Parenting, Health, and Inflammation: The Role of the Autonomic Nervous System

By

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ABSTRACT

Parenting that is warm, supportive, and consistent has been linked to better health outcomes in offspring throughout the lifespan. Functioning of the child's autonomic nervous system may partially mediate this association. Specifically, a parent's positive socialization efforts may lead to the development of neural-physiological systems of stress and affect regulation that are more flexible and moderate, which subsequently lead to better health outcomes. The following research used a diverse array of data and methods to investigate the role of the autonomic nervous system (ANS) in the relation between parenting and offspring health and health-related outcomes.

In Study 1, data from a large sample of 1,255 adults were used to test longitudinal associations between retrospective reports of parental warmth experienced during childhood, resting heart rate variability (HRV) in midlife, and health outcomes measured nine years later. Results revealed that resting HRV mediated the association between warmer parenting and better cardiovascular health, such that warmer parenting predicted higher resting HRV, which in turn predicted lower odds of having a cardiovascular disorder. In Study 2, associations between cardiac autonomic balance (CAB) and changes in inflammatory cytokines during challenge were assessed among children ages 9-11 years old. Children with lower resting CAB, reflecting relatively lower parasympathetic and higher sympathetic modulation of the heart, tended to exhibit greater acute increases in inflammatory markers in the laboratory, compared to children with higher resting CAB. In study 3, the strength of the association between parenting and offspring ANS activity was estimated using meta-analytic techniques. Results from this study revealed non-significant pooled correlations between parenting and multiple measures of the ANS. However, several significant moderators emerged, suggesting that aspects of both (1) the

study design (e.g., *experimental vs. correlational study, child-reported versus parent-reported measures of parenting*) and (2) the participant sample (e.g., *clinical vs. non-clinical*) can lead to stronger associations between parenting and child ANS physiology. Specifically, the positive association between more positive parenting and resting PNS activity was stronger when a study was experimental, when the sample included children with a clinical condition, and when parenting was reported by the child. In sum, these studies provide evidence for the role of the ANS in the link between parenting and health and further suggest that parenting may be more strongly associated with child ANS activity under certain conditions. Finally, inflammation may play a role in understanding links between ANS physiology and health outcomes.

CHAPTER 1

GENERAL INTRODUCTION

From the moment of birth, infants exhibit a near complete reliance on parents or caretakers for protection from distress. Infants have a limited cognitive, behavioral, and physiological repertoire for moderating their responses to external and internal stimuli (Thompson, 1994). Parents, therefore, must serve as primary external regulators of infant affect and stress reactivity. Parents accomplish this through both preemptive efforts to avoid distress (e.g., maintaining predictable daily routines), as well as active engagement with the infant during moments of emotional arousal (e.g., soothing a crying infant; Thompson & Meyer, 2007). How a parent responds to infant distress signals influences not only the amount of distress the infant experiences in the moment, but also how an infant will respond to distress in the future (Thompson, 1994). Consistent, sensitive responding to infant cues can facilitate trust and security in the interpersonal relationship, which allows for emotional expression during distress that is moderate (Cassidy, 1996) and effectively buffered (i.e., reduced) by caretakers (Gunnar & Hostinar, 2015).

As children grow, they begin to rely more on their own regulatory abilities: cognitive, behavioral, and physiological strategies for coping with changing environmental demands, internalized from their history of interactions with caretakers (Thompson & Meyer, 2007). However, the importance of parental *protection*, *teaching*, and *control* for offspring affect and self-regulation does not fade in childhood, but instead changes form in sync with the developing child (Grusec & Davidov, 2010). For instance, parental support during threat can buffer the stress response even into late childhood (Hostinar et al., 2014). Parental emotion coaching, or open and supportive discussion of emotions, can teach children how to better understand and

therefore regulate their own emotional state (Hastings, 2018; Thompson, 2014a). In addition, through the provision of clear, consistent, and developmentally appropriate expectations, parent behavioral control can facilitate autonomy and help guide the child towards active engagement in independent exercise of affective and self-regulatory skills (Barber, 1996; Grusec, 2011; Thompson, 2015).

Conversely, children who develop in unsupportive, harsh, or abusive environments may be exposed to multiple risks, including a lack of experience-expectant warmth, guidance, and control, and increased threat and unpredictability. The consequences of such an upbringing are myriad but include the development of affect and self-regulation strategies that may be evolutionarily adaptive in the short term, but costly across the lifespan (Repetti et al., 2002; Thompson, 2019). In accordance with *life history theory*, the level of threat and unpredictability experienced during early life, modulated by parent socialization, provides important information that may guide the development, or calibration, of physiological systems of affect and stress reactivity (Del Guidice et al., 2011). When the early environment is harsh and unpredictable, a stress reactivity profile that is more vigilant (more reactive and persistent) may provide greater chances of short-term survival, with long term costs to health and wellbeing (Del Guidice et al., 2011; Repetti et al., 2002; Thompson, 2019).

It is not surprising then that differences in parental socialization experienced during the early formative years have been repeatedly linked to direct and indirect measures of health and mortality (Chen et al., 2017). Parenting that is sensitive, consistent, and that provides developmentally appropriate limits predicts better offspring health across the lifespan (G. E. Miller et al., 2011). Harsh, neglectful, or abusive parenting is conversely associated with increased risk for offspring disease and pathology (Chen et al., 2017). Robust correlational

evidence in humans is supported by non-human animal research documenting causal effects of parenting on offspring health and well-being (Cohen et al., 2007). Conceptual models that attempt to describe how parenting gets *under the skin* suggest that the influence of early caregiving on later health can be at least partially explained through the influence of parenting on the development of biological systems of affective and stress reactivity, such as the autonomic nervous system (ANS; Propper & Moore, 2006; Repetti et al., 2002).

The Autonomous Nervous System

The autonomic nervous system (ANS) is an expansive network of nerves that work in combination with the endocrine, immune, and central nervous systems to regulate bodily processes involved in homeostasis, and facilitate context-dependent adaptation to changing environmental demands (Propper & Holochwost, 2013). The ANS is made up of two branches, the sympathetic nervous system (SNS), associated with fight-or-flight behavior, and the parasympathetic nervous system (PNS), conversely associated with returning to a state of rest following physiological arousal (Beauchaine, 2001). Importantly, the PNS and SNS work together, though not always in synchrony, to prepare the body to engage in goal-directed behavior (Berntson et al., 2008; Grossman & Taylor, 2007).

Functioning of the ANS is recognized as an important predictor of health and mortality (Sloan et al., 2007; Thayer et al., 2010). For example, lower resting parasympathetic modulation of the heart is linked to increased odds of cardiovascular disease, diabetes, and all-cause mortality (Thayer et al., 2010). Conversely, elevated sympathetic activity at rest is associated with increased cardiovascular risk (Mancia & Grassi, 2013). The neurovisceral integration model proposes that measurements of autonomic modulation of the heart, reflecting dynamic integration of cognitive and physiological systems of goal-directed behavior, can provide

noninvasive insight into individual differences in self-regulation abilities (Appelhans & Luecken, 2006; Thayer, 2006). These individual differences in psychosocial functioning in turn may explain the connection between measures of ANS physiology and health. Notably, the evidence linking measures of parasympathetic and sympathetic modulation of the heart to psychosocial functioning and well-being is somewhat inconsistent (Sloan et al., 2017), thus more research is needed to understand these associations.

Alternatively, individual differences in ANS physiology may instead predict health and mortality due to bi-directional communication between the ANS and the immune system (Hostinar et al., 2017; Sloan et al., 2007). The parasympathetic nervous system is involved in both monitoring current levels of inflammatory activity and engaging in targeted reduction of inflammation (Tracey, 2002). Evidence for this process, labeled the *cholinergic anti-inflammatory pathway*, is increasing. For example, resting measures of PNS modulation of the heart are inversely related to baseline levels of circulating inflammatory markers (Alen, Parenteau, et al., 2021; Williams et al., 2019). Results from non-human studies add causal support for this mechanism (e.g., Borovikova et al., 2000). Sympathetic activity is also linked to inflammation, though it seems to have both pro- and anti-inflammatory properties (Cooper et al., 2015). Inflammation is an adaptive response to acute infection or injury, which eliminates foreign material and stimulates healing. However, prolonged persistence of inflammation without a clear microbial target (elevated systemic inflammation) is a major contributor to highly prevalent and costly inflammatory based disease (e.g., atherosclerosis; Libby, 2002). Greater autonomic regulation of inflammation may therefore reduce the risk of elevated systemic inflammation.

Overview of Studies

The current set of studies reflect a multi-method investigation into the role of the autonomic nervous system in the link between parenting and health. Conceptual models have proposed that functioning of the ANS partially mediates the relation between parenting experienced during early life and later health, such that more positive parenting leads to the development of a more adaptive ANS profile, which predicts better health and well-being (Calkins et al., 2013; Propper & Moore, 2006). This dissertation had three goals related to this conceptual model: (1) to directly test for mediation by the ANS, (2) to investigate autonomic-immune system links, which may underlie the association between ANS physiology and later health, and (3) to provide a comprehensive assessment of the relation between parenting and child ANS physiology.

The data and methods used in these three studies were diverse. Study 1 used publicly available data from a large, nationally representative sample of adults, the Midlife in the United States (MIDUS) study. This rich dataset includes retrospective reports of childhood parental warmth collected at a mean age of 46 years, measures of resting PNS modulation of the heart collected 10 years later, and health and mortality data collected an additional 9 years later. The hypothesis of this study was that the association between warmer parenting during childhood and better health and longevity would be explained by indirect effects through resting PNS activity, such that greater childhood parental warmth would predict higher resting PNS activity, which would in turn predict better health and longevity. Study 2 involved data I helped to collect in our lab at the University of California, Davis, during my time in this research group. This study was designed to expand our understanding of the role of the ANS in inflammatory processes, by testing associations between resting cardiac autonomic balance, and changes in inflammatory cytokines in response to challenge, in children ages 9 to 11 years old. The hypothesis was that

children who exhibited higher cardiac autonomic balance, indicating relatively greater PNS and less SNS influence over cardiac activity, would exhibit reduced increases in inflammatory marker levels in response to challenge. Study 3 was a meta-analysis of the association between parenting and child ANS physiology. This study was designed to (1) evaluate the strength and direction of the association between parenting and multiple indices of child ANS physiology, and (2) investigate differences in study design and sample characteristics that might explain variability in findings across the literature.

In sum, this dissertation serves to support and improve our understanding of the role of the autonomic nervous system in the association between parenting experienced during childhood and lifelong health. By directly testing theoretical models in longitudinal data (Study 1), engaging in basic science investigations into multi-system biopsychology (Study 2), and conducting a comprehensive quantitative synthesis of the literature (Study 3), this dissertation fills in some gaps in current knowledge about the pathways from parenting quality to later health, while suggesting future avenues of research to strengthen this field of research.

CHAPTER 2

STUDY 1: CHILDHOOD PARENTAL WARMTH AND HEART RATE VARIABILITY IN MIDLIFE: IMPLICATIONS FOR HEALTH

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Abstract

The current study investigated high-frequency heart rate variability (HF-HRV) as a potential mediator between childhood parental warmth and later health and mortality outcomes. Participants were 1,255 adults (56.9% female). Childhood parental warmth was reported retrospectively at mean age 46; resting HF-HRV was measured at mean age 57; cardiovascular health and self-evaluated health were assessed at mean age 57 and 63, and mortality records extracted at mean age 63. Results revealed a positive association between childhood parental warmth and resting HF-HRV, as well as associations between higher HF-HRV and reduced risk of having a later cardiovascular health problem and of mortality by age 63. Mediation analyses revealed a small significant indirect effect of parental warmth, through HF-HRV, on cardiovascular health.

Introduction

The quality of the social environment during childhood has enduring repercussions for offspring health and wellbeing (Chen et al., 2017). In particular, a growing body of research has found associations between characteristics of the parent-child relationship and offspring physiology, with parenting that is high in warmth generally predicting a more moderate and flexible physiological profile (Flannery et al., 2017; Gunnar & Quevedo, 2007; Repetti et al., 2002). However, most prior research has focused on links between parenting and the hypothalamic-pituitary-adrenal (HPA) axis, and much less is known about the potential association between parenting and the autonomic nervous system (ANS). Understanding the relations between childhood parental warmth and ANS physiology has important implications for public health promotion, as more moderate and flexible ANS physiology has been associated with several beneficial health outcomes (Thayer et al., 2010). The present study aimed to (1) address this research gap by testing the association between childhood parental warmth and ANS physiology, indexed through resting high frequency heart rate variability (HF-HRV); (2) add to the growing body of evidence linking HF-HRV to lifelong health and mortality outcomes; and (3) test HF-HRV as a mediator between parental warmth and midlife health and mortality.

Parental Warmth and Health

Parental warmth refers to parenting that is affectionate, consistent, and marked by sensitive responding to the child's needs (Zhou et al., 2002). Past mediation studies attempting to explain the association between parental warmth and health have typically focused on two mechanisms: (1) health behaviors, whereby warmer parenting is associated with healthier behavior patterns –e.g., diet, physical activity (Davids et al., 2017; Graves et al., 1998); and (2) stress physiology and the immune system, such that warmer parenting predicts more moderate

stress reactivity and more adaptive inflammatory processes, which in turn are associated with better health outcomes (Chen et al., 2011; Chen et al., 2017; G. E. Miller & Chen, 2010; Uchino & Way, 2017). However, most studies investigating the link between parental warmth and biological processes have focused on the HPA axis and the immune system, and the relatively fewer studies on parental warmth and the ANS are largely limited to youth, precluding the testing of ANS physiology as a mediator between parental warmth and long-term health outcomes, such as cardiovascular disease and mortality in middle-aged and older adults.

Parental Warmth and Offspring Physiology

Research with children and adolescents has shown that warm parenting can dampen neuroendocrine stress responses (Hostinar et al., 2014) and attenuate the effects of adversity on youth physical health (Chen et al., 2017; Farrell et al., 2016). Warmer parenting may therefore help dampen the offspring's general physiological reactivity during early life, helping to maintain the offspring's physiology within more moderate set points, potentially "programming" the development of physiological profiles that are more moderate and adaptive (G. E. Miller et al., 2011).

