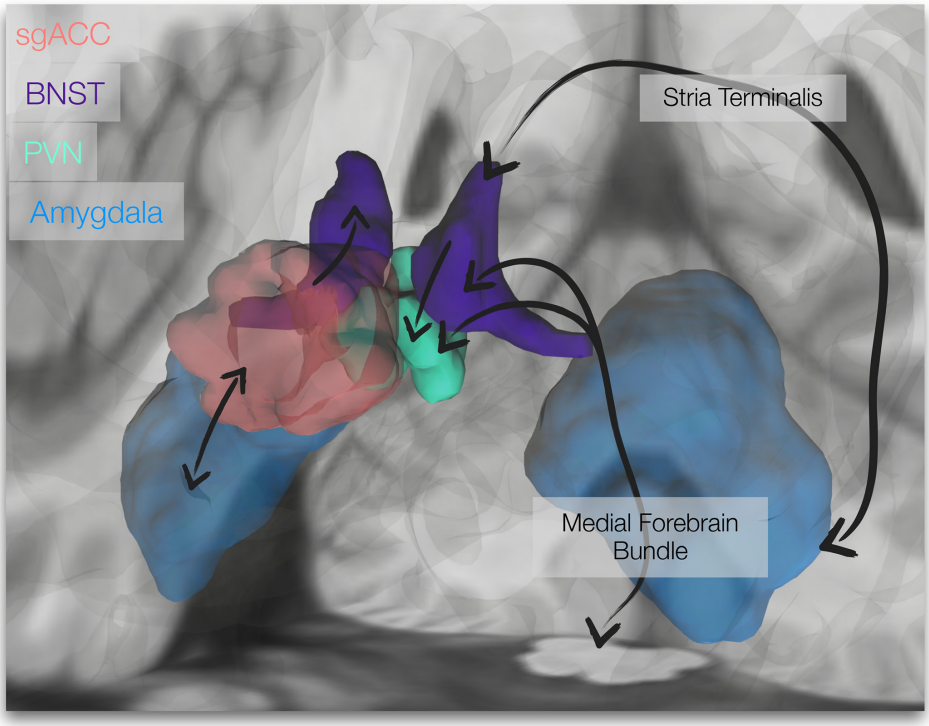

FIGURE 1 | Central Visceral Network. The brain image depicts the regions of interest utilized in our resting-state analyses, the subgenual anterior cingulate cortex (sgACC, red), bed nucleus of the stria terminalis (BNST, violet), paraventricular nucleus of the hypothalamus (PVN, green) and amygdala (blue). Simplified connections are depicted (black arrows; not specific with respect to subnuclei). Ascending viscerosensory and descending preautonomic/visceromotor pathways course through the medial forebrain bundle (BNST and PVN connections depicted). Amygdala, BNST and PVN are connected via the stria terminalis. BNST projections to PVN and sgACC innervation of the BNST are displayed, as well as reciprocal connections between the sgACC and amygdala. The amygdalofugal pathway is also integral to this network (not depicted here). (Unilateral representations are shown).

Our recent work discovered opposing relationships of childhood threat (both abuse and traumatic events) and socioeconomic deprivation with white matter structural integrity (i.e., generalized fractional anisotropy, gFA) of the stria terminalis (Banihashemi et al., 2021), which connects several of our regions of interest (ROIs) (caudomedial amygdala, BNST and hypothalamus) (Rafal et al., 2015; Oler et al., 2017; Weiss et al., 2021). Greater threat was associated with less, while greater deprivation was associated with greater, stria terminalis gFA. Thus, we hypothesized that threat and deprivation would have congruent, opposing effects on resting-state connectivity within this central visceral network (i.e., threat would be associated with lower, while deprivation would be associated with greater, resting-state connectivity). To this end, our goal was to examine differential relationships of threat and deprivation with resting-state connectivity between our central visceral ROIs, as well as to examine how their functional connectivity may contribute to affective symptoms or disorders. These findings may contribute to a greater understanding of how childhood-adversity shapes this central visceral network at rest, how these resting state dynamics may prime functional activity in response to emotionally salient stimuli and how this network may contribute to childhood adversity-related differences in affective symptoms and disorders.

MATERIALS AND METHODS

Participants

Participants were recruited from Allegheny County, Pittsburgh, PA, United States, using various methods (e.g., referrals from other research studies, and online and bus advertisements). Of the 1,020 contacts made, 111 (18.5%) underwent informed consent and were enrolled in the study. Of those consented, 100 (90%) participants completed study procedures. Participants were 59 female and 41 male young adults (n = 100, mean age = 27.28, SD = 3.99). Of the 100 participants that completed the study, 45% self-reported their race as White, 36% as Black or African American, 13% as Asian, 4% as multiracial, and 2% as biracial. Within this sample, 7 individuals reported their ethnicity as Hispanic or Latin American. All participants provided informed consent after receiving an explanation of study protocols and were examined with the approval of the University of Pittsburgh Institutional Review Board.

Exclusion criteria were: Magnetic resonance imaging (MRI) contraindications (e.g., claustrophobia, metal in the body, severe visual or auditory impairment), pregnancy, left-handedness, cardiovascular disease and diabetes, neurological disorders (including seizure disorders, migraine disorder, traumatic brain injury, or neurodegenerative disorders), psychotropic medications or any medications affecting cardiovascular or neural function, suicidality or marked functional impairment, and current psychiatric disorders (bipolar, psychotic disorders, substance abuse or dependence) except for depression, anxiety or trauma-related disorders.

Individuals were also screened using the five childhood physical abuse items from the Childhood Trauma Questionnaire (CTQ) with the goal of achieving an even distribution of participants across four physical abuse severity classifications as defined by CTQ guidelines (Bernstein et al., 1994). The following distribution of physical abuse severity was achieved in the final sample ($n = 100$): 29% None-Minimal, 23% Low-Moderate, 21% Moderate-Severe, 27% Severe-Extreme. A balanced distribution was also achieved across childhood SES (as assessed by maximum parental education level), 31% Low (GED – some college, no degree), 34% Middle (Associate or Bachelor's), and 35% High (Master's or Doctorate). All participants had at least one parent with a GED or higher education level.

Study Protocol and Measures

The study comprised two visits completed within one month (mean number of days between visits: 14.39 ± 10.96), an intake visit followed by an MRI scan visit at the University of Pittsburgh Magnetic Resonance Research Center. At the first visit, eligibility was determined using medical history, two-week medication history, current substance use and traumatic brain injury inventories. Participants were excluded if deemed ineligible by these assessments.

Childhood Threat

Childhood Threat was assessed with the Childhood Trauma Questionnaire (CTQ) and the Trauma History Questionnaire (THQ). The CTQ is a 28-item Likert-type scale that examines five subscales of maltreatment: physical, emotional and sexual abuse, and physical and emotional neglect (Bernstein et al., 1994). Each subscale contains five items with scores ranging from 1-Never to 5-Very Often True. A sum of the three abuse subscales represented our CTQ Threat variable (with 15 indicating no abuse and 75 indicating extreme abuse). (A sum of the two neglect subscales represented our CTQ Deprivation variable, which was used in secondary analyses. See section "Variable Selection").

The THQ is a 24-item questionnaire that assesses the occurrence of traumatic events throughout the life course (Stamm, 1996). An adapted version of the THQ was used in which participants responded yes or no to indicate whether a particular event occurred and then selected the relevant age range(s): age 0–11, age 12–17, and age > 18 (Insana et al., 2012). Traumatic events included experiences with crime, environmental disasters, injury or death, as well as physical or sexual abuse. THQ 0-11 was used as a primary measure of childhood threat and THQ > 18 was used as a covariate (see sections "Variable Selection" and "Data Analysis").

Childhood Socioeconomic Deprivation

A sociodemographic inventory was used to assess childhood and adulthood SES. Maximum parental education level was used to determine childhood SES; the participants' own educational level determined adulthood SES. Both were presented as a 9-point education level scale (0 - No high school diploma, 1 – GED, 2 – High school diploma, 3 – Technical training, 4 – Some college, no degree, 5 – Associate degree, 6 – Bachelor's degree, 7 – Master's degree, 8 – MD/PhD/JD/PharmD). The Childhood Deprivation construct encompasses low SES, socioeconomic disadvantage or neighborhood deprivation (McLaughlin et al., 2014; Webb et al., 2017; Berti and Pivetti, 2019; Morris et al., 2019). Further, education level is often used as a measure of SES and is associated with mental health inequalities (Reiss, 2013), physiological stress (Ursache et al., 2017) and physical health, especially cardiovascular disease risk (Winkleby et al., 1992). Thus, we used maximum parental education level (reverse coded) as our primary measure of childhood socioeconomic deprivation (SED). Adulthood SES was used as a covariate.

Negative Life Events

The 24-item Life Events List assesses significant life events experienced by the participant within the past 12 months (e.g., unemployment, separation or divorce, serious illness, death of someone close) (Cohen et al., 1991). Participants indicate whether or not they have experienced an event in the past year with follow up questions assessing valence and/or details if endorsed. This inventory was used to assess the total number of negative life events, which was used as a covariate.

Affective Symptom Severity

Depression and post-traumatic stress symptom severity were assessed using the Beck's Depression Inventory (BDI-II) and the PTSD Checklist - Civilian Version (PCL-C), respectively. The BDI-II is a 21-item questionnaire that assesses the presence and severity of depression within the past two weeks; it probes whether participants have experienced a thought or behavior related to depressive symptoms on a scale of 0 to 3, with scores > 20 considered moderate-to-severe (Beck et al., 1996). The PCL-C is a 20-item measure that reliably assesses post-traumatic stress symptom severity in the last month on a 5-point Likert scale ranging from not at all (Cuartas et al., 2019) to extremely (M'jid, 2020), with scores > 30 considered moderate-to-severe. It includes assessment of re-experiencing, avoidance and arousal symptoms, as well as negative cognitions (Wilkins et al., 2011).

Diagnostic Assessment

Psychiatric diagnoses of mood, anxiety or trauma-related disorders were evaluated and confirmed via in-person interview using the Structured Clinical Interview for DSM-IV Axis I Disorders by a trained interviewer. Of the 100 participants who completed the study, 29% were healthy (had no history of the affective disorders evaluated), whereas 71% had a history of affective diagnosis (47 participants had one or more current

affective diagnoses). Of those with a diagnostic history, 30 had a trauma-related disorder, 24 had a depressive disorder and 17 had an anxiety disorder, as their primary lifetime diagnosis. Posttraumatic stress disorder was the most frequent diagnosis (30% of the sample) followed by major depressive disorder (15% of the sample). Further, 37% had comorbid lifetime mood and anxiety/trauma-related disorders.

Sample Characterization

Participants also completed questionnaires to characterize the sample, including the Perceived Stress Scale (PSS, 10-item version) to assess frequency of stress-related feelings (Cohen et al., 1983), the State Trait Anxiety Inventory (STAI-Y2) to assess presence and severity of trait anxiety (Spielberger et al., 1983) and the NEO Five-Factor Inventory-3 (NEO-FFI-3, 60 items) to assess personality (McCrae and Costa, 2007). See **Supplementary Table S1** for Participant Characteristics.

Magnetic Resonance Imaging Protocol and Data Acquisition

Magnetic resonance imaging data were collected on a 3-Tesla Trio TIM whole-body MRI scanner (Siemens, Erlangen, Germany), equipped with a 32-channel head coil. Prior to the resting-state sequence, participants were instructed to "gaze at the fixation cross and rest" and reminded to remain as still as possible. A custom, localized shimming procedure was implemented that extended from the bottom-most slice to the ventral aspect of the corpus callosum. Resting-state functional MRI data were acquired using a 7.2-min, T2*-weighted gradient-echo echoplanar imaging (EPI) sequence (TR = 2000 ms, TE = 29 ms, flip angle = 65°, slices = 22, Multiband Factor = 3, FoV = 220 × 220 mm^2, voxel size = 2 × 2 × 2.0 mm^3). The FOV was angled 15–20° to ensure visualization of our ROIs. For registration purposes, anatomical images were acquired using a 4.8-min T1-weighted sagittal MPRAGE sequence (TR = 1500 ms, TE = 3.19 ms, flip angle = 8°, 176 slices, FoV = 256 × 256 mm^2, voxel size = 1 × 1 × 1.0 mm^3). The resting-state sequence followed the MPRAGE acquisition, which was the first sequence in the protocol. Additional sequences were collected during the MR (not reported here) with a total duration of approximately 50–55 min.

Resting-State Functional Magnetic Resonance Imaging Preprocessing and Analysis

Resting state fMRI data were preprocessed using Statistical Parametric Mapping software (SPM12[1]). Motion correction was applied through realignment of each blood-oxygen-level dependent (BOLD) image to the mean reference image. The structural image was then co-registered to the mean functional image. Segmentation was performed on the structural image using probability maps for six tissue classes, generating a deformation field that was then applied to the functional images during normalization of all images to standard Montreal Neurological Institute (MNI) space (2 mm isotropic resolution). Smoothing was applied to functional images using a 4 mm full-width-at-half-maximum Gaussian kernel.

[1]http://www.fil.ion.ucl.ac.uk/spm/

Resting-state connectivity analyses were performed using standard SPM-based functions (in-house MATLAB code was used to wrap these functions). Translation (mm) and rotation (deg) was assessed for each participant; motion was low across the sample of 100 participants (Translation: mean = 1.13 mm, SD = 0.37; Rotation: mean = 0.86 degrees, SD = 0.73). Our threshold for maximum translation was 3 mm of motion and none exceeded this. Motion artifact reduction was applied to smoothed functional images using the SPM BrainWavelet Toolbox wavelet despiking methods to identify and filter spike artifacts. A principal component analysis was performed by extracting five eigenvariates of the BOLD signal principal time series from the white matter and cerebrospinal fluid simultaneously using singular value decomposition. Using multiple linear regression, the time series at each voxel was adjusted by applying these tissue components and the raw values of the six motion parameters (not their derivatives) from preprocessing as covariates. The residual time series was extracted from each voxel and we used a series of cosines to model the band pass Butterworth filter (0.008–0.15 Hz), which was applied on the residuals.

Region of Interest-to-Region of Interest Analyses

The sgACC, BNST and PVN ROI masks were created using manual segmentation with MRIcron on the ch2better template. The BNST and PVN ROIs were based on the Atlas of the Human Brain (Mai et al., 2008) [BNST: plates 18 (Talairach reference systems, $y = -2.7$ mm) through 24 ($y = +2.7$ mm); PVN: plates 20 ($y = -1.3$ mm) through 28 ($y = +8.0$ mm)]. The sgACC ROI was based on its depiction in Cingulate Neurobiology and Disease (Vogt, 2009). These ROIs were described initially (Banihashemi et al., 2015) and utilized/reported elsewhere (Andreescu et al., 2015a,b; Price et al., 2018; Wu et al., 2019). The amygdala ROI was created from the SPM Anatomy toolbox using the 50% probabilistic map (Amunts et al., 2005; Eickhoff et al., 2005). Each ROI was applied as a mask on the covariate-processed functional data. Using principal component analysis, we extracted the first eigenvariate within each ROI for each subject. The correlation (Pearson) between the eigenvariates for each ROI-to-ROI pair was calculated to determine connectivity between the two regions.

Variable Selection

Our rationale for childhood threat and deprivation variable selection has been described previously (Banihashemi et al., 2021). Briefly, preliminary data analyses from the current sample demonstrated that our childhood threat and deprivation variables were correlated (**Table 1**), however, among deprivation measures, socioeconomic deprivation [SED, maximum parental education level (reverse coded, such that higher values reflected greater deprivation)] was the least correlated with the threat measures (Pearson r = 0.175 to 0.411, **Table 1**). CTQ Threat (abuse) and CTQ Deprivation (neglect) were strongly correlated (r = 0.769). As such, CTQ Deprivation was considered only in exploratory analyses (data not shown) and SED was used as the

TABLE 1 | Pearson correlations between childhood threat and deprivation measures ($n = 100$).

		CTQ Threat	THQ 0-11	THQ 12-17	CTQ deprivation	SED
CTQ Threat (abuse)	Pearson *r*	–				
	p (2-tailed)					
THQ 0-11	Pearson *r*	0.535**	–			
	p (2-tailed)	0.000				
THQ 12-17	Pearson *r*	0.580**	0.539**	–		
	p (2-tailed)	0.000	0.000			
CTQ Deprivation (neglect)	Pearson *r*	0.769**	0.462**	0.534**	–	
	p (2-tailed)	0.000	0.000	0.000		
Socioeconomic Deprivation (SED)	Pearson *r*	0.411**	0.175	0.337**	0.404**	–
	p (2-tailed)	0.000	0.081	0.001	0.000	

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

primary measure of childhood deprivation. As early childhood experiences are critical for brain development (Tottenham and Sheridan, 2010), our primary analyses of trauma utilized early traumatic events (THQ 0-11); exploratory analyses examining later traumatic events (THQ 12-17) are included in the **Supplementary Material**. Because CTQ Threat and THQ 0-11 are highly correlated ($r = 0.535$), these threat measures were considered in separate models, allowing separate examination of broader traumatic events (THQ 0-11) and abuse (CTQ Threat). Because threat co-occurs with SED (and these constructs are not independent from one another), we examined the additive effects (Fahrmeir et al., 2013) of threat and deprivation similar to Lawson et al. (2017).

Data Analysis

Childhood Adversity and Resting-State Connectivity

We examined whether childhood threat and SED variables were associated with resting-state connectivity between our ROIs; six resting-state ROI-to-ROI connections were examined (Amygdala-BNST, Amygdala-PVN, Amygdala-sgACC, BNST-PVN, BNST-sgACC and PVN-sgACC). All hierarchical linear regression models covaried for age, race and sex in Step 1 and examined the additive effects of childhood threat and SED together in Step 2 (i.e., Model 1: early traumatic events and SED, and Model 2: abuse and SED). We also evaluated whether our findings remained after multiple comparison correction (FDR < 0.05, for six tests, one for each ROI-to-ROI connection) (Benjamini and Hochberg, 1995) and after adjusting for adulthood trauma (all traumatic events occurring after age 18, THQ > 18), adulthood SES (education level) and negative life events within the past year (Life Events List); these variables were entered together in Step 3. Where a significant relationship was found between abuse (CTQ Threat) and resting-state connectivity, *post hoc* analyses were performed substituting each abuse subscale in the model to examine which type of abuse may have been driving the relationship.

Resting-State Connectivity and Affective Symptoms/Disorders

Where a significant relationship was found between childhood threat and resting-state connectivity between our ROIs, we also examined whether ROI-to-ROI connectivity was associated with depressive or post-traumatic stress symptom severity or the number of lifetime diagnoses. Hierarchical regression models covaried for age, race and sex in Step 1 and examined the effect of ROI-to-ROI connectivity in Step 2 in separate models. We also evaluated whether our findings remained after multiple comparison correction (FDR < 0.05, for three tests, one for each measure of affect) and after adjusting for adulthood trauma (THQ > 18), adulthood SES (education level) and negative life events within the past year (Life Events List); these variables were entered together in Step 3.

RESULTS

Childhood Threat, Deprivation and Central Visceral Network Resting-State Connectivity

Early Traumatic Events (Trauma History Questionnaire, Age 0–11)

Of the six resting-state ROI-to-ROI connections examined, THQ 0-11 had a significant, negative association with BNST-PVN (ß $= -0.224$; $p = 0.033$, **Figure 2A**), Amygdala-sgACC (ß $= -0.312$; $p = 0.003$, **Figure 2B**) and PVN-sgACC connectivity (ß $= -0.264$; $p = 0.008$, **Figure 2C**) (standardized ß values reported throughout; **Table 2**). Among these, relationships between THQ 0-11 and Amygdala-sgACC (adjusted $p = 0.018$) and PVN-sgACC (adjusted $p = 0.024$) survived multiple comparison correction, and both relationships remained significant when adulthood trauma (age > 18), adulthood SES and negative life events were added to the model [Amygdala-sgACC (ß $= -0.328$; $p = 0.005$); PVN-sgACC (ß $= -0.241$; $p = 0.030$) (**Table 2**)]. Socioeconomic deprivation (SED, maximum parental education level reverse coded) did not have a significant association with any ROI-to-ROI connection examined.

An examination of potential outliers is reported in the **Supplementary Material** [Results, Early Traumatic Events (THQ, age 0–11, **Supplementary Tables S2–S4**)]. When removing the largest THQ 0-11 value, the amygdala-sgACC and PVN-sgACC results remain

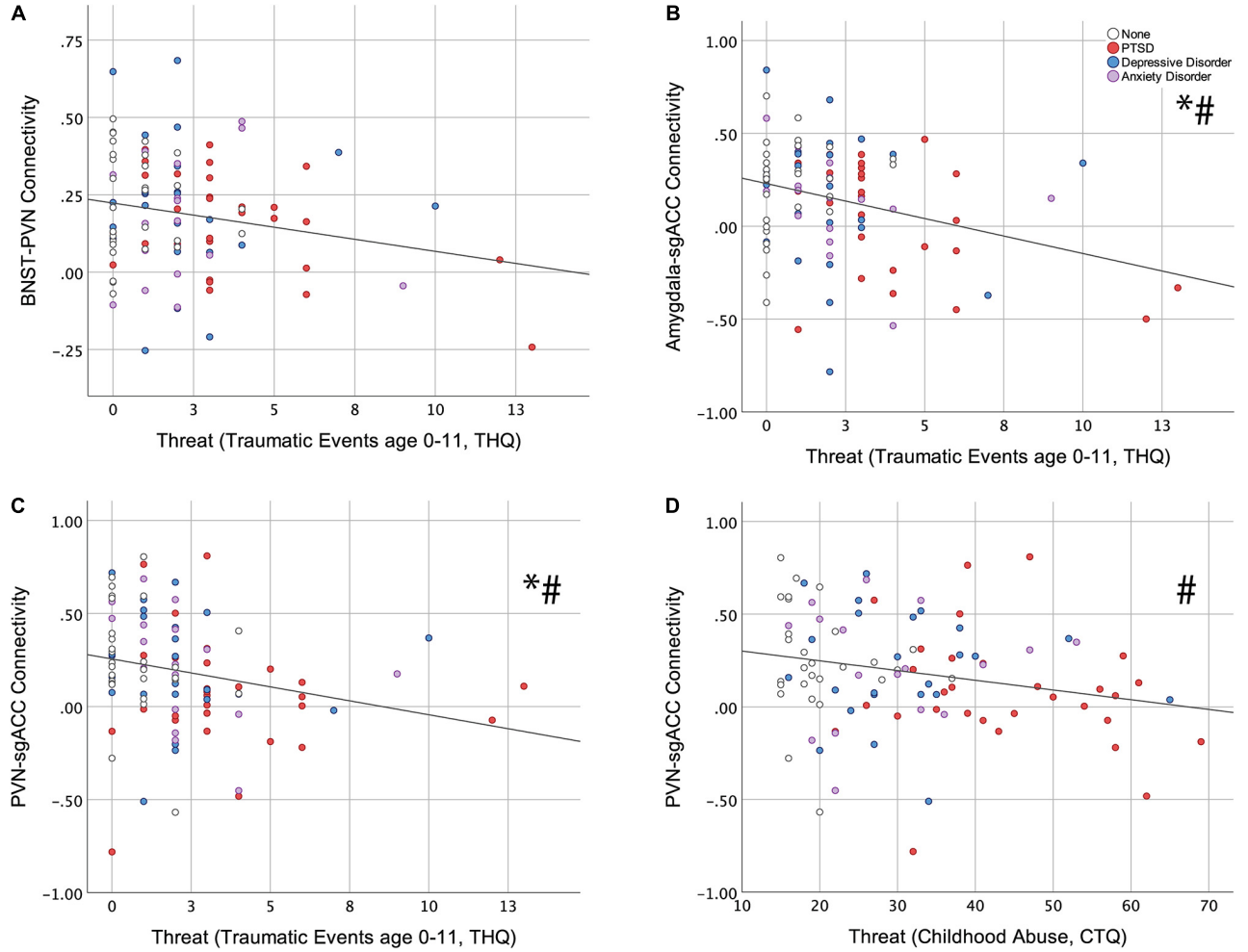

FIGURE 2 | Relationships between childhood threat and central visceral network resting-state connectivity. Hierarchical linear regression was used to examine associations between early traumatic events (Trauma History Questionnaire, THQ, age 0–11) and **(A)** BNST-PVN (ß = −0.224; $p = 0.033$), **(B)** Amygdala-sgACC (ß = −0.312; $p = 0.003$), and **(C)** PVN-sgACC (ß = −0.264; $p = 0.008$) connectivity. **(D)** The association between childhood abuse (Childhood Trauma Questionnaire, CTQ) and PVN-sgACC (ß = −0.258; $p = 0.018$) connectivity. * Indicates survival of FDR correction (0.05) for six tests; # indicates that the childhood threat variable remained significant with the addition of adulthood covariates (adulthood trauma, socioeconomic status and negative life events) to the model. (BNST, bed nucleus of the stria terminalis; PVN, paraventricular nucleus of the hypothalamus; sgACC, subgenual anterior cingulate cortex).

significant, continue to survive multiple comparison correction and remain significant with the additional adulthood covariates.

Abuse (Childhood Trauma Questionnaire Threat)

CTQ Threat had a significant, negative association with only one resting-state ROI-to-ROI connection, PVN-sgACC connectivity (ß = −0.258; $p = 0.018$, **Figure 2D** and **Table 3**). This finding did not survive multiple comparison correction (adjusted $p = 0.108$); however, it did remain significant (ß = −0.228; $p = 0.043$) with the additional adulthood covariates (trauma, SES and negative life events) (**Table 3**). SED did not have a significant association with any ROI-to-ROI connection examined.

Post hoc analyses examining CTQ Threat subscales (physical, emotional and sexual abuse) revealed that physical (ß = −0.255; $p = 0.023$, **Supplementary Table S5**) and sexual (ß = −0.250; $p = 0.014$, **Supplementary Table S6**) abuse were each negatively associated with PVN-sgACC connectivity. Both findings survived multiple comparison correction for 3 tests (one for each abuse type) [physical abuse (adjusted $p = 0.035$); sexual abuse (adjusted $p = 0.042$)]; however, only sexual abuse remained significant (ß = −0.248; $p = 0.015$) with the additional adulthood covariates (**Supplementary Tables S5, S6**).

Exploratory Analyses

Exploratory analyses examining later traumatic events (THQ 12-17) are included in **Supplementary Table S7**.

When CTQ Deprivation (Neglect) was substituted for SED in the THQ 0-11 or CTQ Threat models, no significant associations of CTQ Deprivation with any ROI-to-ROI connection were observed (data not shown).

TABLE 2 | Hierarchical linear regression results: childhood threat (early traumatic events, age 0–11) and central visceral network resting-state connectivity.

		BNST-PVN			Amygdala-sgACC			PVN-sgACC		
Step	**Variable**	**St. Beta**	***t***	***p***	**St. Beta**	***t***	***p***	**St. Beta**	***t***	***p***
1	Age	−0.107	−1.050	0.296	−0.036	−0.358	0.721	0.113	1.166	0.247
	Race	0.092	0.910	0.365	−0.177	−1.750	0.083	−0.038	−0.388	0.699
	Sex	0.096	0.943	0.348	0.007	0.068	0.946	0.301	3.111	**0.002**
2	Age	−0.085	−0.809	0.421	−0.007	−0.069	0.945	0.152	1.529	0.130
	Race	0.135	1.330	0.187	−0.117	−1.184	0.240	0.010	0.104	0.917
	Sex	0.097	0.961	0.339	0.009	0.093	0.926	0.295	3.102	**0.003**
	THQ 0-11	−0.224	−2.170	**0.033**	−0.312	−3.103	**0.003***	−0.264	−2.707	**0.008***
	Socioeconomic Deprivation	0.084	0.800	0.425	0.119	1.161	0.249	0.049	0.492	0.624
3	Age	0.008	0.067	0.947	−0.025	−0.210	0.834	0.161	1.417	0.160
	Race	0.121	1.183	0.240	−0.119	−1.170	0.245	0.003	0.026	0.979
	Sex	0.073	0.686	0.495	0.015	0.143	0.886	0.257	2.511	**0.014**
	THQ 0-11	−0.151	−1.312	0.193	−0.328	−2.887	**0.005***	−0.241	−2.201	**0.030**
	Socioeconomic Deprivation	0.074	0.639	0.524	0.108	0.944	0.348	0.053	0.487	0.628
	THQ > 18	−0.182	−1.385	0.169	0.039	0.299	0.766	0.048	0.384	0.702
	Adulthood SES	−0.139	−1.301	0.197	−0.006	−0.057	0.955	−0.037	−0.364	0.717
	Negative Life Events	−0.047	−0.387	0.699	0.013	0.103	0.918	−0.134	−1.143	0.256

Bold values indicate significance at $p < 0.05$; an asterisk indicates survival of FDR correction (0.05) for six tests.

Central Visceral Network Resting-State Connectivity and Affective Symptoms or Diagnoses

Of the three ROI-to-ROI connections that showed an association with childhood threat (early traumatic events and/or childhood abuse) (BNST-PVN, Amygdala-sgACC, PVN-sgACC), only BNST-PVN connectivity was associated with affective (depressive or post-traumatic stress) symptoms or diagnoses. BNST-PVN connectivity was negatively associated with depressive symptoms (ß = −0.138; $p = 0.169$, non-significant), post-traumatic stress symptoms (ß = −0.202; $p = 0.045$) and the number of lifetime affective diagnoses (ß = −0.236; $p = 0.011$, **Table 4**). The relationship between BNST-PVN connectivity and the number of lifetime diagnoses survived multiple comparison correction (adjusted $p = 0.033$) and remained significant when adulthood trauma, adulthood SES and negative life events were added to the model (ß = −0.191; $p = 0.032$, **Table 4**). Relationships between childhood adversity and affective symptoms/diagnoses are in **Supplementary Table S8**.

TABLE 3 | Hierarchical linear regression results: childhood threat (abuse) and central visceral network resting-state connectivity.

		PVN-sgACC		
Step	**Variable**	**St. Beta**	***t***	***p***
1	Age	0.113	1.166	0.247
	Race	−0.038	−0.388	0.699
	Sex	0.301	3.111	**0.002**
2	Age	0.150	1.494	0.139
	Race	0.004	0.043	0.966
	Sex	0.262	2.696	**0.008**
	CTQ Threat	−0.258	−2.398	**0.018**
	Socioeconomic Deprivation	0.105	0.986	0.327
3	Age	0.189	1.660	0.100
	Race	0.003	0.028	0.978
	Sex	0.214	2.081	**0.040**
	CTQ Threat	−0.228	−2.057	**0.043**
	Socioeconomic Deprivation	0.124	1.070	0.287
	THQ > 18	−0.004	−0.033	0.974
	Adulthood SES	−0.029	−0.284	0.777
	Negative Life Events	−0.166	−1.448	0.151

Bold values indicate significance at $p < 0.05$.

DISCUSSION

An expanding literature has linked childhood adversity to neural measures of brain structure, (e.g., gray matter volume, van Harmelen et al., 2010; Walsh et al., 2014) and white matter structural integrity (Choi et al., 2012; Hanson et al., 2013, 2015) and function [e.g., emotion or threat processing (Fani et al., 2010; McCrory et al., 2011, 2013; van Harmelen et al., 2012) and resting-state connectivity] (Teicher et al., 2016; Ho and King, 2021). Further, threat and deprivation dimensions of childhood adversity may have different neural correlates (McLaughlin et al., 2014; Sheridan and McLaughlin, 2014) and/or influence the same neural circuits in different ways (Banihashemi et al., 2021). How threat and deprivation may differentially influence a proximally stress-responsive, central visceral network (PVN, BNST, amygdala and sgACC) is unclear; previous work demonstrated that early experience may shape the sensitivity of these regions to stress (Banihashemi et al., 2011, 2015), however, childhood adversity-related differences in resting-state connectivity specific to this network have not been examined. To this end, the present study examined effects of

childhood threat (traumatic events and childhood abuse) and socioeconomic deprivation on the resting-state connectivity of this neural circuit. We hypothesized that threat and deprivation would have differential, potentially opposing effects on resting-state connectivity within this central visceral network.

Overall, we found that childhood threat (namely, early traumatic events, age 0–11) was associated with lower resting-state-connectivity among our central visceral, limbic forebrain-hypothalamic ROIs (BNST-PVN, Amygdala-sgACC and PVN-sgACC). Of these, our most robust findings were that greater exposure to early traumatic events was associated with less PVN-sgACC and amygdala-sgACC connectivity, both of which withstood multiple comparison correction, as well as the addition of adulthood covariates to the model. Contrary to our hypothesis of differential effects of threat and deprivation, we only identified childhood threat as being related to resting-state connectivity within our network, with no significant associations of socioeconomic deprivation (SED) on any ROI-to-ROI connections. Lastly, despite the well-known clinical significance of amygdala-sgACC connectivity, only BNST-PVN connectivity was associated with affective symptoms and disorders, implicating this connection as a potential mediator between childhood threat and affective vulnerability.

Relationships Between Childhood Threat and Subgenual Anterior Cingulate Cortex-Related Resting-State Connectivity

Two of the three identified ROI-to-ROI relationships with childhood threat involved the sgACC (PVN-sgACC and amygdala-sgACC), a central visceral/visceromotor limbic forebrain region (Vertes, 2004; Alexander et al., 2020) involved in negative affect (Shackman et al., 2011) and emotion regulation, that is also dysregulated in affective disorders (Gotlib et al., 2005; Drevets et al., 2008a,b; Matthews et al., 2009; Alexander et al., 2019). The present study demonstrated a relationship between childhood threat and PVN-sgACC connectivity; this was shown with both early traumatic events (THQ 0-11) and childhood abuse (CTQ Threat), where greater threat was associated with lower PVN-sgACC connectivity. Interestingly, the sgACC has little to no direct projection to the PVN (Öngür et al., 1998; Freedman et al., 2000; Floyd et al., 2001). The sgACC may influence PVN activity via its direct innervation of the BNST (Freedman et al., 2000; Dong et al., 2001a), which sends dense projections to the PVN from its anterolateral and fusiform subnuclei (**Figure 1**; Dong et al., 2001b; Dong and Swanson, 2004; Maita et al., 2021). Indeed, our findings did indicate that greater exposure to early traumatic events was associated with less BNST-PVN connectivity (discussed further below, Relationship between Childhood Threat and BNST-PVN Resting-State Connectivity).

Our findings also revealed a negative relationship between early traumatic events and amygdala-sgACC resting-state connectivity. The amygdala and sgACC are directly and reciprocally connected (**Figure 1**); from amygdala to sgACC, projections primarily stem from basal, accessory basal and lateral nuclei (Kim et al., 2018; Sharma et al., 2019). Projections from sgACC to amygdala innervate various subnuclei, including basal, accessory basal, medial and intercalated nuclei (Freedman et al., 2000). Blunt dissection and tractography techniques have also identified putative connections between them (Johansen-Berg et al., 2008; Vergani et al., 2016). To further elaborate the white matter these connections traverse, elegant work by Folloni et al. (2019) demonstrated that in both macaques and humans the amygdalofugal pathway and the uncinate fasciculus extend between the amygdala and sgACC. Our present finding that greater exposure to early traumatic events was associated with less amygdala-sgACC connectivity may indicate microstructural differences in these white matter pathways. Indeed, childhood adversity has been associated with less uncinate fasciculus fractional anisotropy (Eluvathingal et al., 2006; Kumar et al., 2013; Hanson et al., 2015; McCarthy-Jones et al., 2018); however, only a medial bundle from the uncinate extends along the sgACC, while a major section of the amygdalofugal pathway extends along the sgACC (Folloni et al., 2019). Thus, the amygdalofugal pathway may be a promising candidate neural mechanism underlying the relationship between childhood threat and amygdala-sgACC connectivity found here. Further, a recent study showed greater neurite density within the ventral amygdalofugal pathway with age, perhaps indicating greater fiber packing density and/or myelination of the tract (Azad et al., 2021). Future work will be needed to examine childhood adversity-related microstructural differences within this pathway across development and to determine its multimodal relationship to functional connectivity among these ROIs.

Our finding that greater exposure to early traumatic events is associated with less amygdala-sgACC connectivity in a sample of transdiagnostic young adults converges with that of Herringa et al. (2013) who found that greater childhood maltreatment was associated with less amygdala-sgACC connectivity in a late adolescent sample. In younger individuals, however, this relationship may be reversed. Thomason et al. (2015) found that trauma-exposed youth displayed greater centromedial amygdala-sgACC connectivity compared to controls; this work highlights the need for future work examining the connectivity of this central visceral network across development.

The amygdala-sgACC connection has long been thought to be clinically important (Drevets et al., 2008b). Herringa et al. (2013) found that amygdala-sgACC connectivity contributed substantially in mediating the relationship between maltreatment and internalizing symptoms. Depressed adolescents display elevated sgACC-amygdala connectivity (Connolly et al., 2013; Ho et al., 2014) or weaker bottom-up amygdala-sgACC connectivity (Musgrove et al., 2015). Amygdala-sgACC connectivity may also predict treatment response (Taylor et al., 2018; Nakamura et al., 2021). Recent studies highlight the role of amygdala-sgACC connectivity in fear-related encoding, emotional processing/regulation and anxiety (Hakamata et al., 2020; Scharnowski et al., 2020). Hakamata et al. (2020) demonstrated that greater fear encoding strength is associated with greater basolateral amygdala-sgACC

TABLE 4 | Hierarchical linear regression results: central visceral network resting-state connectivity and affective symptoms or diagnoses.

		BDI-II			PCL-C			Lifetime Diagnoses		
Step	**Variable**	**St. Beta**	***t***	***p***	**St. Beta**	***t***	***p***	**St. Beta**	***t***	***p***
1	Age	0.223	2.238	**0.028**	0.190	1.885	0.062	0.337	3.618	**0.000**
	Sex	−0.148	−1.486	0.141	−0.117	−1.167	0.246	−0.296	−3.189	**0.002**
	Race	−0.004	−0.042	0.967	0.029	0.286	0.776	−0.042	−0.450	0.653
2	Age	0.208	2.088	**0.039**	0.168	1.688	0.095	0.311	3.427	**0.001**
	Sex	−0.134	−1.354	0.179	−0.098	−0.986	0.327	−0.273	−3.019	**0.003**
	Race	0.009	0.086	0.932	0.047	0.477	0.634	−0.020	−0.221	0.826
	BNST-PVN Connectivity	−0.138	−1.385	0.169	−0.202	−2.032	**0.045**	−0.236	−2.603	**0.011***
3	Age	0.039	0.352	0.725	−0.049	−0.451	0.653	0.131	1.320	0.190
	Sex	−0.029	−0.288	0.774	0.031	0.314	0.754	−0.170	−1.885	0.063
	Race	−0.021	−0.218	0.828	0.016	0.176	0.861	−0.057	−0.665	0.508
	BNST-PVN Connectivity	−0.088	−0.898	0.372	−0.128	−1.347	0.181	−0.191	−2.177	**0.032**
	THQ > 18	0.186	1.560	0.122	0.247	2.149	**0.034**	0.220	2.078	**0.040**
	Adulthood SES	−0.048	−0.491	0.624	0.014	0.145	0.885	−0.101	−1.169	0.245
	Negative Life Events	0.253	2.264	**0.026**	0.320	2.973	**0.004**	0.227	2.285	**0.025**

Bold values indicate significance at $p < 0.05$; an asterisk indicates survival of FDR correction (0.05) for six tests.

connectivity, and that this connectivity was also elevated in anxious participants. Scharnowski et al. (2020) have examined the role of amygdala-sgACC connectivity during automated and effortful emotion regulation; during more automated/less effortful emotion regulation, they found greater amygdala-to-sgACC connectivity. Additionally, they found greater amygdala-to-sgACC modulation among anxious participants during effortful emotion upregulation (Scharnowski et al., 2020). In this context, our amygdala-sgACC findings may suggest less adaptive emotional processing or regulation related to fear-inducing or emotionally salient stimuli, however, such childhood threat-related differences could be indicative of functional impairments that yield vulnerability to affective disorders and/or neuronal adaptations to the early environment that yield resilience (Champagne et al., 2003; Teicher and Samson, 2016; Teicher et al., 2016; Ioannidis et al., 2020).

Relationship Between Childhood Threat and Bed Nucleus of the Stria Terminalis-Paraventricular Nucleus of the Hypothalamus Resting-State Connectivity

The present study also revealed an association between early traumatic events and BNST-PVN resting-state connectivity; however, this effect was less robust (i.e., did not withstand multiple comparison correction or the addition of adulthood covariates). This relationship did, however, converge with our previous finding that greater childhood threat (both traumatic events and childhood abuse) was associated with less stria terminalis white matter structural integrity (Banihashemi et al., 2021), a white matter bundle that connects these regions (**Figure 1**; De Olmos and Ingram, 1972; Nieuwenhuys et al., 2008). Taken together, these findings may indicate a reciprocal relationship between BNST-PVN structural and functional connectivity. Further, previous work in rodents shows that ascending noradrenergic/viscerosensory pathways from caudal brainstem collateralize to both BNST and PVN, thus, enabling coordinated modulation of both structures' response to stress (Banihashemi and Rinaman, 2006). These viscerosensory pathways course through the medial forebrain bundle (**Figure 1**), which our previous study also revealed may be diminished by childhood threat (Banihashemi et al., 2021). Thus, the medial forebrain bundle may be an indirect pathway underlying the resting-state relationship between BNST and PVN, as well as a neural mechanism underlying the current findings.

The BNST regulates physiological responses to stress not only via its own preautonomic projections but also through its direct connections to the PVN (Maita et al., 2021). Various BNST subnuclei differentially regulate physiological responses to stress (Choi et al., 2007; Crestani et al., 2013). PVN-projecting BNST neurons are primarily GABAergic and recent work has shown that the anteroventral BNST exerts inhibitory influence over HPA responses to stress (Radley et al., 2009; Johnson et al., 2016; Radley and Johnson, 2018) via potential peptidergic mechanisms (Zheng et al., 2019; Povysheva et al., 2021). Considered together, our finding that childhood threat (early traumatic events) was associated with lower BNST-PVN connectivity may indicate the BNST's diminished capacity to constrain the PVN and stressor-evoked HPA responses, perhaps yielding greater stress reactivity.

It has been proposed that anteroventral BNST-related circuitry is recruited by stress-inducing stimuli, but is uninvolved in tonic HPA regulation (Johnson et al., 2016). Our findings suggest that childhood threat may shape basal BNST-PVN connectivity, however, effects of childhood threat on sgACC-related connectivity (PVN-sgACC and amygdala-sgACC) were more robust, despite BNST-PVN connectivity having closer proximity to the control of stress responses. It is possible that childhood threat may shape the resting-state connectivity of this central visceral network in ways that prime the network to engage differently during stress, with indirect connections

(sgACC-related connectivity) more active at rest and direct connections (BNST-PVN) more active during stress.

Relationship Between Bed Nucleus of the Stria Terminalis-Paraventricular Nucleus of the Hypothalamus Resting-State Connectivity and Affective Disorders

The BNST's involvement in mediating responses to more distant, less predictable threats implicate it in future-oriented anxiety states, as well as addiction and other psychiatric disorders (Avery et al., 2016; Lebow and Chen, 2016; Clauss, 2019; Clauss et al., 2019; Limbachia et al., 2020). Recent work also indicates stronger BNST-hypothalamus structural connectivity in women, which may underlie sex differences in symptoms related to abstinence from alcohol and risk for relapse (Flook et al., 2021). As the BNST's anatomical connection to the PVN contributes in part to its ability to respond to threat, our findings may indicate childhood threat-related differences in vulnerability to affective disorders. Indeed, the present study found that greater BNST-PVN resting-state connectivity was associated with less affective symptoms and disorders (i.e., fewer lifetime diagnoses), implicating this connection as a potential mediator between childhood threat and affective vulnerability, although future, larger studies will be necessary to test formal mediation models (Fritz and MacKinnon, 2007).

Convergence With Large-Scale Networks

The sgACC is considered to be part of the default mode network (DMN), which is involved in self-related mental activity; the DMN is most active when individuals are not engaged in goal-oriented tasks and is deactivated when engaged in cognitive processing (Menon, 2013; Seitzman et al., 2019). The sublenticular extended amygdala and hypothalamus are considered to be part of the salience network (Menon, 2013), although the amygdala may also be considered part of the affective or limbic network (Seitzman et al., 2019). Nevertheless, our findings involved childhood threat-related differences in functional connectivity in cortico-amygdalar-hypothalamic regions that overlap with DMN and salience networks. Expanding literatures indicate that these networks, their nodes and connections between them are altered by childhood adversity (Werff et al., 2012; Marusak et al., 2015; Hoffmann et al., 2018; Cheng et al., 2021; Huang et al., 2021; Rakesh et al., 2021a; Merrick et al., 2018; Silveira et al., 2021), and that these networks are dysregulated in affective disorders (Greicius et al., 2007; Seeley et al., 2007; Jacobs et al., 2014, 2016; Iadipaolo et al., 2018). Thus, our findings may also reflect alterations within these large-scale networks that impact emotion regulation processes (DMN) and orientation to salient internal and external stimuli (salience) (Menon, 2013). Additionally, Kleckner et al. (2017) provided evidence of a large-scale, intrinsic allostatic-interoceptive system and demonstrated that stronger connectivity between hubs within this system supported greater interoceptive ability. This allostatic-interoceptive system is comprised of DMN and salience network regions and includes limbic cortices and subcortical and brainstem visceromotor regions (Kleckner et al., 2017; Ruiz-Rizzo et al., 2020; Sennesh et al., 2022) that converge with our central visceral network of interest (Myers et al., 2005; Banihashemi and Rinaman, 2006; Rinaman et al., 2011; Banihashemi et al., 2015, 2021). Further, Schaan et al. (2019) have shown that childhood maltreatment was associated with less stress-related interoceptive accuracy during a heartbeat perception task. Taken together, our findings indicating lower childhood threat-related central visceral network connectivity may have implications for diminished interoceptive ability and/or accuracy. Future work will be necessary to explicitly examine the neural mechanisms underlying links between childhood adversity and interoceptive ability/capacity.

Differential Relationships of Childhood Threat and Deprivation on Resting-State Connectivity

Several studies have examined differential relationships between resting-state connectivity and aspects of threat and deprivation dimensions (Cheng et al., 2021; Fadel et al., 2021; Park et al., 2021; Rakesh et al., 2021a). A study examining mesocorticolimbic circuitry in young children found opposing influences of threat and socioeconomic deprivation on ventral tegmental area (VTA)-related resting-state connectivity (Park et al., 2021), with greater threat associated with less VTA-somatomotor connectivity and greater deprivation associated with greater VTA-intraparietal sulcus connectivity. In a large adolescent sample, Rakesh et al. (2021a) found differential effects of threat and deprivation across development: at age 16, greater abuse was associated with less within salience network connectivity, while at age 19, greater neglect was associated with greater within-salience network connectivity, potentially indicating different trajectories for adversity dimensions. Fadel et al. (2021) also found differential relationships of threat and deprivation on salience network connectivity; in a sample of healthy and depressed adults they found opposing relationships of abuse and neglect on within salience network connectivity (i.e., prefrontal cortex-insula), in which greater abuse was associated with greater resting-state connectivity and greater neglect was associated with less resting-state connectivity. The present study did not find effects of socioeconomic deprivation, as defined by maximum parental education level (reverse coded), on any ROI-to-ROI connection. Effects of CTQ Deprivation (neglect) on central visceral network connectivity were also explored and no significant relationships were found (data not shown). It is possible that socioeconomic deprivation will have a greater impact on stressor-evoked activity and connectivity within this central visceral network than on its resting-state connectivity. Future work on this network will be needed to investigate different aspects of the deprivation construct (e.g., neighborhood and cognitive deprivation).

Limitations and Future Directions

A limitation of this study is its cross-sectional design examining young adults; however, participants were specifically recruited across a continuum of physical abuse severity, with individuals

across a spectrum of affective symptom severity including those with depression, anxiety and trauma-related disorders. This recruitment strategy achieved a relatively even distribution across childhood socioeconomic status, as well. Nevertheless, future prospective work will be needed to examine distinct dimensions of childhood adversity and how they differentially impact this central visceral network across development. Additionally, future studies designed to be statistically powered for detecting realistic effect sizes for mediation are necessary to further examine central visceral network components as mediators of the relationship between childhood adversity and affective symptoms/disorders.

Regions of interest in the present study were defined using a template for manual segmentation [sgACC, BNST and PVN (Banihashemi et al., 2015; Wu et al., 2019)]. Greater accuracy and precision are necessary to define specific subnuclei within these ROIs and to examine additional components of the network (e.g., brainstem nuclei), which may benefit from high-field acquisitions. Improvements in manual segmentation approaches for these regions and continued advancements in automated segmentations would also benefit the examination of these brain regions, particularly in humans. Future work will be needed to capitalize on current advances (Avery et al., 2014; Saygin et al., 2017; Wolff et al., 2018).

SUMMARY AND CONCLUSION

This study provides novel evidence that childhood threat may influence a central visceral network. Analyses revealed that childhood threat is associated with lower connectivity among our ROIs (PVN-sgACC, amygdala-sgACC and BNST-PVN). These findings have functional and clinical implications that suggest potential alterations in emotion regulation and processing, orienting responses to salient stimuli, and stress and threat reactivity. Further, our results demonstrate that BNST-PVN connectivity may provide a novel link between childhood threat and affective symptoms and disorders. In conclusion, exposure to threat during early development may entrain altered patterns of resting-state connectivity between these stress-related regions in ways that contribute to dysregulated neural and physiological responses to stress and subsequent affective psychopathology. Investigating how this network links childhood adversity and affective symptoms may elucidate underlying neural mechanisms of affective disorders, as well as guide interventions targeting these brain structures.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they are still undergoing primary analyses. The data that support the findings of this study will be made available from the corresponding author upon request in the future. Requests to access the datasets should be directed to LB, layla.banihashemi@pitt.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Pittsburgh Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LB conceptualized the research, acquired funding, conducted the research, performed formal analysis, wrote the original draft, and reviewed and edited the manuscript. CP conducted the research, managed and coordinated the research, performed formal analysis, and wrote portions of the Methods. AR performed formal analysis and implemented code and algorithms. HK provided programming, implemented code and algorithms, and reviewed and edited the manuscript. MW contributed to creation of models and reviewed and edited the manuscript. BS wrote portions of the Discussion and reviewed and edited the manuscript. JS wrote portions of the Introduction. MS provided data curation. AG provided mentorship, oversight, and resources. HA provided mentorship, oversight, and resources and reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.805049/full#supplementary-material

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Peer Victimization Influences Attention Processing Beyond the Effects of Childhood Maltreatment by Caregivers

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Background: Different types of maltreatment (emotional, physical, and sexual) lead to distortions in emotion and attention processing. The present study investigated whether the experience of peer victimization in childhood and adolescence has an additional influence on attention processing in adulthood.

Methods: Two non-clinical samples consisting of individuals with different levels of experiences of maltreatment were recruited. In an evaluative conditioning task, images of faces with neutral emotional expression were either associated with short videos of intense negative statements, or associated with neutral videos. Subsequently, these faces were used as stimuli in an emotional Stroop task as well as a dot-probe task.

Results: In both tasks, hierarchical regression analyses revealed that retrospective reports of relational peer victimization made an incremental contribution to the prediction of attentional biases beyond child maltreatment. In the emotional Stroop task, emotional abuse was the strongest predictor for an attentional bias showing delayed responses to negatively associated faces, while peer victimization was associated with faster responses to negatively associated faces. In the dot-probe task, relational peer victimization was the strongest predictor for an attentional bias. When the attentional bias was examined in more detail, though, peer victimization did not show incremental contributions although emotional abuse remained the strongest predictor for facilitated attention toward negatively associated neutral faces.

Conclusion: Experiences of peer victimization leave additional cognitive scars beyond effects of childhood maltreatment by caregivers. It is likely that attentional biases in the aftermath of victimization put individuals at risk for the development of psychopathology.

Keywords: child maltreatment, peer victimization, attentional bias, emotional Stroop, dot-probe

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INTRODUCTION

Attentional biases are characterized by a selective and differential allocation of attention toward emotional stimuli in comparison to neutral stimuli (for a review, see Cisler and Koster, 2010). Specifically, attentional biases can be divided into facilitated attention (i.e., faster detection of threatening stimuli), difficulty in disengagement (i.e., disengaging attention from threat stimuli

is more difficult than disengaging from neutral stimuli), and attentional avoidance (i.e., shifting attention toward locations opposite the location of threat; Cisler and Koster, 2010). In addition to a large body of research showing that attentional biases robustly emerge among clinical populations (e.g., Bar-Haim et al., 2007; Cisler and Koster, 2010), studies indicated that experiences of childhood maltreatment are also associated with altered attentional processes in the processing of threatening information (e.g., Pollak et al., 2001; Grant et al., 2011; Günther et al., 2015). However, the kinds of attentional biases that have been linked to childhood maltreatment have differed across studies. For example, individuals reporting a history of childhood maltreatment showed an enhanced sensitivity to detect threatening cues from emotionally ambiguous faces which was thought to be indicative of a facilitated processing of threatening information (Pollak and Sinha, 2002; Gibb et al., 2009). Attentional avoidance of threatening faces and difficulties in disengaging from sad faces, though, have been reported in samples of children who had experienced physically abuse (Pine et al., 2005; Romens and Pollak, 2012). Since childhood maltreatment is a heterogenous phenomenon that includes various types of abuse and neglect, it is likely to assume that different forms of maltreatment, such as abuse and neglect, influence attentional biases toward threatening stimuli differently. Similarly, various kinds of childhood maltreatment have differential psychopathological outcomes (Danielson et al., 2005; Teicher et al., 2006; Lobbestael et al., 2010; Teicher and Samson, 2013). This is also supported by recent reports of differential effects of abuse and neglect on neural mechanisms that may link childhood maltreatment to psychopathology and alterations in emotional functioning (Dong et al., 2004; McLaughlin et al., 2014; Sheridan and McLaughlin, 2014; Humphreys and Zeanah, 2015; Zeanah and Sonuga-Barke, 2016; Roth et al., 2018). Critically, however, there are a limited number of studies examining differential effects of specific kinds of childhood maltreatment on attentional biases.

In one study of childhood maltreatment and attentional biases, Günther et al. (2015) analyzed the differential impact of five factors of childhood maltreatment (emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse) on attentional biases in a dot-probe task and reported that sustained attention toward sad facial expressions was associated with emotional forms of maltreatment and physical neglect, but not with physical and sexual abuse. Notably, the relationship of childhood maltreatment and sustained attention was not confounded by the severity of symptoms of depression, even though a sample of depressed individuals was examined. Similarly, attentional processes varied as a function of different forms of childhood maltreatment in a study using a visual search paradigm combining a social conditioning paradigm with a face in the crowd recognition task (Iffland and Neuner, 2020). Specifically, emotional forms of maltreatment were particularly associated with an altered sensitivity in detecting faces. While emotional abuse was associated with faster recognition of negatively associated faces, emotional neglect was related to slower detection of both negative and neutral faces. Experiences of physical abuse were shown to be associated with slower detection of negatively associated faces compared to neutrally associated faces. Past experiences of sexual abuse, however, did not have an impact on individuals' performance in this study (Iffland and Neuner, 2020). In addition, processing of emotional cues varied between types of maltreatment in a facial emotion recognition task (Pollak et al., 2000). In this study, physically abused children showed a response bias for angry facial expressions, whereas physically neglected children presented with difficulties in differentiating among emotional expressions. Reports of differential effects of maltreatment types on attentional processes were not supported by Fani et al. (2011), though. In their study with a sample of patients with posttraumatic stress disorder (PTSD), childhood maltreatment uniquely predicted attentional biases toward happy faces relative to neutral faces. However, differing associations between attention processing and different types of childhood maltreatment were not found. Although there is growing body of literature indicating that different types of maltreatment affect attentional biases differently, further research is needed to examine the extent to which the various kinds of maltreatment account for differences in attentional processes.

In addition, most studies examined attentional biases as a function of childhood maltreatment including emotional, physical, or sexual abuse and neglect by caretakers (e.g., Günther et al., 2015; Iffland and Neuner, 2020). However, maltreatment is not isolated within the context of families alone. There are also experiences of maltreatment that involve emotional forms of abuse by peers (Storch et al., 2005; Siegel et al., 2009). This relational peer victimization is characterized by bullying, verbal threats or aggression, malicious manipulation of a relationship, friendship withdrawal, and damaging another's peer relationships (Siegel et al., 2009). Prevalence rates of repeated peer victimizations range between 10 to 20% in school children, with periodic adversities being indicated even more frequently (e.g., Rudolph et al., 2010). Similar to experiences of maltreatment by caretakers, a history of relational peer victimization increases the risk of various forms of psychopathology, with peer victimization predicting psychological symptoms even beyond the effects of child maltreatment (Storch et al., 2005; Sansen et al., 2014). For instance, it has been demonstrated that emotional peer abuse is associated with increased rates of depression, anxiety disorders, suicidality, psychosomatic complaints, sleep and eating disorders, self-injurious behavior, dissociation, substance use, and psychosis (e.g., Gladstone et al., 2006; Teicher et al., 2010; Copeland et al., 2015). In particular, the relationship of peer victimization to social anxiety is well established (e.g., Storch et al., 2003; Storch and Masia-Warner, 2004; Ranta et al., 2009; Siegel et al., 2009; Iffland et al., 2012; Sansen et al., 2015).