Parenting may also influence the development of offspring physiology by shaping the development of emotion regulation. During early life, parents act as primary regulators of their offspring's affect and physiology (Morris et al., 2007). Because of this, parents who sensitively respond when their child is in distress, providing scaffolding assistance to the child's attempt to regulate their own physiological reaction, help create internalized patterns of regulatory processes (Thompson, 1994), potentially leading to the development of more moderate and well-regulated ANS physiology. While most studies investigating early life "programming" of offspring biology have focused on the HPA axis, there is growing evidence supporting the need

to better understand how early life environmental characteristics, particularly parenting, may predict the development of ANS physiology (Propper & Moore, 2006).

Heart Rate Variability

A common technique for investigating individual differences in ANS physiology is to measure heart rate variability (HRV; Laborde et al., 2017). HRV is a measurement of the beat-to-beat changes in heart rate, and high frequency HRV (HF-HRV) is often used as an index of parasympathetic influence, via the vagus nerve, over cardiovascular activity (Porges, 2007). High resting HF-HRV is believed to represent ANS physiology that can flexibly adapt to changing environmental demands, increasing heart rate during times of threat, then quickly returning to a calm resting state once the threat has subsided (Appelhans, & Luecken, 2006).

Previous research on the association between parenting characteristics and resting HF-HRV is somewhat limited. Nevertheless, the evidence so far suggests an association between positive parenting characteristics and high resting HF-HRV. For example, infants of mothers who warmly responded to their infant's communication cues had higher resting HF-HRV (Porter, 2003). In addition, warmer parenting (e.g., high involvement, high support) has been shown to predict higher resting HF-HRV in adolescents (Graham et al., 2017), and reduced decreases in resting HF-HRV over a one-year period (Fox et al., 2018). Experimental evidence from randomized controlled trials has also revealed associations between (1) increased sensitivity following parenting intervention and higher resting HF-HRV in preschoolers (Bell et al., 2018), and (2) reductions in negative parenting following intervention and higher resting HF-HRV in 9-year-olds (Tabachnik et al., 2019).

There is also evidence of associations between parenting quality and HRV change during challenge, sometimes referred to as vagal withdrawal, though findings have been mixed, with

warmer or more sensitive parenting sometimes predicting increased HRV change (Calkins et al., 2008; Perry et al., 2012), and sometimes predicting decreased HRV change (Hastings, Kahle, et al., 2019). While these mixed results highlight the complexity of HRV change research, it suggests that parenting quality may influence child state-level ANS physiology in addition to the trait-level ANS physiology captured by resting measures.

HF-HRV and Health

High resting HF-HRV has been previously associated with better physical health and reduced mortality risk. Low resting HF-HRV has been linked to hypertension (Singh et al., 1998), high cholesterol (Christensen et al., 1999), and coronary heart disease (Liao et al., 2002). In addition, low resting HF-HRV has also been previously associated with increased risk for diabetes (Liao et al., 1995) and all-cause mortality (Gerritsen et al., 2001; Tsuji et al., 1994). However, some studies have failed to find associations between HRV and cardiovascular risk factors (Klutting et al., 2010). Given this mixed evidence, it is important to further test the relation between HRV and health outcomes using large samples.

Current Study

The present study aimed to (1) expand our current understanding of the association between childhood parental warmth and adult ANS physiology, (2) investigate the relations between ANS physiology and long-term health and mortality outcomes in older adulthood, and (3) test HF-HRV as a potential mediator of the relation between parental warmth and health and mortality. Considering some of the previously reported associations between warm parenting and high resting HRV, and high resting HRV and better health and reduced mortality risk, we developed three hypotheses: (1) we hypothesized that adults who reported retrospectively to have received warmer parenting during childhood would exhibit higher resting HF-HRV in midlife;

(2) we hypothesized that higher resting HF-HRV would predict better physical health outcomes (cardiovascular health, self-evaluated health) and reduced risk of mortality, and (3) we hypothesized that resting HF-HRV would mediate the relation between childhood parental warmth and health and mortality outcomes in older adulthood.

Methods

Participants

Data for this study were drawn from the Midlife Development in the United States (MIDUS) longitudinal study. The first MIDUS wave involved phone and mail surveys to a nationally representative sample of adults (N = 7,108). In 2004-2009, a subset of this sample (n = 1,255) were recruited for a follow up study, the Biomarker Project of MIDUS 2, involving assessments of biological markers. The third wave, MIDUS 3 began in 2013, and involved phone survey assessments similar to the first wave. Complete details on the MIDUS study are available at www.midus.wisc.edu.

Participants in the current study include individuals who participated in all three MIDUS waves. Of the 1,255 participants who took part in the MIDUS 2 Biomarker Project, 1,148 had technically acceptable resting HF-HRV data. Of the individuals who returned for MIDUS 3, 938 had data on cardiovascular health, and 943 had data on self-evaluated health. Participants included in the current study were: middle-aged, with a mean age at MIDUS 2 of 57.3 (range = 35 to 86); and predominantly Caucasian (78.7%), though a large subset of the sample were African American (17.2%), 1.4% were Native American, 0.2% Asian, and 2.5% Other (please see Table 1.1 for complete sample demographics). On average, participants had moderate childhood socioeconomic status (SES), with 41.3% of participants reporting that at least one of

their parents completed some college. Just over half of participants were female (56.8% female; 43.2% male).

Measures

Childhood Parental Warmth. Childhood parental warmth was measured retrospectively at MIDUS 1 (mean age 46) using a validated questionnaire (Rossi, 2001). Participants were asked to reflect on their childhood experiences and answer seven questions regarding the quality of their relationship with each parent (participants completed separate 7-item scales for their mother and their father). Questions assessed how much that parent understood the participant's worries; how much attention, effort, and affection that parent provided; as well as the participant's subjective interpretation of the overall quality of the relationship (e.g., *"How would you rate your relationship with your mother/father during the years you were growing up?"*). Responses were coded on a 4-point Likert-type scale, ranging from "*Not at all*" to "*A lot*"; or, regarding quality of the relationship, from "*Poor*" to "*Excellent*"; such that higher scores reflected more parental warmth. Both maternal and paternal warmth scales showed high internal consistency (Cronbach's alpha of .91 and .92, respectively). The maternal and paternal scores were averaged together to provide a measure of combined parental warmth.

High-Frequency Heart Rate Variability. High-frequency heart rate variability (HF-HRV) was measured during MIDUS 2, using a 3-lead electrocardiogram (ECG) attached to the chest in Einthoven's triangle configuration. ECG recordings took place in the morning, after an overnight clinic stay, following breakfast, with no caffeine consumption permitted. ECG data were recorded during an 11-minute seated, resting baseline period, as part of a larger ECG protocol involving cognitive tasks. The current study utilized data from the resting baseline measure. ECG data were digitized at 500 Hz by a 16-bit National Instruments analog-to-digital

board. ECG wave R peaks were visually inspected and cleaned. Arrhythmias were handled using interpolation. Interbeat-intervals (IBIs) were processed through a Fast Fourier transformation algorithm, with a high frequency band filter set at 0.15 – 0.50 Hz, providing mean HF-HRV from two 300-second epochs, which were then averaged together. If uncleanable noise precluded the collection of a minimum of 180 continuous seconds, data from that participant were not calculated.

Cardiovascular Health. To create a measure of cardiovascular health, we used participants' answers to ten questions, during MIDUS 3 (mean age 63), regarding the presence or absence of heart problems as diagnosed by a physician. Participants were asked if they had ever been diagnosed by a physician with any of the following: stroke, heart attack, high blood pressure, valve disease, blocked artery, irregular heartbeat, heart murmur, or heart failure; participants were also asked if they had ever had a major heart procedure, and if they currently experience chest pain while walking. Participant responses to these questions were used to create a dichotomous variable, such that individuals who answered "*No*" to all questions were coded as "0" (excellent cardiovascular health), and individuals who answered "*Yes*" to at least one question were coded as "1". We also created a count variable by summing the total number of "*Yes*" responses, such that higher scores represented more cardiovascular health problems.

Self-Evaluated Health. Self-evaluated health was measured during MIDUS 3 via phone surveys. This measure was indexed using one item, answered on a 5-point Likert-type scale: *"In general, would you say your physical health is excellent, very good, good, fair, or poor?"* Responses to this question were reverse coded from the original coding scheme so that higher scores indicated better self-evaluated health (e.g. "*poor*" = 0; "*excellent*" = 4). This question has

been found in previous studies to be predictive of objective health outcomes such as mortality (Benjamins et al., 2004).

Mortality. Mortality data were collected through October 2015, using three methods: (1) tracing conducted by the University of Wisconsin Survey Center, which used a variety of database searches to confirm participant identity and status, (2) formal searches through the National Death Index (NDI), and (3) longitudinal sample maintenance procedures, including regular participant outreach.

Covariates. Additional demographic and health data were collected during MIDUS 2, when the ECG protocol was conducted. Demographic information included: age, sex, race, and childhood SES. Race was entered as binary code (Caucasian = 0, Non-Caucasian = 1) given that other racial categories had very low frequencies and did not allow sufficient statistical power for inclusion. Childhood SES was indexed through parental education level, as an ordinal variable with 12 categories ranging from "*Some primary school"* = 1 to "*Doctoral or professional degree"* = 12, in line with prior publications from MIDUS (Fuller-Rowell et al., 2018). When parents had different education levels, the highest education level between parents was used. Health information included: binary coded exercise habits (*engages in regular exercise* = 1), binary coded smoking status (*current smoker* = 1), and whether or not the participant was taking medication that may influence HF-HRV. Medication regimen was coded into two dummy variables representing whether or not the participant was currently taking (1) medications known or believed to increase HF-HRV (*parasympathomimetic agents, beta-blockers*), and (2) medications known or believed to decrease HF-HRV (*anticholinergic agents, anti-depressants, sedatives, anti-arrhythmic agents, cardiac drugs, antipsychotics*), a method previously used in research on HF-HRV with the MIDUS cohort (Sloan et al., 2017). Menopause status, collected

during MIDUS 2, was dummy coded such that both females who had yet to go through menopause and males were assigned a "0", and females who had gone through menopause were assigned a "1", in line with previous MIDUS research on HF-HRV (Sloan et al., 2017). Health data (cardiovascular health, self-evaluated health) were also collected during MIDUS 2 and included as covariates in analyses predicting respective MIDUS 3 health outcomes.

Data Analysis

Bivariate correlations and regression analyses were calculated using IBM SPSS Statistics version 25, and mediation analyses were performed using structural equation modeling in Mplus version 6.12. To address Aim 1 examining the relation between childhood parental warmth and HF-HRV, a multiple linear regression was performed. Linear regression analysis was performed in 2 steps: first, resting HF-HRV was regressed on parental warmth, then demographic and health related covariates (age, sex, race, childhood SES, exercise, smoking, medication regimen, menopause status) were added to the model. HF-HRV data were positively skewed, so in accordance with standard methods (Malik, 1996), we performed a natural log transformation prior to analyses. Due to the well documented correlation between HF-HRV and heart rate (HR), we followed recent recommendations (de Geus et al., 2018) and calculated HF-HRV adjusted for concurrent HR (aHF-HRV), using the following equation: $aHF\text{-}HRV = 100*(HF\text{-}HRV/(IBI)^2)$. Initial analyses were performed using unadjusted HF-HRV; post hoc sensitivity analyses were performed for all analyses using aHF-HRV. Positively skewed aHF-HRV data were log transformed prior to analyses. Participants excluded from regression analysis due to missing one or more variables were on average 6.3 years older, thus we adjusted for age statistically in all analyses. Participants with missing data did not significantly differ from those included in regards to any other variable. Sample size varies across analyses depending on data availability.

In order to correct for multiple comparisons, we utilized the Benjamini-Hochberg False Discovery Rate (FDR). With this method an estimate is significant if the p-value is smaller than the corresponding FDR q-value.

To address Aim 2, testing the relation between resting HF-HRV and health and mortality outcomes, four separate regression models were performed. The association between HF-HRV and cardiovascular health was investigated through two models: (1) a binary logistic regression predicting the dichotomous cardiovascular health problem variable, and (2) a generalized linear model with a Poisson distribution predicting the total number of cardiovascular health problems. A Poisson distribution allows for better modeling of the distribution of count data, which is characterized by the absence of values below zero and a positive skew (Atkins & Gallop, 2007). To test the association between HF-HRV and self-evaluated health, we performed a multiple linear regression with resting HF-HRV as a predictor of self-evaluated health. Finally, to test the association between HF-HRV and mortality we performed a binary logistic regression. All models, with the exception of the model predicting mortality, were run in three steps: (1) first without covariates, then (2) controlling for respective health measured during MIDUS 2, then (3) with demographic and health covariates (age, sex, race, childhood SES, exercise, smoking, medication regimen, menopause status) added to the model. The model predicting mortality was tested in two steps: (1) first without covariates, then (2) with demographic and health covariates.

To address Aim 3, testing HF-HRV as a mediator between childhood parental warmth and later health and mortality outcomes, we performed four mediation analyses using bias-corrected bootstrapping methods (Hayes, 2009), with 1000 samples, in Mplus software. With this method an indirect effect is significant if the 95% bootstrapped confidence interval does not span zero. In order to address missing data in our mediation analysis, Full Information Maximum

Likelihood (FIML) was used. Mplus FIML employs Ecker-Huber-White estimation, which accounts for non-normality and the non-independence of data clustered within families, a method previously used with this data set (Donoho et al., 2015; Wiley et al., 2016).