With respect to attention processes, children who reported more frequent experiences of peer victimization showed less interference when confronted with victim-related words in an emotional Stroop task (Rosen et al., 2007). Accordingly, within the framework of a modified social-information-processing model, the authors proposed that peer victimization was associated with preemptive, defensive processing of threatening cues (Rosen et al., 2007). On the contrary, individuals who

had experienced peer victimization showed delayed responses in color-naming negative adjectives compared to neutral adjectives in an emotional Stroop task (Iffland et al., 2019). However, in line with Rosen et al. (2007), an additional dot-probe task applied in the same sample revealed that participants with a history of peer victimization avoided negative adjectives rather than detecting them faster or allocating their attention toward negative words. Even more, since the pattern of results did not differ between negative and positive adjectives, the results of this study indicated that peer victimized individuals presented with a general emotion-avoidant, rather than threat avoidant, attentional style (Iffland et al., 2019). Most notably, in this sample of psychiatric inpatients and healthy controls, attentional avoidance of emotional words was more closely associated with experiences of peer victimization than with the current diagnostic status (Iffland et al., 2019). It may be that attentional avoidance of emotional stimuli could increase the risk of victims of peer abuse for the development of psychopathology.

Recent studies in clinical as well as healthy samples suggest that negative life experiences influence the magnitude of attentional biases (Field et al., 2001; Gibb et al., 2009; Aishu and Chunmei, 2014; Günther et al., 2015; Iffland et al., 2019). Indeed, attentional biases may play a crucial role in the link between childhood maltreatment experiences and the development of psychopathology (Pollak, 2003). Still, knowledge about the unique contributions of different forms of childhood maltreatment to the development of attentional biases is scarce. Moreover, to our knowledge, there are no studies examining the incremental effect of relational peer victimization on attentional biases when controlling for experiences of child maltreatment. Therefore, the purpose of the current sample was to extend the previous research (e.g., Günther et al., 2015; Iffland and Neuner, 2020) by examining differential associations between various types of childhood maltreatment and peer victimization and attentional biases in healthy adult samples.

As experimental tasks to measure attentional biases, we applied both an emotional Stroop task (Stroop, 1935) and a dot-probe task (MacLeod et al., 1986; Koster et al., 2004; for a review see Cisler and Koster, 2010). Following previous studies (Rosen et al., 2007; Iffland et al., 2019), we decided to use the emotional Stroop task. The emotional Stroop task is the most commonly used task to measure attentional biases indicating interference by higher response times to color-naming of threat words compared to neutral words (Cisler and Koster, 2010). Because of several shortcomings in the interpretation of attentional biases measured with the emotional Stroop task (Cisler and Koster, 2010), however, the dot-probe task was additionally used. The advantage of the dot-probe task is that is was developed to distinguish different aspects of attentional biases, i.e., difficulty in disengaging and facilitated attention (Cisler and Koster, 2010). Moreover, the dot-probe task allows for the measurement of spatial attention allocation (MacLeod et al., 1986). In line with a previous study extending the evolutionary theory of attentional biases (Iffland and Neuner, 2020), we postulated that not only the detection of emotional facial expressions, but also the detection of differently evaluated individuals, represented by neutral faces that are associated with different emotions, may be shaped by life experiences differently. That is, threat is not always linked to overt facial expressions of negative emotions in real-world settings. Thus, rather than perceptual features of their faces, the rapid identification of potential perpetrators should initiate a quick location, recognition, and response to potential social threats (Iffland and Neuner, 2020). And the rapid identification should depend on previous experiences with specific persons (e.g., childhood maltreatment). Therefore, we applied a more ecologically valid test for attentional biases in maltreated individuals by combining an evaluative conditioning task with an emotional Stroop and a dot-probe task. As a first step, we coupled still images of neutral faces with short videos of negative/disapproving evaluations vs. neutral statements of the same actors from the E.Vids video set in the evaluative conditioning task (Blechert et al., 2013; see also Iffland and Neuner, 2020). Second, the images of neutral faces were used as stimuli in the emotional Stroop and dot-probe tasks. By doing this, we aimed at extending previous research using a visual search paradigm (Iffland and Neuner, 2020). Response times (RTs) were used to detect whether neutral faces evaluated as being negative were associated with different attention processes than neutral faces with a neutral evaluation.

The aim of the present study was to examine differential unique contributions of various forms of childhood maltreatment to attentional biases in facial emotion processing. Particularly, extending previous research (e.g., Günther et al., 2015; Iffland and Neuner, 2020), the incremental contribution of experiences of peer victimization in the prediction of attentional biases when controlling for histories of childhood maltreatment was assessed. With respect to previous studies reporting that peer victimization predicts psychopathology beyond the effects of childhood maltreatment (Sansen et al., 2014), we hypothesized that peer victimization would make a significant incremental contribution of variance to the prediction of attentional biases. Specifically, in line with a previous study (Iffland et al., 2019), we assumed that peer victimization would be associated with attentional avoidance of negatively associated faces. Regarding the unique contributions of forms of childhood maltreatment by caretakers, in line with previous studies (Günther et al., 2015; Iffland and Neuner, 2020), we assumed that attentional biases would be particularly associated with emotional forms of childhood maltreatment.

MATERIALS AND METHODS

Participants

Two samples were recruited to address the study's aims. The first sample completed the emotional Stroop task and the second completed the dot-probe task. Participants of both samples were recruited through online advertisements and bulletins on the Bielefeld University campus advertising a study examining the consequences of personality traits on attention. Inclusion criteria were age between the ages of 18 and 65 and sufficient knowledge of German language (clearly able to understand the information and instructions). No further exclusion criteria were applied. The emotional Stroop task sample consisted of 94 participants (54

females, 57.4%) ranging in age from 18 to 65 years with a mean of 26.40 (*SD* = 10.65). The dot-probe task sample consisted of 89 participants (56 females, 62.9%) ranging in age from 18 to 60 years with a mean of 25.10 (*SD* = 7.44). In both samples, each participant read and signed an informed consent form that was approved by the Ethics Committee of Bielefeld University. The demographic characteristics of the samples and participants' means on the assessments are presented in **Table 1**.

Stimuli, Design, and Apparatus

In line with a previous study (Iffland and Neuner, 2020), we utilized a social conditioning paradigm using 3000 ms duration videos of negative and neutral sentences from the E.Vids video set (Blechert et al., 2013) for the conditioning of neutral faces to negative/disapproving vs. neutral valence. Within this paradigm, still images of neutral faces from four different actors (two female) served as conditioned stimuli (CSs) predicting dynamic videos of negative/disapproving evaluations (e.g., 'You're ridiculous,' 'I hate you,' 'I can't stand you') vs. neutral statements (e.g., 'The bus is stopping,' 'It's windy outside,' 'It's 4 o'clock') of the same actors as unconditioned stimuli (US) (for details see Wiggert et al., 2017). No information about CS-US contingencies was provided. The conditioning consisted of 64 trials, 32 trials (16 per actor) coupling CSs with a negative US and 32 trials (16 per actor) coupling CSs with a neutral US. Each of the four actors spoke eight different sentences, each sentence presented twice. For each participant, two actors were presented in the socially negative and two actors were presented in the neutral condition. Actors' conditions were counterbalanced over participants. Video volume was constant across participants. Each trial started with the presentation of a black fixation cross in the center of a white screen for 500 ms before being replaced by the CS. Conditioned stimuli were shown for 1000 ms and were followed by the presentation of a black fixation cross in the center of a white screen for 1500 ms. Then, the USs were presented for 3000 ms. Inter-trial intervals varied randomly between 5000 and 7000 ms. Stimuli were presented on a 23-inch LCD monitor with a resolution of 1920 × 1080 pixels and 120 Hz refresh rate, using E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA, United States).

For both the emotional Stroop and the dot-probe task, we used the four still images of neutral faces that were negatively or neutrally associated in the social conditioning paradigm.

Participants viewed stimuli at a distance of 60 cm. Stimuli were presented on a 23-inch LCD monitor with a resolution of 1920 × 1080 pixels and 120 Hz refresh rate. We used the software package Inquisit 4.0.3 (Millisecond Software, Seattle, WA, United States) to deliver stimuli and record responses and reaction times (RTs).

The emotional Stroop task consisted of 128 trials. In total, 64 negatively and 64 neutrally associated neutral faces were shown, in each case 16 faces were colored in red, 16 in blue, 16 in green, and 16 were colored in yellow. For this purpose, we used black-and-white (binary) images of the faces, in which the white parts were colored in the respective colors. Each single face was presented 32 times, eight times in each color. Each image was 20.5 cm (width) × 18 cm (height) and presented on a black background. Stimuli were shown throughout until the participants responded. After an intertrial interval of 200 ms the next stimulus was presented. Responses were made on an external keyboard in which four keys were activated. The participants' task was to identify the color of the presented faces as quickly and as accurately as possible. Participants indicated their response by pressing buttons on an external keyboard with the index and middle fingers of both hands. In order to ensure that the participants were able to assign the colors to the appropriate buttons, the assignment of buttons and colors was presented on the screen throughout the experiment. The assignment of buttons was counterbalanced across participants. The order of faces, face valences, and colors was randomized. No feedback on accuracy was provided.

The dot-probe task consisted of two blocks of 64 trials each, with a short break between the blocks. There were two different types of trials in the present task: negative–neutral and neutral-neutral, with negatively and neutrally, and neutrally and neutrally associated neutral faces combined, respectively. For each trial, two faces were presented simultaneously. The face pairs were presented with one face beside the other (horizontal) in the middle of the screen. Each image was 8 cm (width) × 6.7 cm (height). The dot-probe experiment began with 12 practice trials using neutral–neutral face pairs to familiarize participants with the task. Each trial started with a black fixation cross presented in the center of a white screen for 500 ms. Then, a face pair appeared with one face beside the other for 500 ms. A gray dot emerged in one of the face locations immediately after the offset of the faces. The location of the target face (left or right) and probe (left or right) was randomized for all trials. The inter-trial interval for all trials was 500 ms. Responses were made on an external keyboard in which two keys were activated. Participants were instructed to

TABLE 1 | Subject characteristics and mean values on the assessments.

	Emotional Stroop task (*N* = 94)	Dot-probe task (*N* = 89)
Age, *M* (*SD, range*)	26.40 (10.65, 18–65)	25.10 (7.44, 18–60)
Gender,% *female* (*n*)	57.4 (54)	62.9 (56)
Family status,% *single* (*n*)	57.4 (54)	49.4 (44)
Educational level,% high school graduation and higher (*n*)	83.0 (78)	88.7 (79)
Symptoms of Depression[1], *M* (*SD*)	8.83 (6.23)	8.97 (5.22)
General Psychopathology[2], *M* (*SD*)	0.48 (0.38)	0.50 (0.40)
Trait Anxiety[3], *M* (*SD*)	39.30 (11.60)	41.05 (9.54)
Childhood Trauma Questionnaire, *M* (*SD*)	34.59 (9.76)	35.16 (11.35)
Emotional Abuse, *M* (*SD*)	7.87 (3.24)	8.21 (4.14)
Emotional Neglect, *M* (*SD*)	9.05 (3.60)	8.96 (3.99)
Physical Abuse, *M* (*SD*)	5.64 (2.30)	5.79 (2.04)
Physical Neglect, *M* (*SD*)	6.61 (2.06)	7.04 (2.65)
Sexual Abuse, *M* (*SD*)	5.41 (1.28)	5.16 (0.82)
Peer Victimization[4], *M* (*SD*)	9.52 (6.96)	9.13 (5.71)

[1]Beck Depression Inventory; [2]Brief Symptom Inventory — Global Severity Index; [3]State Trait Anxiety Inventory-Trait; [4]Fragebogen zu belastenden Sozialerfahrungen.

respond as quickly and as accurately as possible and to indicate the location of the gray dot (left or right) by pressing either the "E" (left) or "I" (right) keys on an external keyboard with the index fingers of both hands. The two types of face pairs were randomly formed. Each face was presented 64 times (32 times on each side) for a total of 128 experimental trials. The combination and order of face pairs varied randomly for each participant. No feedback on accuracy was provided.

Instruments

The *Fragebogen zu belastenden Sozialerfahrungen* (*FBS;* [Adverse Social Experiences Questionnaire]) was used to assess relational peer victimization (Sansen et al., 2013). This self-report questionnaire consists of 22 items describing aversive social situations like rejection, exclusion, being laughed at, insulted, and teased by peers (e.g., "I was excluded from games or activities by other children or adolescents," "I have been laughed at in the presence of other children"). For each situation, respondents were asked whether or not they have experienced this situation during childhood (age 6–12) or adolescence (age 13–18). The total score was calculated as a sum of "Yes" responses across both age periods and ranged from 0 to 44. The total-score of the FBS presented with a satisfying stability over a 20-month period (r = 0.89) (Sansen et al., 2013). Moderate correlations with the scales of the Childhood Trauma Questionnaire (Wingenfeld et al., 2010), as well as an incremental contribution to the prediction of psychopathology, support the idea that the FBS assesses an additional construct of child maltreatment (Iffland et al., 2012; Sansen et al., 2013).

Childhood maltreatment was measured using the German Version of the Childhood Trauma Questionnaire (CTQ; Wingenfeld et al., 2010; Klinitzke et al., 2012). With the CTQ, all common types of childhood maltreatment (emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse) that have occurred before the age of 18 can be assessed. In the present study, dimensional sum scores for each CTQ subscale were used in the statistical analyses. The CTQ physical neglect subscale was not included in the following statistical analyses because it was highly correlated with the other CTQ subscales, and presented with a weak internal consistency in comparison to the other subscales in a validation study (Klinitzke et al., 2012). For the sake of a comparison with other samples, however, mean score and frequency of the CTQ physical neglect subscale are presented. **Table 2** presents the bivariate Pearson correlation coefficients of different types of maltreatment and peer victimization for both samples.

Moreover, the assessment battery included a socio-demographic questionnaire as well as well-established questionnaires for symptoms of depression (German version of the Beck Depression Inventory II, BDI-II; Hautzinger et al., 2006; Kühner et al., 2007), general psychopathology and psychological distress (German version of the Brief Symptom Inventory, BSI; Derogatis and Melisaratos, 1983; Derogatis, 1993; Franke, 2000), and trait anxiety (German version of the State Trait Anxiety Inventory-Trait, STAI-T; Spielberger et al., 1970; Laux et al., 1981).

TABLE 2 | Bivariate Pearson correlation coefficients of different types of maltreatment and peer victimization for samples of the emotional Stroop (N = 94) and the dot-probe task (N = 89).

Emotional Stroop task	**Emotional abuse**	**Emotional neglect**	**Physical abuse**	**Sexual abuse**	**Peer victimization**
	r	***R***	***r***	***r***	***r***
Emotional abuse	–				
Emotional neglect	0.68***	–			
Physical abuse	0.47***	0.45***	–		
Sexual abuse	0.56***	0.49***	0.50***	–	
Peer victimization	0.37***	0.51***	0.42***	0.23*	–
Dot-probe task	**Emotional abuse**	**Emotional neglect**	**Physical abuse**	**Sexual abuse**	**Peer victimization**
	r	***R***	***r***	***r***	***R***
Emotional abuse	–				
Emotional neglect	0.74***	–			
Physical abuse	0.71***	0.53***	–		
Sexual abuse	0.43***	0.45***	0.27**	–	
Peer victimization	0.49***	0.45***	0.28**	0.38***	–

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Procedure

Procedures were identical in both tasks. Prior to the laboratory session, participants were asked to complete the assessment battery described above. Afterward, participants were tested individually in a darkened room. All instructions for the tasks were presented on the computer screen for the participants to read. Participants were informed that they would see a series of images and videos of different people and they would be asked to evaluate them. During a pre-conditioning rating phase, subjects evaluated neutral still images of the actors (for details see Wiggert et al., 2017) for valence, arousal, and disapproval using an on-screen visual analog scale to control for baseline differences in the evaluation of the four actors that were presented in the social conditioning paradigm. Next, participants attended to the 64 trials of the social conditioning paradigm followed by a post-conditioning evaluative rating phase of each actor's still image using the same rating scales described above. Post-conditioning evaluative rating served to evaluate whether social conditioning was successful. Next, participants completed either the emotional Stroop tasks or the dot-probe task. Before the emotional Stroop task, participants were informed that they would see faces presented in different colors and that their task was to identify the color of the presented faces. Participants indicated their response by pressing either the button "D," "F," "J," or "K" on a keyboard with their index and middle fingers of both hands. Assignment of buttons to colors alternated between participants. Before the dot-probe task, participants were informed that they would see

pairs of faces and that their task was to indicate the location of the gray dot (left or right). Participants indicated their response by pressing either the button "E" (left) or "I" (right) on a keyboard with the index fingers of both hands. Following completion of the attention tasks, another rating phase was completed using the same steps as the pre- and post-conditioning phase. This was used to examine if the effect of social conditioning lasted throughout the attention tasks. After these tasks were completed, participants were debriefed.

Data Reduction

In the emotional Stroop task an attentional bias was indicated by greater color-naming latencies following negatively associated faces in comparison with neutrally associated faces (Williams et al., 1996). Therefore, a difference score for the reaction times (RT) in color-naming negative and neutral trials was calculated (emotional Stroop Index = RT negatively associated faces – RT neutrally associated faces). Positive scores indicate a greater attentional bias in the processing of negatively associated faces. Furthermore, RTs of trials with negatively associated faces and trials of neutrally associated faces can be used to identify underlying mechanisms of attentional biases. That is, positive emotional Stroop index scores could be either caused by higher RTs in color-naming negatively associated faces or by lower RTs in color-naming neutrally associated faces. Initially, 95 participants were tested using the emotional Stroop task. Consistent with procedures of prior studies, trials with reaction times lower than 300 ms or higher than 4000 ms were excluded from analyses (Moritz et al., 2008; Wittekind et al., 2010). In addition, trials where participants indicated the wrong color (error trials) were excluded. Over 128 trials, participants indicated between 0 and 13 wrong colors (M = 5.96, SD = 4.81). No participants were excluded due to error rates higher than 25%. Outliers were defined as participants presenting mean reaction times that deviated more than three SDs from sample mean reaction times and were removed from analyses (n = 1). Accordingly, the remaining sample for the analyses of the emotional Stroop task consisted of 94 participants. Further, individual RT outliers, defined as ±2 SDs from the individual's mean (4.7% of all correct trials), were excluded from the calculation of that participant's mean score.

In the dot-probe task an attentional bias was indicated by either lower RTs to the probe if it emerged at the location where the participants were focusing their attention, or higher RTs to the probe when it appears in the location where the participants were not attending (Roberts et al., 2010). The attentional bias scores were calculated by subtracting participants' RTs to the probe when it appeared in the same position as the target face (congruent trials) from participants' RTs to the probe when it did not appear in the same position as the target face (incongruent trials; MacLeod and Mathews, 1988; Roberts et al., 2010). In the present study, the target faces were the negatively associated faces in the negative–neutral trials. According to previous research (MacLeod and Mathews, 1988; Roberts et al., 2010), significant positive bias scores indicate that participants were focusing their attention on the area around the target faces when the probe occurred, whereas significant negative bias scores indicate that participants were not attending to the area around the target faces when the probe occurred (i.e., avoidance).

To differentiate the mechanisms underlying the attentional bias (vigilance vs. difficulty to disengage), additional index scores were calculated (Koster et al., 2004). Vigilance should lead to faster responses on trials where the probe appeared where participants were attending compared to neutral trials. Difficulties in disengaging attention from negatively associated faces would result in slower reaction times on trials where the probe appeared in a location they were not attending to due to the time needed to shift attention from the negatively valenced location to the neutral location. Specifically, the Orienting Index score was calculated by subtracting participants' RTs to the probe when it occurred in the same position as the target face (congruent trials) from participants' RTs to the probe when two neutrally associated faces were presented (neutral trials; Koster et al., 2004). The Disengaging Index score was calculated by subtracting participants' RTs to the probe when two neutrally associated faces were presented (neutral trials) from participants' RTs to the probe when it did not occur in the same position as the target face (incongruent trials; Koster et al., 2004).

Initially, 94 participants were tested using the dot-probe task. In line with previous studies, trials with reaction times lower than 150 ms or higher than 2000 ms were excluded from analyses (Koster et al., 2004; Dewitte et al., 2007; Bardel et al., 2013). In addition, trials where participants indicated the incorrect location of the probe (error trials) were excluded. Out of 128 trials, participants indicated between 0 and 53 incorrect locations (M = 11.38, SD = 12.43). One participant was excluded due to error rates greater than 25%. Outliers were defined as participants presenting mean reaction times that deviated more than three SDs from mean reaction times and were removed from analyses (n = 4). Accordingly, the remaining sample for the analyses of the dot-probe task consisted of 89 participants. Moreover, individual RT outliers, defined as ±2 SDs from the individual's mean (5.6% of all correct trials), were excluded from the calculation of that participant's mean score.

Statistical Analyses

For the planned multiple linear regression analyses using RTs as outcome variable, a statistical power analysis was performed for sample size estimation using G*Power 3.1 (Faul et al., 2009). With respect to previous results (Günther et al., 2015; Iffland and Neuner, 2020), the effect size (ES) in this study was considered to be medium to large using Cohen's (1988) criteria (Cohen's f^2 = 0.25). With an α = 0.05, power = 0.95, and inclusion of seven predictors (emotional abuse, emotional neglect, physical abuse, sexual abuse, peer victimization, age, gender), the projected sample size needed with this ES was N = 86. We anticipated a loss of data of approximately 10 percent due to error trials and outliers. Therefore, we aimed at recruiting 94 participants for each attention task.

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) 27. Consistent with procedures utilized in prior research (Iffland et al., 2018; Iffland and Neuner, 2020), we calculated experiential rating composite scores (mean-score of the arousal, valence, and disapproval

ratings) for analyses of differential conditioning effects on self-report data in both samples. Experiential data was assessed through a 2 (CS-type: CS-negative, CS-neutral) x 3 (time of assessment: pre-conditioning, post-conditioning, post attention task) analysis of variance (ANOVAs) with repeated measures on CS-type and time of assessment. When necessary, additional *post hoc t*-tests were conducted separately for different times of assessment. When Mauchly's test indicated violation of the sphericity assumption, Greenhouse–Geisser corrections were applied and the original degrees of freedom together with Greenhouse–Geisser ε are reported.

In order to determine the relative contribution of child maltreatment and relational peer victimization for the prediction of attentional bias indices, several sets of hierarchical multiple regression analysis were conducted. For this purpose, we used the continuous sum scores of the CTQ subscales emotional abuse, emotional neglect, physical abuse, and sexual abuse as well as the continuous sum score of the FBS. In the hierarchical regression analyses, age and gender were included as predictors in a first step. In a second step, emotional abuse, emotional neglect, physical abuse, and sexual abuse were added. Relational peer victimization was added in a third step. In the emotional Stroop task sample, regression analyses were conducted separately for the emotional Stroop index score and RTs of trials with negatively associated faces and trials of neutrally associated faces. Here, preliminary analyses showed no violation of the assumption of multicollinearity (tolerances > 0.40; variance inflation factors < 2.48). In the dot-probe task sample, hierarchical regression analyses were conducted separately for each of the three indices of the dot-probe task presented above. Preliminary analyses showed no violation of the assumption of multicollinearity in this sample (tolerances > 0.29; variance inflation factors < 3.50).

RESULTS

Emotional Stroop

Social-Conditioning Paradigm

A CS-type × Time of assessment ANOVA using the experiential rating composite score was conducted to test whether the association of the neutral faces with negative and neutral valences was successful. The ANOVA revealed significant main effects of CS-type and time of assessment [CS-type: $F(1,93) = 93.15$; $p < 0.001$; $\eta^2 = 0.500$; time of assessment: $F(2,186) = 78.98$; $p < 0.001$; $\eta^2 = 0.459$; $\varepsilon = 0.87$]. Moreover, a significant interaction of CS-type and time of assessment was found [$F(2,186) = 40.46$; $p < 0.001$; $\eta^2 = 0.303$; $\varepsilon = 0.88$]. While

TABLE 3 | Means and standard deviations on the experiential rating composite scores and the experiential ratings of arousal, valence, and disapproval for the emotional Stroop ($N = 94$) and the dot-probe task ($N = 89$).

	Pre-conditioning	Post-conditioning	Post attention task
Emotional Stroop task			
Experiential rating composite score			
Negatively associated neutral faces, *M* (*SD*)	42.97[a] (10.29)	71.32[a] (17.86)	61.23[a] (18.49)
Neutrally associated neutral faces, *M* (*SD*)	44.81[a] (10.14)	38.25[b] (15.88)	41.06[b] (20.23)
Arousal			
Negatively associated neutral faces, *M* (*SD*)	42.72[a] (11.67)	66.31[a] (20.94)	58.05[a] (18.26)
Neutrally associated neutral faces, *M* (*SD*)	43.22[a] (11.70)	34.04[b] (17.38)	38.41[b] (20.72)
Valence			
Negatively associated neutral faces, *M* (*SD*)	42.11[a] (13.03)	71.67[a] (19.61)	60.40[a] (20.90)
Neutrally associated neutral faces, *M* (*SD*)	44.90[a] (11.69)	37.58[b] (18.15)	40.59[b] (21.42)
Disapproval (inverted)			
Negatively associated neutral faces, *M* (*SD*)	55.91[a] (13.62)	24.03[a] (18.86)	34.77[a] (19.94)
Neutrally associated neutral faces, *M* (*SD*)	53.69[a] (12.61)	56.88[b] (15.94)	55.81[b] (21.25)
Dot-probe task			
Experiential rating composite score			
Negatively associated neutral faces, *M* (*SD*)	42.83[a] (11.30)	76.98[a] (17.31)	68.88[a] (17.51)
Neutrally associated neutral faces, *M* (*SD*)	43.50[a] (11.58)	29.85[b] (15.41)	32.36[b] (15.96)
Arousal			
Negatively associated neutral faces, *M* (*SD*)	39.76[a] (14.73)	71.88[a] (18.41)	64.68[a] (18.45)
Neutrally associated neutral faces, *M* (*SD*)	40.95[a] (13.81)	25.81[b] (17.03)	30.70[b] (17.18)
Valence			
Negatively associated neutral faces, *M* (*SD*)	41.43[a] (12.71)	76.76[a] (19.91)	67.75[a] (19.74)
Neutrally associated neutral faces, *M* (*SD*)	41.32[a] (14.20)	27.93[b] (17.19)	31.43[b] (17.67)
Disapproval (inverted)			
Negatively associated neutral faces, *M* (*SD*)	52.71[a] (13.92)	17.71[a] (19.67)	25.79[a] (18.81)
Neutrally associated neutral faces, *M* (*SD*)	51.77[a] (15.97)	64.19[b] (17.44)	65.04[b] (16.27)

Means in the same column sharing the same superscript letter do not differ significantly from one another at $p \leq 0.05$.

there were no significant differences in experiential ratings of the neutral faces before the conditioning task [$t(93) = 1.36$, $p = 0.176$], *post hoc t*-tests showed that experiential ratings of the negatively associated familiar faces were rated significantly more negative than the neutrally associated familiar faces immediately after the conditioning task as well as after the emotional Stroop task [post-conditioning: $t(93) = 10.85$, $p < 0.001$; post emotional Stroop task: $t(93) = 5.44$, $p < 0.001$]. Means and standard deviations of experiential rating scores as well as the experiential ratings of arousal, valence, and disapproval are presented in **Table 3**.

Attention Task

Means and standard deviations of the emotional Stroop index score and RTs of trials with negatively as well as neutrally associated faces of the emotional Stroop task are shown in **Table 4**. **Table 5** presents bivariate Pearson correlation coefficients of different types of maltreatment and the emotional Stroop index score and RTs of trials with negatively as well as neutrally associated faces of the emotional Stroop task. Separate gender- and age-adjusted hierarchical regression analyses were carried out for each of the three indices to examine the unique contributions of different kinds of child maltreatment and relational peer victimization in the prediction of attential biases (**Table 6**). With respect to the emotional Stroop index score, relational peer victimization made a significant incremental contribution of variance (4%) to the prediction of the score beyond the variance explained by child maltreatment. In the final model [$F(7, 86) = 2.27$, adjusted $R^2 = 0.09$, $p = 0.036$], however, emotional abuse was the strongest predictor showing a positive association, while peer victimization was negatively associated with the emotional Stroop index score. In the prediction of RTs of trials with negatively associated faces, neither child maltreatment (2%) nor peer victimization (1%) made significant incremental contributions. Here, age was the only significant predictor in the final model [$F(7, 86) = 14.35$, adjusted $R^2 = 0.50$, $p < 0.001$]. Similarly, age was the strongest predictor for RTs of trials with neutrally associated faces. Though, showing a positive association, peer victimization contributed significantly to the prediction of RTs with neutrally associated faces, explaining additional 3% of the variance, after controlling for the influence of child maltreatment [final model: $F(7,86) = 11.79$, adjusted $R^2 = 0.45$, $p < 0.001$].