Results

Preliminary Analysis

Table 1.1 provides characteristics of participants included in the analysis. We highlight some of the significant correlations (for complete bivariate correlational results, please see Table 1.2; note that Spearman rank correlations were used for this correlation table given that some of our outcome variables were skewed). Parental warmth was positively correlated with HF-HRV (r_s = .06, p = .04), such that warmer parenting predicted higher HF-HRV. Higher HF-HRV was associated with better cardiovascular health and reduced mortality risk: HF-HRV was negatively correlated with having a cardiovascular health problem (r_s = -.13, p < .001), total number of cardiovascular health problems (r_s = -.13, p < .001), and mortality (r_s = -.09, p = .002). Cardiovascular health and self-evaluated health were moderately correlated (r_s = -.32, p < .001), suggesting that these two measures represent different aspects of physical health outcomes. Mortality by the end of the follow-up period was negatively correlated with previous report of self-evaluated health (r_s = -.08, p = .02).

The Relation Between Childhood Parental Warmth and HF-HRV

Results from a multiple linear regression revealed a significant positive relation between self-reported childhood parental warmth and HF-HRV at the univariate level, β = .06, p = .04. Results from the final model, presented in Table 1.3, which included covariates, also revealed a significant positive association between childhood parental warmth and HF-HRV, β = .07, p = .01 (*FDR* q = .025). Raw data are presented in Figure 1.1.

HF-HRV and Cardiovascular Health

To test the relation between HF-HRV and cardiovascular health we conducted two models. First, using a dichotomous dependent variable representing presence or absence of any cardiovascular health problems, we conducted a binary logistic regression. Results revealed a significant association between HF-HRV and cardiovascular health both at the univariate level, B = -.24, SE = .06, $p < .001$, OR = .79, 95% CI [0.71, 0.89], and after including demographic covariates, B = -.14, p = .02, OR = .87, 95% CI [0.77, 0.98]. The final model, including covariates related to HF-HRV, again revealed a significant association between HF-HRV and cardiovascular health, B = -.17, SE = .06, p = .007 ($FDR\ q$ = .0125), OR = .84, 95% CI [0.74, 0.95], such that greater HF-HRV predicted lower odds of having a cardiovascular health problem at mean age 63. Raw data for this association are presented in Figure 1.2. In order to test the robustness of this relation we also conducted a generalized linear model (GLM) to see if HF-HRV could predict the total number of cardiovascular health problems. Results from this model again revealed a significant association between HF-HRV and the total number of cardiovascular health problems (please see Table 1.4 for GLM results).

HF-HRV and General Self-Evaluated Health in Midlife

Results from this model revealed no significant association between HF-HRV and self-evaluated health. This outcome was consistent at the univariate level, β = .03, p = .31, after controlling for previous self-evaluated health, β = .04, p = .27, and in the final model with the addition of covariates, β = .05, p = .18 ($FDR\ q$ = .05).

HF-HRV and Mortality

Results from a binary logistic regression revealed a significant association between HF-HRV and subsequent mortality at the univariate level, B = -.36, SE = .11, p = .001, OR = .70,

95% CI [0.57, 0.86]. The final model, presented in Table 1.5, which included all covariates, also revealed a significant association between HF-HRV and subsequent mortality, *B* = -.23, *SE* = .11, *p* = .035 (*FDR q* = .037), *OR* = .79, 95% CI [0.64, 0.99], such that greater HF-HRV predicted decreased odds of mortality within the follow-up period.

Testing the Mediation Models

Mediation analysis revealed a significant indirect effect of childhood parental warmth, through HF-HRV, on cardiovascular health, *B* = -.02, *SE* = .01, 95% CI [-.043, -.003], presented in Figure 1.3. Results from our robustness check, using sum of cardiovascular problems, again revealed a significant indirect effect of parental warmth, through HF-HRV, on sum of cardiovascular health problems, *B* = -.01, *SE* = .005, 95% CI [-.022, -.002]. Results from the mediation model predicting mortality revealed that the indirect effect of parental warmth, through HF-HRV, on mortality was not significant, *B* = -.002, 95% CI [-.01, .00]. The indirect effect of parental warmth, through HF-HRV, on self-evaluated health was also not significant, *B* = .11, 95% CI [-.002, .01].

Post-Hoc Sensitivity Analysis

***Adjusted HF-HRV*.** Using HF-HRV adjusted for concurrent HR (aHF-HRV), controlling for the same covariates in the initial models, results were unchanged: parental warmth was positively associated with aHF-HRV (*B* = .16, *p* = .014); higher aHF-HRV was associated with better cardiovascular health, using both a dichotomous variable (*B* = -.17, *p* = .006), and a count variable (*B* = -.09, *p* = .004); aHF-HRV predicted reduced odds of mortality (*B* = -.14, *p* = .014); and aHF-HRV did not significantly predict self-evaluated health (*B* = .02, *p* = .48). In addition, mediation results were unchanged, with aHF-HRV only significantly mediating the relation between parental warmth and cardiovascular health.

***Moderation by Age*.** Due to the large age range of this sample, and the retrospective methods used for measuring childhood parental warmth, a sensitivity analysis was conducted to test age as a moderator of the relation between parental warmth and resting HF-HRV. Without covariates the interaction term between age and parental warmth was significant, B = -.01, SE = .005, p = .049. A Johnson-Neyman region of significance test revealed that the relation between parental warmth and HF-HRV was only significant for individuals younger than 59 years old. After including covariates, the interaction term was no longer significant, B = -.007, p = .17.

Discussion

Parenting that is affectionate, consistent, and sensitive has often been associated with better physical health outcomes for offspring (G. E. Miller et al., 2011; Newland, 2015). A comprehensive understanding of the mechanisms involved in this association, including biological mechanisms, is still needed. The present study set out to investigate the associations between childhood parental warmth, resting high-frequency heart rate variability (HF-HRV), and health and mortality outcomes. Furthermore, we aimed to test whether ANS physiology may mediate the relation between parental warmth and health indices in older adulthood. Findings from the current study suggest that (1) retrospective measures of childhood parental warmth has small but significant associations with resting HF-HRV in midlife, (2) resting HF-HRV can predict cardiovascular health over a nine year period, controlling for baseline cardiovascular health, and can also predict mortality, and (3) resting HF-HRV may act as a mediator between childhood parental warmth and health in older adulthood, though the indirect influence of parental warmth through HF-HRV on health may depend on the specific physical health outcomes measured.

Consistent with our first hypothesis, we found that individuals who reported greater parental warmth during childhood exhibited higher HF-HRV during rest. This is consistent with previous research on parental warmth and HRV with infants and adolescents (Graham et al., 2017; Porter, 2003). In general, these results shed light on the potential influence of parenting on ANS physiology (Propper & Moore, 2006). Warm parenting may influence the offspring's life-long autonomic physiology by providing stable, predictable environments that keep their physiological reactivity within certain set points (Flannery et al., 2017). This has important implications, as HF-HRV has been associated with several significant health outcomes (Thayer & Lane, 2007).

The effect size was relatively small within our sample, compared to previous research in infants and adolescents (Graham et al., 2017; Porter, 2003). This may be attributed to a weakening association across development, as additional variables (e.g., health behavior, age) continue to influence ANS physiology into midlife. Alternatively, given the large sample and robust statistical power in the current study, this may reflect a true small effect. Nevertheless, a small effect of parental warmth on lifelong offspring physiology may have significant consequences at the population level and the individual level, particularly if it co-varies with early-life adversities, such as poverty. Results from our unadjusted model examining moderation by age provide some evidence that parental warmth may exhibit reduced influence on HF-HRV with age, though these results should be interpreted with caution as they were post-hoc and did not hold up to the inclusion of covariates. Alternatively, moderation by age may reflect increasing memory bias with age, such that older individuals' retrospective reports may have had more measurement error. Further research using longitudinal designs and multiple measures of retrospective accounts of childhood experiences could help clarify these moderation results.

For the second aim of this study, we hypothesized that higher resting HF-HRV would predict better health outcomes, indexed through participants' reports of physician diagnosed cardiovascular health problems and self-evaluated health. Our findings were generally supportive of this hypothesis, and the effect was specific for cardiovascular health rather than a general effect on overall self-evaluated health. Specifically, we found that higher resting HF-HRV was associated with better cardiovascular health, indexed through (1) absence or presence of any diagnosed cardiovascular disorders, and (2) total number of cardiovascular health disorders. This association remained significant after statistically controlling for prior cardiovascular health, indicating that higher resting HF-HRV may protect against worsening in cardiovascular health over a 9-year period. These findings add to the large body of evidence suggesting an association between low resting HF-HRV and cardiovascular disease. While low resting HF-HRV has been associated with other health diagnoses, such as diabetes (Carnethon et al., 2003), the majority of past associations between low resting HF-HRV and physical health have focused on cardiovascular health, including: hypertension (Singh et al., 1998), high cholesterol (Christensen et al., 1999), and coronary heart disease (Liao et al., 2002). It has been proposed that vagal activity has beneficial effects for cardiovascular health through multiple pathways, including a vagal anti-inflammatory pathway (Sloan et al., 2007; Tracey, 2007) that may reduce risk of atherosclerosis (Libby, 2002). Furthermore, low HF-HRV may also lead to poor health through its association with poor psychosocial functioning (Appelhans & Luecken, 2006; Kemp & Quintana, 2013).

The large and nationally representative sample of adults and the longitudinal design of the MIDUS study provided a unique opportunity for also investigating the relation between HF-HRV and mortality. Previous research on HRV and mortality suggests that higher resting HF-

HRV predicts reduced all-cause mortality risk (Thayer et al., 2010); the results were consistent with these past findings. While the association between HRV and cardiovascular disease may partially explain these findings, the all-cause mortality data included causes of death not directly related to cardiovascular health, such as cancer. However, considering the previously mentioned associations between low resting HRV and both (1) inflammatory processes (Tracey, 2007) and (2) poor psychosocial functioning (Kemp & Quintana, 2013), it is possible that the mechanisms underlying the relation between low resting HF-HRV and cardiovascular disease are similar to those that drive the association between low resting HF-HRV and all-cause mortality.

The absence of a significant association between HF-HRV and global self-evaluated health suggests that HF-HRV may be more strongly related to specific health conditions, such as cardiovascular disease. It is possible that this global measure of self-evaluated health aggregates across many different aspects of health (e.g., mental health, physical limitations) that have weaker connections to high-frequency heart rate variability.

For the third aim of this study, we hypothesized that resting HF-HRV would mediate the relation between childhood parental warmth and health outcomes. Our findings were generally supportive of this, and the effect was specific for cardiovascular health rather than a general effect on overall self-reported health. Specifically, we found that childhood parental warmth was indirectly associated with better cardiovascular health, indexed through both absence of any diagnosed cardiovascular health disorders and fewer cardiovascular health disorders, and that this indirect association was explained through (1) the association between high childhood parental warmth and high resting HF-HRV, and (2) the association between high resting HF-HRV and better cardiovascular health. These results are consistent with the model proposed by Repetti et al. (2002) whereby early-life family-environmental characteristics are theorized to

affect offspring life-long health outcomes through their influence on offspring physiology. However, the weak indirect effect suggests it is not likely that HF-HRV fully mediates the relation between parental warmth and cardiovascular health, and instead may work in addition to, or in an interaction with, other biological mediators (e.g., inflammation, the HPA axis).

While we did not observe a direct, bivariate relation between childhood parental warmth and cardiovascular health among this sample, contemporary mediation analysis no longer requires a direct association to be significant as a prerequisite to mediation analysis (MacKinnon et al., 2000; Shrout & Bolger, 2002; Zhau et al., 2010). Using simulation models, quantitative researchers have shown that mediation can occur even when an initial direct effect is not found (Hayes, 2009; Rucker et al., 2011). Such a phenomenon has been explained through (1) suppression, whereby unmeasured mediators express an indirect effect in the opposite direction, or (2) unbalanced statistical power, such as when the mediator has less measurement error than the independent or dependent variables, and therefore significant relations between either the independent or dependent variable and the mediator are easier to find than a significant relation between the independent and dependent variables (Rucker et al., 2011). Considering the expansive literature on the association between warmer parenting and better health (Chen et al., 2017), suppression is an unlikely explanation of our results. Instead, for the current study, the greater precision in the measurement of the biological mediator relative to the self-report methods employed for both the independent and dependent variables may have contributed to unbalanced statistical power, which allowed us to detect significant associations between parental warmth and HF-HRV, as well as HF-HRV and cardiovascular health outcomes, but not between self-reported parental warmth and cardiovascular health outcomes.

Limitations and Future Directions

While the current study addressed an important gap in the literature and has a number of strengths, there are some limitations that should be considered for future research. The first limitation is the use of a retrospective measure of parental warmth, which may be subject to memory bias (Hardt & Rutter, 2004). However, due to the logistical constraints associated with longitudinal designs that span decades from childhood into middle/older age when chronic diseases begin to manifest, retrospective measurements are frequently utilized for investigating the long-term outcomes associated with parenting characteristics (Rothrauff et al., 2009; Wright et al., 2017). Stability of retrospective reports over time (Silva & Maia, 2013) and modest but significant associations between observational and later retrospective measures of parenting (Newbury et al., 2018) provide some support for the validity of retrospective methods. In addition, the limitations associated with retrospective measures may be particularly important to consider within the current study due to the large age range, considering memory bias may increase with age. Concerns over this limitation may be partially alleviated by the inclusion of age as a covariate in our analyses.

Lastly, future research could benefit from employing an experimental design, for instance, by randomly assigning parents to receive parental warmth training; and from measuring HF-HRV at more than one time point, in order to directly observe change. The correlational design utilized in the current study limits our ability to interpret causality or direction of effects; it is possible that offspring autonomic physiology may influence parental warmth, as some have suggested (Hastings, Grady, & Barrieau, 2019; Kennedy et al., 2004), or that the relation is bidirectional. It is also possible that the association between childhood parental warmth and HF-HRV may be in part explained by shared genetics related to autonomic physiology. For example, it is possible that parents who themselves have high resting HF-HRV may be more likely to

engage in warmer parenting, and pass on a genetic predisposition to high resting HF-HRV to their offspring. However, previous research has shown both intraindividual change in HRV across early years of development (Bornstein & Suess, 2000), and discordant HRV among monozygotic twin pairs (Healy, 1992), suggesting substantial environmental contributions to HRV that need to be clarified.