TABLE 4 | Means and standard deviations on the index scores and reaction times for the emotional Stroop ($N = 94$) and the dot-probe task ($N = 89$).

	M (*SD*)
Emotional Stroop task	
Emotional Stroop index score	0.44 (79.65)
RTs of trials with negatively associated faces	912.06 (222.24)
RTs of trials with neutrally associated faces	911.61 (217.67)
Dot-probe task	
Attentional bias score	–0.34 (17.93)
Orienting index score	–0.26 (18.08)
Disengaging index score	–0.08 (14.43)

TABLE 5 | Bivariate Pearson correlation coefficients of different types of maltreatment and the indices of the emotional Stroop ($N = 94$) and the dot-probe task ($N = 89$).

Emotional Stroop task	**Emotional Stroop index score**	**RTs of trials with negatively associated faces**	**RTs of trials with neutrally associated faces**
	r	*R*	*r*
Emotional abuse	0.25*	0.23*	0.14
Emotional neglect	0.07	0.27**	0.25*
Physical abuse	0.08	0.16	0.14
Sexual abuse	0.13	0.22*	0.18
Peer victimization	-0.16	0.09	0.15
Dot-probe task	**Attentional bias score**	**Orienting index score**	**Disengaging index score**
	r	*R*	*r*
Emotional abuse	0.08	0.13	–0.07
Emotional neglect	–0.04	–0.06	0.02
Physical abuse	–0.06	–0.05	–0.01
Sexual abuse	–0.15	–0.20	0.05
Peer victimization	0.29**	0.14	0.18

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Dot-Probe

Social-Conditioning Paradigm

To test whether the association of the neutral faces with negative and neutral valences was successful, a CS-type × Time of assessment ANOVA using the experiential rating composite score was conducted. The ANOVA revealed significant main effects of CS-type and time of assessment [CS-type: $F(1,88) = 188.39$; $p < 0.001$; $\eta^2 = 0.682$; time of assessment: $F(2,176) = 52.36$; $p < 0.001$; $\eta^2 = 0.373$; $\varepsilon = 0.69$]. Moreover, a significant interaction of CS-type and time of assessment was found [$F(2,176) = 181.49$; $p < 0.001$; $\eta^2 = 0.673$; $\varepsilon = 0.79$]. There were no significant differences in experiential ratings of the neutral faces before the conditioning task [$t(88) = 0.46$, $p = 0.646$]. However, *post hoc t*-tests revealed that experiential ratings of the negatively associated familiar faces were rated significantly more negatively than the neutrally associated familiar faces immediately after the conditioning task as well as after the dot-probe task [post-conditioning: $t(88) = 16.53$, $p < 0.001$; post dot-probe task: $t(88) = 12.26$, $p < 0.001$]. Means and standard deviations of experiential rating scores are presented in **Table 3**.

Attention Task

Means and standard deviations of the index scores are shown in **Table 4**. **Table 5** presents bivariate Pearson correlation coefficients of different types of maltreatment and the indices of the dot-probe task. For each of the three indices separate gender- and age-adjusted hierarchical regression analyses were carried out to investigate the unique proportion of variance

TABLE 6 | Hierarchical multiple regression analysis for the prediction of attentional bias scores in the emotional Stroop task (N = 94).

	Variable	β	R^2	Adjusted R^2	ΔR^2	ΔF
Emotional Stroop index score						
Step 1			0.05	0.02	0.05	2.14
	Gender	0.10				
	Age	0.11				
Step 2			0.12	0.06	0.07	1.76
	Emotional abuse	0.37*				
	Emotional neglect	–0.09				
	Physical abuse	0.07				
	Sexual abuse	–0.05				
Step 3			0.16	0.09	0.04	4.07*
	Peer victimization	–0.25*				
RTs of trials with negatively associated faces						
Step 1			0.51	0.49	0.51	46.47***
	Gender	0.06				
	Age	0.72***				
Step 2			0.53	0.50	0.02	1.06
	Emotional abuse	0.15				
	Emotional neglect	–0.06				
	Physical abuse	0.01				
	Sexual abuse	–0.02				
Step 3			0.54	0.50	0.01	1.96
	Peer victimization	0.13				
RTs of trials with neutrally associated faces						
Step 1			0.45	0.44	0.45	37.06**
	Gender	0.02				
	Age	0.69***				
Step 2			0.46	0.42	0.01	0.37
	Emotional abuse	0.01				
	Emotional neglect	–0.03				
	Physical abuse	–0.02				
	Sexual abuse	0.00				
Step 3			0.49	0.45	0.03	5.33*
	Peer victimization	0.22*				

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
β *coefficients of the final models are presented.*

TABLE 7 | Hierarchical multiple regression analysis for the prediction of attentional bias scores in the dot-probe task (N = 89).

	Variable	β	R^2	Adjusted R^2	ΔR^2	ΔF
Attentional bias score						
Step 1			0.08	0.06	0.08	3.59*
	Gender	0.23*				
	Age	0.06				
Step 2			0.18	0.12	0.10	2.44
	Emotional abuse	0.34				
	Emotional neglect	–0.22				
	Physical abuse	–0.19				
	Sexual abuse	–0.28*				
Step 3			0.26	0.19	0.08	9.03**
	Peer victimization	0.35**				
Orienting index score						
Step 1			0.00	0.02	0.00	0.10
	Gender	–0.02				
	Age	0.07				
Step 2			0.17	0.11	0.17	4.11**
	Emotional abuse	0.56**				
	Emotional neglect	–0.29				
	Physical abuse	–0.28				
	Sexual abuse	–0.30*				
Step 3			0.19	0.12	0.02	2.39
	Peer victimization	0.19				
Disengaging index score						
Step 1			0.12	0.10	0.12	5.95**
	Gender	0.31**				
	Age	–0.01				
Step 2			0.14	0.08	0.02	0.40
	Emotional abuse	–0.29				
	Emotional neglect	0.10				
	Physical abuse	0.11				
	Sexual abuse	0.03				
Step 3			0.17	0.09	0.03	2.61
	Peer victimization	0.20				

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
β *coefficients of the final models are presented.*

accounted for by retrospective reports of child maltreatment and relational peer victimization. As reported in **Table 7**, relational peer victimization made a significant incremental contribution of variance (8%) to the prediction of the attentional bias score beyond the variance explained by child maltreatment. In the final model [$F(7,81) = 4.02$, adjusted $R^2 = 0.19$, $p = 0.001$], peer victimization was the strongest predictor with gender and sexual abuse also remaining significant. While sexual abuse showed a negative association, peer victimization and gender were positively associated with the attentional bias score. With respect to the orienting index score, child maltreatment contributed significantly to the prediction (17%) whereas peer victimization did not show a significant incremental contribution of variance (2%). Here, emotional and sexual abuse remained the only significant predictors when entering peer victimization as an additional predictor in the final model [$F(7,81) = 2.76$, adjusted $R^2 = 0.12$, $p = 0.013$]. Being the strongest predictor, emotional abuse showed a positive association with the orienting index score, while a negative association was found for sexual abuse. For the disengaging index score, neither child maltreatment nor peer victimization showed significant incremental contribution of variance beyond the variance explained by gender [final model: $F(7,81) = 2.29$, adjusted $R^2 = 0.09$, $p = 0.035$].

DISCUSSION

Using a facial emotional Stroop and a facial dot-probe task, we examined the contribution of peer victimization to the prediction of attentional biases beyond experiences of child maltreatment using hierarchical regression analyses in two different samples with varying levels of childhood maltreatment and peer victimization. Consistent with our hypotheses, the present study showed that retrospective reports of relational peer

victimization made a significant, incremental contribution to the prediction of attentional biases beyond child maltreatment. In the emotional Stroop task, however, emotional abuse was the strongest predictor for an attentional bias showing a positive association, while peer victimization was negatively associated with the emotional Stroop index score. In the dot-probe task, relational peer victimization was the strongest predictor for an attentional bias. However, when the attentional bias was examined in more detail, peer victimization did not show incremental contributions but again emotional abuse was the strongest predictor for facilitated attention toward negatively associated neutral faces.

In line with prior research, experiences of child maltreatment and peer victimization were related to altered attention and emotion processing in both samples (Field et al., 2001; Pollak and Sinha, 2002; Gibb et al., 2009; Fani et al., 2011; Grant et al., 2011; Dannlowski et al., 2013; van Harmelen et al., 2013; Günther et al., 2015; Iffland et al., 2019; Iffland and Neuner, 2020). Most notably, relational peer victimization predicted attentional biases over and above experiences of physical, sexual and emotional maltreatment within the family context. This is consistent with findings that child maltreatment and peer victimization significantly and independently predict psychopathology (Gren-Landell et al., 2011; Fisher et al., 2012; Sansen et al., 2014). Hence, our findings emphasize on experiences of peer abuse being as detrimental as histories of child maltreatment but also indicate that peer victimization may have a qualitatively different impact on the processing of emotional faces than other adverse childhood experiences. Further, attentional biases as a result of peer victimization may increase the risk of victims of peer abuse for the development of psychopathology (Iffland et al., 2019).

In line with previous results reported by Rosen et al. (2007), retrospective reports of experiences of peer victimization were associated with differentiated color-naming of negatively associated faces compared to neutrally associated neutral faces in the present emotional Stroop task. In prior studies, faster responses in trials with threatening compared to non-threatening cues were reported and have been suggested to indicate more defensively preemptive cognitive processing patterns as attentional avoidance (Newman and McKinney, 2002; Rosen et al., 2007). Accordingly, attentional avoidance in individuals who have experienced peer victimization has also been reported in a previous dot-probe study using emotional and neutral adjectives (Iffland et al., 2019). In the present study, however, RTs of trials with negatively and neutrally associated faces contradicted the suggestion of attentional avoidance in individuals who have experienced peer victimization. While peer victimization is associated with delayed responses to neutrally associated faces, responses to negatively associated faces were not affected by ratings of peer abuse. Hence, the faster responses in trials with threatening compared to non-threatening faces were rather caused by an enhanced interference in trials with neutrally associated faces than by a preemptive and implicit cognitive and emotional reaction to negatively associated faces (Rosen et al., 2007). It may be speculated that the ambiguity of neutrally associated faces is more difficult to process for individuals who have experienced peer victimization. Accordingly, Rudolph et al. (2010) reported increased anticipatory physiological activation in children who had been victimized who were informed that they would be interacting with unfamiliar peers, reflecting a hyper-alertness to social threat. In line with this argument, the present findings in individuals with experiences of peer victimization may also illustrate a hyper-alertness or hyper-vigilance to social threat. That is, individuals who experienced peer victimization may be more likely to anticipate social threat and negative consequences even when confronted with neutral stimuli. Indeed, a previous study using the same set of social-evaluative and neutral videos reported similar psychophysiological responses to both kinds of videos in peer victimized participants (Iffland et al., 2018). Accordingly, peer victimization has been linked to a rather generalized emotion and attention processing style when confronted with different emotions (Iffland et al., 2019). Similarly, childhood bullying has been reported to be associated with paranoid thinking (Campbell and Morrison, 2007; Shakoor et al., 2015) which in turn is linked to a generalized attentional bias toward threatening and neutral stimuli (Jack and Egan, 2016, 2018). Furthermore, attentional avoidance in those who had experienced peer victimization was not supported by the results of the present dot-probe task. Instead, our findings indicated an attentional bias toward negatively associated faces. Accordingly, peer victimization was not associated with avoidance but enhanced interference in an emotional Stroop task in a previous study (Iffland et al., 2019). However, whether this is caused by facilitated attention or by difficulty in disengagement could not be identified in our data (Cisler and Koster, 2010).

It could be that differences in attentional processing styles associated with peer victimization were caused by different demands of the paradigms. Being confronted by a single face indicating social threat as utilized in the emotional Stroop task may elicit different emotion processing than being simultaneously confronted with a face indicating social threat and a neutral face in the dot-probe task. Thus, different attention tasks may address different victim schemas as proposed in the modified social-information-processing model (Rosen et al., 2007). In this model, a victim schema is defined as a cognitive structure comprising an individual's expectations, cognitions, emotions, and behavior that develop out of repeated patterns of interaction (Rosen et al., 2007). That is, based on previous experiences, an attentional bias toward socially threatening individuals may be adaptive to enable victims of peer victimization to escape from potentially abusive situations when confronted with different individuals as in the dot-probe task (Iffland and Neuner, 2020). However, in situations where no active coping or behavioral resources based on fight or flight stress responses are available, such as being directly confronted with a perpetrator as in the emotional Stroop task, attentional avoidance may reflect an attempt to regulate negative emotions (Williams et al., 1988; Mogg and Bradley, 1998; Bar-Haim et al., 2007; Iffland et al., 2019). Accordingly, attentional avoidance has been reported to be linked to emotional regulation strategies (Mogg et al., 2004; Koster et al., 2005, 2006; Pflugshaupt et al., 2005; Cisler and Koster, 2010). Similarly, Carroll et al. (2019) proposed that attentional biases associated with peer victimization not only

enhance threat related attention but also broad selective attention processes toward detecting goal-relevant stimuli. Moreover, it is possible that the use of pictures of faces instead of words in the present tasks have led to different results because of differing underlying mechanisms of processing and their link to semantic memory. Though, comparisons of picture and word versions of the paradigms used in the present study showed similar results so it has been suggested that they can be used equally (Stormark and Torkildsen, 2004; Hester et al., 2006).

Although the present study showed that experiences of peer victimization contribute uniquely and additionally to the prediction of attentional biases, the direction and the magnitude of its influence still remains open. That is, when looking at the specific tasks, the results of the present study were in opposition to results reported in previous studies (Rosen et al., 2007; Iffland et al., 2019). Hence, from an aggregational perspective, it may also be suggested that no association of peer victimization and attentional biases is present. Therefore, conclusions from the results of the present study have to be drawn with caution and further research is needed to specify underlying mechanisms and the impact of potential paradigm peculiarities (e.g., kinds of stimuli, task demands).

With respect to the effects of childhood maltreatment within the family context on attentional processes, as hypothesized, our results were consistent with previous findings indicating that particularly emotional forms of maltreatment are associated with attentional biases in the processing of emotional cues (Pollak et al., 2000; Günther et al., 2015; Iffland and Neuner, 2020). In both the emotional Stroop and the dot-probe task emotional abuse was related to facilitated orientation toward negatively associated neutral faces. Faster recognition of negatively associated faces as well as an attentional bias toward sad facial expressions had previously been associated with more frequent reports of emotional abuse (Günther et al., 2015; Iffland and Neuner, 2020). Similarly, the present results were consistent with previous findings of greater sensitivity in detecting threatening cues from emotionally ambiguous faces in healthy individuals with a frequent proportion of emotional maltreatment (Gibb et al., 2009). Emotional neglect, however, was not linked to attentional bias scores within the present study, although bivariate correlations indicated that experiences of emotional neglect were related to slower color-naming of both negatively and neutrally associated neutral faces in the emotional Stroop task. This finding is in line with associations of emotional neglect with slower detection of negatively and neutrally associated familiar faces in a crowd of unfamiliar faces reported in a previous study using the same stimulus set (Iffland and Neuner, 2020). Hence, it may be that emotional neglect causes generalized interference in reaction to social stimuli, such as emotional and neutral faces. As argued by Iffland and Neuner (2020), limited emotional expressiveness of their parents may result in difficulties in distinguishing between emotional expressions in victims of emotional neglect. This may impede effective recognition and appropriate response to social cues, especially when individuals are confronted with emotionally indistinct facial expressions (Pollak et al., 2000; Iffland and Neuner, 2020). Consistently, physical neglected children showed impaired emotion recognition abilities in prior research (Pollak et al., 2000).

Consistent with Günther et al. (2015), our findings indicated that physical abuse was not associated with attentional biases when controlling for other forms of maltreatment. However, additional research is needed to reconcile the present findings with prior reports of impeded recognition of negative faces, attentional avoidance of threatening faces, and response biases for angry faces in physically abused individuals (Pollak et al., 2000; Pollak and Sinha, 2002; Pine et al., 2005; Iffland and Neuner, 2020). For instance, the stimulus set used in the social conditioning paradigm of the present study may have caused stronger associations of peer victimization and emotional forms with alterations in attention processes. The social evaluative connotation of the stimuli may be stronger related to emotionally abusive experiences than to physical forms of maltreatment. Hence, future studies using other kinds of stimuli may reveal effects of physical abuse on emotion processing, even when controlling for effects of emotional forms of maltreatment.

Contrasting with previous studies examining differentiated effects of maltreatment forms on attention processes (Günther et al., 2015; Iffland and Neuner, 2020), the present findings indicated threat avoidance in individuals reporting more frequent experiences of sexual abuse. Cognitive interference in survivors of childhood sexual abuse with current PTSD has been reported previously (Freeman and Gayle Beck, 2000; Field et al., 2001; Martinson et al., 2013). However, the presence of a diagnosis of PTSD has been shown to have a greater impact on attentional biases than having a history of sexual trauma alone. Further, contrasting with our findings, a recent meta-analytic review promoted a positive relationship between experiences of sexual victimization and attentional bias toward sexual threat stimuli (Latack et al., 2017). While most studies used explicit sexually threatening stimuli, the more subtle, social evaluative stimuli in the present study may have elicited a different processing style. In line with Klein et al. (2019), socially threatening stimuli may be associated with peri-traumatic experiences of victimis of sexuals abuse and therefore suitable to evoke differential processing in these individuals.

Contrasting with previous studies applying facial emotional Stroop or dot-probe tasks, modified versions of these tasks using faces with neutral facial expressions were utilized in the present study. Therefore, comparing our results to previous findings must be done with caution because the present tasks may refer to different cognitive mechanisms. However, our findings suggest that differential processing of threatening information does not rely on actual threatening facial expressions, but mental representations of threat through associations are sufficient to modify attentional processes. At this point, the present study replicated the findings presented by Iffland and Neuner (2020) using different tasks measuring attention in additional samples of healthy individuals. As depicted by the experiential ratings, negatively associated neutral faces were perceived as significantly more negative than the neutrally associated faces increasing the likelihood of an activation of the proposed victim schemas or mental representations of maltreatment (Rosen et al., 2007). Assuming that emotion processing in victims of childhood

maltreatment and peer victimization is influenced by mental representations rather than by facial expressions alone (Iffland and Neuner, 2020), encountering potential perpetrators could already trigger a cascade of attentional, emotional, and behavioral processes without the counterpart even having expressed, said, or done anything. Hence, the present study presents an ecologically valid attempt to expand the understanding of information processing in the aftermath of childhood maltreatment and peer victimization. It is possible, though, that the stimulus set may not have been arousing or threatening enough to generate general attentional biases to the negatively associated neutral faces. While clearly and strongly threatening stimuli could mask different processing, it may be assumed that less arousing and more ambiguous stimuli are better suited to evoke differentiated processing in maltreated samples (Pollak and Sinha, 2002; Gibb et al., 2009). In line with this conceptualization, even less arousing and more ambiguous stimuli elicit experience-specific information-processing biases in maltreated children due to adaptively increased sensitivity to signals of danger (Pollak, 2003; Gibb et al., 2009). However, future studies are needed to examine whether the absence of absolute attentional biases in the present study were due to stimulus characteristics or paradigm modifications and to better understand which performances are reflected in the modifications.

To our knowledge, this is the first study that simultaneously investigated different forms of maltreatment in the family context and relational peer victimization as predictors of attentional biases. Extending previous research indicating differential associations between various forms of maltreatment and emotion processing (Pollak et al., 2000; Günther et al., 2015; Iffland and Neuner, 2020), our findings suggest that peer victimization can be considered to be at least as detrimental for emotion processing in adulthood as other forms of childhood maltreatment, which may be a risk factor for the development of psychopathological symptomatology. Moreover, the results emphasize that emotional and social forms of maltreatment have at least the same predictive value concerning attentional biases as sexual and physical abuse. However, further studies using a wide range of paradigms and methods (e.g., eye tracking in addition to reaction times) including additional sets of stimuli (e.g., positive stimuli, physical abuse related stimuli) are needed to examine the specific effects of different forms of maltreatment and peer victimization on information processing.

The present study has several limitations that must be considered when interpreting the results of the present study. Because of the cross-sectional design of the study, conclusions about the causal relationship between child maltreatment, peer victimization, and altered emotion processing cannot be drawn. In addition, the assessment of adverse experiences in family and peer context was based on self-report and retrospective accounts which may be subject to recall biases (Häuser et al., 2011). However, this is a limitation common to the field, as investigating the consequences of the full range of childhood maltreatment often lacks valid alternatives to restrospective reports. Particularly emotional forms of maltreatment and victimization are not reliably documented in child protection service, clinical, or medical records. It has been reported, though, that recall biases in reporting childhood maltreatment were not large enough to invalidate retrospective reports (Hardt and Rutter, 2004). For the purpose of examining causality, future research using longitudinal prospective designs is needed. Furthermore, the generalizability of our findings is limited. The sample was relatively young and highly educated, with participants who were predominantly female. This should be addressed in future studies using larger and more representative samples. Additionally, attentional biases in the present study were affected by individual characteristics. In the emotional Stroop task, age was positively associated with RTs of trials with both negatively and neutrally associated faces supporting previous findings that participants become slower with age (Ashley and Swick, 2009; Agustí et al., 2017; Gajewski et al., 2020). Moreover, in accordance with previous studies (Pfabigan et al., 2014; Campbell and Muncer, 2017; Torrence and Troup, 2018), the dot-probe task revealed differences between genders in processing emotional faces. While women tended to show threat avoidance, men showed an attentional bias toward negatively associated faces, particularly showing a difficulty in disengaging from these faces. Future research is needed to examine influences of individual characteristics as age and gender on attentional processes in association with childhood maltreatment and peer victimization. While mean scores of emotional abuse, physical abuse, and sexual abuse were comparable to mean scores of child maltreatment in a representative sample of the German population (Häuser et al., 2011; Iffland et al., 2013), results may have been influenced by lower levels of emotional neglect. Similarly, variance of the CTQ subscales differed within the present samples. Thus, restricted variability may explain the lack of significant associations for some kinds of maltreatment. Hence, replication of the current findings in samples with more varying levels of childhood maltreatment exposure is desirable. The present study is further limited by its focus on the unique effects of peer victimization and types of child maltreatment on attentional processes. Since different forms of maltreatment are intercorrelated and often co-occur (Häuser et al., 2011), it is likely that interactions between maltreatment types as well as maltreatment types and peer victimization influence emotion processing beyond the unique effects of each. Therefore, future studies should investigate cumulative and interactive effects of types of maltreatment associations. Lastly, it has been documented that childhood maltreatment increases the risk for experiencing adversities later in life (e.g., Dong et al., 2004; Finkelhor et al., 2007). Because exposure to adverse experiences in adolescence and adulthood were not measured in the present study, potential effects of these additional adversities could not be controlled for in our analyses, which should be addressed in future research.

CONCLUSION

Prevalence rates of peer victimization in school children of 10–20% are alarming (Rudolph et al., 2010), particularly with respect to the strong associations of peer victimization and psychopathology (e.g., Storch et al., 2005). The current study contributes to a better understanding of potential paths linking

peer victimization and psychopathology by expanding previous reports of altered processing of incoming emotional information in the aftermath of childhood maltreatment within the family context (e.g., Wells et al., 2014; Günther et al., 2015; Iffland and Neuner, 2020). It has been suggested that cognitive alterations in victims of maltreatment contribute to inadequate and maladaptive responding to social interactions, setting individuals at risk for further victimization and later psychopathology (Rosen et al., 2007; Masten et al., 2008; Fani et al., 2011; Wells et al., 2014). In addition to supporting prior studies that indicate that particularly emotional maltreatment is associated with alterations in attentional processes (Iffland and Neuner, 2020), the results of the present study indicate that peer victimization leaves additional cognitive scars that may contribute to a broad range of psychopathology. A better understanding of the specific characteristics in the processing of emotional stimuli in the wake of peer victimization and other forms of childhood maltreatment is therefore needed to address short and long term consequences and treatment offers for victims.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Bielefeld University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BI participated in the conception and design of the study, collected the data, performed the statistical analyses and interpretation of findings, and drafted the manuscript. FN participated in the conception and design of the study, made substantial contributions to the statistical analyses and interpretation of findings, and helped to draft and revise the manuscript. Both authors read and approved the final manuscript.

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Childhood Trauma and Cortisol Reactivity: An Investigation of the Role of Task Appraisals

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Background: Childhood adversity is linked to adverse health in adulthood. One posited mechanistic pathway is through physiological responses to acute stress. Childhood adversity has been previously related to both exaggerated and blunted physiological responses to acute stress, however, less is known about the psychological mechanisms which may contribute to patterns of physiological reactivity linked to childhood adversity.

Objective: In the current work, we investigated the role of challenge and threat stress appraisals in explaining relationships between childhood adversity and cortisol reactivity in response to an acute stressor.

Methods: Undergraduate students (n = 81; 61% female) completed an online survey that included general demographic information and the Risky Families Questionnaire 24 h before a scheduled lab visit. In the lab, a research assistant collected a baseline salivary cortisol sample. Following the baseline period, participants were read instructions for the Trier Social Stress Test (TSST), a validated psychological lab stressor. Next, they completed a challenge vs. threat task appraisal questionnaire and completed the speech and math portion of the TSST. Twenty minutes following the start of the TSST, a second salivary sample was collected to measure changes in salivary cortisol following the TSST.

Results: Linear regression analyses adjusted for age, sex, childhood socioeconomic status (SES), and baseline cortisol levels, showed childhood adversity associated with changes in cortisol levels [B = –0.29 $t(73)$ = –2.35, p = 0.02, $R^{2=0.07}$]. Linear regression analyses controlling for age, sex, and childhood SES showed childhood adversity associated with both challenge [B = –0.52 $t(74)$ = –5.04, $p < 0.001$, $R^{2=0.24}$] and threat [B = 0.55 $t(74)$ = 5.40, $p < 0.001$, $R^{2=0.27}$] appraisals. Significant indirect effects of childhood trauma on cortisol reactivity were observed through challenge appraisals [B = –0.01 (95% confidence interval = –0.02, –0.003)], and threat appraisals [B = –0.01 (95% confidence interval = –0.01, –0.003)].

Conclusion: Childhood adversity may contribute to blunted cortisol reactivity, a pattern of response which is linked to obesity, addiction, and other behavior-related diseases. Our findings suggest that this relationship is in part a product of stress appraisals.

Keywords: childhood trauma and adversity, cortisol, stress, challenge and threat appraisals, blunted reactivity

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INTRODUCTION

When individuals experience or perceive a stressor, the body produces a physiological response which is designed to aid in overcoming the stressor. This response involves activation of the hypothalamic-pituitary-adrenal (HPA) axis, releasing cortisol into the blood stream which promotes energy mobilization (Smith and Vale, 2006). The pattern and quantity of cortisol release in response to acute psychological stress varies across individuals, with some individuals displaying exaggerated or blunted responses. Exaggerated cortisol response is characterized by increases in cortisol levels that are greater than the average response which may include slower recovery to baseline. Previous research indicates that these exaggerated responses may leave an individual at higher risk for deleterious health effects such as chronic disease and early mortality through biological wear and tear on bodily systems (Lovallo, 2015). A separate body of research has shown that cortisol reactivity to stress may also be blunted or diminished, which is characterized as increases in cortisol which are below the average response. Blunted cortisol reactivity has previously associated with downstream health-relevant outcomes such as addiction, obesity, and depression (Lovallo, 2011; Phillips et al., 2013; al'Absi et al., 2021).

Differences in cortisol responses to stress have also been related to childhood adversity (Lovallo et al., 2012; Voellmin et al., 2015; Young et al., 2021). In prior work, childhood adversity was related to stress sensitization and vulnerability to future stressful events (Bunea et al., 2017) which may be hallmarked by dysregulation in HPA functioning characterized as increased sensitivity to stress and diminished physiological capacity to respond and combat stress (McEwen, 1998). Childhood adversity puts individuals at high risk for extreme and chronic levels of stress exposure during critical developmental stages (Ridout et al., 2018). Research suggests that cortisol responsivity may become diminished in response to chronic and elevated incidences of stress exposure (Fries et al., 2005) especially during early stages of brain development (VanTieghem and Tottenham, 2018). This hypothesis is highlighted in a body of research showing that individuals who report childhood adversity exhibit dysregulated stress reactivity characterized by diminished cortisol reactivity in response to a lab induced stressor (Carpenter et al., 2011; Voellmin et al., 2015; Bunea et al., 2017). In turn, these diminished cortisol responses to stress may explain the previously documented relationship between childhood adversity and chronic inflammation (for review; see Coelho et al., 2014).