Despite these limitations, the current study adds to the limited literature on the relation between parental warmth and ANS physiology and is the first to investigate ANS physiology as a mediator between parental warmth, and health and mortality. Among a nationally representative sample of adults, we found that retrospective measures of childhood parental warmth were positively associated with resting HF-HRV, and that higher resting HF-HRV predicted better cardiovascular health and decreased all-cause mortality risk. We also found that HF-HRV may partially mediate the relation between parental warmth and health, and that this relation may be specific to cardiovascular health. A better understanding of the biological mechanisms behind the association between family-environmental factors and health contributes important evidence of potentially lasting beneficial implications of warm parenting, and provides unique opportunities for intervention, such as biofeedback training.

CHAPTER 3

STUDY 2: AUTONOMIC NERVOUS SYSTEM ACTIVITY PREDICTS INCREASING SERUM INFLAMMATORY CYTOKINES IN CHILDREN

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Abstract

Systemic inflammation is associated with increased risk for prevalent and costly diseases, and animal models implicate the autonomic nervous system in the control of inflammatory processes. In humans, research on autonomic-immune connections has been much more limited and has focused on single branch autonomic measures (i.e., either parasympathetic or sympathetic). The current study utilized cardiac autonomic balance (CAB), derived from dual-branch cardiac autonomic recordings, to test the relation between resting autonomic function and inflammatory reactivity to challenge in children. Participants included 96 children (51 boys, 45 girls) ages 9 to 11 years (mean age = 9.93 years, *SD* = .57 years). CAB values were calculated as the standardized relative contribution of parasympathetic to sympathetic activity, derived from resting respiratory sinus arrhythmia and pre-ejection period data, respectively. Children provided

two blood samples, one before and one following exposure to an acute social stressor or control condition. Serum was assayed for four cytokines that orchestrate inflammation: interleukin-6 (IL6), interleukin-8 (IL8), interleukin-10 (IL10), and tumor necrosis factor-alpha (TNFa). We discovered large individual differences in inflammatory marker production across children, and no average main effect of stress condition. CAB significantly predicted these individual differences, such that children lower on CAB showed increasing serum cytokines from time 1 to time 2. In contrast, children with greater CAB tended to show declining inflammatory markers across the session. Low cardiac autonomic balance may be a useful marker of proinflammatory tendencies in children, suggesting novel paths for early risk detection and intervention.

Introduction

Extensive preclinical and clinical studies have implicated systemic inflammation in the pathophysiology of prevalent chronic diseases. These include coronary heart disease (Libby et al., 2018), obesity and metabolic disorders (Odegaard & Chawla, 2013), cancer (Crusz & Balkwill, 2015), and several psychiatric disorders including depression (A. H. Miller & Raison, 2016). Inflammation involves an acute response by innate immune cells to injury and infection, which eradicates invading pathogens, promotes tissue healing, and then terminates. Although beneficial in the short term, prolonged persistence of inflammation without a clear microbial target is a major contributor to highly prevalent and costly chronic diseases with inflammatory underpinnings (Libby, 2002; G. E. Miller et al., 2011). Thus, understanding risk factors for the development of elevated inflammation would pave the way for effective early intervention.

Motivated by the vision of early intervention, recent studies have begun assessing inflammatory markers in childhood. Importantly, childhood inflammatory markers can predict later health outcomes in a dose-response manner. For example, inflammatory markers in children

under the age of 10 predict subsequent increases in body mass index (BMI) over baseline BMI (Bernard et al., 2019; Lourenco et al., 2014). Additionally, one large population-based study in England with 4500 children found that the inflammatory marker IL6 assessed in serum at age 9 predicted depressive symptomatology at age 18 in a dose-response manner (Khandaker et al., 2014). These patterns suggest the need to identify early risk factors that explain elevations in inflammatory markers during childhood, which could then become targets for early intervention.

Prevailing theory suggests that neuro-immune communication is an important driver of inflammation (Hostinar et al., 2017; Irwin & Cole, 2011). For example, connections between the autonomic nervous system (ANS) and peripheral inflammation have been documented in both animal models and in humans. These studies have shown that sympathetic activation stimulates pro-inflammatory gene expression and cytokine production (Irwin & Cole, 2011; Nance & Sanders, 2007), whereas parasympathetic activity reduces the production of inflammatory markers by immune cells (Borovikova et al., 2000; Tracey, 2002). For instance, rodent studies have revealed a cholinergic anti-inflammatory pathway, such that electrical or pharmacological stimulation of the efferent vagus nerve inhibits systemic inflammation in response to endotoxin, reducing production of cytokines such as IL6 and TNFa (Borovikova et al., 2000; Tracey, 2002).

Consistent with this notion, human studies show that greater parasympathetic and less sympathetic modulation of cardiac activity at rest is associated with lower circulating levels of inflammatory markers such as IL6 (Cooper et al., 2015; Lockwood et al., 2017; Révész et al., 2014; Sloan et al., 2007), and reduced production of inflammatory cytokines in response to a bacterial product (Marsland et al., 2007). However, to date these questions have not been examined in children, leaving open the question whether cardiac autonomic markers could serve as a risk factor for inflammation during development.

In addition, previous research on the relation between the ANS and immune processes has been largely limited to measures of a single branch of the ANS in isolation (i.e., either sympathetic or parasympathetic). The sympathetic and parasympathetic branches of the ANS do not always work in coordination (Berntson et al., 1991; Quigley & Moore, 2018). Considering evidence for both sympathetic and parasympathetic influences on the immune response, single branch ANS measures may therefore preclude a comprehensive understanding of neuro-immune connections.

In order to address these gaps in the literature, the current study tested the relation between autonomic functioning and inflammatory responses to challenge in children. We utilized calculations of cardiac autonomic balance, derived from sympathetic and parasympathetic autonomic recordings. We hypothesized that children exposed to an acute social stressor would exhibit greater increases in inflammatory markers, compared to controls. We also hypothesized that children who received social support from parents prior to acute stress exposure would exhibit changes in cytokine levels similar to controls, based on prior literature in adults suggesting that social support is associated with lower levels of serum inflammatory markers (Marsland et al., 2007; Uchino et al., 2018). Lastly, we hypothesized that children with lower cardiac autonomic balance, indicating relatively lower parasympathetic and higher sympathetic modulation of cardiac activity at rest, would exhibit greater increases in inflammatory markers following challenge.

Methods

Participants

Participants included children, ages 9 to 11 years old, recruited from the Sacramento-Davis area through the University of California, Davis Participant Pool system and

advertisements on Facebook. Exclusion criteria included: developmental disorder, chronic health condition, speech or language disorder, and currently taking psychotropic or steroid medication. Participants' parents were also asked if their child was, or had recently been, ill (e.g., the flu), and if so their lab visit was scheduled two weeks after symptoms abated. This study was part of a larger study looking at the social and emotional development of children; in such, sample size was determined for reasons not directly related to the current analysis. A total of 133 children were recruited for a laboratory visit. Of these children, 37 children did not participate in the blood draw procedure (21 participants declined to participate in one or both blood draws; the phlebotomist had a scheduling conflict for 13 visits; the phlebotomist was unable to draw sufficient blood from two participants; and one participant ended the session before the first blood draw). This resulted in a sample of $N = 96$ children with data available for the current analysis. Participants in the current study included 51 boys and 45 girls (mean age = 9.93 years, $SD = .57$ years). Participants were 54.2% non-Hispanic white, 33.3% mixed race/ethnicity, 4.2% Black/African American, 3.1% Hispanic/Latino, 3.1% Asian, and 2.1% American Indian or Alaska Native. Participants' families had a mean yearly household income of $127,194 ($SD$ = $72,934). The study was approved by the Institutional Review Boards of the University of California-Davis and the State of California Committee for the Protection of Human Subjects.

Procedure

Experiments were performed in late afternoon to account for diurnal variation in cytokine levels. Upon arrival at the laboratory, informed consent was obtained from the participant's parent or guardian, and informed assent was obtained from the participant. Participants were randomly assigned to one of three conditions, (1) the *alone* condition ($N = 29$), (2) the *parent* condition ($N = 33$), or (3) the *control* condition ($N = 34$), as described next.

Trier Social Stress Test – Modified (TSST-M). The Trier Social Stress Test (TSST) is the most widely used laboratory social stressor for adults, and it involves a public speaking and an arithmetic challenge while being evaluated by judges and video-recorded for 10 minutes (Kirschbaum et al., 1993). The TSST-M is a modification of the TSST designed for children in our age range (Yim et al., 2010). The TSST-M is very similar to the adult TSST, with two differences: the prompt for the public speaking task was adapted to ask children to imagine introducing themselves to a new classroom and the mental arithmetic task was modified to be age-appropriate (see Yim et al., 2010 for additional details on conducting this protocol). In the current study, the procedure consisted of the following steps: participants were told that they had ten minutes to prepare a speech that would be evaluated by judges and recorded on camera to be later analyzed. In the *alone* condition, participants prepared alone in a room. In the *parent* condition, participants prepared with the help of their parent, who was instructed to support their child in any way they find natural. After the ten-minute preparation period, participants were taken to a novel room where there were two judges wearing white lab coats and a video camera. The participant then engaged in a five-minute speech followed by a five-minute arithmetic subtraction task. Judges refrained from showing facial affect or providing feedback to the child during the process.

Children randomly assigned to the *control* condition engaged in a placebo TSST-M that consisted of the following steps: participants were informed that they were part of a calm comparison group and were asked to spend 10 minutes with their parent, thinking about their favorite book or movie, and writing down some ideas about the plot of the book or movie. Following this 10-minute period, participants were taken to a novel room where they engaged in five minutes of friendly conversation about the chosen book or movie with the experimenter,

matching the speaking demands of the TSST-M but excluding the elements of social evaluation (i.e., judges and video camera). To match the mental arithmetic component of the TSST-M, the participants were then asked to play a Sudoku game (level: easy) for five minutes. Participants were told that their performance on the Sudoku was not important, and the experimenter spent time tidying up the room during this part of the task, to prevent the participant from feeling watched and evaluated on their performance.

Blood Draw and Serum Processing Procedure. The first blood draw occurred 30 minutes after arrival at the laboratory to allow children to acclimate to the new environment, before administration of the TSST-M or TSST-M placebo; the second blood draw occurred 100 minutes after the TSST-M, consistent with some evidence in adults that cytokines such as IL6 peak in blood 90-120 minutes post-stress (Marsland et al., 2017; Steptoe et al., 2007). Blood draws were performed by trained and certified phlebotomists with previous experience drawing blood from pediatric samples. Blood draws were taken from the median cubital vein. Blood samples were inverted gently 5 times, and then left to clot in Serum Separator Tubes for 60 minutes. Following the 60-minute clotting time, samples were centrifuged at 2700 RPM for 10 minutes, after which sample serum was aliquoted into micro vials and stored at -80 degrees Celsius, until being shipped to Northwestern University for assaying.

Measures

Demographic data were collected from participants and parents through self-report or parent-report questionnaires. This included: participant age, sex, and highest parental education level. Highest parental education level was the highest level of education among parents, either mother or father, that culminated in the attainment of a degree, and was coded as an ordinal variable: 0 = *less than high school* (1%); 1 = *high school diploma or GED* (11.5%); 2 = *2-year*

or vocational degree (12.5%); 3 = *4-year degree* (31.3%); 4 = *master's level degree* (32.2%); 5 = *doctoral level degree* (11.5%). Children's weight (kg) and height (cm) were measured using a physician beam-scale and stadiometer, for the calculation of body mass index (BMI).

Respiratory Sinus Arrhythmia. Respiratory Sinus Arrhythmia (RSA) was utilized as a marker of parasympathetic activity, where higher RSA reflects greater parasympathetic modulation of cardiac activity (Laborde et al., 2017). RSA was collected with a MindWare ambulatory electrocardiogram (ECG; MindWare, Westerville, OH), using three silver electrodes with a 7% chloride wet gel attached to the child's chest in Einthoven's triangle configuration. RSA data were collected during a resting 5-minute period, as part of a larger ECG data collection procedure. Current analysis focused on the resting period, during which children were in a seated position on a comfortable couch. All children were tested in the same room, on the same couch, and instructed to sit in the same seated position. Participants were instructed to not engage in any activity, to refrain from speaking to their parent, and to attempt to relax for the five-minute duration.

Interbeat Interval (IBI) data were calculated using an automated algorithm in the MindWare Biolab acquisition software. A high-frequency band pass filter set at .24 – 1.04 Hz was used to correspond to the average breathing rate of this age range (Quigley & Stifter, 2006). Sampling rate was set at 500 Hz. R-peaks were inspected and cleaned for artifacts by trained researchers using MindWare Heart Rate Variability software. Arrhythmias (e.g., ectopic beats, sinus pauses) were corrected using the MindWare mid-beat function, which averages the IBI interval and minimizes the influence of artifacts. RSA was calculated, using a Fast Fourier transformation algorithm, in 60-second epochs (Berntson et al., 1997). A 60-second epoch was considered usable when it met two criteria: (1) at least 30-seconds of clean, continuous data were

available, and (2) less than 10% of R-peaks were estimated. Manual inspection of respiration rate ensured that participant respiration rate did not fall outside of the high-frequency band pass filter range. RSA during the individual 60-second epochs were then averaged together, producing a mean resting RSA value. Three participants were missing resting RSA data for the following reasons: excessive, un-cleanable noise (n = 2), and ECG technical malfunction (n = 1).

Pre-ejection Period. Pre-ejection period (PEP) was utilized as a marker of sympathetic activity, where longer PEP reflects less SNS modulation of cardiac activity (Berntson et al., 2004). PEP has been widely used as a non-invasive index of sympathetic modulation of the heart (Bagley & El-Sheikh, 2014; Forouzanfar et al., 2018), and has been previously validated using pharmacological blockade (Berntson et al., 1994; Cacioppo et al., 1994; Mezzacappa et al., 1999; Schächinger, Weinbacher et al., 2001; Winzer et al., 1999).

PEP was calculated from cardiac impedance data measured concurrently to ECG data collection using a MindWare ambulatory device (MindWare, Westerville, OH). Four silver electrodes with a 7% chloride wet gel were attached to the child's chest and back in standard configuration (Sherwood et al., 1990), including two on the chest (one at the top of the sternum and one at the xiphisternal junction) and two on the back (one over the C4 vertebrae and one over the thoracic spine). The impedance signal was used to derive dZ/dt, the first derivative of the change in thoracic impedance. PEP was defined as the amount of time in milliseconds between the Q-wave of the ECG signal and the B-notch of the dZ/dt signal (Berntson et al., 2004). For the identification of the B-notch we employed a two-stage approach recommended by Lozano and colleagues (2007). When impedance data provided a clear signal with a visible B-notch, an algorithm was utilized that identified the B-notch as the peak of the second derivative of the dZ/dt; when impedance data did not provide a clear visible B-notch, the B-notch was

estimated using a percentage of the R-peak to Z-peak interval (RZ interval) in milliseconds plus a constant, set at 4 milliseconds: B-notch = .55*RZ interval + 4, (Lozano et al., 2007). Due to the small percentage of participants with impedance data that showed a clear visible B-notch (< 3%), all PEP values were calculated using the second estimation method for consistency. Current analysis focused on a 5-minute resting baseline measure of PEP, during which participants were in a seated position on a comfortable couch. All children were tested in the same room, on the same couch, and instructed to sit in the same seated position. Six participants were missing resting PEP data for the following reasons: excessive, un-cleanable noise (n = 5), and ECG technical malfunction (n = 1).

Inflammatory Cytokines. Cytokine assays were performed at Northwestern University in the Foundations of Health Research Center using the following procedure: after the serum aliquots had been thawed, they were assayed in triplicate for the following cytokines: interleukin-6 (IL6), interleukin-8 (IL8), interleukin-10 (IL10), and tumor necrosis factor-alpha (TNFa). The assays were performed with a custom four-plex assay on the Simple-Plex Platform (Protein Simple, San Jose, CA). This integrated system conducts automated fluorescence immunoassays using disposable microfluidic cartridges. It yields data with high levels of accuracy and reproducibility (Aldo et al., 2016.) In the current study, the mean inter-assay CVs for triplicate runs were: 4.89% for IL6, 4.70% for TNFa, 3.41% for IL10, and 2.33% for IL8.

Primary Outcomes

Cardiac Autonomic Balance. Cardiac autonomic balance was calculated as the relative contribution of parasympathetic to sympathetic modulation of cardiovascular activity, using a method developed by Berntson and colleagues (2008). RSA was used as an index of parasympathetic modulation of cardiovascular activity. PEP was utilized as an index of

sympathetic modulation of cardiovascular activity. Due to differences in the scaling of these two indices, values were z-scored, producing: z-scored RSA (zRSA) and z-scored PEP (zPEP). RSA is positively related to parasympathetic activity, whereas PEP is negatively related to sympathetic activity, we therefore multiplied zPEP times (-1). CAB was calculated as: CAB = zRSA – (–zPEP), as previously described (Berntson et al., 2008).

Cytokine Change Scores. Of the 96 participants who completed both blood draws, IL6 levels for one participant were deemed abnormally high and indicative of illness by the laboratory that conducted the assaying procedure. This value was therefore excluded from analysis. From the remaining cytokine data, three IL6 values, two IL8 values, and two IL10 values, were outliers (> 4 *SD* from the mean), these were therefore Winsorized to the highest value within 4 *SD* from the mean. Cytokine change scores were computed by subtracting Time 1 cytokine levels from Time 2 cytokine levels, such that higher change scores represent greater increases in circulating cytokine levels from Time 1 to Time 2.

Statistical Analysis

Statistical analysis was conducted using SPSS version 25. To test the effects of condition (*alone*, *parent,* or *control*) we conducted four multiple linear regressions, regressing each cytokine change score (IL6, IL8, IL10, & TNFa) onto two dummy-coded variables representing the *alone* condition, and the *parent* condition, compared to controls. To test the relation between CAB and cytokine change CAB values were included in the models, in addition to the following covariates: child age, child sex, child BMI, and highest parental education level. To control for inflated Type-I error due to multiple comparisons involving the four cytokines, estimate significance was assessed using the Benjamini-Hochberg False Discovery Rate (FDR) correction (Benjamini & Hochberg, 1995).

Missingness. Little's MCAR test was non-significant, X^2 (25) = 36.41, p = .07, consistent with a missing completely at random (MCAR) pattern. In addition, individuals with and without cytokine change score data did not differ significantly in resting CAB, age, sex, BMI, or highest parental education level.

Results

Sample descriptives for the main study variables and demographics are presented in Table 2.1. Complete bivariate correlational results are presented in Table 2.2.

Cardiac Autonomic Correlates

Consistent with its denotation as a spectrum from sympathetic dominant to parasympathetic dominant cardiac autonomic balance (CAB), CAB values were highly positively correlated with both RSA (r = .71, p < .001) and PEP (r = .75, p < .001; note: longer PEP indicates lower sympathetic activity). Unsurprisingly, CAB was significantly negatively correlated with heart rate (HR, r = -.62, p < .001), consistent with previous research in adults (Berntson et al., 2008). CAB was not significantly correlated with any demographic variable, or with participant BMI. RSA was significantly correlated with participant sex (r = -.22, p = .03), such that girls exhibited lower RSA. Consistent with lower parasympathetic modulation of cardiac activity (i.e., lower RSA) in girls, girls also exhibited higher HR compared to boys (r = .23, p = .03).

Cytokine Change Correlates

Change in IL6 was positively correlated with IL8 change (r = .23, p = .03), and TNFa change (r = .29, p = .005). IL8 change was also correlated with change in IL10 (r = .42, p < .001), and change in TNFa (r = .29, p = .004). IL10 change was positively correlated with TNFa change (r = .24, p = .02). IL8 change was higher in girls, compared to boys (r = .23, p =

.03). No other significant relations between cytokine change and participant demographics were observed. Although inflammatory marker change scores were not associated with BMI, we found significant relations between baseline (i.e., Time 1) cytokine levels and BMI, as would be expected. Specifically, BMI was positively correlated with baseline IL6 (r = .28, p = .004) and baseline IL10 (r = .23, p = .02).

Condition Effects and Cytokine Change

Regression results revealed no significant differences in cytokine change by condition. Specifically, individuals in the *alone* condition did not differ from those in the *control* condition in: IL6 change (B = -.29, p = .13), IL8 change (B = .02, p = .94), IL10 change (B = -.14, p = .21), or TNFa change (B = -.32, p = .23). In addition, individuals in the *parent* condition did not differ from controls in: IL6 change (B = .15, p = .42), IL8 change (B = .12, p = .61), IL10 change (B = -.03, p = .76), or TNFa change (B = -.17, p = .51). IL6 levels by condition are presented in Figure 2.1 to illustrate both the non-significant main effects and large individual differences within each condition.

CAB and Cytokine Change

Across all four cytokine change scores, lower CAB was associated with greater increase in circulating cytokines over the course of the experiment. Specifically, at the bivariate level, CAB was negatively correlated with IL6 change (r = -.25, p = .02), IL8 change (r = -.22, p = .04), and IL10 change (r = -.30, p = .004). CAB was also negatively correlated, at the trending level, with TNFa change (r = -.21, p = .05).

Multiple linear regression results (Table 2.3) revealed that, after controlling for covariates, lower CAB remained significantly associated with greater increase in IL6 (B = -.14, SE = .06, β = -.26, p = .015), and IL10 (B = -.09, SE = .03, β = -.30, p = .005). Lower CAB was

also marginally significantly associated with greater increase in IL8 (B = -.11, SE = .07, β = -.19, p = .09), and TNFa (B = -.14, SE = .08, β = -.19, p = .09). The associations between CAB, and change in IL6 and IL10, remained significant after controlling for multiple comparisons. FDR calculations are presented in supplemental Table 2.4. The relations between CAB and cytokine change scores are presented in Figure 2.2.

Post-hoc Exploratory Analysis

Post-hoc exploratory analysis was conducted to test associations between CAB and cytokine change within each condition. Within the TSST-M *alone* condition, CAB was correlated with change in IL8 (r = -.47, p = .02), IL10 (r = -.42, p = .03), and at the trending level with change in IL6 (r = -.34, p = .09), but not with change in TNFa (r = -.23, p = .26). Within the TSST-M *parent* condition, CAB was correlated with change in IL10 (r = -.47, p = .007), TNFa (r = -.46, p = .009), and at the trending level with change in IL6 (r = -.33, p = .07), but not with change in IL8 (r = -.14, p = .45). Within the non-stress *control* condition, CAB was not significantly correlated with any cytokine change score: IL6 (r = -.14, p = .45), IL8 (r -.07, p = .68), IL10 (r = -.01, p = .94), and TNFa (r = .07, p = .71).

Discussion

This is the first study to test the relation between autonomic function and changes in inflammatory markers in response to acute stress in children, to our knowledge. Increasing evidence suggests early risk detection may be crucial in implementing successful interventions in the etiology of inflammatory-based mental and physical health conditions (Chen et al., 2017). In addition, this is the first study to utilize measures of both sympathetic and parasympathetic modulation of cardiac activity, to test the association between cardiac autonomic balance and serum inflammatory markers. There is increasing understanding that single branch autonomic

measures may not provide a full picture of individual differences in autonomic functioning (Quigley & Moore, 2018).

Surprisingly, we did not find condition effects of acute stress exposure on changes in circulating cytokine levels. Previous meta-analytic results suggest that in adults acute stress exposure leads to average increases in circulating IL6 (Steptoe et al., 2007), IL10, and TNFa (Marsland et al., 2017). However, several individual differences factors have been found to moderate stress-induced inflammatory responses in adults. For example, a greater inflammatory response to acute stress has been observed in individuals with depression (G. E. Miller et al., 2005), low self-esteem (O'Donnell et al., 2008), a history of childhood trauma (Carpenter et a., 2010), those of a lower socioeconomic status (Brydon et al., 2004; Steptoe et al., 2002), and individuals with higher adiposity (Brydon et al., 2008). This suggests that individuals with poorer psychosocial functioning and physical health tend to exhibit greater increases in inflammatory markers in response to acute stress. Our non-clinical community sample consisted of healthy children with BMI in the normal range and middle-to-high SES, given the composition of the existing Participant Pool. This may explain why we did not find average main effects of acute stress exposure. Our future directions include the recruitment of lower-SES samples and children with mental and physical health diagnoses.

Alternatively, these results may suggest lower average stress-induced immune responses in children compared to adults. Acute stress effects on circulating IL6 levels have been previously documented in adolescents, but only in those with higher BMI (Chiang et al., 2017), and in those who reported high peer-victimization and hopelessness (Giletta et al., 2018). There is very limited research on inflammatory responses to challenge in children, using salivary samples, and results are mixed. For example, no significant changes in salivary interleukin-1β

following challenge have been observed in preschool children (Tyrka et al., 2015). A different study found stress induced increases in salivary IL6 for girls ages 8 to 10 years, but decreases for boys (El-Sheik et al., 2007). A third study, with preschoolers, found no significant changes in salivary IL6 following an emotionally challenging task, but found decreases in TNFa and IL8 (Riis et al., 2017). Future research in pediatric populations is needed to better understand if and when acute stress exposure leads to average increases in circulating cytokine levels in children.

For our second hypothesis, we predicted that lower cardiac autonomic balance (CAB) would be associated with greater increases in cytokine levels. Consistent with this hypothesis, we found that children with lower resting CAB exhibited greater increases in IL6 and IL10 across the experimental protocol. Importantly, these results remained significant after controlling for covariates and adjusting for multiple comparisons. These findings are consistent with previous research showing that higher baseline circulating cytokine levels are observed in adults with either low parasympathetic activity or high sympathetic activity (Révész et al., 2014; Williams et al., 2019). These findings are also consistent with prior studies in human and non-human animal models supporting modulation of inflammatory activity by the autonomic nervous system (Borovikova et al., 2000; Irwin & Cole, 2011; Nance & Sanders, 2007; Tracey, 2002). Lower CAB was also associated with greater increases in IL8 and TNFa, though these relations were only trending and were not significant after controlling for multiple comparisons. This suggests that in children, CAB may be more strongly related to IL6 and IL10 increases during challenge compared to IL8 and TNFa increases. This could reflect differential associations between the autonomic nervous system and the four cytokines assayed in the current study. A recent meta-analysis found that lower parasympathetic modulation of cardiac activity (RSA) was consistently associated with higher circulating IL6 levels but was not associated with TNFa

levels (Williams et al., 2019). Too few studies have tested associations between ANS activity and either IL10 or IL8 to facilitate meta-analysis, thus further research is needed on these cytokines. Post hoc analysis of achieved power suggested that we were underpowered to detect relations between CAB and both IL8 and TNFa (achieved power was only .71 and .67, respectively, which is below the recommended .8 power), largely due to missing data. Future research should therefore aim for a larger sample size, taking into account missing data problems associated with high rates of blood draw refusal in children. This will resolve the issue of whether non-significant links with TNFa and IL8 are true null effects or simply need larger samples to detect.

There are two possible interpretations for the increasing serum cytokine levels from Time 1 to Time 2. One interpretation is that these increases are stress-related, but only some children exhibited them so the group averages did not reflect these tendencies well, resulting in non-significant main effects of condition. As can be seen in Figure 2.2, all cytokine change scores showed a broad spread with many children showing increases and many showing decreases in cytokine levels across conditions. Supporting the interpretation that cytokine increases may be stress-related in some children, our post-hoc exploratory analysis found stronger and significant associations between CAB and cytokine change within the two conditions experiencing the TSST-M stressor (alone or with prior parent support), but non-significant correlations in the non-stress *control* condition. This suggests that CAB may exhibit a stronger association with increases in inflammatory markers within contexts characterized by threat. These results should be interpreted with caution, given the exploratory methods utilized and the small sample sizes within each condition. The second possible interpretation is that our results reflect relations between children's CAB and differential diurnal trajectories of circulating cytokines. There is

very limited literature on diurnal variation in serum cytokines, particularly in children. However, there is some evidence in adults that inflammatory cytokine levels display regular patterns throughout the day (Izawa et al., 2013), with cytokines increasing from afternoon to evening. Thus, our results may suggest that children with low cardiac autonomic balance show greater increases in cytokines across the afternoon as evening approaches. Future research involving repeated sampling throughout the day could provide insight into how autonomic function may influence immune system diurnal patterns in children, and how these underlying patterns can be differentiated from the effects of acute challenge.