The psychological mechanisms which may contribute to the documented relationship between childhood adversity and cortisol reactivity to stress are less understood. Prior research has shown that differences in the psychological appraisal of a stressor informs the pattern of physiological responses to stress. A large body of work on stress appraisals focuses on challenge (i.e., having adequate resources to meet the demand) compared to threat appraisals (i.e., not having adequate resources to meet the demand) (Uphill et al., 2019). Compared to challenge appraisals, threat appraisals have previously been related to increased reports of stress (Tomaka et al., 1993) and other poor cognitive, behavioral and affective responses to laboratory stressors (Drach-Zahavy and Erez, 2002; Jamieson et al., 2012). According to the biological embedding model, childhood is a period of heightened sensitivity and plasticity (Miller et al., 2011). The model posits that in addition to affecting the programming of biological systems, high levels of adversity in the childhood environment give rise to excessive vigilance for threat. As such, individuals who experience high levels of adversity during childhood may be more likely to appraise future events as threatening rather than challenging.

In past work, challenge and threat appraisals have also been found to have distinct profiles of cardiovascular activity in response to stress (Quigley et al., 2002). A threat profile, viewed as a less efficient cardiovascular response, is characterized by blunted cardiac output reactivity and increased vascular resistance compared to that which is observed in challenge states (Mendes et al., 2008). In previous work, threat appraisals were identified as a mediator in the relationship between depression and blunted systolic blood pressure (Brindle et al., 2013). Separately, previous literature indicates that cortisol and cardiovascular reactivity are linked to similar cortical and limbic regions of the brain (Gianaros and Wager, 2015; Gianaros et al., 2017; Ginty et al., 2017). Based on these findings, it is possible that as previously observed with cardiovascular reactivity (Brindle et al., 2013), threat appraisals of stressors may be linked to blunted cortisol reactivity.

It is currently unclear if differential perceptions of stress contribute to the association between childhood trauma and blunted cortisol reactivity. In the current work, we test our hypothesis that individuals who report higher levels of childhood adversity will exhibit blunted cortisol reactivity to stress, in part due to greater threat and lower challenge appraisals of an acute psychological stressor.

METHODS AND METHODS

Procedure

Participants were college students enrolled in an introductory to psychology course at a 4-year state university. As part of the course requirements, students are asked to participate in research studies managed by the Psychology department. Participants were recruited through an online database in which they found and signed up for timeslots. All sessions were run during a 3-h time block (between 1 and 4 p.m) in order to control for time of day effects on cortisol levels. Twenty-four hours before their scheduled lab visit, participants who signed up were sent an online survey by email containing an informed consent form, general demographic information survey, and the Risky Families Questionnaire. Participants were required to complete the survey in order to participate in the lab portion of the study. Participants came to the lab during their scheduled lab visit and were seated in a chair. A research assistant asked them to limit their movement for a 10-min baseline period. During the last minute of the baseline period, participants provided a salivary sample for measurement of cortisol. A double tube salivary cortisol device (Salimetrics, CA, United States), was utilized to

collect cortisol. The participant was instructed to remove a piece of cotton from the tube and chew on it for 60 s. The participant returned the piece of chewed cotton immediately to the collection tube upon completion.

Following the baseline period, all participants completed the Trier Social Stress Test (TSST), a validated social stressor, known to elicit changes in cortisol levels (Kirschbaum et al., 1993). Two research assistants were present in the room and evaluated participants for the duration of the TSST. One research assistant communicated all instructions for the task and answered any questions. The participant was seated for the duration of the TSST facing the two evaluators and a video camera that they believed was taping their performance. One research assistant explained the instructions for the Trier Social Stress Test (TSST) as follows, "You are being asked to complete a speech task detailing why you would be the ideal candidate for your dream job. The speech task will last for 5 min, and you will have the next 5 min to prepare for the speech. You will also complete a 5- min arithmetic task. Your performance will be videotaped and evaluated by a panel of judges trained in public speaking. Do you have any questions before we begin?" Once the research assistant answered any questions, the participant completed a brief stress appraisal measure and then began the 5-min speech task.

After the 5-min speech period, the research assistant read the instructions for a 5-min math task. The participant was given the following instructions: "You are now being asked to complete a math task. You will sequentially subtract the number 13 from 1,022. If you make a mistake, you will be asked to start over from 1,022. If you complete the sequence before time is up, please start over from 1,022". The research assistant answered any questions before the participant began the task. At the conclusion of the 5-min period, a 10-min recovery period began during which the participant was asked to remain comfortably seated in their chair. At the end of the 10-min recovery period, the participant provided a second salivary cortisol sample using the method previously described. The research assistant concluded the study by explaining the true nature of the study and informed the participant that their performance was not actually being recorded.

Measures

Childhood Adversity

We used the Risky Families Questionnaire (RFQ), a 13 item self-report measure to assess the degree of risk of physical, mental, and emotional adversity that an individual faced in their childhood and adolescent family environment (Taylor et al., 2004). Participants indicate how frequently certain events or situations occurred during the ages of 5–15 years using a 5-point likert scale (1 = not at all and 5 = very often). Example questions from this scale include, "How often did a parent or other adult in the household make you feel that you were loved, supported and cared for?" and "How often did a parent or other adult in the house push, grab, shove or slap you?" Items measuring the presence of positive qualities or experience were reversed scored and all 13 items were then summed to reflect overall risk in the family environment.

Challenge and Threat Appraisal

After research assistants described the upcoming TSST, all participants were provided with the following statement "A challenge state is experienced when an individual perceives they have sufficient, or nearly sufficient, resources to meet the demands of a task or situation, whereas a threat state is experienced when an individual perceives they have insufficient resources to meet the demands of a task or situation." And then asked to indicate the degree to which they agreed with a series of 6 statements as a measure of their appraisal of the task as a challenge or as a threat (Williams et al., 2010; Trotman et al., 2018), adapted from McGregor and Elliot (2002). The statements which measured challenge appraisal were the following: "I view this task as a challenge," "The task presents itself as a challenge to me," and "I feel challenged by this task." The statements used to measure task appraisals were identical apart from replacing the word "challenge" with "threat." Participants rated the extent to which they agreed with each statement ranging from 1 (*not at all true*), to 7 (*very true*). The challenge and threat scales had adequate reliability, with Cronbach's alpha being 0.81 and 0.83, respectively, which is in line with previous research using the scale (Williams et al., 2010; Trotman et al., 2018). Previous research has demonstrated that the challenge and threat subscales are independent of one another and not the same construct (Williams et al., 2010).

Cortisol

Upon collection, all salivary samples were immediately stored in a fridge and were transferred to a −80°C freezer located in the Stress, Adversity, Resilience and Health (SARAH) lab located on the Montana State University campus within 4 h of collection. Samples were thawed on the day of analyses and centrifuged at 1500 × *g* for 15 min. All samples were processed by trained SARAH lab research staff using a high sensitivity ELISA (Salimetrics, CA, United States). The inter-assay and intra-assay coefficient were below 8%. As we have done in previous research (John-Henderson et al., 2020), we calculated a cortisol difference score using the sample collected during baseline and the post-stressor sample (i.e., the sample collected 20 min after the start of the TSST).

Covariates

Based on previous research indicating relationships between biological sex, age, childhood socioeconomic status, oral contraceptive use, symptoms of depression and anxiety and cortisol reactivity to a social stressor (Kudielka et al., 2004; Liu et al., 2017; Lê-Scherban et al., 2018; Mazurka et al., 2018; Fiksdal et al., 2019; Gervasio et al., 2022), we measured these variables as covariates for our analyses. Participants self-reported their biological sex and age. As a measure of childhood socioeconomic status (SES), we used the MacArthur scale of subjective childhood SES, which is used to capture SES during childhood across objective SES indicators. Participants are presented with a 10-rung ladder and are asked to indicate where they feel their family stood during childhood relative to other families in the United States (Adler et al., 2000). Scores ranged from 1 (lowest SES) to 9 (highest SES). The question explains that the top of

the ladder represents those families with more money, higher levels of education, and better jobs, while the bottom of the ladder represents those families with the lowest incomes, less education, and had low paying jobs or were unemployed. Female participants self-reported whether they were currently using oral contraceptives, and current symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression scale (HADS; Zigmond and Snaith, 1983).

Statistical Analyses

Analyses were conducted using SPSS (version 24; IBM, Armonk, NY, United States). Continuous covariates were centered before being used in analyses. A two-way repeated measures ANOVAs (baseline, 20 min after stress onset) using cortisol was conducted to determine if the stress task successfully perturbed the HPA axis. We tested our primary hypotheses using linear regression models. We examined relationships between childhood adversity and stress appraisals, stress appraisals and changes in levels of salivary cortisol, and the relationship between childhood adversity and changes in levels of salivary cortisol. Next, we explored potential indirect effects of childhood adversity on changes in levels of salivary cortisol. To test for indirect effects, following suggestions by Preacher and Hayes (2008), we used a bootstrapping approach in which a point estimate of the indirect effect was derived from the mean of 5000 estimates of the indirect pathways, and 95% confidence intervals were computed using the cutoffs for the 2.5% highest and lowest scores of the distribution. Indirect effects were considered statistically significant if the confidence interval did not include 0. For these analyses, demographics, oral contraceptive use, symptoms of depression and anxiety were used as covariates based on documented relationships between these measures and our outcome of interest as referenced earlier.

RESULTS

Descriptive statistics for the sample are listed in **Table 1** and bivariate correlations between main variables of interest are listed in **Table 2**. A two-way repeated- measures ANOVA using cortisol activity during baseline (Mean = 0.36, Standard Deviation = 0.30) and 20 min after stress onset (Mean = 0.57, Standard Deviation = 0.37) demonstrated that the TSST significantly perturbed cortisol activity, $F(1,80) = 62.02$, $p < 0.001$, ${}_p\text{eta}^2 = 0.437$. Over 90% of participants showed an increase in cortisol activity from baseline to 20 min post stress onset. There were no statistically significant differences related to biological sex for reported levels of childhood adversity [$t(79) = -0.62$, $p = 0.54$], reported challenge appraisals [$t(79) = -0.74$, $p = 0.46$], or observed cortisol reactivity [$t(79) = -1.05$, $p = 0.29$].

TABLE 1 | Means and standard deviations.

Variable	*M*	*SD*	% Female
Gender			61.7%
Childhood socioeconomic status	3.12	1.23	
Age (years)	21.16	4.04	
Baseline cortisol (ug/dL)	0.36	0.30	
Post-task cortisol (ug/dL)	0.57	0.37	
Change in cortisol (ug/dL)	0.21	0.25	
Challenge appraisal average	3.30	1.54	
Threat appraisal average	2.50	1.58	
Risky family questionnaire	19.31	7.24	
Anxiety symptoms	20.53	3.35	
Depressive symptoms	10.03	3.96	

Childhood Adversity and Stress Appraisals

We utilized a linear regression controlling for age, biological sex, childhood SES, and symptoms of depression and anxiety to examine relationships between childhood adversity (as measured by the Risky Family Questionnaire) with stress appraisals. We found that childhood adversity was positively related to threat appraisals [$B = 0.55$ $t(74) = 5.40$, $p < 0.001$, $R^{2=0.27}$] and negatively related to challenge appraisals [$B = -0.52$ $t(74) = -5.04$, $p < 0.001$. $R^{2=0.24}$].

Stress Appraisals and Changes in Salivary Cortisol

In a linear regression model controlling for age, biological sex, childhood SES, symptoms of depression and anxiety, oral contraceptive use and baseline levels of cortisol, challenge and threat appraisals were significant predictors of changes in levels of salivary cortisol [$B = 0.48$ $t(73) = 4.61$, $p < 0.001$, $R^{2=0.21}$] and [$B = -0.44$ $t(73) = -4.21$, $p < 0.001$, $R^{2=0.18}$], respectively.

Childhood Adversity and Changes in Salivary Cortisol

Separately, in a linear regression model controlling for the same previously described covariates including baseline levels of cortisol, we examined the relationship between childhood adversity and changes in cortisol from baseline to after the TSST. Childhood adversity was negatively associated with changes in cortisol [$B = -0.29$ $t(73) = -2.35$ $p = 0.02$, $R^{2=0.07}$], with greater reports of childhood adversity relating to smaller increases in levels of salivary cortisol.

Using the previously described method (Preacher and Hayes, 2008), with the same covariates described previously, and with the addition of each respective stress appraisal, we found a significant indirect effect of childhood adversity on changes in cortisol through challenge appraisals and threat appraisals. The bootstrapped unstandardized indirect effect of childhood adversity on cortisol reactivity through challenge appraisals was −0.01, and the 95% confidence interval ranged from −0.02 to −0.003. The bootstrapped unstandardized indirect effect of childhood adversity on cortisol reactivity through threat appraisals was −0.01, and the 95% confidence interval ranged from −0.01 to.003[1]. The direct effect of childhood adversity on

[1]Based on previously documented relationships between biological sex and cortisol reactivity patterns, we tested whether biological sex moderated the statistically significant mediation we reported here. Biological sex was not a statistically significant moderator of this mediation model.

TABLE 2 | Correlations.

Variable	1	2	3	4	5	6	7	8	9	10	11
1 Childhood socioeconomic status											
2 Age	– 0.12										
3 Gender	0.16	– 0.29**									
4 Baseline cortisol	0.09	0.04	0.02								
5 Post-task cortisol	0.02	0.12	0.10	0.75**							
6 Change cortisol	– 0.07	0.13	0.12	– 0.10	0.59**						
7 Challenge appraisal average	– 0.24*	– 0.10	0.08	– 0.08	0.24*	0.46**					
8 Threat appraisal	0.27∗	– 0.11	0.15	0.14	– 0.18	– 0.43**	– 0.60**				
9 Risky family questionnaire	0.18	– 0.08	0.07	0.12	– 0.09	– 0.29**	– 0.54**	0.57**			
10 Anxiety symptoms	– 0.04	– 0.07	0.05	0.13	0.16	08	0.24*	0.91	– 0.22		
11 Depressive symptoms	– 0.01	– 0.10	0.08	– 0.04	– 0.08	– 0.07	– 0.08	0.85	– 0.05	– 0.40**	

*** indicates correlation is significant at the 0.01 level (2-tailed), * indicates correlation is significant at the 0.05 level (2-tailed).*

cortisol reactivity when controlling for challenge appraisals was $B = -0.001$, $t(77) = -0.26$, $p = 0.79$, and the direct effect of childhood adversity on cortisol reactivity when controlling for threat appraisals was $B = -0.002$, $t(77) = -0.45$, $p = 0.65$.[2]

DISCUSSION

The findings reported here contribute to a significant body of work documenting relationships between childhood adversity and future patterns of cortisol responses to social stressors. In line with prior work (Carpenter et al., 2011; Lovallo et al., 2012; Voellmin et al., 2015; Bunea et al., 2017; al'Absi et al., 2021; Young et al., 2021; Brindle et al., 2022), our findings indicated a relationship between childhood adversity and cortisol reactivity such that individuals who reported more adversity during their childhood (age 5–15), had blunted cortisol reactivity compared to those individuals who reported less adversity.

Our findings extend previous work in this area by highlighting a potential psychological mechanism which may account for observed relationships between childhood adversity and cortisol responses to stress later in life. Specifically, our findings suggest that differences in challenge and threat stress appraisals linked to childhood adversity, may contribute to blunted cortisol responses. Specifically, individuals who reported more childhood trauma reported greater threat appraisals (i.e., not having adequate resources to meet demand) and lower challenge appraisals (i.e., having adequate resources to meet demand) compared to those who reported lower levels of childhood trauma. In previous research, threat appraisals have also been linked to poor behavioral, cognitive and affective responses to stress (Tomaka et al., 1993; Drach-Zahavy and Erez, 2002; Jamieson et al., 2012).

The present study is not without limitations. The second sample which was meant to reflect changes in salivary cortisol associated with completing the stressor, was collected at 20 min following the start of the task. While we observed a statistically significant increase in cortisol activity from baseline to this collection timepoint and over 90% of participants displayed an increase in cortisol from baseline to the collection timepoint, we may have missed the "peak" response time by collecting saliva too early. Methodological approaches to calculating stressor-evoked cortisol reactivity differ. Some work suggests calculating area under the curve (Pruessner et al., 2003), while other work suggests calculating a difference score between the maximum and minimum values (Miller et al., 2018). Nevertheless, in future work, multiple salivary samples should be collected over a longer time period in order to better understand how childhood trauma and related psychological appraisals of stressors map on to trajectories of salivary cortisol in response to a stressor. Additionally, the current sample was predominantly composed of non-Hispanic White college students. In future work, a more diverse sample would allow us to understand if the observed relationships are specific to this racial group or if they would differ in other racial and ethnic groups. In addition, simultaneous measurement of reactivity across multiple physiological systems would further develop our understanding of correspondence or divergence of responses across systems.

Prior work indicates that for females, the point in the menstrual cycle at the time of data collection could affect cortisol levels and cortisol reactivity. We did not collect this information in the current study and so were unable to account for the potential effect of this measure on our outcome. Finally, since we allowed for questions between the speech task and the math task of the TSST, there is some variability in the total time of the TSST across participants, however, this variability should be very limited (i.e., under 1 min).

Overall, the findings presented here raise the possibility that stress appraisals may contribute to the link between childhood trauma and cortisol responses to stress. As noted previously, the blunted pattern of cortisol response, which was linked to low challenge appraisals, high threat appraisals, and high reports of childhood trauma, is related to a host of behavioral outcomes which in turn relate to poor mental and physical health outcomes.

Previous work demonstrates the feasibility of manipulating or directing stress appraisals toward either challenge or threat, and provides evidence that these distinct appraisals correspond with

[2]We conducted sensitivity analyses for which we excluded two outliers who were 3 standard deviations above the average age of our sample. The pattern of our findings did not change after excluding these outliers.

unique physiological responses to the stressor (John-Henderson et al., 2015; Williams et al., 2017). As such, it is possible that interventions which aim to reshape stress appraisals (i.e., toward challenge) for individuals who report high levels of childhood trauma may reduce risk for chronic health conditions and behavioral outcomes which are linked to blunted cortisol reactivity. Finally, with regards to implications of our findings, as discussed previously, blunted cortisol reactivity is related to obesity, addiction, and depression (Phillips, 2011; Phillips et al., 2013; al'Absi et al., 2021). It is possible that psychological interventions which work to reshape stress appraisals (i.e., toward challenge rather than threat) may increase cortisol reactivity to social stressors in individuals who experienced childhood adversity, and in doing so could reduce the high incidence of obesity, addiction, and depression observed in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Montana State University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC designed the study, collected the data, analyzed the data, wrote the manuscript, and helped with revisions. AG helped with the conceptual framing of the manuscript, data analyses and interpretation, and manuscript revisions. JL and TK helped with the literature review, table creation, and manuscript revisions. NJ-H helped design the study and helped with data analyses and with writing and revision of the manuscript.

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Planful Self-Control, Metabolic Risk, and Psychosocial Outcomes Among Young, Black Men: A Test of Skin-Deep Resilience Theory

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Research on skin-deep resilience suggests that for youth and young adults from disadvantaged backgrounds, high levels of planful self-control may promote positive psychosocial outcomes while simultaneously conferring vulnerabilities to chronic diseases related to aging. In this study, we investigated the divergent effects of planful self-control on young Black American men's psychosocial well-being and their metabolic risk. We expected that high levels of planful self-control in emerging adulthood would predict positive outcomes in young adulthood (educational attainment, low depressive symptoms, job satisfaction); however, the combination of high levels of planful self-control and the experience of contextual adversity either in emerging adulthood or in childhood would forecast poor metabolic health. Hypotheses were tested with prospective data from 504 Black American men followed from age 20 to age 26. Planful self-control in emerging adulthood directly forecasted low levels of depressive symptoms, one's likelihood of obtaining a bachelor's degree, increased job satisfaction, and increases in metabolic risk. Exposure to childhood deprivation moderated the influence of planful self-control on metabolic risk. Men with high levels of deprivation and high levels of planful self-control exhibited the worst metabolic profiles in the sample. In contrast, men with high levels of childhood deprivation and low levels of planful self-control exhibited the best metabolic profiles. Documenting the health consequences associated with planful self-control provides a foundation from which to identify modifiable psychosocial factors that affect the course of psychosocial problems and health.

Keywords: metabolic risk, skin-deep resilience, black men, self-control, childhood adversities

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INTRODUCTION

Residence in the rural South of the US takes a toll on Black men's health (Quarells et al., 2012). Research indicates that their life expectancy averages 67.7 years, more than 6 years less than rural white men (Thorpe et al., 2013; Singh and Siahpush, 2014). Although accidents and violence play an important and tragic role in reducing life expectancy, particularly among younger men, much

of this disparity is a consequence of morbidity and mortality related to chronic diseases of aging (Gilbert et al., 2016; Pathak, 2018). For example, compared with Caucasians, Black men evince earlier onset and greater prevalence of, and greater mortality from, coronary heart disease (CHD; Graham, 2015). They are twice as likely to develop type 2 diabetes and are more extensively affected by its complications, including CHD, blindness, and amputation (Mainous et al., 2004). These chronic health problems can take decades to develop and to begin to manifest clinically. However, risk for and resilience to these health problems can be studied earlier in development by tracking intermediate biological processes that are known to contribute to disease progression. Specifically, studies have examined markers of future cardiovascular and metabolic health problems, including elevated blood pressure, lipids, insulin resistance, and obesity (Cornier et al., 2008). We focus in this study on health risks among young adult Black men.

For Black Americans in general, and Black men in particular, life in rural areas can be more challenging than in other areas due to restricted educational and employment opportunities, barriers to physical and mental health care, and a lack of public transportation (Probst and Fozia, 2019). The challenge of overcoming the environmental obstacles associated with chronic economic stress is exacerbated by institutional and interpersonal experiences with racial discrimination (Kogan and Bae, 2020). Stressful experiences proliferate in high poverty environments and during childhood, rural Black men experience elevated rates of adverse childhood experiences associated with poverty (National Advisory Committee on Rural Health and Human Services, 2018). The challenges continue as men transition to the labor force. Although approximately 50% pursue postsecondary education or training programs, completion rates are low: fewer than half of the men who enroll will complete postsecondary training programs or obtain a university degree (Shapiro et al., 2017). Due to poor preparation in schools and discriminatory hiring practices, most young men obtain part- or full-time employment in low-wage jobs that offer little training and no opportunity for advancement (Bucknor, 2015). Job turnover rates are high, and prolonged periods of unemployment grow increasingly common. For men with little stake in conventional educational or occupational systems, the transition to independent adult roles can be a demoralizing and protracted process that taxes their self-efficacy.

Despite the challenges associated with living in a low-resource rural environment, many rural Black American men are able to protect themselves from negative effects of their environment (Brown, 2008; Zapolski et al., 2014; Kogan and Bae, 2020). These men have been called *resilient* because their competence develops in the face of the contextual adversity with which they must contend, enabling them to adapt and "beat the odds" that their lives have presented to them (Teti et al., 2012; Denckla et al., 2020). Research suggests that high levels of *planful self-control* may be critical to resilient outcomes. Planful self-control is a group of attributes involved in the self-regulation of cognition, emotion, and behavior (de Ridder et al., 2012). It involves planning, persistence, and a future goal orientation which supports academic and vocational achievement, and psychological adjustment despite a lifetime of exposure to the barrier's endemic to the rural South (Brody et al., 2020). Common outcomes of high levels of planful self-control include lower rates of depression, and high educational and vocational involvement (Spencer, 2001; Silverstein et al., 2021).

Recent research focused on rural Black Americans has documented a paradoxical effect whereby youths from low-income families who are exhibiting high levels of planful self-control and striving hard to succeed experience good mental health but are at elevated risk for adverse health outcomes. These studies find that higher planful self-control during childhood among youths growing up in either economically disadvantaged families or impoverished neighborhoods is associated with better psychosocial outcomes, as reflected in less drug use, lower levels of depressive symptoms, and college attendance. Examination of health vulnerabilities, however, reveals that high levels of planful self-control are associated with higher allostatic load scores (Brody et al., 2013; Chen et al., 2015), a metric that reflects future health vulnerability. The diverging effects of planful self-control have been termed, "skin-deep resilience," wherein outward indicators of competence co-occur with poor health in upwardly mobile Black young people exposed to social adversity.

Skin-deep resilience research suggests that the stress of surmounting adversity to achieve positive developmental outcomes, such as greater educational and vocational success, may tax physiological systems that respond to stress, including the sympathetic nervous system (SNS), and the hypothalamic–pituitary–adrenal (HPA) axis (Merritt et al., 2011). Young Black men exposed to social adversity develop a range of strategies to cope with chronic and acute stressors (Ellis et al., 2015). Some men will use maladaptive coping strategies such as anger, resignation, or substance use. These coping strategies can promote a range of negative psychosocial outcomes including depression, limited educational attainment, and vocational distress. In contrast, some young people who encounter chronic challenges "put their heads down" and persist in pursuit of life goals with even greater determination to succeed. This high effort coping style that promotes success in many life pursuits and deters depressive symptoms appears to tax the physiological systems that respond to stress, leading to a greater risk of elevations in markers for metabolic problems (DeAngelis, 2020).

In this study, we investigated the divergent effects of planful self-control on young adult, Black American men's psychosocial well-being and their metabolic risk. To advance understandings regarding the skin-deep resilience phenomenon, we investigated hypotheses related to the timing and type of social adversity men have experienced. Several studies examining the link between adversity and factors associated with dysregulation in the HPA axis and sympathetic nervous system suggest that childhood exposures to stress have life-course-persistent effects (Miller et al., 2011; Evans et al., 2012). Even if an individual exposed to adversity as a child experience a more optimal environment as a young adult, the physiological "residue" of childhood adversity

remains and manifests as increased allostatic load, metabolic risk, and systemic inflammation (Miller et al., 2011; Evans et al., 2012). We thus examine separately the potential influences of adversity experienced during childhood and adolescence vs. stressors experienced during emerging adulthood.

Recent research also indicates the importance of considering distinct dimensions of childhood adversity. McLaughlin et al. (2014) highlighted two dimensions: the absence of cognitive and social stimulation, termed *deprivation*, and the presence of experiences involving harm or risk thereof, termed *threat*. Unique emotional, cognitive, and neurobiological pathways have been proposed that underlie the association of these dimensions of adversity with downstream outcomes (McLaughlin et al., 2014). Deprivation affects mental health via influences on the development of higher-order cognitive processes, such as linguistic processing and executive function. Threat in childhood affects mechanisms involved in the acquisition and extinction of fear, with downstream consequences on emotion processing. The extent to which deprivation or threat modulates the effect of planful self-control on metabolic risk has not been investigated.

Figure 1 presents a summary of the skin-deep resilience hypotheses we investigated. We first examined the direct influence of planful self-control on three psychosocial outcomes: educational attainment, vocational satisfaction, and depressive symptoms. Consistent with past research on similar outcomes with youth and young adults (Brody et al., 2013, 2016, 2020; Chen et al., 2020), we expect planful self-control to forecast greater educational attainment and vocational success, along with low levels of depressive symptoms. In contrast, we expect the effects of planful self-control on metabolic risk to depend on men's exposure to social adversity including exposure to deprivation and threat during childhood, and contextual stressors during emerging adulthood. Specifically, in the context of high levels of social adversity, planful self-control in emerging adulthood will forecast worse metabolic outcomes in young adulthood.

METHODS AND MEASURES

Participants

We tested study hypotheses with data from 504 Black American men recruited from 11 rural counties in South Georgia. Eligibility criteria included self-identifying as Black or African American and male, residing in the sampling area, and being between 19 and 22 years of age (M_{age} = 20.29; SD_{age} = 1.10) at baseline (Time 1 [T1]). We recruited participants using respondent-driven sampling (Heckathorn, 2002), an effective method for recruiting hard-to-reach samples of young adults (Kogan et al., 2011). Emerging adult rural Black men are a hard-to-reach population due to frequent transitions in living arrangements, changing contact information, and the lack of reliable lists from which to randomly sample. Community liaisons recruited 45 initial participants from 11 contiguous, rural counties in South Georgia, representing areas of rural poverty in the Southeastern U.S. (Probst and Fozia, 2019). These initial participants were members of the community liaisons' social networks, or individuals who responded to advertisements and outreach in the community. The 45 initial participants completed baseline surveys and were then asked to identify three other Black American men in their community that qualified for the study. Project staff then contacted the referred participants. After the referred participants completed the survey, they were asked to refer three more men from their networks. Each referring participant received $25 per person who completed the survey. This continued until the sampling goal ($N \geq 500$ per *a priori* power analysis) was reached.