Finally, a strength of our study is that it highlights the utility of cardiac autonomic balance measures in neuro-immune research. Our bivariate correlation matrix revealed several significant associations of cytokine change scores with individual parasympathetic (RSA) or sympathetic (PEP) measures, though notably all correlation coefficients were smaller between inflammatory markers and either RSA or PEP, compared to correlation coefficients between inflammatory markers and CAB. This suggests that the integrated relative contribution of parasympathetic to sympathetic activity may provide a stronger signal than single branch measures. Researchers interested in the association between autonomic and immune processes could benefit from utilizing valid indices of CAB, such as that derived from simultaneous recordings of RSA and PEP.

Limitations and Future Directions

This study contributes novel information towards a more comprehensive understanding of the connection between the autonomic and immune systems, extending past findings to include cardiac autonomic balance and inflammatory reactivity in children. Nevertheless, some limitations warrant attention.

First, our sample size was reduced due to missing serum data. Although our analysis of missingness did not reveal any systematic patterns, it is still possible that children who declined the blood draw were different from those who completed the blood draw in some unmeasured characteristic. Considering the challenges associated with pediatric research involving the collection of multiple biological samples, some missing data are expected. However, future research should consider the practical advice provided below, in order to help limit missing data in pediatric samples.

Second, it is important to note that CAB reflects the relative contribution of parasympathetic to sympathetic innervation of the heart, and therefore can only serve as a non-invasive proxy of autonomic activity in other bodily organs. Autonomic effects on immune activity are theorized to occur primarily through innervation of the spleen or liver, which are major sources of cytokine production (Tracey, 2007). Our results are also limited by the low-risk, healthy sample, which limits generalizability. We plan to examine these processes in more at-risk children in our future directions. Lastly, our findings are limited by the correlational design, which precludes causal inferences. Future research could benefit from creative methods of experimentally manipulating CAB, for example through random assignment to biobehavioral feedback training, in order to better test how CAB affects inflammatory processes. It is important to consider that the effects we detected may underestimate true effects due to the random error introduced by the inter-assay CV for serum cytokine assays. Nevertheless, our assay error was lower than most studies (average CV of 2.3 – 4.9%) and we assayed samples in triplicate to minimize such error.

Practical Recommendations and Theoretical Implications.

Pediatric research involving the collection of multi-system biological data has the potential to help further our understanding of how important biological systems, such as the immune system and the autonomic nervous system, interact across development. It is therefore critical to properly address the challenges to such a research endeavor, in order to mitigate reservations and promote the expansion of research in multi-system developmental psychobiology. With this in mind, we provide here several practical methodological strategies that we found to be helpful for the collection of autonomic and serum biomarkers in children. During ECG and impedance electrode placement, we found it necessary to refer to electrodes as *stickers* in order to avoid participant misconception, and resulting anxiety, that the ambulatory ECG would shock or electrocute them. We also found that expressing excitement about the ECG device, comparing it to an astronaut's computer, and asking the participant to help identify the placement locations (e.g., *can you point to your lowest rib?*), helped make the participant feel more involved, less like a subject, and therefore more comfortable during the process.

During blood draws, we found that having several friendly and colorful images on the walls (e.g., smiling animals, jungle scenes) provided a distraction for the participant, and helped create a warm environment in an otherwise sterile phlebotomy room. The use of an oversized adult phlebotomy chair enabled us to allow parents to sit next to their child if the participant requested, which eased reservations in some participants. Phlebotomists were most successful when they provided a more concise description of the process before the blood draw; a lengthy and detailed introduction often led to increased participant anxiety and refusal to continue. Lastly, we provided participants with an optional topical anesthetic approved for pediatric use (lidocaine 4%) if requested; this numbing gel was offered when a participant expressed fear of

the blood draw hurting. It is our goal that these recommendations can serve as a guide for researchers interested in developmental psychobiology.

In conclusion, this study found that children with low cardiac autonomic balance exhibited greater increases in circulating inflammatory cytokines. Importantly, we observed this association in healthy, low-risk children, under conditions of relatively mild challenge. This is a critical consideration, as it suggests that low CAB may represent a risk factor even in relatively favorable conditions. As such, it is possible that for children with poor mental and physical health, who may exhibit a greater inflammatory response to challenge, low CAB may represent an even greater risk factor. In addition, it is possible that CAB may be more strongly related to immune responses under conditions of greater environmental threat (e.g., abuse). If these contextual and individual risk factors co-occurred, we might find low CAB to be a crucial determinant of the development of inflammatory disease in at-risk populations. A comprehensive understanding of risk factors in the etiology of systemic elevated inflammation could pave the way for the development and application of targeted early risk identification and intervention.

CHAPTER 4

STUDY 3: A META-ANALYSIS OF THE ASSOCIATION BETWEEN PARENTING AND CHILD AUTONOMIC NERVOUS SYSTEM PHYSIOLOGY

Abstract

Parental socialization of affect and self-regulation may influence the development of the autonomic nervous system (ANS), a key stress-response system. However, to date no systematic quantitative synthesis of the literature linking parenting and child ANS physiology has been conducted. To address this gap, we conducted a meta-analysis. A comprehensive search of the literature identified 103 unique studies (n = 13,044 participants) that had available effect sizes describing the relation between parenting, or parent-child relationship quality and either parasympathetic nervous system (PNS) or sympathetic nervous system (SNS) activity in children. The overall analysis revealed non-significant associations between parenting and child ANS physiology. However, substantial between-study heterogeneity in effect size was observed that was predicted by study methodology and sample characteristics. Specifically, the positive relation between more positive parenting and resting PNS activity was stronger when a study was experimental rather than correlational, when the sample included children with a clinical condition, and when parenting was reported by the child. In conclusion, certain study designs and reliance on correlational data may undermine the ability to detect associations between parenting and child ANS physiology. Implications for future research on parental socialization and the development of child autonomic physiology are discussed.

Introduction

During the earliest years of life parents play a critical role in helping shape children's affect and self-regulatory abilities (Grusec & Davidov, 2010; Thompson, 2014a). Parenting that is characterized by sensitivity, consistency, and developmentally appropriate levels of control, is associated with better physiological and behavioral affect and self-regulation (Feldman, 2012; Thompson & Mayer, 2007). Parenting may influence child functioning in these domains through socialization and biological programming of neural-autonomic stress and affect regulatory systems, such as the autonomic nervous system (ANS; Calkins et al., 2013; J. G. Miller & Hastings, 2019; Propper & Moore, 2006; Thompson, 2015). High-quality narrative reviews of the relation between parenting and child ANS physiology have been written (Chiang et al., 2015; Propper & Holochwost, 2013; Quigley & Moore, 2018). However, substantial heterogeneity in both results and study methodology make interpretation of the literature difficult. ANS functioning has been implicated in both health and social-emotional outcomes (Beauchaine et al., 2013; J. G. Miller, 2018; Thayer et al., 2010). As such, improving our understanding of the early-life environmental predictors of child ANS physiology is a crucial task for developmental science. To provide a systematic integration of the literature, we conducted a meta-analysis of the association between parenting during early life and child ANS physiology.

The Autonomic Nervous System

The autonomic nervous system (ANS) is an expansive network of efferent and afferent nerves that work in conjunction with the central nervous and endocrine systems to adaptively respond to change in the environment and maintain the body in dynamic, context-appropriate homeostasis (Propper & Holochwost, 2013). The ANS is comprised of two branches, the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). In general,

the SNS is involved in mobilizing the body to deal with threat or challenge (i.e., "fight-or-flight"), such that increases in sympathetic output in response to a stressor is expected. Conversely, the relatively faster acting PNS facilitates return to calm (i.e., "rest-and-digest"). During moments of relative rest, cardiovascular activity is under constant influence by the PNS, which actively reduces heart rate through innervation of the sinoatrial node, termed the heart's *pacemaker* (Beauchaine, 2001). As such, the initial physiological response to perceived changes to the environment is a reduction in parasympathetic modulation of the heart, referred to as parasympathetic, or vagal, withdrawal (Porges, 2007).

Several theoretical models have been proposed to account for observed associations between ANS functioning and well-being. Polyvagal theory proposes that the highly myelinated ventral vagus nerve plays a central role in dynamic physiological responding to stimuli, which has allowed for flexible attending to subtle social environmental cues among species with relatively high metabolic demands (Porges, 2007). While polyvagal theory has contributed much to our appreciation for the important dynamic interplay between the parasympathetic and sympathetic branches of the nervous system in social situations, its evolutionary and anatomical claims have been challenged (Grossman & Taylor, 2007). According to the neurovisceral integration model, higher and lower order neural and endocrine systems organize the body for goal-directed behavior partially through sympathetic and parasympathetic nerves, which innervate with the heart (Thayer & Lane, 2000). As such, measurements of autonomic modulation of the heart can provide noninvasive insight into individual differences in cognitive and self-regulation abilities (Appelhans & Luecken, 2006; Thayer, 2006). Grossman and Taylor theorized that respiratory sinus arrhythmia (RSA), a common index of PNS modulation of cardiac activity, can reflect general physiological and neural plasticity to changing environmental

needs (i.e., flexibility), as information from multiple bodily systems is integrated to enhance metabolic efficiency (2007).

Measures of the Parasympathetic Nervous System. Several biomarkers exist that are regularly used to index parasympathetic nervous system activity. Most biomarkers approximate parasympathetic modulation of cardiovascular activity via heart rate variability (HRV), an index of the beat-to-beat changes in heart rate over time (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Three commonly used measures of HRV have been well validated to reflect PNS modulation of the heart through the vagus nerve, which is often referred to as "vagal tone" (Laborde et al., 2017). High-frequency heart rate variability (HF-HRV), the log of which is an index of RSA, is a measure of variations in HR associated with normative increases and decreases in HR during inhalation and exhalation, respectively (Laborde et al., 2017). When HF-HRV is portioned into developmentally appropriate frequencies, it is a relatively pure approximation of PNS influence over cardiac activity (Shader et al., 2018). Root mean squared successive differences (RMSSD) and RSA, as derived through the peak-to-valley method, are time-series measures that are highly correlated with HF-HRV (Grossman et al., 1990) and have also been validated as indices of PNS modulation of the heart (Laborde et al., 2017). Another, less common, index of PNS modulation of the heart is the cardiac vagal index (CVI), which has been validated using pharmacological blockade (Toichi et al., 1997).

Resting measures of HRV are positively associated with emotion and self-regulation (Appelhans & Luecken, 2006), executive function (Gillie, Vasey, & Thayer, 2015), and better physical health (Alen, Sloan, et al., 2020; Thayer et al., 2010). However, some studies have found negligible associations between HRV and psychosocial functioning (Klutting et al., 2010;

Sloan et al., 2017). Some recent evidence suggests the relation between resting HRV and social-emotional outcomes may not be linear (J. G. Miller, 2018).

HRV change in reaction to challenge or threat (i.e., vagal withdrawal) represents a physiological mobilization of resources important in attending to changing environmental demands, and has also been associated with better social and emotional functioning (Calkins & Keane, 2004; Thompson et al., 2008; J. G. Miller et al., 2015). However, the appropriateness of vagal withdrawal is context dependent (Hastings et al., 2014), and in some instances (e.g., normatively non-threatening situations) may reflect reactivity that is ill suited to situational demands (Beauchaine et al., 2007; Davis et al., 2016; Hastings et al., 2008).

Measures of the Sympathetic Nervous System. The activity of the sympathetic nervous system can be measured using various indices. First, pre-ejection period (PEP) is an index of the mechanical aspects of the heart (i.e., contractility; Sherwood et al., 1990). PEP is derived from cardiac impedance data, with shorter PEP representing more SNS influence over cardiac activity (Schächinger et al., 2001). Second, the SNS can also be indexed through skin conductance level (SCL), which measures electrodermal activity related to sympathetic innervation of sweat glands, and is positively related to SNS activity (Beauchaine, 2001). Additionally, salivary alpha amylase (sAA) has been suggested to reflect primarily sympathetic activity (Nater et al., 2007). However, production of saliva is influenced by both sympathetic and parasympathetic innervation of salivary glands, and therefore sAA levels do not purely index SNS activity (Rohleder & Nater, 2009). Toichi and colleagues also derived a validated, though less common, measure of SNS activity, termed the cardiac sympathetic index (CSI; 1997).

Increased sympathetic activity at rest is associated with greater cardiovascular risk (Mancia & Grassi, 2013), making SNS activity a valuable clinical marker of cardiovascular

health and risk of mortality. Research has also linked increased sympathetic activity to increased behavioral problems (internalizing and externalizing) in preschoolers (Esposito et al., 2015), though studies have also found the opposite relation (Beauchaine et al., 2013), or no relation (Nelson et al., 2021). Sympathetic reactivity has been associated with health and psychosocial functioning, with elevated reactivity predicting cardiovascular risk (Treiber et al., 2003), and reduced reactivity predicting increased substance use (Brenner & Beauchaine, 2011), poorer emotion regulation abilities (Stifter et al., 2011), and increased aggression (Posthumus et al., 2009) in children. It should be noted that, like PNS reactivity, sympathetic reactivity results must consider the contextual demands of the task.

Developmental Trajectories and Stability of ANS Functioning. Past findings have revealed increases in resting PNS activity, indexed through resting HF-HRV, from infancy to early childhood (Wagner et al., 2021), and from early childhood into late childhood (Quas et al., 2000; Rigterink et al., 2010). PNS reactivity (i.e., withdrawal) to challenge tends to decrease in magnitude from preschool to adolescence, though among clinical samples (e.g., high externalizing behavior problems) the opposite has been observed (Shader et al., 2018). Under normative conditions resting HF-HRV exhibits moderate to high rank-order stability after 3 months of age (Wagner et al., 2021). In contrast, HF-HRV change in response to challenge has been found to exhibit instability in both infancy and childhood (Bornstein & Seuss, 2000; Calkins & Keane, 2003; Doussard-Roosevelt et al., 2003), and low rank-order stability in late childhood and adolescence (Salomon, 2005).

Measures of sympathetic activity also exhibit consistent developmental changes during early life. For example, resting PEP has been shown to increase over 3 years in childhood (Matthews et al., 2002), and children exhibit shorter resting PEP (more SNS activity) compared

to adolescents (Matthews et al., 2002) and adults (Quigley & Stifter, 2006). Sympathetic reactivity to challenge tends to be lower in children compared to adolescents (Matthews et al., 2002) and adults (Quigley & Stifter, 2006), and has been shown to increase with age during childhood (Hinnant et al., 2011; Matthews et al., 2002).

In summary, resting PNS activity tends to increase and resting SNS activity tends to decrease across infancy and childhood, and both reach moderate stability in adolescence. PNS reactivity decreases from infancy to adolescence, and SNS reactivity increases. Moderate rank-order stability is found for resting measures, but less so for measures of reactivity.

Parental Socialization and the Autonomic Nervous System

Parental socialization of children's affect and self-regulatory abilities is a complex and intricate process that involves several aspects of both the parent's behavior towards the child, and the parent-child relationship (Grusec, 2011; Thompson & Meyer, 2007). Established theoretical perspectives suggest that a child's ability to regulate emotional states and adaptively respond to changing environmental demands is most likely influenced by parenting in three domains: *protection*, *teaching*, and *control* (Grusec & Davidov, 2010). More specifically, parents can help facilitate the development of affect and self-regulation through: (1) sensitive responding to distress, (2) socialization of emotional understanding, and (3) consistent and developmentally appropriate discipline (Grusec, 2011; Thompson, 2015). In addition, a child's ability to practice self-regulatory skills early in life depends on internalized conceptualizations of safety and dependability in close relationships (Waters et al., 2010). We will briefly touch on these four aspects of parent socialization, and how they may relate to differences in child ANS functioning.

The development of affect and self-regulation skills is aided by parental sensitivity and support, as parents engage in efforts to protect infants and children from both internal and

external sources of threat (Grusec, 2011). In infancy and early childhood parents act as primary sources of emotion and affect regulation (Thompson, 1994). Without adequately developed internal cognitive and physiological mechanisms, infants and young children rely on caregivers to help recover following affective arousal. Through guided socialization processes, parents' efforts to help children manage their internal affective state may over time lead to the entrainment of cognitive strategies and physiological response patterns critical in the development of adaptive emotion and self-regulatory skills (Cole et al., 2004; Thompson, 2015).

In addition, through social buffering processes, parental support can help maintain infant and child endocrine and sympathetic responses to external stimuli within moderate and more manageable levels (Hostinar, Sullivan, & Gunnar, 2014). At the same time, parental support leads to increased reliance on parasympathetic withdrawal as a physiological mechanism of engagement (Calkins & Keane, 2004; Calkins et al., 2007), which is thought to be a more adaptive physiological response pattern (Beauchaine, 2001). Over time, parental support may lead to the programming of stress physiology that is more moderate in reactivity, more flexible, and therefore better able to respond appropriately to changing environmental demands (Flannery et al., 2017; G. E. Miller et al., 2011). As such, sensitive and supportive parenting may act as an experience-expectant environmental contributor to the development of adaptive physiological regulatory systems. Harsh or abusive parenting, on the other hand, may pose a double risk of (1) an absence of experience expectant caretaker warmth, and (2) an increased level of threat and environmental unpredictability. Children who develop in abusive or unpredictable interpersonal environments may develop physiological reactivity patterns that are evolutionarily adaptive for the short term (e.g., hyper-vigilant), with long term costs to health and well-being (Blair & Raver, 2012; Del Guidice et al., 2011; Repetti et al., 2002).

Child autonomic physiology may also be influenced by parent efforts to teach children emotional understanding. More specifically, a parent's open discussion of, and measured reactions to, their child's and their own emotional expressions can help engender the child's understanding of emotions, and ability to effectively identify and moderate them (Eisenberg et al., 1998). Conversely, parental invalidation of child negative emotions can lead to rigid or avoidant cognitive and physiological emotion response patterns (Crowell et al., 2013). In such, differences in emotion coaching, or a parent's contribution to a child's understanding of their own affective state, can have substantial influence on the child's ability to regulate their own emotions, which may manifest itself in physiological systems implicated in affect and self-regulation (e.g., ANS physiology; Thompson, 2014b).

Children also benefit from developmentally appropriate levels of control and discipline. Parental behavioral control, that includes active monitoring, clear and realistic expectations, and developmentally appropriate involvement of the child in the decision-making process, guides the child towards practicing self-regulation (Barber, 1996; Grusec, 2011), which may become internalized and reflected at a physiological level. Parental control that is strict, overcontrolling, or that leverages the personal relationship (e.g., psychological control) can undermine autonomy and rob the child of chances to engage in independent self-regulation (Barber & Harmon, 2002; Hastings et al., 2008). Furthermore, harsh or inconsistent discipline can be a source of threat to the child (Morris et al., 2007), which may lead to the canalization of physiological and affective response patterns that are more vigilant (i.e., reactive) and more difficult to regulate (Gunnar & Cheatham, 2003; Repetti et al., 2002).

Lastly, these parental socialization processes share a bidirectional association with the child's style of attachment to the parent. According to attachment theory, infants and children

incorporate characteristics of their caregiver's behavior patterns into an internal working model, or a dynamic representation of how their caregiver, and the larger social world, will respond to their emotional signals (Bowlby, 1969; Thompson, 2008a). When a child believes the caregiver will be responsive to distress signals, this facilitates trust in the interpersonal environment and can give rise to a developmentally appropriate balance between interdependence and independence (Thompson, 2008b). Children who are securely attached to their caregiver can thus feel safe using their caregiver as a secure base from which to explore the world and returning to them to seek comfort in moments of distress (Ainsworth et al., 1974; Cassidy, 1994). This means that a secure attachment enables the caregiver to act as an effective buffer in times of acute stress (Gunnar & Hostinar, 2015; Thompson et al., 2008), while also permitting the growing child to practice the self-regulatory processes essential in the development of a flexible physiological approach and avoidance system (e.g., the ANS; Thompson, 2015).

Current Study

Parent socialization theory, supported by substantial empirical evidence, links parenting experienced during early life to individual differences in affect and self-regulation, which may be reflected in differences in autonomic physiology. In order to synthesize the literature, we conducted a meta-analysis of the association between parenting (or related constructs) and child ANS physiology. In the current study, we had two goals: (1) to quantify the magnitude and direction of the association between parenting experienced during early life and measures of child parasympathetic and sympathetic nervous system physiology, and (2) to investigate sample-level and study-level characteristics that might explain variability in findings across studies. As such, this study was designed to both review the current literature and provide directions for future research.

Methods

Literature Search and Study Screening

Search strategy and study methods were pre-registered at the International Prospective Register of Systematic Reviews (PROSPERO; Alen, Shields, & Hostinar, 2020). Study reporting adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page et al., 2021). To identify possible studies for inclusion we searched for relevant publications through two databases: PubMed and PsychINFO (ProQuest). Searches were conducted initially in April 2020 and then during a second time point in February 2021, using the following search string, with asterisks indicating a wildcard symbol that stands for any one or more characters that may follow the provided word stem:

(parent* OR maternal OR paternal OR mother OR father OR attachment OR maltreatment OR abuse OR neglect) AND ("autonomic nervous system" OR parasympathetic OR sympathetic OR "heart rate variability" OR "respiratory sinus arrhythmia" OR "heart period variability" OR vagal OR vagus OR "pre-ejection period" OR "skin conductance" OR "salivary alpha amylase")

This search resulted in the identification of 2,486 studies, from which 307 duplicates were removed (2,179 unique studies; see Figure 3.1 for PRISMA flow chart). An additional 11 studies were identified through hand searching reference lists from relevant literature reviews and inquiries within our research network. Screening procedures were conducted using the web-based platform Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Titles and abstracts for these 2,190 studies were screened for relevance twice independently by trained research assistants (RAs); disagreements during this process were resolved by the lead author (NVA). Title and abstract screening resulted in the exclusion of

1,831 irrelevant studies. The lead author independently reviewed 10% (k = 183) of these excluded studies and found no errors (i.e., zero incorrectly excluded studies). Full texts were retrieved and screening of Methods sections was then conducted by the lead author to make inclusion decisions on the remaining 359 studies.

Inclusion and Exclusion Criteria

To be considered for inclusion the following had to true:

- *The study must be peer reviewed, written in English, and present unique data*. Studies were limited to peer-reviewed articles to increase confidence in the quality of study methodology. Concerns of publication bias were low considering a large portion of studies were not designed to test direct relations between parenting and child ANS physiology, and instead collected both variables in order to test a different hypothesis (e.g., ANS physiology moderates the relation between parenting and some child outcome). If more than one article described the same sample and data, the article with the most information (e.g., more participants, more measures) was used (k = 4). If neither article presented more information, then the earliest published article was used (k = 8). If two studies used the same sample and each described different data (e.g., different measures), then all unique data were used and data were grouped together into a single study for analysis (k = 3).
- *The study must contain either a measure of parenting, a measure of the parent-child relationship, or a parenting intervention*. Given insufficient prior knowledge on which aspects of parental socialization are most strongly associated with child ANS physiology, the current synthesis adopted an inclusive approach and examined any study that included a measure of parenting or parent-child relationship quality. A parenting measure was

considered acceptable if it (1) could be placed conceptually within a spectrum ranging between negative (e.g., harsh, aggressive, abusive) to positive (e.g., warm, sensitive, supportive) parenting, or (2) if it described a parent's socialization of the child's emotions (e.g., emotion coaching), or (3) if it described a manner of parental control or discipline. Documented history of maltreatment was included as a parenting measure if the study explicitly stated that the perpetrators of maltreatment were all parents or primary caregivers. Acceptable measures of the parent-child relationship included measures of attachment security and measures of subjective quality of the relationship. Parenting interventions were only included if they were specific to the parent (i.e., did not involve child-directed intervention).

- *The study must contain a well-validated single branch (PNS or SNS) measure of the infant/child/adolescent ANS physiology (e.g., HRV, PEP, SCL).* For thoroughness, salivary alpha amylase (sAA) was also included, although this measure has been described as reflecting both sympathetic and parasympathetic influence (Rohleder & Nader, 2009). Sensitivity analyses were conducted to test models with and without this additional biomarker.
- *The study must provide sufficient information for the calculation of an effect size*. If a study met inclusion criteria but did not provide sufficient information for the calculation of an effect size, requests for information were sent to the study corresponding author and principal investigator.
- *For studies of ANS reactivity, reactivity must be calculated as either a raw change score (e.g., task level minus resting level) or a residualized change score (task level controlling for resting level)*. If a study provided only an effect size for the association between

parenting and ANS physiology *during a task* without baseline correction, requests were sent to the corresponding author for effect sizes that use either change scores or residualized change scores.

Studies were excluded if any of the following were true:

- The sample included participants that were older than 18 years of age at the time of ANS physiology measurement.
- The sample included participants with a neurological or cardiovascular disorder.
- The ANS physiology measure was obtained in the hospital shortly after birth (less than 1 week after birth).
- The ANS physiology measure was obtained at an earlier time point than the parenting measure. This exclusion criterion was implemented in order to support the conceptual framework of parenting influencing the development of the child's ANS. If a study presented both effect sizes that met inclusion criteria (e.g., cross-sectional or parenting measured before child ANS) *and* effect sizes that failed to meet inclusion criteria, the study was included but only the acceptable effect sizes were used in meta-analysis.

Full text screening resulted in $K = 153$ eligible studies, of which $k = 90$ studies provided sufficient data for the calculation of an effect size. Requests for necessary data to compute effect sizes were sent to 63 study authors; this resulted in the inclusion of $k = 16$ additional studies (Bosquet et al., 2014; Clark et al., 2016; Del Guidice et al., 2012; Giuliano et al., 2015; Laurent et al., 2012; Mezulis et al., 2015; J. G. Miller et al., 2013; Noll et al., 2015; Partington et al., 2018; Perrone et al., 2016; Rousseau et al., 2014; Rudd et al., 2017; Skowron et al. 2011; Tabachnick et al., 2019; Tharner et al., 2013; Willemen et al., 2008). Most studies reported more

than one effect size (e.g., due to multiple types of parenting measures or repeated assessments of ANS physiology). All effect sizes were retained for use in meta-analysis with one caveat: if a study contained repeated assessments of the *same* parenting measure, only the first assessment was included. A total of $K = 103$ unique samples, from $n = 106$ citations, provided $n = 418$ effect sizes ($n = 13{,}044$ unique participants).

Data Extraction

Data for calculating effect sizes, effect size weights, and for coding moderators were extracted by a team of highly trained RAs. Each study was extracted twice independently by highly trained RAs, and discrepancies were handled by the lead author. The lead author then conducted an additional check of the information used to calculate effect sizes and weights (i.e., correlation coefficient and sample size) on all studies. Lastly, the principal investigator (CEH) checked 10% of all extracted data for accuracy.

Coding of Moderators

The following categorical moderators were coded for use in primary analysis: (1) type of ANS physiology measure, (2) positive or negative parenting measure, (3) study design, (4) whether the parent was present or not during the ANS physiology recording, (5) clinical vs. non-clinical sample, and (6) type of change score used. In addition, two continuous moderators were coded (1) mean sample age at time of ANS measurement, and (2) percent female of sample. Continuous moderator variables were mean centered, within each individual model. Lastly, moderators were coded for exploratory analysis to further investigate moderation by: (1) relationship/attachment measures vs. parenting measures, (2) the specific type of parenting measure used (sensitivity/harshness, emotion socialization, control/discipline), (3) the type of

report used (parent-report, child-report, observed, composite), (4) country of sample, (5) percent minority sample, and (6) the type of task used during ANS reactivity measurement.