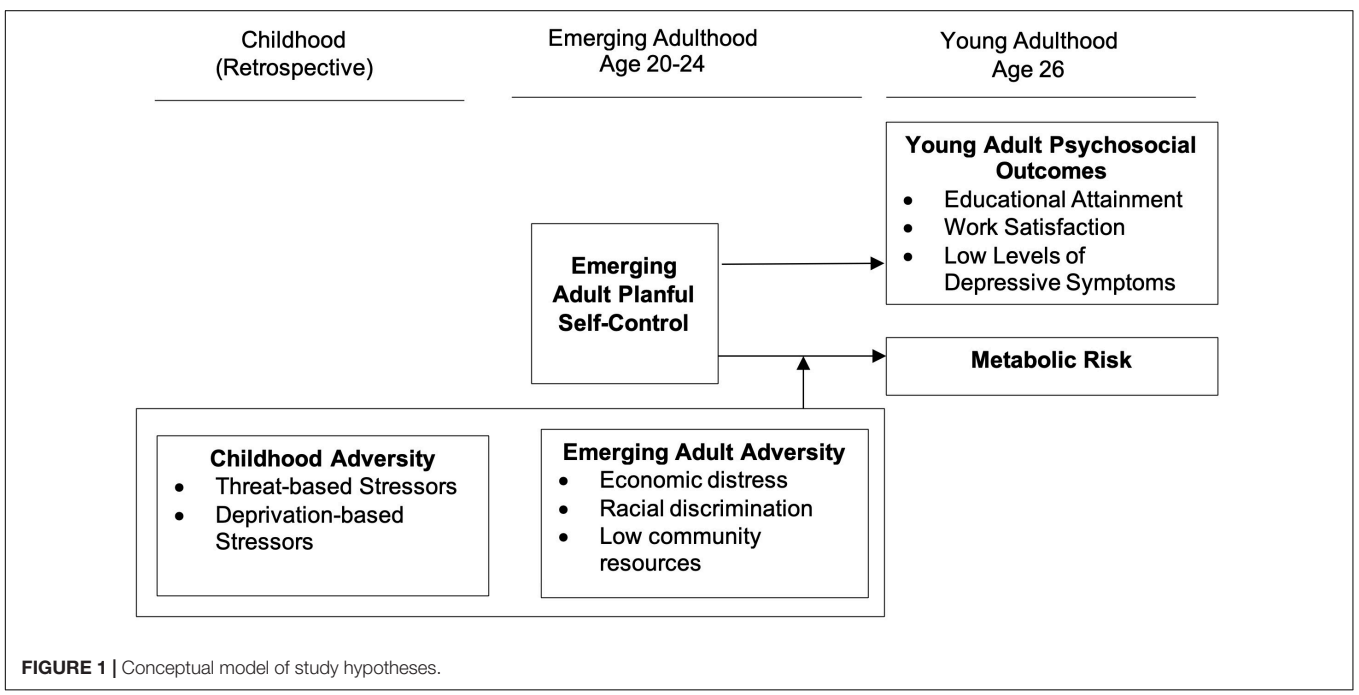

FIGURE 1 | Conceptual model of study hypotheses.

Respondent-driven sampling methods compensate for the non-random recruitment of the sample (Heckathorn, 2002). Analyses of network data at baseline suggested that the sample evinced negligible levels of bias arising from the characteristics of the initial participants, recruitment efficacy, and differences in the sizes of participants' networks (Kogan et al., 2016). Thus, we used raw data in the current analysis.

Procedures

Participants completed surveys in their homes or at a convenient location in the community. Research staff administered surveys on a laptop computer using an audio computer-assisted self-interview protocol, which provides survey navigation with voice and video enhancements to alleviate literacy concerns. Participants were compensated $100 for completing the survey. Participants provided written informed consent; all study protocols were approved by the University's Human Subjects Review Board. The study operated under a federal certificate of confidentiality issued by the U.S. National Institute of Health.

Men provided survey data at three additional waves (T2, T3, and T4; see **Figure 2**). Data from waves T1, T2, and T3 were collected during men's emerging adult years. Baseline data were collected between January 2012 and August 2013 when participating men's mean age was 20.26 (SD = 1.08). A follow-up survey at T2 was conducted in the same manner between August 2013 and March 2015. The T3 data collection took place between April 2015 and December 2016 when participants' mean age was 23.11 (SD = 1.25). The young adult data collection (T4) was conducted between March 2019 and March 2021, when the mean age of the sample was 27.67 (SD = 1.39). At T4, about 70% (n = 351) of participants remained in the study.

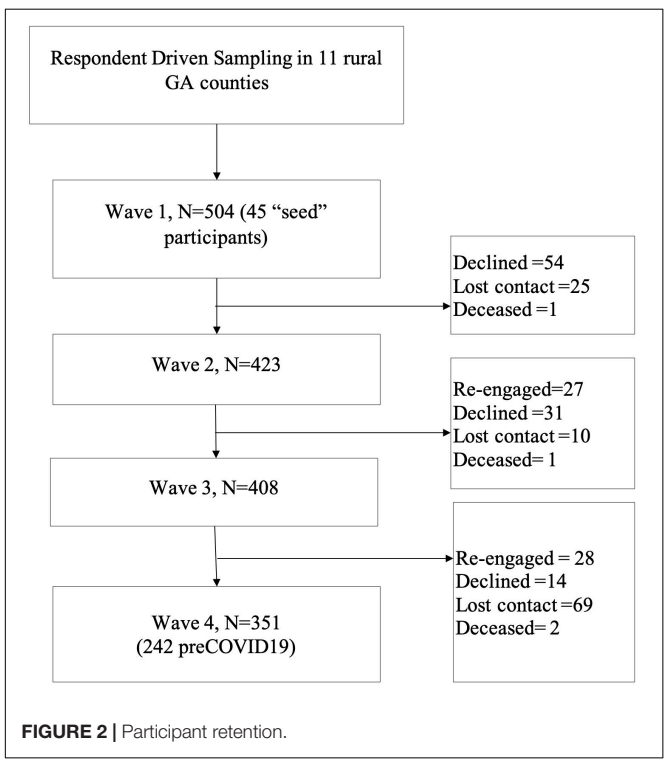

FIGURE 2 | Participant retention.

At T4, blood spot specimens were collected; research staff conducted a finger prick and helped the participant deposit blood spots on data collection cards. Specimen cards were sent to ZRT Laboratories (Beaverton, OR) where levels of cholesterol, triglycerides, and glycosylated hemoglobin (HbA1c) were assayed. Research staff collected participant's blood pressure using an Omeron automatic blood pressure cuff. The research staff also measured the participants' waist circumference at the midpoint between the upper iliac crest and lower costal margin. All anthropomorphic measurements were taken twice and subsequently averaged.

COVID and Study Protocols

In March 2020, when T4 data collection for 242 participants was completed, COVID-19 related lockdowns and in-person visit restrictions were imposed. This resulted in a 2-month pause in research visits when we could only collect data remotely (N = 21). Participants were sent a link to the study survey and no biomarkers were measured. In October 2020, when data collection resumed, study procedures had to be adapted to provide for additional COVID-19 protections for both study participants and research staff. The adapted procedures entailed limiting close contact with participants to 15 min or less. Thus, for the survey part of the data, participants were sent a survey link and they completed the survey on their own devices. Research assistants then delivered a kit with data collection instructions to each participant's home. Study staffs were available by video chat for assistance, and participants were instructed on how to measure their own height, weight, waist and hip circumference, and blood pressure. Then, blood samples were collected outside the home by trained research staff using the same procedures as pre-COVID. Of 351 men who participated at T4, 242 participated before COVID restrictions were imposed, with 177 of them providing blood sample (73.14%); After COVID restrictions were imposed, 109 men participated in the study with 69 of them (63.3%) submitting blood samples through contact-limited procedures.

We ran independent sample T-tests to see if study variables were significantly different between data collected pre-COVID and post-COVID. T-tests revealed that data collected pre- and post-COVID did not differ significantly for planful self-control (p = 0.21), childhood threat (p = 0.90), childhood deprivation (p = 0.80), or contextual stress (p = 0.45). T-tests revealed a significant difference in metabolic risk between participants whose data were collected pre-COVID vs. post-COVID (p = 0.02). Thus, COVID-19 data collection timing was controlled in all analyses. We conducted a second independent sample T-test to compare planful self-control, childhood threat, childhood deprivation, and contextual stress between the participants who submitted biodata compared to the participants who completed the survey only. T-tests suggest in-person visits, compared with survey-only data collection, did not differ significantly for planful self-control (p = 0.40), childhood threat (p = 0.32), childhood deprivation (p = 0.64), or contextual stress (p = 0.94).

Measures

Metabolic Risk

Bloodspots and anthropometric protocols yielded assessments of central adiposity, high-density lipoprotein (HDL), cholesterol, triglycerides, HbA1c, and blood pressure. We made an index variable summing the number of health risk factors at T4. Following previous studies (Han et al., 1995; Expert Panel on Detection, 2001), we dichotomized measures so that they indicate presence (1) or absence (0) of risk per International Diabetes Federation (IDF) criteria (Alberti et al., 2009). Central adiposity was coded as 0 (waist circumference $<$ 94 cm) or 1 (waist circumference $\geq$ 94 cm). HDL was coded as 0 ($>$40 mg/dL) or 1 ($\leq$40 mg/dL). Triglycerides were coded as 0 ($<$150 mg/dL) or 1 ($\geq$150 mg/dL). HbA1c was coded as 0 ($\leq$7) or 1 ($>$7). Elevated blood pressure was coded as 1 when systolic pressure was above or equal to 130 millimeters of mercury (mm Hg) and/or diastolic blood pressure was at or above 85 mm Hg, or 0 if systolic blood pressure was below 130 mm Hg and/or diastolic blood pressure was below 85 mm Hg. The resulting metabolic risk index ranged from 0 to 5 (M = 1.38, SD = 1.09).

Planful Self Control

Planful self-control was measured at T1, T2, and T3 using three measures. Self-regulation was measured using a 10-item version of the Self-Regulation Questionnaire (Brown et al., 1999). The response scale ranged from 1 (*strongly disagree*) to 4 (*strongly agree*). Example items included, "If I wanted to change, I am confident that I could do it," and "I usually keep track of my progress toward my goals." Cronbach's α was as follows: T1 α = 0.90, T2 α = 0.95, T3 α = 0.96. Self-regulation scales across time were correlated ($rs > 0.54$, $p < 0.00$) and subsequently averaged. State hope was measured using the 6-item State Hope Scale (Snyder et al., 1996). The response scale ranged from 1 (*strongly disagree*) to 4 (*strongly agree*). Example items included, "I can think of many ways to reach my current goals," and "Right now, I see myself as being pretty successful." Cronbach's α was 0.85 at T1, 0.90 at T2, and 0.93 at T4, and the scores across time were correlated ($rs > 0.25$, $p < 0.00$). They were averaged to form a composite. Men completed the nine-item Perceived Life Chances scale (Jessor et al., 1998). The scale provided a list of positive life experiences and asked men how sure they were that they would achieve them. The response scale ranged from 1 (*not sure at all*) to 4 (*very sure*). Example items included, "You will have a job that pays you well," and "You will be respected in your community." Alphas were as follows: T1 α = 0.90, T2 α = 0.92, T3 α = 0.95, and the scores across time were correlated ($rs > 0.32$, $p < 0.00$). To provide a reliable index of emerging adult planful self-regulation, the scales were averaged across T1, T2, and T3. The resulting three composites were all significantly correlated at or above 0.50, standardized and summed to create a T1–T3 planful self-control composite measure.

Childhood Threat

At T1, men reported on childhood experiences of threat using eight-items from the Adverse Childhood Experience Questionnaire (Felitti et al., 1998). The scale lists a range of experiences involving physical abuse, sexual abuse, and witnessing domestic violence and asks men if the experiences occurred to them in their first 16 years of life. The response scale was 1 (*yes*) or 0 (*no*). Example items include "Did a parent or other adult hit you do hard that you had marks or were injured?," "Did an adult or person at least 5 years older than you ever attempt or actually have oral, anal, or vaginal intercourse with you" and "Was your mother or stepmother often pushed, grabbed, slapped, or had something thrown at her?" Items were summed to create a childhood threat scale that ranged from 0 to 8. Cronbach's α was 0.80.

Childhood Deprivation

Childhood deprivation was assessed with measures of neglect and childhood poverty at T1. Neglect was measured using four items from the Adverse Childhood Experience Questionnaire (Felitti et al., 1998). Men were asked if a list of experiences occurred to them within their first 16 years of life, including, "you didn't have enough to eat, had to wear dirty clothes, and had no one to protect you?" and "your parents were too drunk or high to take care of you or take you to the doctor if you needed it?" Cronbach's α was 0.70. Childhood family poverty was measured with a 15-item scale (Curtis et al., 2021). The scale asked men how often they experienced poverty-related events in their first 16 years of life. Example items include, "My family often had to move due to money problems" and "I often did not have clothes that fit." The response scale ranged from 0 (*never*) to 3 (*almost always*). Cronbach's α was 0.81. The neglect and poverty scales were significantly correlated (r = 0.30). They were standardized and summed to create a childhood deprivation measure.

Emerging Adult Contextual Stress

We constructed a contextual stress index using three indicators (economic distress, racial discrimination, and low community resources) assessed at T1, T2, and T3. Men reported on their experience of economic distress in the past 6 months with five statements about their economic resources such as, "I have enough money to afford the kind of food I need," and "I have enough money to afford the kind of medical care I need." The men's responses ranged from 1 (*strongly disagree*) to 4 (*strongly agree*). All items were reverse-scored and summed to create a total economic stress variable. Cronbach's α was as follows: T1 = 0.79, T2 = 0.84, T3 = 0.87. Racial discrimination was assessed using the nine-item Racist Hassles Questionnaire (Brody et al., 2006). Men's responded to the items on a scale ranging from 0 (*never*) to 3 (*frequently*). Cronbach's α was as follows: T1 = 0.84, T2 = 0.86, T3 = 0.87. Examples of items include, "have you been ignored, overlooked, or not given service because of your race," and "have you been called a name or harassed because of your race." Men responded to the 12-item community resources subscale of the Community Resources and Problems Scale (Forehand et al., 2000). Men were asked how well their community was at providing a list of resources including "finding full-time jobs," "public transportation" and "finding places to live on your own." The response scale ranged from 1 (*very poor*) to 5 (*very good*). All items were reversed scored and summed, so higher scores reflected lower community resources. Cronbach's α was as follows: T1 = 0.94, T2 = 0.96, T3 = 0.94. All measures

were significantly correlated (rs > 0.25) and were standardized and summed to create the contextual stress variable.

Depressive Symptoms

At T4, men responded to the 20-item Center for Epidemiological Studies Depression scale (Radloff, 1977). The scale asks participants to rate how often they experienced a range of depressive symptoms over the previous week. Example items include, "How often were you bothered by things that usually do not bother you" and "How often did you feel sad?" The response scale ranged from 0 (*rarely or none of the time*) to 4 (*most or all of the time*). Items were summed to create a total depressive symptom scale that ranged from 0 to 60. Cronbach's alpha was 0.86 at T4.

Job Satisfaction

Job satisfaction was measured at T4 using an 18-item scale (Gattiker and Larwood, 1986). The scale asked men who reported that they worked full or part-time (n = 279) if they agreed or disagreed with a list of statements about their job, such as "I am in a position to do mostly work which I really like" and "I am receiving fair compensation compared to my peers." The response scale ranged from 1 (*strongly disagree*) to 4 (*strongly agree*). Cronbach's alpha was 0.88.

Educational Attainment

At T4 men reported their educational attainment on a 6-point scale ranging from 1 (10th grade or less) to completing 6 (*receipt of a graduate degree*). Educational attainment was recoded as 0 (*no bachelor's degree*) or 1 (*bachelor's degree or higher*).

Covariates

To isolate the individual and interaction effects of planful self-control and social adversity on Black men's metabolic risk in emerging adulthood, we controlled for several pre-existing factors that may be associated with metabolic risk. At T1, Men reported on their mother and father's highest level of education. Responses ranged from 1 (*10th grade or less*) to 6 (*receipt of a graduate degree*). At T4 men reported on the number of hours they spent doing moderate or vigorous exercise in the previous week. Physical activity was coded as the average number of hours the participant engaged in moderate and/or vigorous exercise per week. The final psychical activity score ranged from 0 to 28 h (M = 6.58, SD = 7.9).

Men reported on their alcohol and tobacco use at T4. Men were asked how many cigarettes or cigars they had smoked in the previous 3 months. The response scale ranged from 0 (*none at all*) to 7 (*more than 40 per day; M* = 3.08*, SD* = 4.37). Men were then asked on average, how many alcoholic drinks they consume each month (M = 4.27, SD = 5.77).

Men reported on their consumption of a healthy diet at T4 using the 23-item Food Habits Checklist (Johnson et al., 2002). The checklist asked men about their diet choices with a response option of 1 (*true*) or 0 (*false*). Example items include, "I try to keep my overall fat intake down," "I make sure I eat at least one serving of vegetables or salad a day," and "I rarely eat fast food meals." Items were summed to create a healthy diet scale that ranged from 0 to 23. Cronbach's alpha was 0.70.

Age was measured at T1 via birth dates (M = 20.1, SD = 1.27). COVID-19 occurred during the fourth wave of data collection in the current study. We created a dummy variable that indicated whether the data had been collected prior to the first national lockdown on March 11th, 2020. The variable was coded as 0 (*prior to March 11th, 2020*) and 1 (*post-March 11th, 2020*). Data collection timing vis-á-vis COVID-19 was controlled in all analyses.

Data Analysis

Tests of study hypotheses were conducted using Mplus 8 (Muthén and Muthén, 1998-2017). Little's Missing Completely at Random test indicated that our data were missing completely at random for all study variables [$\chi^2_{(679)}$ = 614.63, p = 0.96]. Accordingly, missing data were managed with full information maximum likelihood (FIML) estimation (Little and Rubin, 2019). FIML tests hypotheses with all available data; therefore, no cases were dropped due to missing data (Arbuckle, 1996; Little and Rubin, 2019). Data from all 504 participants were included in tests of study hypotheses.

Analyses were conducted in stages. First, we assessed the impact of planful self-control on each psychosocial outcome (depressive symptoms, job satisfaction, educational attainment). Linear regression analyses were used to examine the effects on continuous outcomes (depressive symptoms and job satisfaction), and logistic regression was used to analyze the effects on the dichotomous outcome (educational attainment). In all analyses childhood threat, childhood deprivation, emerging adult contextual stress, age, parental education, and COVID-19 data collection were controlled. Comparative Fit Index (CFI) values greater than 0.95, Root Mean Square Error of Approximation (RMSEA) values less than 0.08, and a χ^2/df ratio less than 3.0 indicate acceptable model fit (Hu and Bentler, 1999). Educational attainment was a dichotomous outcome, and therefore a logistic regression was used.

Next, we conducted interaction analyses to test our hypotheses regarding the moderating influence of, threat, deprivation, and contextual stress on the association between planful self-control and metabolic risk. We used ordinal regression analysis to model the main effects of planful self-control behavior on metabolic risk while controlling for diet, physical activity, age, and COVID-19 data collection. To test our hypotheses regarding the moderating effects of childhood threat, deprivation, and contextual stress on the association between planful self-control and metabolic risk, we created interaction terms for each moderator and conducted hierarchical ordinal regressions (Marsh et al., 2013). Models with significant interaction effects were plotted using the Johnson-Neyman plot in Mplus (Johnson and Neyman, 1936; Muthén and Muthén, 1998-2017).

RESULTS

Table 1 presents the means, standard deviations, and frequencies among study variables. At T4, men were, on average, 27 years old (SD = 1.23). Men in the study had an average of 1.38 metabolic risk factors (SD = 1.09). Approximately 13.5% (n = 68) of men

TABLE 1 | Means, standard deviations, and frequencies of study variables.

	Mean/*n**	SD/%*
Metabolic risk index (0–5)	1.38	1.09
Central adiposity (waist circumference ≥94 cm)	107*	35.00*
High-density lipoprotein cholesterol (≤40 mg/dL)	121*	49.20*
Triglycerides (≥150 mg/dL).	69*	28.10*
HbA1c (>7)	7*	2.85*
Blood pressure (SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg)	156*	63.41*
Planful self-control	0	0.86
Childhood threat	1.31	1.87
Childhood deprivation	0	1.45
Contextual stress	0	2.09
Depressive symptoms	4.05	4.25
Job satisfaction	54.50	8.65
Educational attainment (≥Bachelor's degree)	55*	15.67*
Age in years	20.10	1.27
Healthy diet	9.10	4.76
Physical exercise (hours/week)	13.16	4.33
COVID onset (data collected post COVID onset)	109*	31.05*
Maternal education	3.89	6.12
Paternal education	4.10	6.16
Tobacco use	3.08	4.37
Alcohol use (drinks/month)	4.26	5.77

*SD, standard deviation. *In the left column signifies total number at the corresponding cut-off; *In the right column signifies the percent at the corresponding cut-off. HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure.*

had 0 metabolic risk factors, 38.6% (n = 120) had 1 risk factor, 24.1% (n = 75) had 2 risk factors, and 15.4% had 3 or more risk factors (n = 48). Despite 72% of participants being employed (86% full time, 14% part-time), the average monthly income among working men was $871. Correlations of all study variables can be found in **Supplementary Table 1**.

Table 2 presents the results and model fit indices for the linear regression (depressive symptoms and job satisfaction) and logistic regression (educational attainment) analyses on psychosocial outcomes. Per Model 1, increased levels of planful self-control behaviors predicted reductions in depressive symptoms ($\beta = -0.13$, $p = 0.03$, 95% CI [−0.24, −0.01]). Per Model 2, planful self-control had a significant association with job satisfaction ($\beta = 0.24$, $p < 0.01$, 95% CI [0.12, 0.36]). Per Model 3 planful self-control was a significant predictor of educational attainment ($\beta = 0.36$, $p < 0.01$, 95% CI [0.17, 0.54]). Participants with more planful self-control behavior were 2.36 times more likely per unit change in the scale to graduate from college than those with less planful self-control.

Table 3 presents the results and model fit indices of the ordinal regression analyses on metabolic risk. Model 1 presents the main effects of planful self-control, childhood threat, childhood deprivation, contextual stress, and confounding variables on metabolic risk. Planful self-control was significantly associated with T4 metabolic risk ($\beta = 0.12$, $p = 0.04$). Participants with high planful self-control behaviors were 1.3 times more likely to have increased metabolic risk. Model 2 includes the interaction term (planful self-control × childhood deprivation) which was significant ($\beta = 0.15$, $p = 0.02$). Model 3 includes the interaction term between planful self-control and threat, which was non-significant ($\beta = -0.01$, $p = 0.87$). Model 4 includes the interaction term between planful self-control and contextual stress. This interaction was also non-significant ($\beta = -0.06$, $p = 0.23$). The Johnson-Neyman plot (see **Figure 3**) presents the effect of planful self-control on metabolic risk (y-axis) and the 95% confidence intervals across different values of childhood deprivation (x-axis). The shaded area on the right side of the plot indicates that for men who experienced higher levels of childhood deprivation, planful self-control is associated with elevated metabolic risk. This region of significance begins slightly below the mean, when childhood deprivation reaches -0.01, which comprises 34.1% of the sample.

DISCUSSION

Emerging research suggests that investigations of resilience among Black American men must content with the possibility that a resilience observed in psychosocial functioning may take a tool on health. The current study investigated the divergent effects of planful self-control on young adult, Black American men's psychosocial well-being and metabolic risk. Specifically, we used a prospective design to (a) examine the direct relationship between Black American men's planful self-control and specific psychosocial outcomes (e.g., educational attainment, job satisfaction, and depressive symptoms) and (b) examine the moderating effects of childhood and young adult adversities on the relationship between emerging adult Black American men's planful self-control and metabolic risk. Study findings revealed that increased levels of planful self-control were directly associated with (a) lower levels of depressive symptoms, (b) higher levels of job satisfaction, (c) an increased likelihood of earning a bachelor's degree, and (d) increased metabolic risk. Our findings indicated that within the context of high levels of childhood deprivation, increased levels of planful self-control were associated with elevated metabolic risk.

Planful self-control was directly associated with positive psychosocial outcomes and with increased metabolic risk. These findings are consistent with emerging research documenting the protective effects of planful self-control on psychosocial health and socioeconomic outcomes at the detriment of physiological health (Sellers and Neighbors, 2008; Chen et al., 2020). According to Brody et al. (2013), planful self-control can be emotionally and socioeconomically beneficial as men are able to develop competencies in the face of adversity, enabling them to *beat the odds*. However, prior evidence indicates that high-effort coping can be physiologically strenuous, which contributes to increased stress on the body that eventually results in poor physical health (Bennett et al., 2004). For example, Robinson and Thomas Tobin (2021) examination of the associations between high effort coping, and physical and mental health, among 627 Black Americans found that high effort coping was associated with decreases in depressive symptoms but increases in allostatic load (i.e., an indicator of physiological dysregulation that occurs as a response to stress). Our findings extend prior

TABLE 2 | Effects of planful self-control, childhood threat, deprivation, and contextual stress on psychosocial outcomes.

	Depressive symptoms					Job satisfaction					Educational attainment				
	β	*p*	*b*	SE	95% CI	β	*p*	*b*	SE	95% CI	β	*p*	OR	SE	OR 95% CI
Predictors															
Planful self control	−0.13	0.03*	−0.77*	0.36	−1.47, −0.07	0.24***	0.00	2.41***	0.63	1.18, 3.64	0.36**	0.00	2.36	0.62	1.41, 3.94
Deprivation	0.07	0.27	0.24	0.22	−0.19, 0.67	−0.01	0.93	−0.03	0.38	−0.77, 0.71	−0.20	0.08	0.75	0.13	0.54, 1.05
Threat	0.06	0.34	0.15	0.16	−0.16, 0.46	0.03	0.66	0.13	0.29	−0.44, 0.69	0.16	0.07	1.20	0.12	0.98, 1.45
Contextual stress	0.18**	0.00	0.46**	0.14	0.19, 0.73	−0.21**	0.00	−0.87**	0.27	−1.40, −0.35	−0.02	0.78	0.98	0.07	0.85, 1.13
Covariates															
Maternal education	−0.18	0.42	−0.15	0.19	−0.52, 0.22	0.20	0.38	0.28	0.32	-0.35, 0.91	0.72	0.06	1.28	0.14	1.04, 1.57
Paternal education	0.15	0.50	0.13	0.19	−0.24, 0.50	−0.15	0.52	−0.21	0.32	-0.84, 0.42	-0.55	0.11	0.83	0.09	0.68, 1.02
Age	−0.08	0.16	−0.30	0.21	−0.71, 0.12	0.01	0.89	0.06	0.42	=0.77, 0.88	−0.06	0.48	0.91	0.11	0.71, 1.18
COVID onset	−0.01	0.93	−0.05	0.65	−1.33, 1.22	−0.00	0.95	−0.08	1.26	−2.56, 2.40	−0.07	0.45	0.73	0.30	0.33, 1.65
Model fit															
χ^2	16.60					16.65					–				
DF	12					12					–				
CFI	0.89					0.91					–				
RMSEA	0.02					0.03					–				

**Significant at the 0.05 level (2-tailed). **Significant at the 0.01 level (2-tailed). ***Significant at the 0.001 level (2-tailed). SE, standard error; 95% CI, unstandardized 95% confidence interval; OR, odd's ratio; DF, degrees of freedom; CFI, comparative fit index; RMSEA, root mean square error of approximation.*

TABLE 3 | Effects of childhood threat, deprivation, and contextual stress by striving on metabolic risk.

	Model 1				Model 2				Model 3				Model 4			
	b	SE	Odds ratio	95% CI	*b*	SE	Odds ratio	95% CI	*b*	SE	Odds ratio	95% CI	*b*	SE	Odds ratio	95% CI
Predictors																
Planful self-control	0.27*	0.13	1.30	1.00, 1.69	0.28*	0.13	1.31	1.01, 1.71	0.27*	0.13	1.31	1.01, 1.69	0.26*	0.14	1.30	1.01, 1.69
Deprivation	−0.03	0.10	0.99	0.81, 1.20	−0.01	0.09	1.00	0.83, 1.20	−0.03	0.10	0.99	0.81 1.20	−0.02	0.10	0.98	0.80, 1.19
Threat	−0.08	0.08	0.92	0.79, 1.08	−0.07	0.08	0.93	0.80, 1.09	−0.08	0.09	0.92	0.78, 1.09	−0.09	0.08	0.92	0.78, 1.08
Contextual stress	0.04	0.05	1.04	0.93, 1.15	0.031	0.05	1.03	0.93, 1.14	0.04	0.06	1.04	0.93, 1.15	0.05	0.06	1.05	0.94, 1.17
Interactions																
Planful SC × Deprivation		-	-	-	0.22*	0.09	1.24	1.04, 1.49	-	-	-	-	-	-	-	-
Planful SC × Threat	-	-	-	-	-	-	-	-	−0.01	0.08	0.99	0.85, 1.14	-	-	-	-
Planful SC × Contextual stress	-	-		-	-	-	-	-	-	-	-	-	−0.06	0.05	0.94	0.86, 1.04
Covariates																
Healthy diet	0.00	0.03	1.00	0.96, 1.05	0.01	0.02	1.00	0.96, 1.05	0.01	0.03	1.00	0.96, 1.05	0.01	0.03	1.01	0.96, 1.06
Phys. exercise	0.00	0.01	1.00	0.99, 1.02	−0.00	0.01	1.00	0.98, 1.01	0.00	0.01	1.00	0.99, 1.02	0.00	0.01	1.00	0.99, 1.02
Age	0.07	0.09	1.07	0.90, 1.28	0.06	0.09	1.06	0.89, 1.26	0.08	0.09	1.06	0.89, 1.26	0.07	0.09	1.07	0.90, 1.28
COVID onset	−0.80*	0.26	0.45	0.27, 0.75	−0.85*	0.26	0.43	0.26, 0.72	−0.82*	0.27	0.45	0.27, 0.75	−0.81*	0.27	0.44	0.26, 0.75
Tobacco use	0.03*	0.01	1.03	1.00 1.05	0.03*	0.01	1.03	1.00 1.05	0.03*	0.01	1.03	1.00 1.05	0.03*	0.01	1.03	1.00 1.05
Alcohol use	−0.01	0.02	0.99	0.96 1.03	−0.01	0.02	0.99	0.96 1.03	−0.01	0.02	0.99	0.96 1.03	−0.01	0.02	0.99	0.96 1.03
Model fit																
AIC	18859.526				20560.001				20872.686				20938.261			
BIC	19197.490				20952.885				21265.570				21331.145			

**Significant at the 0.05 level (2-tailed). SC, self-control; AIC, akaike information criterion; BIC, Bayesian information criterion. Model 1 shows the effects of planful self-control, threat, deprivation, contextual stress, and covariates on metabolic risk. Model 2 shows the effects of planful self-control, threat, deprivation, contextual stress, covariates, and the interaction between striving and deprivation on metabolic risk. Model 3 shows the effects of planful self-control, threat, deprivation, contextual stress, covariates, and the interaction between striving and threat on metabolic risk. Model 4 shows the effects of planful self-control, threat, deprivation, contextual stress, covariates, and the interaction between striving and contextual stress on metabolic risk.*

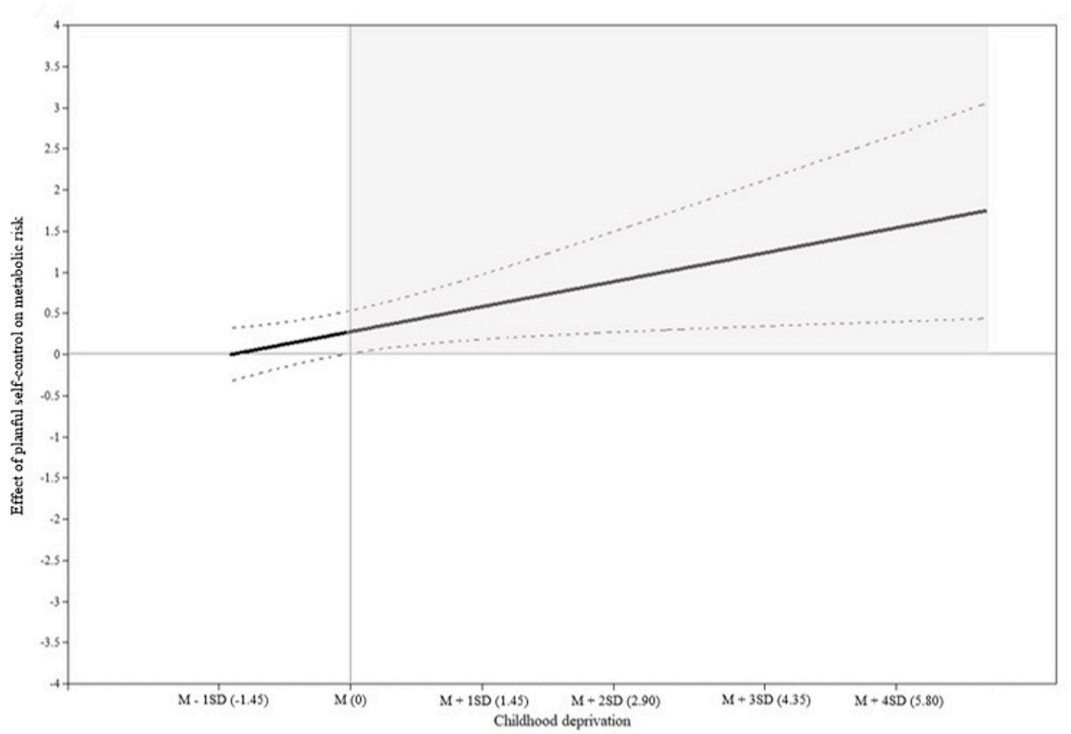

FIGURE 3 | Johnson-Neyman plot. The gray shaded areas indicated the region of significance. The x-axis indicates the score of childhood deprivation and the y-axis represents the effects of planful self-control on metabolic risk. The black solid line represents the effects of planful self-control on metabolic risk corresponding to the values of childhood deprivation. Dashed lines show the 95% confidence interval.

examinations of skin-deep resilience by demonstrating the direct benefits that planful self-control can have on young Black men's outcomes related to depressive symptoms, job satisfaction, and educational attainment, while simultaneously demonstrating the direct detrimental effects that planful self-control can have on men's cardiovascular health.

We hypothesized that the influence of planful self-control on metabolic risk would be particularly pronounced among men experiencing contextual adversity in their lives. A contextual stress by planful self-control interaction did not emerge. This is inconsistent with previous studies (Brody et al., 2013, 2020; Chen et al., 2020); however, these studies tended to be with younger samples and did not focus solely on men. It may be the case that skin deep resilience emerges earlier in development. We leveraged retrospective data on childhood adversity to consider if exposure to different childhood adversities would interact with planful self-control to predict increases in metabolic risk. Consistent with a skin-deep resilience pattern, we found that childhood deprivation interacted with planful self-control to predict metabolic risk, high levels of planful self-control combined with childhood deprivation was associated with increases in men's metabolic risk. This pattern characterized about one-third of the sample. Our findings are consistent with prior developmental research that suggests that restricted access to resources in childhood can have enduring effects on physiological health (Brody et al., 2013). For example, Gaydosh et al.'s (2018) study examining the effects of childhood deprivation on the association between college attainment and metabolic risk demonstrated that within the context of high levels of childhood deprivation, college completion was associated with higher metabolic syndrome among young Black and Hispanic adults.

Our results indicate that Black men who have experienced childhood deprivation may experience a "zero-sum" game regarding planful self-control and their well-being. Should Black men choose to strive for success, they increase their risk of experiencing significant long-term physical health issues. Yet should Black men choose not to strive for success, they may then experience significant psychosocial challenges. These findings highlight the need for (a) further research documenting the complicated effects of skin-deep resilience and Black American men's health, and (b) targeting childhood deprivation screening tools and interventions.

Inconsistent with hypotheses, childhood experiences of threat did not significantly influence the relationship between planful self-control and metabolic risk. The insignificance of this interaction may be related to the differential developmental effects of childhood threat, in comparison to childhood experiences of deprivation (Kinniburgh et al., 2005). For example, adults who experience significant threat during childhood may prioritize physical and emotional safety and security over their

potential futures and adult socioeconomic stability (Edwards et al., 2021). Behaviorally this priority may be represented by men choosing to enter the workforce, often at dissatisfying jobs, instead of pursuing higher education to gain independence. In this instance, men's focus may not be on upward mobility, or planful self-control, but instead on safety, and stabilization. Prior theorizing, coupled with our results, indicate that planful self-control and skin-deep resilience may be heavily influenced by men's psychological desire for upward socioeconomic mobility due to their experiences of resource deprivation in childhood (Pitesa and Pillutla, 2019). In comparison, men's psychological need for physical and emotional safety in adulthood following experience of abuse in childhood may not interact with planful self-control to compromise men's physiological health.

Limitations to the study are notable. Findings may not generalize to women or to men from urban areas or of other racial groups. Information on planful self-control during childhood and adolescence and baseline information on metabolic risk, would allow better specification of when the skin-deep resilience pattern emerges. There are contextual factors that affect rural Black men's health (e.g., community norms) that are not measured in this study. Study findings may not generalize to non-rural Black men or to Black women. The use of biomarker measurements allows us to investigate risk before disease onset when many conditions are asymptomatic or undetected via traditional clinical screening. Nevertheless, it remains unknown whether such risk will ultimately manifest in morbidities, or if high planful self-control individuals will be able to translate their accumulating advantage into better health as they age. RDS sampling may be subject to selection biases and self-report measures are subject to response bias. Documenting the health consequences associated with planful self-control in early adulthood provides a foundation from which to understand different aging trajectories among those from disadvantaged backgrounds.

DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this article will be made available by the authors under a limited disclosure agreement. Requests to access the datasets can be directed to the corresponding author SK, smkogan@uga.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Georgia Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SK, AR, and MC wrote the first draft of the manuscript. AR conducted statistical analyses. CC, HZ, EK, and DA provided feedback on versions of the manuscript. All authors collaboratively conceptualized the study, developed hypotheses, interpreted study results, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.806955/full#supplementary-material

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Associations Between Child Maltreatment, Inflammation, and Comorbid Metabolic Syndrome to Depressed Mood in a Multiethnic Urban Population: The HELIUS Study

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Background: Child maltreatment is a common negative experience and has potential long-lasting adverse consequences for mental and physical health, including increased risk for major depressive disorder (MDD) and metabolic syndrome. In addition, child maltreatment may increase the risk for comorbid physical health conditions to psychiatric conditions, with inflammation as an important mediator linking child maltreatment to poor adult health. However, it remains unresolved whether experiencing child maltreatment increases the risk for the development of comorbid metabolic syndrome to MDD. Therefore, we investigated whether child maltreatment increased the risk for comorbid metabolic syndrome to depressed mood. Subsequently, we examined whether C-reactive protein (CRP), as an inflammatory marker, mediated this association. In addition, we investigated whether effects differed between men and women.

Methods: Associations were examined within cross-sectional data from the multiethnic HELIUS study (N = 21,617). Adult residents of Amsterdam, Netherlands, self-reported on child maltreatment (distinct and total number of types experienced before the age of 16 years) as well as current depressed mood (PHQ-9 score $\geq$ 10), and underwent physical examination to assess metabolic syndrome. The CRP levels were assessed in N = 5,998 participants. Logistic and linear regressions were applied for binary and continuous outcomes, respectively. All analyses were adjusted for relevant demographic, socioeconomic, and lifestyle characteristics, including ethnicity.

Results: A higher number of maltreatment types as well as distinct types of emotional neglect, emotional abuse, and sexual abuse were significantly associated with a higher risk for current depressed mood. Child maltreatment was not significantly associated with the risk for metabolic syndrome in the whole cohort, nor within individuals with depressed mood. As child maltreatment was not significantly associated with the CRP levels, subsequent mediation analyses were not performed. No significant moderating effects by sex were observed.

Conclusion: In this multiethnic urban cohort, child maltreatment was associated with a higher risk for depressed mood. Contrary to our expectations, child maltreatment was not significantly associated with an increased risk for metabolic syndrome, neither in the whole cohort nor as a comorbid condition in individuals with depressed mood. As the data were cross-sectional and came from a non-clinical adult population, longitudinal perspectives in relation to various stages of the investigated conditions were needed with more comprehensive assessments of inflammatory markers.

Keywords: child maltreatment, depressed mood, metabolic syndrome, CRP, HELIUS study

INTRODUCTION

During childhood, biopsychological development occurs relatively fast, leading to vulnerability to lifelong adverse health effects of negative influences from within the environment (Hensch, 2005; Fumagalli et al., 2007). Child maltreatment, as reported by 34–62% of healthy adults during their childhood in Western countries, is such a common negative experience that may have potential long-lasting adverse consequences for mental and physical health (Felitti et al., 1998; Gilbert et al., 2015; Hughes et al., 2017; Merrick et al., 2018). Child maltreatment involves both direct (i.e., sexual, physical, emotional abuse, or neglect) and indirect (i.e., parental conflict and parental substance abuse) sources of stress (Felitti et al., 1998; Gilbert et al., 2015; Merrick et al., 2018; World Health Organization [WHO], 2017). Health may be either directly or indirectly influenced by maltreatment, due to abnormal functioning of biological systems leading to disturbances in emotional, cognitive, physical, and social functioning (Pechtel and Pizzagalli, 2011; Danese and McEwen, 2012) or by reinforcement of abnormal behavior (e.g., smoking, physical inactivity, and unhealthy diet), respectively (Anda et al., 1999; Ford et al., 2011; Midei and Matthews, 2011; Al Odhayani et al., 2013; Bellis et al., 2014; Danese and Tan, 2014; Hughes et al., 2017; Elkins et al., 2019).

Child maltreatment has been shown to increase the risk for major depressive disorder (MDD) and metabolic syndrome (Scott et al., 2011; Danese and Tan, 2014; Mandelli et al., 2015; Otte et al., 2016; Hughes et al., 2017). MDD, defined as experiencing a depressive episode lasting at least 2 weeks, is the most prevalent psychiatric disorder affecting 163,000 million people in 2017 worldwide (American Psychiatric Association, 2013; Otte et al., 2016; Gbd 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Metabolic syndrome is defined as the presence of a specific set of components that constitute risk factors for cardiovascular disease and type 2 diabetes, including increased abdominal obesity, triglyceride levels, blood pressure, fasting glucose levels, and low high-density lipoprotein (HDL) cholesterol. Metabolic syndrome forms a leading public health concern as it affects approximately one-quarter of the population worldwide in 2018 (Alberti et al., 2005; Gheshlagh et al., 2016; Saklayen, 2018). According to the World Health Organization (WHO), the number of people affected by MDD and metabolic syndrome will increase significantly in the next decades, resulting in an expected higher contribution to overall morbidity and mortality (World Health Organization; Vaccarino et al., 2008; Dzherieva et al., 2011). According to a recent meta-analysis, the prevalence of the co-occurrence of MDD and metabolic syndrome is 30.5% (Vancampfort et al., 2014). Individuals with MDD are at 1.5 times higher odds ratio of developing metabolic syndrome than individuals without MDD (Moradi et al., 2021). Metabolic syndrome thus is a common comorbid condition of MDD (Muhtz et al., 2009; Foley et al., 2010; Pan et al., 2012; Penninx et al., 2013; Whooley and Wong, 2013; Gheshlagh et al., 2016; Hiles et al., 2016; Moradi et al., 2021; Vancampfort et al., 2014). This comorbidity is associated with higher societal costs and a further increase of the burden of disease compared to the isolated occurrence of both disorders (Alberti et al., 2005; Penninx et al., 2013).

Child maltreatment has been found to increase the risk for comorbid physical health conditions to psychiatric conditions, including MDD (Widom et al., 2007; Scott et al., 2011). Three previous studies investigated the association between child maltreatment and comorbid (components of) metabolic syndrome to MDD (McIntyre et al., 2012; Wingenfeld et al., 2017; Hosang et al., 2018). These previous studies showed inconsistent findings regarding the association between child maltreatment and risk for comorbid metabolic syndrome to MDD (McIntyre et al., 2012; Wingenfeld et al., 2017; Hosang et al., 2018). It thus remains unresolved whether experiencing child maltreatment increases the risk for the development of comorbid metabolic syndrome to MDD.

Inflammation may be an important mediator linking child maltreatment to poor adult mental and physical health (Danese et al., 2007, 2009; Widom et al., 2007; Capuron et al., 2008; Berens et al., 2017). Several studies have found that child maltreatment significantly impacts inflammatory markers, including higher C-reactive protein (CRP) (Baumeister et al., 2016). CRP is an acute-phase protein synthesized by the liver. Increased circulating CRP is an indicator of ongoing inflammation and is considered a risk factor for developing metabolic syndrome (Sluzewska et al., 1996; Berk et al., 1997; Hornig et al., 1998; Festa et al., 2000; Han et al., 2002; Coelho et al., 2014). Rethorst et al. (2014) previously demonstrated a positive association between the MDD and CRP levels. In addition, previous studies have shown that CRP, as an inflammatory marker, impacts the association between MDD and metabolic syndrome (Rethorst et al., 2014; Chirinos et al., 2017; Lamers et al., 2020). For instance, a former study has found a positive association between CRP and the presence of comorbid metabolic syndrome within individuals with depressed mood (Rethorst et al., 2014). As a result of the previous research, CRP as an inflammatory marker could be a potential mediator in the assumed association between child maltreatment and the development of comorbid metabolic syndrome to MDD.

Against this background, our primary focus was to investigate whether child maltreatment increased the risk of comorbid occurrence of metabolic syndrome and its individual components to the current depressed mood as a self-reported proxy for MDD. Subsequently, the role of CRP as a mediator for these associations was examined. In all analyses, we investigated potential moderating effects by sex, as an increasing amount of literature shows that associations between child maltreatment and adverse health outcomes can differ between men and women (Garad et al., 2017; Ehrlich et al., 2021). This study used data from the Healthy Life in an Urban Setting (HELIUS) study which is a multiethnic urban cohort including several ethnic groups living in Amsterdam, Netherlands. The design of the HELIUS study forms a representative cross-section of this Western European capital's population in terms of demographic factors (e.g., socioeconomic status, educational level, and ethnicity) (Stronks et al., 2013; Snijder et al., 2017). With this study, we extend on previous findings within the same population that individual child maltreatment types were associated with a higher risk for current depressed mood, without significant moderating effects of sex (Sunley et al., 2020).

The association between the number of child maltreatment types experienced and the risk for current depressed mood was not yet investigated in this population, nor were associations between child maltreatment, metabolic syndrome, and CRP.

MATERIALS AND METHODS

Participants and Procedure

This study describes baseline data from the HELIUS study which is a multiethnic cohort study performed in Amsterdam, Netherlands. It aims to investigate the impact of ethnicity on common major physical and mental health problems. Between 2011 and 2015, baseline data were collected among N = 23,942 Amsterdam residents of South-Asian Surinamese, African Surinamese, Turkish, Moroccan, Ghanaian, and Dutch origin. Full details on the study and recruitment method are described elsewhere (Stronks et al., 2013; Snijder et al., 2017). In brief, individuals between the ages of 18 and 70 years were randomly sampled, stratified by ethnicity, from the municipality register of Amsterdam, and invited to participate. We were able to contact 55% of those invited, either by response card or after a home visit by an ethnically matched interviewer. Of those, 50% agreed to participate (participation rate). Therefore, the overall response rate was 28% with some variations across ethnic groups (33% among Dutch, 31% among Surinamese, 22% among Turks, 21% among Moroccans, and 35% among Ghanaians).

Previous non-response analyses indicated that the HELIUS cohort is representative of the investigated ethnic groups in Amsterdam, as only minor differences in socioeconomic characteristics were observed between participants, non-participants, and non-invited eligible individuals. Written informed consent was obtained prior to any study procedures. Participants completed an extensive questionnaire and a physical examination that included the collection of biological samples. The study was approved by the Institutional Review Board of the Amsterdam University Medical Centers located at Academic Medical Center.

For this study, baseline questionnaire and physical examination data were available for n = 22,165 participants. We excluded participants of Javanese Surinamese origin (n = 233), other/unknown Surinamese origin (n = 267), and participants with unknown ethnic background (n = 48) due to their comparatively small sample sizes. This resulted in a total sample size of n = 21,617. The CRP levels were determined in random subsamples of n = 1,000 participants from each ethnic group (total n = 6,000), for whom complete data on cardiovascular measurements and stored blood samples were available. The CRP levels could not be assessed in two participants due to very less material, resulting in n = 5,998 participants.

Measures

Child Maltreatment

Participants self-reported on experienced child maltreatment using a short self-report questionnaire derived from the NEMESIS Trauma questionnaire (De Graaf et al., 2010). It contains 4 items, each reflecting a specific type of maltreatment experienced before the age of 16 years, namely, emotional neglect (ignored or unsupported), physical abuse (kicked, hit, bitten, or hurt), emotional abuse (yelled at, insulted, or threatened), and sexual abuse (any unwanted sexual experience). Items were scored on a Likert scale (never-once-sometimes-often-would rather not say). The items inquiring about emotional neglect, physical abuse, and emotional abuse were considered endorsed when experienced sometimes or often. The item inquiring about sexual abuse was considered endorsed when experienced at least once (De Graaf et al., 2010). Subsequently, the total number of endorsed maltreatment types was calculated (range: 0–4). Missing data were imputed (refer to below details on the applied imputation strategy).

Depressed Mood

Depressed mood was determined using the self-report questionnaire Patient Health Questionnaire-9 (PHQ-9), which inquiries about the presence of depressive symptoms over the past 2 weeks (Kroenke et al., 2010). Its cross-cultural validity across the ethnic groups in the HELIUS study was previously demonstrated (Galenkamp et al., 2017). The questionnaire consists of nine items, with a Likert response scale ranging from never (0) to nearly every day (3). A maximum of one missing item was allowed, in which case the mean score on the other eight items was used to replace it. The cutoff score ≥ 10 indicated a depressed mood (Kroenke et al., 2001). Both the sensitivity and specificity for current MDD at this cutoff score were previously established to be 0.88 (Kroenke et al., 2001).

Metabolic Syndrome

Metabolic syndrome was determined using the harmonized definition of the International Diabetes Federation (Alberti et al., 2009), which considers metabolic syndrome to be present if a minimum of three of five criteria are met: (a) elevated fasting glucose ($\geq$ 5.6 mM, or current use of glucose-lowering medication); (b) elevated blood pressure (systolic $\geq$ 130 and/or diastolic $\geq$ 85 mm Hg, or current use of blood pressure-lowering medication); (c) reduced HDL cholesterol ($<$ 1.0 mM for men, $<$ 1.3 mM for women, or current use of lipid-lowering medication); (d) elevated triglycerides ($\geq$ 1.7 mM, or current use of lipid-lowering medication); and (e) elevated waist circumference (ethnic-specific cutoff values; for all women $\geq$ 80 cm, South-Asian men $\geq$ 90 cm, and other men $\geq$ 94 cm).

To assess these criteria, blood samples were collected during the physical examination after overnight fasting. Glucose was determined using spectrophotometry with hexokinase as the primary enzyme, and triglycerides and HDL-C were determined using colorimetric spectrophotometry (Roche Diagnostics, Tokyo, Japan) from heparin plasma. Blood pressure was measured in a seated position using a semiautomatic sphygmomanometer (Microlife WatchBP Home; Microlife AG, Widnau, Switzerland) using appropriate cuff sizes after being seated for at least 5 min. The mean of duplicate measurements was used. Waist circumference was measured during the physical examination, also determined as the mean of duplicate measurements. If the difference between the two measurements was greater than 1.0 cm, a third measurement was obtained and the mean of the two measurements that were closest together was calculated.

C-Reactive Protein

Blood samples for CRP determination were collected during the physical examination after overnight fasting. Highly sensitive CRP was determined from heparin plasma using particle-enhanced immunoturbidimetric assay (Cobas 702c analyzer; Roche Diagnostics, Mannheim, Germany).

Covariates

Socioeconomic and demographic covariates were age, sex, ethnicity, and educational level. Ethnicity was defined according to the countries of birth of the participant and his/her parents. Participants were considered to be of Dutch origin if the person and both parents were born in Netherlands. Participants were considered to be of non-Dutch origin if the person was either born abroad with at least one parent born abroad (first generation) or was born in Netherlands with both his/her parents born abroad (second generation). Surinamese subgroups (i.e., African and South-Asian) were classified according to self-reported ethnic origin. Dummy variables were created contrasting each ethnic minority group (i.e., South-Asian Surinamese, African Surinamese, Ghanaian, Turkish, and Moroccan) to the Dutch group.

Educational level was used as an indicator of socioeconomic status and was defined as the highest qualification obtained, either in Netherlands or in the country of origin. For educational level, we created dummy variables for lower vocational or general secondary education; intermediate vocational or higher secondary education; and higher vocational education or university, contrasting each to no completed or elementary schooling only as the reference group.

The following information regarding health-behavioral and chronic stress characteristics was also included as they represent potential mediating pathways in the associations under investigation, and we aimed to investigate additional effects of child maltreatment over and above these previously described mediating pathways: smoking (in estimated pack-years), alcohol use in the past 12 months (yes/no), and negative life events experienced in the past 12 months (yes/no), all determined by the self-report questionnaire. In addition, the current use of any of the following psychopharmacological medication was included as covariate: antipsychotics (ATC code N05A), anxiolytics (ATC codes N05BA and N03AE), hypnotics (ATC coded N05C and R06AD02), and antidepressants (ATC coded N06AB, N06AA, N03AF, N03AG, N05AN, and N03AX or without ATC code).

Statistical Analyses

All analyses were performed using SPSS version 26.0. The total number of endorsed types of maltreatment initially could not be calculated for 8.8% of participants because of one or more missing child maltreatment items (either left at least one of the items blank or answered as "would rather not say," refer to **Supplementary Table 1**). Missingness was significantly correlated with all dependent and covariate variables, except smoking. To avoid biased estimations of the investigated associations concerning child maltreatment, missing data for the 4 child maltreatment items were imputed using Markov Chain Monte Carlo imputation with fully conditional specification using predictive mean matching. We included auxiliary variables to account for the fact that missingness was not at random (main effects and two-way interactions among categorical predictors). All variables included in our final analyses were included as auxiliary variables (Alberti et al., 2009). In total, 10 imputations were needed to obtain adequate imputation efficiency. All findings reported concern the pooled results from these 10 imputed datasets (refer to **Supplementary Table 1** for a comparison of the child maltreatment prevalence in the pooled imputed vs. non-imputed data). PHQ-9 scores to determine the current depressed mood were missing for $n = 211$ (0.98%), and information on metabolic syndrome diagnosis was

missing for n = 120 (0.56%); these data were pair-wise deleted from the analyses.

Stepwise logistic regression models were applied to assess the association between the number of experienced maltreatment types and the presence of current depressed mood and metabolic syndrome (diagnosis and its 5 individual components) in the full sample and to assess the association between the number of maltreatment types and the presence of co-morbid metabolic syndrome (diagnosis and its 5 individual components) in participants with current depressed mood only. To aid in the interpretation of observed effects, the number of child maltreatment types was included as an ordinal categorical variable, using indicator contrasts with 0 types experienced as the reference group. These analyses were subsequently repeated including the effects of the four distinct child maltreatment types within one analysis, instead of the total number of types experienced.

For each outcome, the first step included the main effect of the number of experienced maltreatment types, sex, and interaction terms between the number of maltreatment types and sex. The next step included all covariates regarding demographic, socioeconomic, health-behavioral, and chronic stress characteristics and current medication use as described earlier. We refer to these models as the simple and full models, respectively. In the latter model, we assess the associations between child maltreatment and the outcomes of interest over and above these previously described potential confounders and mediators. If the interaction effects between child maltreatment and sex were non-significant, these effects were removed from the respective step of the model and the analysis was repeated including only the main effects of child maltreatment and sex.

The Bonferroni corrections were applied to correct for K = 26 regressions performed, k = 14 in the full sample (1: depressed mood, 2: metabolic syndrome diagnosis, and 3–7: individual metabolic syndrome components), k = 12 in participants with current depressed mood (1: metabolic syndrome diagnosis and 2–6: individual metabolic syndrome components), resulting in $\alpha < 0.002$.

Subsequently, we investigated potential mediation by CRP. As CRP was not normally distributed, a log10(+1) transformation was applied. We excluded N = 27 outliers (0.005%) with standardized log-transformed values $> \pm$ 3.29. We first performed a linear regression analysis on the association between the number of maltreatment types endorsed and CRP, followed by a regression including the effects of the four distinct child maltreatment types. For these analyses, we applied the same stepwise approach as described earlier, with an applied Bonferroni correction for K = 2 analyses, resulting in $\alpha < 0.025$. As the association between child maltreatment and CRP proved non-significant, no further analyses regarding this potential mediation effect were performed.

RESULTS

Sample characteristics of the full sample are shown in **Tables 1**, **2**. On average, participants were 44.3 (SD = 13.2) years old. Women constituted 57.8% (n = 12,488) of the sample. Within the total sample, the prevalence of current depressed mood was 14.8% (n = 3,193). In addition, 31.8% (n = 6,482) of the participants within the total sample met the diagnostic criteria for metabolic syndrome. Of the n = 3,193 participants with current depressed mood, 38.4% (n = 1,221) of the participants also met the criteria for comorbid metabolic syndrome. The average number of experienced maltreatment types was 0.60 (SD = 1.06): 31.3% (n = 6,174) of participants reported to have experienced at least one child maltreatment type.

Association Between Child Maltreatment and Depressed Mood

Women were at increased risk for depressed mood, but sex did not significantly moderate the association between the number of child maltreatment types and depressed mood (**Supplementary Table 2**). Therefore, the interaction effects were removed from the models. The number of experienced child maltreatment types was significantly associated with the risk for current depressed mood, both in the simple and full models (**Table 3**). Similarly, for the four distinct child maltreatment types, sex did not significantly moderate the association with depressed mood (all p-Values > 0.002). The experience of emotional neglect [simple: OR: 1.966 (95% CI: 1.763–2.192) $p < 0.001$; full: OR: 1.929 (95% CI: 1.707–2.180) $p < 0.001$] and emotional abuse [simple: OR: 1.621 (95% CI: 1.429–1.838) $p < 0.001$; full: OR: 1.599, 95% CI: 1.400–1.826, $p < 0.001$] was significantly associated with depressed mood in both the simple and full models. The effect of sexual abuse was only significant within the full model [simple: OR: 1.211 (95% CI: 1.069–1.371) $p = 0.003$; full: OR: 1.434, (95% CI 1.246–1.650), $p < 0.001$], while the effect of physical abuse was non-significant in both the simple and full models [simple: OR: 1.192 (95% CI: 1.051–1.354) $p = 0.007$; full: OR: 1.149 (95% CI: 1.007–1.312) $p = 0.039$].

Association Between Child Maltreatment and Metabolic Syndrome

Men were at increased risk for metabolic syndrome, but sex did not significantly moderate the association between child maltreatment and metabolic syndrome (**Supplementary Table 3**). The number of experienced maltreatment types was not significantly associated with the risk for metabolic syndrome diagnosis, both in the simple and full models (**Table 4**).

Similarly, for the four distinct child maltreatment types, sex did not significantly moderate the association with metabolic syndrome, nor were distinct maltreatment types significantly associated with the risk for metabolic syndrome diagnosis, both in the simple and full models (all p-Values > 0.002).

The number of experienced maltreatment types (either as main effect or interaction effect with sex) was also not significantly associated with the risk for the presence of the individual components of the metabolic syndrome, except for a significantly decreased risk for the presence of elevated blood pressure upon reporting child maltreatment (refer to **Supplementary Tables 4A**–**E**).

Regarding the distinct maltreatment types, the only effect that remained significant within the full model was a significantly decreased risk for the presence of elevated blood pressure upon reporting emotional neglect specifically [simple model: OR: 0.814 (95% CI: 0.747–0.887) $p < 0.001$; full model: OR: 0.807 (95% CI: 0.732–0.889), $p < 0.001$].

The effect of physical abuse was also significant in the simple model, but no longer within the full model [simple: OR: 1.275 (95% CI: 1.160–1.402) $p < 0.001$; full: OR: 1.051 (95% CI: 0.994–1.171) $p = 0.363$]. All other effects were non-significant, including the moderation effects by sex (all p-Values > 0.002).

Association Between Child Maltreatment and Comorbid Metabolic Syndrome to Depressed Mood

Men were at increased risk for comorbid metabolic syndrome, but sex did not significantly moderate the impact of the number of child maltreatment types on metabolic syndrome (**Supplementary Table 5**). The number of experienced maltreatment types was not significantly associated with the risk for comorbid metabolic syndrome in participants with current depressed mood, both in the simple and full models (**Table 5**). The number of experienced maltreatment types was also not significantly associated with the individual components of the metabolic syndrome in participants with current depressed mood, either as main effects or interaction effects with sex (refer to **Supplementary Tables 6A–E**).

Similarly, non-significant results regarding the moderation by sex and main effects on comorbid metabolic syndrome were observed for the four distinct child maltreatment types (all p-Values > 0.002).

Association Between Child Maltreatment and C-Reactive Protein

Women had significantly higher CRP levels, but sex did not significantly moderate the associations between child maltreatment and CRP (**Supplementary Table 7**).

TABLE 1 | Participant characteristics.

	Total sample	Depressed mood		Metabolic syndrome		Depressed Mood with co-morbid metabolic syndrome	
	All (n = 21617)	Yes (n = 3193)	No (n = 18213)	Yes (n = 6842)	No (n = 14655)	Yes (n = 1221)	No (N = 1955)
Sex (% female)	12488 (57.8%)	2128 (66.6%)	10233 (56.2%)	3556 (52.0%)	8860 (60.5%)	740 (60.6%)	1377 (70.4%)
Age	44.26 (13.20)	43.35 (12.65)	44.38 (13.31)	51.64 (10.51)	42.47 (13.61)	50.32 (9.91)	39.01 (12.22)
Ethnicity							
Dutch	4564 (21.1%)	329 (10.3%)	4230 (23.2%)	1077 (15.7%)	3464 (23.6%)	95 (7.8%)	231 (11.8%)
South-Asian-Surinamese	3043 (14.1%)	562 (17.6%)	2461 (13.5%)	1388 (20.3%)	1646 (11.2%)	288 (23.6%)	273 (14.0%)
African-Surinamese	4151 (19.2%)	444 (13.9%)	3668 (20.1%)	1302 (19.0%)	2815 (19.2%)	171 (14.0%)	270 (13.8%)
Ghanaian	2339 (10.8%)	210 (6.6%)	2074 (11.4%)	663 (9.7%)	1661 (11.3%)	65 (5.3%)	144 (7.4%)
Turkish	3614 (16.7%)	835 (26.2%)	2731 (15.0%)	1301 (19.0%)	2291 (15.6%)	340 (27.8%)	490 (25.1%)
Moroccan	3906 (18.1%)	813 (25.5%)	3049 (16.7%)	1111 (16.2%)	2778 (19.0%)	262 (21.5%)	547 (28.0%)
Education (highest level completed)							
Low	3818 (17.8%)	835 (26.3%)	2921 (16.1%)	1884 (27.8%)	1916 (13.2%)	444 (36.7%)	388 (20.0%)
Medium-low	5633 (26.3%)	901 (28.4%)	4678 (25.9%)	2188 (32.3%)	3411 (23.5%)	388 (32.1%)	508 (26.1%)
Medium-high	6235 (29.1%)	944 (29.8%)	5256 (29.1%)	1569 (23.2%)	4623 (31.8%)	267 (22.1%)	670 (34.5%)
High	5736 (26.8%)	490 (15.5%)	5234 (28.9%)	1134 (16.7%)	4578 (31.5%)	111 (9.2%)	377 (19.4%)
Any negative life events (past 12 months, yes)	14095 (65.6%)	2707 (84.9%)	11322 (62.2%)	4608 (67.8%)	9410 (64.5%)	1051 (86.1%)	1639 (83.9%)
Alcohol use (past 12 months, yes)	10885 (50.6%)	1200 (37.8%)	9633 (53.1%)	3747 (55.2%)	7785 (53.4%)	375 (30.9%)	819 (42.1%)
Smoking (pack-years)	6.07 (15.18)	7.59 (16.68)	5.81 (14.90)	9.03 (19.46)	4.70 (12.50)	9.81 (18.64)	6.19 (15.14)
Medication use (current)							
Antipsychotics	221 (1.0%)	98 (3.1%)	122 (0.7%)	110 (1.6%)	110 (0.8%)	57 (4.7%)	41 (2.1%)
Antidepressants	810 (3.7%)	374 (11.7%)	423 (2.3%)	360 (5.3%)	445 (3.0%)	167 (13.7%)	206 (10.5%)
Anxiolytics	262 (1.2%)	129 (4.0%)	132 (0.7%)	122 (1.8%)	137 (0.9%)	57 (4.7%)	71 (3.6%)
Hypnotics	199 (0.9%)	90 (2.8%)	104 (0.6%)	83 (1.2%)	116 (0.8%)	36 (3.0%)	54 (2.8%)

*Continuous variables are depicted as mean (SD), categorical variables are depicted as N (%). *Low, No schooling or elementary schooling; Medium-low, Lower vocational or secondary schooling; Medium-high, Intermediate vocational or secondary schooling; High, Higher vocational schooling or university.*

TABLE 2 | Descriptive information regarding child maltreatment, depressed mood, metabolic syndrome, and C-reactive protein (CRP).

	Total sample	**Depressed mood**		**Metabolic syndrome**		**Depressed mood with co-morbid metabolic syndrome**	
	All (*n* = 21617)	**Yes (*n* = 3193)**	**No (*n* = 18213)**	**Yes (*n* = 6842)**	**No (*n* = 14655)**	**Yes (*n* = 1221)**	**No (*N* = 1955)**
Emotional neglect[$]	4817 (23.6%)	1271 (43.6%)	3534 (20.3%)	1441 (22.6%)	3351 (24.0%)	457 (41.8%)	809 (44.7%)
Emotional abuse[$]	3143 (15.3%)	916 (31.2%)	2216 (12.7%)	951 (14.8%)	2177 (15.6%)	336 (30.2%)	577 (31.9%)
Physical abuse[$]	3145 (15.2%)	797 (26.7%)	2334 (13.3%)	1026 (15.8%)	2106 (15.0%)	299 (26.4%)	497 (27.1%)
Sexual abuse[$]	1704 (8.2%)	412 (13.85)	1289 (7.3%)	485 (7.4%)	1210 (8.6%)	147 (13.0%)	263 (14.2%)
Child maltreatment types, mean number of types experienced[$]	0.60 (1.06)	1.12 (1.34)	0.52 (0.98)	0.58 (1.06)	0.54 (1.01)	1.07 (1.36)	1.15 (1.32)
Child maltreatment types, number of types experienced[$]							
0 types	13545 (68.7%)	1348 (49.3%)	12127 (71.8%)	4349 (70.8%)	9124 (67.7%)	539 (52.3%)	801 (47.4%)
1 type	2816 (14.3%)	472 (17.3%)	2336 (13.8%)	778 (12.7%)	2021 (15.0%)	167 (16.2%)	303 (17.9%)
2 types	1494 (7.6%)	343 (12.6%)	1148 (6.8%)	427 (6.9%)	1061 (7.9%)	111 (10.8%)	231 (13.7%)
3 types	1351 (6.9%)	382 (14.0%)	964 (5.7%)	414 (6.7%)	932 (6.9%)	134 (13.0%)	247 (14.6%)
4 types	513 (2.6%)	188 (6.9%)	323 (1.9%)	178 (2.9%)	332 (2.5%)	79 (7.7%)	109 (6.4%)
Depressed Mood (past 2 weeks, based on PHQ-9)	3193 (14.8%)	3193 (100%)	0 (0%)	1221 (18.1%)	1955 (13.5%)	1221 (100%)	1955 (100%)
PHQ-9 mean	4.77 (5.21)	14.92 (4.47)	2.99 (2.67)	5.15 (5.73)	4.59 (4.94)	15.35 (4.63)	14.66 (4.35)
Metabolic Syndrome diagnosis	6842 (31.8%)	1221 (38.4%)	5537 (30.6%)	6842 (100%)	0 (0.0%)	1221 (100%)	0 (0.0%)
Metabolic Syndrome component							
High waist circumference	14044 (65.0%)	2309 (72.4%)	11579 (63.6%)	6447 (94.3%)	7524 (51.4%)	1164 (95.4%)	1136 (58.1%)
Raised Triglycerides or lipid lowering medication	4155 (19.3%)	793 (25.0%)	3314 (18.3%)	3752 (54.9%)	401 (2.7%)	730 (59.8%)	63 (3.2%)
Reduced HDL cholesterol or lipid lowering medication	6808 (31.7%)	1326 (41.8%)	5041 (29.8%)	4753 (69.5%)	2047 (14.0%)	945 (77.5%)	380 (19.4%)
Raised blood pressure or blood pressure lowering medication	10065 (46.7%)	1420 (44.6%)	8525 (46.9%)	5763 (84.3%)	4249 (29.1%)	970 (79.4%)	443 (22.7%)
Raised fasting glucose or glucose lowering medication	6578 (30.6%)	1034 (32.6%)	5466 (30.2%)	4999 (73.2%)	1571 (10.7%)	865 (71.0%)	169 (8.6%)
CRP (mg/L)#	2.59 (4.14)	3.18 (4.16)	2.49 (4.12)	3.39 (4.88)	2.21 (3.67)	3.67 (3.94)	2.87 (4.26)

Continuous variables are depicted as mean (SD), categorical variables are depicted as N (%). [$]Child maltreatment descriptive represent the non-imputed data for participants completing the respective items only, descriptive concerning the total number of maltreatment types include only those participants with a fully completed child maltreatment questionnaire (n = 19719). #CRP was available for a random subset of participants (N total sample: 5998; N Depressed mood – yes: 897; N depressed mood – no = 5101; N Metabolic syndrome – yes: 1931; N Metabolic syndrome – no: 4067; N Depressed mood no metabolic syndrome: 552; N depressed mood comorbid metabolic syndrome: 345).

Therefore, the interaction effects were removed from the models. The number of experienced maltreatment types was not significantly associated with circulating CRP levels in the simple and full models (**Table 6**). There were also no significant associations between the four distinct maltreatment types and CRP, nor significant moderation effects by sex (all p-Values > 0.002) Therefore, mediation analyses for the associations between maltreatment, depressed mood, and (co-morbid) metabolic syndrome were not performed.

DISCUSSION

In this study, we investigated whether child maltreatment increases the risk for the presence of co-morbid metabolic syndrome to the current depressed mood among a representative multiethnic urban cohort from Amsterdam, Netherlands. Extending previous research within the cohort in which we showed that individual types of child maltreatment were associated with a higher risk for current depressed mood (Sunley et al., 2020), we observed that a higher number of experienced child maltreatment types were positively associated with a higher risk for current depressed mood. Contrary to our expectations, child maltreatment was not significantly associated with increased risk for metabolic syndrome, neither in the whole sample nor as a comorbid condition to depressed mood. Subsequently, we aimed to investigate whether CRP as an inflammatory marker mediated these associations. However, this mediation analysis was not performed since the association between child maltreatment and CRP was not significant.

We did not observe significant associations between child maltreatment and increased risk for metabolic syndrome or its separate components within the whole sample, in either men or women. Our findings regarding the absent association between the number of child maltreatment types and metabolic syndrome diagnosis are in line with findings from Li et al. (2019) who neither observed an association between the number of experienced child maltreatment types, as reported both in childhood and adulthood, nor a risk for metabolic syndrome at mid-adulthood in women and men from a birth cohort that included both British-born residents and immigrants. Yet, Li et al. (2019) observed specific associations between distinct types of maltreatment and increased risk for specific components of

TABLE 3 | Results of the logistic regression analyses assessing associations between the number of experienced child maltreatment types and the presence of current depressed mood in *N* = 20,740 participants.

	Odds Ratio	*P*	95% Confidence Interval Odds Ratio	
Simple model:				
Child maltreatment – 1 type vs. 0 types	1.864	<0.001	1.659	2.094
2 vs. 0	2.784	<0.001	2.452	3.161
3 vs. 0	3.523	<0.001	3.091	4.014
4 vs. 0	4.619	<0.001	3.813	5.595
Sex– female vs. male	1.479	<0.001	1.362	1.606
Constant	0.092	<0.001	0.085	0.099
Full model:				
Child maltreatment – 1 type vs. 0 types	1.869	<0.001	1.641	2.129
2 vs. 0	2.819	<0.001	2.452	3.241
3 vs. 0	3.376	<0.001	2.919	3.906
4 vs. 0	5.156	<0.001	4.162	6.388
Constant	0.045	<0.001	0.034	0.060

Full model: adjusted for sex, age, educational level, smoking, alcohol use, psychopharmacological medications, ethnicity (reference group Dutch), any negative life events (12 months).

TABLE 4 | Results of the logistic regression analysis assessing the association between the number of experienced child maltreatment types and metabolic syndrome diagnosis in *N* = 20,714 participants.

	Odds ratio	*P*	95% confidence interval odds ratio	
Simple model:				
Child maltreatment– 1 type vs. 0 types	0.901	0.020	0.826	0.984
2 vs. 0	0.937	0.247	0.839	1.046
3 vs. 0	0.973	0.649	0.863	1.096
4 vs. 0	1.167	0.105	0.968	1.407
Sex– female vs. male	0.700	<0.001	0.660	0.743
Constant	0.577	<0.001	0.550	0.605
Full model:				
Child maltreatment – 1 type vs. 0 types	0.882	0.013	0.799	0.974
2 vs. 0	0.918	0.181	0.811	1.041
3 vs. 0	0.822	0.004	0.720	0.938
4 vs. 0	1.068	0.527	0.871	1.310
Constant	0.014	<0.001	0.011	0.018

Full model: adjusted for sex, age, educational level, smoking, alcohol use, psychopharmacological medications, ethnicity (reference group Dutch), any negative life events (12 months).

the metabolic syndrome, with the largest effects observed for physical abuse and childhood neglect (Li et al., 2019), while in our study the distinct child maltreatment types were not associated with increased risk for the metabolic syndrome components. We did, however, unexpectedly observe negative associations between distinct maltreatment types as well as the total number of maltreatment types and the presence of elevated blood pressure. The effects of emotional abuse and having experienced once vs. no types of child maltreatment remained significant in the full model including demographic, socioeconomic, health-behavioral, and chronic stress characteristics and current medication use, and warrant further investigation.

In addition, Midei et al. (2013) also did not observe an association between exposure to physical, sexual, and emotional abuse and risk for metabolic syndrome in premenopausal or early perimenopausal women in midlife. Yet, they did observe that physical abuse specifically increased the risk for incident metabolic syndrome in the following 7 years. This effect was specifically related to two components of metabolic syndrome, namely high waist circumference and high fasting glucose (Midei et al., 2013). Contrastingly, Lee et al. (2014) observed that child maltreatment was associated with increased risk for the presence of a higher number of metabolic syndrome components as well as metabolic syndrome diagnosis in both women and men in mid-adulthood within a US study. Moreover, in this study, emotional and physical abuse increased the risk of developing metabolic syndrome across women and men, whereas sexual abuse only increased the risk for metabolic syndrome in women (Lee et al., 2014). Together these studies suggest that there is no general association between childhood maltreatment and metabolic syndrome, rather associations might differ based on interactions between sex, maltreatment type, participant age, and type of cohort. Furthermore, all these studies including this study were cross-sectional, except for Midei and Matthews (2011) who investigated both cross-sectional and longitudinal data. This hampers the interpretation of the nature of the observed associations. It would, therefore, be of interest to investigate longitudinal associations between the various distinct child maltreatment types and the prospective incidence of metabolic syndrome in the planned follow-up assessments within our cohort, especially since the mean age of our cohort is 44.3 years and the associations between child maltreatment and adverse outcome may strengthen with age (Midei et al., 2013).

Within the participants with current depressed mood, childhood maltreatment was not significantly associated with the risk for the presence of co-morbid metabolic syndrome, nor with its separate components. Again, these effects did not differ between men and women. In concordance with this study, the study by Wingenfeld et al. (2017), Hosang et al. (2018) also did not find an association between self-reported maltreatment and medical comorbidities related to metabolic syndrome (e.g., diabetes type 1 and 2, heart problems, and hypertension) in people with recurrent and current unipolar depression, respectively. However, a cross-sectional study by McIntyre et al. (2012) reported that a history of any self-reported childhood trauma was associated with increased risk for one component of the metabolic syndrome in people with MDD, i.e., lower HDL levels. In our study, we used self-reported current depressed mood in the past 2 weeks as a proxy for probable current MDD, whereas McIntyre et al. (2012), Wingenfeld et al. (2017), Hosang et al. (2018) included a clinical MDD diagnosis. Although it is not completely substitutable for a diagnostic interview, the PHQ-9 has been repeatedly found to be a valid diagnostic screener to measure current depressed mood and has good sensitivity and specificity for the detection of current MDD (Kroenke et al., 2001). Nonetheless, potentially our use of a more lenient definition of depressed mood might explain the contrasting findings between studies, and this should be further investigated in the future.

TABLE 5 | Results of the logistic regression analysis assessing the association between the number of experienced child maltreatment types and co-morbid metabolic syndrome diagnosis to current depressed mood in *N* = 3,061 participants.

	Odds ratio	*P*	95% confidence interval odds ratio	
Simple model:				
Child maltreatment – 1 type vs. 0 types	0.889	0.270	0.721	1.096
2 vs. 0	0.769	0.033	0.604	0.979
3 vs. 0	0.815	0.103	0.638	1.042
4 vs. 0	1.006	0.971	0.736	1.374
Sex– female vs. male	0.623	<0.001	0.534	0.727
Constant	0.923	0.293	0.795	1.072
Full model:				
Child maltreatment– 1 type vs. 0 types	0.957	0.721	0.754	1.215
2 vs. 0	0.887	0.397	0.673	1.17
3 vs. 0	0.766	0.060	0.58	1.011
4 vs. 0	1.136	0.489	0.792	1.63
Constant	0.015	<0.001	0.008	0.027

Full model: adjusted for sex, age, educational level, smoking, alcohol use, psychopharmacological medications, ethnicity (reference group Dutch), any negative life events (12 months).

TABLE 6 | Results of the linear regression analysis assessing the association between the number of experienced child maltreatment types and circulating CRP in *N* = 5,879 participants.

	B	SE	*t*	*p*
Simple model:				
Child maltreatment – 1 type vs. 0 types	−0.013	0.011	−1.211	0.226
2 vs. 0	0.005	0.015	0.351	0.726
3 vs. 0	−0.004	0.016	−0.275	0.783
4 vs. 0	0.031	0.024	1.256	0.209
Sex– female vs. male	0.084	0.007	11.253	< 0.001
Constant	0.377	0.006	60.443	< 0.001
Full model:				
Child maltreatment– 1 type vs. 0 types	−0.010	0.010	−0.955	0.340
2 vs. 0	0.003	0.015	0.229	0.819
3 vs. 0	−0.016	0.015	−1.068	0.286
4 vs. 0	0.027	0.024	1.138	0.255
Constant	0.215	0.025	8.722	< 0.001

Full model: adjusted for sex, age, educational level, smoking, alcohol use, psychopharmacological medications, ethnicity (reference group Dutch), any negative life events (12 months).

In support of our approach to investigating comorbid metabolic syndrome to depressed mood, a meta-analysis by Blaine (2008) showed that people with depression were more likely to develop obesity over time than people without depression. Conversely, in a 5-year-longitudinal study, Roberts et al. (2003) showed that the presence of obesity at baseline predicted the subsequent development of a major depressive episode among middle-aged men and women. A recent meta-analysis extends this evidence, as they observed that three surrogate measures of insulin resistance at baseline and development of prediabetes within the first 2 years were associated with a greater risk of incident MDD among healthy adults with no history of MDD or anxiety in a 9-year follow-up (Watson et al., 2021). These findings emphasize the need to also investigate the association between child maltreatment and comorbid depressed mood to metabolic syndrome, preferably in a design that allows for drawing temporal causal inferences. Again, longitudinal studies could help to determine the direction of the effect in the relationship between depression and metabolic syndrome and potential effects of child maltreatment.

We also aimed to investigate whether circulating CRP levels mediated the association between child maltreatment and comorbid metabolic syndrome in participants with current depressed mood. The actual mediation analysis was not performed since the main association between child maltreatment and CRP levels was not significant. Our finding of the absence of an association between childhood maltreatment and CRP is in line with a recent systematic review (Kerr et al., 2021) that showed that previous retrospective studies with retrospective reporting on child maltreatment in adulthood including non-clinical samples have also found no association between maltreatment and CRP. Yet, in contrast, three prospective studies using objective assessment of maltreatment already in childhood, including non-clinical samples, all observed that maltreatment was associated with elevated CRP levels (Danese et al., 2007; Nikulina and Widom, 2014; Osborn and Widom, 2020).

Baldwin et al. (2019) previously investigated the validity of self-report vs. objective measurements of maltreatment. They emphasize that retrospective self-report measures should be used with caution since it may not accurately reflect the experiences of maltreatment due to memory biases which can result in overreporting or underreporting of actual experiences (Baldwin et al., 2019). This might be especially relevant for individuals with depressed mood or MDD, as this might influence the recall and interpretation of previous negative events such as child maltreatment (negative cognitive bias) (Łosiak et al., 2019). Therefore, future longitudinal studies should ideally use a combination of retrospective self-report and prospective objective measures to capture the experiences of maltreatment.

xsx Furthermore, we measured inflammation with just one single marker, i.e., CRP. Although CRP is an established indicator of ongoing inflammation and is commonly used as a diagnostic biomarker for inflammation, individual inflammatory markers in general do not adequately reflect all aspects of inflammatory processes (Del Giudice and Gangestad, 2018). Therefore, future studies should ideally include a more comprehensive assessment of inflammatory markers for a more detailed investigation of the potential mediating role of inflammatory processes.

Moreover, in our multiethnic cohort, the minority groups were previously found to have an increased risk for multiple diseases, including cardiovascular diseases and asthma (Aarab et al., 2019; Perini et al., 2019). Therefore, the observed elevated CRP levels in four out of the five minority groups compared to the ethnic Dutch reference group are not unexpected. Yet, it is well conceivable that these larger effects confounded more subtle associations between child

maltreatment and CRP, even though we accounted for ethnicity in our analyses.

Strengths and Limitations

This study investigated child maltreatment and comorbid metabolic syndrome to current depressed mood in a large representative urban multiethnic cohort in Western Europe (Snijder et al., 2017). The assumed generalizability of the findings is further supported by the fact that the self-reported prevalence rate of child maltreatment of approximately 30% is similar to that previously reported in the general Dutch population (De Graaf et al., 2010).

Nevertheless, our study has several limitations that should be addressed. First, as already mentioned earlier as this study had a cross-sectional design, it is not possible to draw causal or inferences on directionality of effects. Our study suggests that child maltreatment is not associated with increased risk for comorbid metabolic syndrome to depressed mood. However, there is a possibility that the effects of child maltreatment do exist at a more nuanced level and will only come to light when depressed mood and metabolic syndrome development are investigated longitudinally. Next, this study used self-report questionnaires which could have led to decreased reporting reliability. However, in contrast, self-report questionnaires may also represent the respondent's perspective more reliably and stimulate disclosing as compared to interview situations, specifically on sensitive topics, i.e., child maltreatment and depressed mood (McNeeley, 2012). In addition, with respect to child maltreatment, recall bias may have occurred, as child maltreatment may happen at a young age in which children do not have the cognitive ability to recall these events. Moreover, our measure of child maltreatment only included four types of maltreatment (i.e., emotional neglect, psychological abuse, physical abuse, and sexual abuse), which obviously does not cover all the various types of child maltreatment. The measurement of child maltreatment used was developed for use in a Dutch community population. Unfortunately, the questionnaire's cross-cultural validity has not yet been investigated, and we cannot exclude differences in the reliability of retrospective child maltreatment reporting between the different ethnic groups included in our study population, nor in the interpretation of what constitutes child maltreatment and was, therefore, endorsed as such in the questionnaire. Furthermore, in line with previous investigations on the associations between child maltreatment and adverse physical health outcomes within the HELIUS study (Bakema et al., 2020), we solely investigated the associations between the occurrence of the distinct child maltreatment types and the total number of experienced maltreatment types. The developmental timing and chronicity of maltreatment was also not assessed, which could have had an impact on the results, as previous studies have shown that the exact timing of maltreatment within childhood impacts the occurrence of physical and mental health and neurobiological correlates in adulthood (Pechtel et al., 2014).

Finally, while we included ethnicity as a covariate in our analyses, we did not explicitly investigate whether there were differences in the associations between child maltreatment and the various outcomes of interest between our included ethnic groups, nor in the associations of these outcomes with the included covariates on demographic, socioeconomic, health-behavioral, and chronic stress characteristics and current medication use in the statistical models.

CONCLUSION AND FUTURE IMPLICATIONS

This multiethnic urban cohort study provides insights into the association between child maltreatment and comorbid metabolic syndrome in people with current depressed mood, and the potential mediating effect of the inflammatory marker CRP. No significant association was found between child maltreatment and comorbid metabolic syndrome in people with current depressed mood. As child maltreatment was not significantly associated with circulating CRP, mediation was excluded. The observed associations did not differ between men and women. Although our cohort was cross-sectional and consisted of a non-clinical adult population, our study findings provide additional support for the notion that although child maltreatment has debilitating effects on wellbeing and many health outcomes, it does not unequivocally increase the risk for all adverse health outcomes at any moment throughout life. In future research, it is essential to gain prospective longitudinal perspectives regarding different stages of the examined conditions with more comprehensive measures of maltreatment, depressed mood, metabolic syndrome, and inflammation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the HELIUS research cohort, but restrictions apply to the availability of these data which were used under license for the current study, and so are not publicly available. Galenkamp is the Scientific Coordinator of HELIUS and may be contacted with further questions (h.galenkamp@amsterdamumc.nl).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Amsterdam University Medical Centers, location Academic Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MZ and AL conceptualized and designed the current study. FW, SR, B-JB, AH, KT, MS, and LE contributed to the conceptualization and interpretation of results. MZ organized the database and performed the statistical analyses. FW and MZ wrote the first draft of the manuscript. AL and JZ wrote

sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.787029/full#supplementary-material

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