Type of ANS Measure. Parasympathetic and sympathetic nervous system measures were tested separately. However, within these separate models, different types of biomarkers were included together. For parasympathetic models (resting and reactivity) three biomarkers were used: high-frequency heart rate variability (HF-HRV), root mean squared successive differences (RMSSD), and RSA as derived using the peak-to-valley method. For sympathetic models the following biomarkers were included: skin conductance level (SCL), also known as electrodermal activity, pre-ejection period (PEP), and salivary alpha amylase (sAA).

Type of Parenting Measure. A dichotomous dummy-coded variable was created to reflect whether a parenting variable measured a *positive* construct or a *negative* construct. Specifically, positive parenting measures reflect measures where higher values or scores on the measure would be theorized to lead to better emotion or self-regulation (e.g., parental warmth, sensitivity, emotional support). Conversely, negative parenting measures reflect measures where higher values or scores on the measure would be theorized to lead to poorer emotion or self-regulation (e.g., parental hostility, harshness, corporal punishment).

Type of Reactivity Measure. Reactivity effect sizes were calculated and reported as either raw change scores (e.g., task level minus resting level) or as regression-based residualized change scores in source studies. To control for this heterogeneity in methods we created a dummy coded variable, *residualized*, such that effect sizes that came from residualized scores = 1, and effect sizes that came from raw change scores = 0.

Study Design. Study design was coded into two variables reflecting (1) whether an effect size was *experimental* (e.g., parenting intervention effect) vs. correlational, and (2) whether an

effect size was *longitudinal* vs. cross-sectional. All experimental effect sizes were longitudinal due to the need for pre- and post-intervention measurement, but correlational studies were either cross-sectional or longitudinal.

Clinical vs. Non-clinical. Studies were coded as *clinical* if 50% or more of the sample had a diagnosed clinical disorder (e.g., attention deficit hyperactive disorder) or health condition (e.g., premature birth).

Parenting Measure Type. Due to the large heterogeneity in parenting measures found in our search results, we further coded effect sizes for parenting measure type. We created four dummy coded variables reflecting whether a parenting measure was (1) an *emotion socialization* measure, (2) a measure of a parent's manner of *control or discipline* over the child, (3) a measure of the parent-child *relationship quality*, or (4) a measure of *attachment security*.

Country of Sample and Percent Minority. Due to the distribution of the sample country of origin (i.e., 79% were USA samples), we tested country of sample as a dichotomous moderator, such that USA samples = 1, and all other country samples = 0. *Percent minority* reflected the percent of the sample that was reported to belong to a minority racial or ethnic group for the respective country of the sample.

Reactivity Task Type. ANS reactivity effect sizes were coded into whether they were from ANS reactivity to tasks designed to be challenging (e.g., frustration tasks, conflict tasks, stressors), or tasks not designed to be challenging (e.g., free play, joint interaction). A dummy coded variable *non-challenging* was created such that non-challenging task effect sizes = 1, and challenging task effect sizes = 0.

Computation and Coding of Effect Sizes

The primary effect size observed was a Pearson's correlation, *r*, describing the association between two continuous variables. If a study reported a different effect size, such as Cohen's *d* (*n* = 1) or partial eta^2 (*n* = 1), this was transformed into a Pearson's correlation. If a study reported means, standard deviations (SDs), and sample sizes by group (e.g., attachment classification), this was used to first calculate a Cohen's *d*, which was then transformed into a Pearson's correlation (*n* = 23). When a study only reported an F-test (*n* = 2) or t-test (*n* = 1) statistic, this was used in combination with group sample sizes to first calculate a Cohen's *d*, which was then transformed into a Pearson's correlation. If a study only provided information to calculate effect sizes from correlations that were significant (selective reporting), requests were sent to study authors for the non-significant correlations. If study authors did not respond to requests, correlations described as non-significant in study text were imputed as *r* = 0 (this occurred for *n* = 7 effect sizes). This is considered a conservative method for handling selective reporting, as it is unlikely true correlations were exactly zero.

Due to the heterogeneity in both (1) parenting measures, and (2) type of ANS measures, effect sizes needed to be coded so that they would all reflect the same direction of effect. For resting ANS models, effect sizes were coded such that larger positive effect sizes reflect a greater positive relation between more *positive* parenting and higher levels of the respective resting ANS physiology measure. This was accomplished by multiplying effect sizes with *negative* parenting measures by -1.

For reactivity ANS models, effect sizes were coded such that larger positive effect sizes reflect a stronger positive relation between more *positive* parenting and greater "reactivity". This coding had to take into consideration (1) the type of parenting measure (i.e., *positive* vs. *negative*), (2) the way in which the change scores were calculated (i.e., resting minus task vs.

either task minus resting or residualized), and (3) the specific ANS biomarker used. For all included measures of PNS activity, a reduction in levels during a task, known as withdrawal, reflects physiological engagement and/or a fight-or-flight stress response. For SCL or sAA, exposure to a significant stressor should result in increasing levels. However, PEP is inversely related to sympathetic output, and therefore decreases in PEP during threat exposure are expected. In order to have all SNS measures be positively associated with SNS activity, PEP effect sizes were multiplied by -1. A complete description of the effect size coding scheme is available in the appendix. Positive effect sizes in reactivity models subsequently represent positive relations between more *positive* parenting and either greater PNS withdrawal (decreases), or greater SNS augmentation (increases).

Sample size was utilized to calculate variance of the sampling distribution, the inverse of which was used as a weight specific for each effect size during analysis. If sample size for each specific correlation was not clearly provided in the article, requests for clarification were sent to study authors. If study authors did not respond, then all available information was used to approximate sample size. We adopted a conservative approach to approximating sample size. For example, if a study only provided a range of missingness across all variables, the maximum missingness of the range was assumed.

Missing Moderator Data

When data for moderators were unavailable or unclear in the publication, authors were contacted for clarification. We received responses from eight study authors providing the requested data (Kochanska et al., 2017; Laurent et al., 2012; McQuade et al., 2021; Nelson et al., 2017; Oshri et al., 2020; Perry et al., 2013; Taylor et al., 2015; & Willemen et al., 2008). As a result of this effort all moderators in the primary analysis, with the exception of sample *percent*

female, had complete data. *Percent female* data were missing for $k = 3$ studies. Considering the low variability in *percent female* across studies with available data (mean = .50, *SD* =.08), likely due to researchers' efforts to have equal distributions of participant sex within their samples, we used mean imputation for these three studies. For a sensitivity analysis we reran all analyses (1) excluding *percent female* as a moderator, and (2) without imputing the missing data (list-wise deletion of these three studies). A total of $k = 6$ studies did not have sufficient information on race or ethnicity to calculate *percent minority*. However, since this moderator was exploratory, we did not impute values and instead ran analysis on available data only.

Statistical Analysis

All analyses were conducted using Rstudio Version 1.38, running R language Version 4.0.0 (R Core Team, 2020; RStudio Team, 2019). We used random-effects meta-analytic modeling, instead of fixed-effects modeling, due to the high heterogeneity in study design (Hedges & Vevea, 1998). A total of four meta-analytic models were tested looking at the relation between parenting and (1) resting PNS activity, (2) PNS reactivity, (3) resting SNS activity, and (4) SNS reactivity. Pearson's correlations were transformed into Fisher's Z, using the *escalc* function in the *metafor* package (Viechtbauer, 2010), for analysis. This is recommended practice, due to bias introduced when calculating the variance estimate for Pearson's *r* effect sizes (Borenstein & Hedges, 2019). Specifically, the sampling distribution variance for a Pearson's correlation depends on the correlation itself and is therefore biased. However, the formula for calculating the sampling distribution variance estimate for a Fisher's Z is simply:

$$Fisher's\ Z\ Variance = \frac{1}{(n-3)}$$

Where *n* is the sample size for each specific effect size. Fisher's Z is therefore an unbiased estimate. To increase interpretability, pooled effect sizes were back transformed and presented as Pearson's *r* in the text.

Many studies reported more than one effect size per sample, as previously stated. This was most often due to studies collecting multiple parenting measures, but also resulted from repeated measures of ANS physiology. Methods for obtaining a single effect size per study, for example by averaging effect sizes or arbitrarily selecting a single effect size, result in a loss of information (loss of statistical power) and biased pooled estimates (Assink & Wibbelink, 2016). In order to properly handle this within-study dependency, we employed robust variance estimation (RVE) methods with a correlated effects structure, which produces effect size weights that are corrected for the shared covariance between effect sizes clustered within a given sample (Hedges et al., 2010). Random effects meta-analysis with RVE was conducted using the R package *robumeta* (Version 2.0; Fisher et al., 2017). Unlike alternative methods for handling within-study dependency (i.e., generalized linear modeling), RVE does not require precise knowledge of the covariance structure among study effect sizes, or rho (ρ; Hedges et al., 2010). In the current analysis, rho was set to $\rho = .8$, reflecting high covariance among parenting measures and/or repeated measures of ANS physiology. Sensitivity analyses were then conducted that vary rho in increments of .1, ranging from $\rho = 0$ to $\rho = 1$; consistent with the robustness of RVE methods, results were unchanged. We implemented a small sample size bias correction for both models looking at SNS activity (resting and reactivity), due to the small number of studies available (*K*'s < 23). This correction is recommended when less than 40 studies are available (Tipton, 2015).

Intercept-only models were initially conducted, which provides a weighted pooled estimate of the effect, across biomarker types. To test for heterogeneity, we calculated the I^2 statistic. I^2 is a measure of the proportion of variability in effect sizes that is due to between study differences (true heterogeneity; Cheung, 2014). This statistic ranges from 0 to 1, with higher values reflecting greater heterogeneity. It has been suggested that an $I^2 < .30$ (less than 30% of variance attributed to heterogeneity) reflects low heterogeneity, I^2 values of .30 to .50 reflect moderate heterogeneity, and values above .70 reflect high heterogeneity (Deeks et al., 2008). It should be noted that other guides for interpreting the I^2 have been proposed (e.g., Higgins et al., 2003).

We next conducted a no-intercept model, with the inclusion of a dummy variable for each biomarker for a given model. For example, the no-intercept model for PNS activity could be written as:

$$Zr_i = B_1(\mathrm{HF-HRV}_i) + B_2(\mathrm{RMSSD}_i) + B_3(\mathrm{Peak-to-Valley}_i)$$

whereby the resulting estimates $B_{1\text{-}3}$ represent the estimated weighted pooled effect size for the association between parenting and HF-HRV, RMSSD, and peak-to-valley, respectively. Covariates (moderators) can then be added to this model, which will estimate the relation between each covariate and effect sizes across biomarkers, while accounting for the different pooled estimates (i.e., intercepts) for each biomarker.

Moderation analysis was conducted using meta-analytic regression. All moderators were entered into the model simultaneously. Only categorical moderators that had five or more effect sizes per level were included in a given model. Because of this, the list of moderators varied between models. The full list of moderators included: *positive parenting measure*, *experimental study*, *longitudinal study*, *parent absent during ANS recording*, *clinical sample, sample mean*

age, and *sample percent female*; an additional moderator *residualized* was included in reactivity models. *Experimental study* was not tested in the resting SNS model, or the SNS reactivity model, due to too few effect sizes being experimental (*n*'s = 1). *Clinical sample* was not tested in the resting SNS model, as too few effect sizes were from clinical samples (*n* = 4). In addition, *longitudinal study* was not tested in the SNS reactivity model because too few effect sizes were longitudinal (*n* = 3).

Publication bias was assessed through visual inspection of funnel plots and through Egger's regression. Egger's regression tests were conducted by calculating *SE*s and including this as a moderator in the intercept only RVE models. This method can account for dependency among effect sizes within studies. A significant association between *SE* and effect size, suggesting an asymmetrical distribution of effect sizes, is evidence for publication bias (Egger et al., 1997).

Results

Study Characteristics

Of the 103 total selected studies, *K* = 74 studies provided *n* = 178 effect sizes for resting PNS activity (HF-HRV, *k* = 61, *n* = 142; peak-to-valley, *k* = 8, *n* = 14; RMSSD, *k* = 4, *n* = 18; CVI, *k* = 1, *n* = 4), *K* = 50 studies provided *n* = 137 effect sizes for PNS reactivity (HF-HRV, *k* = 38, *n* = 105; peak-to-valley, *k* = 8, *n* = 18; RMSSD, *k* = 4, *n* = 14), *K* = 25 studies provided *n* = 51 effect sizes for resting SNS activity (SCL, *k* = 13, *n* = 23; PEP, *k* = 6, *n* = 11; sAA, *k* = 5, *n* = 13; CSI, *k* = 1, *n* = 4), and *K* = 27 studies provided *n* = 61 effect sizes for SNS reactivity (SCL, *k* = 17, *n* = 34; PEP, *k* = 9, *n* = 23; sAA, *k* = 1, *n* = 4). Biomarkers with less than five effect sizes (CVI, CSI, sAA reactivity) were excluded from analysis.

A vast majority of the studies came from the United States (77%), but studies were also obtained from Canada (7%), the Netherlands (7%), Israel (5%), and other countries (4%). Mean sample age ranged from *term age* (preterm sample) to 16.8 years (mean = 6.6, *SD* = 4.8, years), and on average samples were half female (mean = 50%, *SD* = 8%, female). Study sample sizes ranged from $n = 18$ to $n = 450$ (mean sample size = 127, *SD* = 95).

Publication Bias and Outliers

Investigation of publication bias did not reveal evidence for publication bias. In the resting PNS activity model the Egger's regression only revealed a marginally significant association between *SE* and effect size ($p = .09$). This association was driven by a single outlier (effect size > 4 *SD* above the mean) with a small sample size ($n = 18$). After removing this outlier, the Egger's regression test was non-significant ($p = .20$). Removing this outlier did not change any primary study results; we therefore present the funnel plot with this outlier removed (Figure 3.2). Egger's regression was non-significant for all other models (p's > .38), suggesting lack of publication bias. In addition, visual inspection of the funnel plots, presented in Figure 3.2, revealed a relatively symmetrical distribution of data points on the left and right side of the average effect size, thus there was no evidence for publication bias.

Pooled Estimates

The test for pooled estimates with intercept-only models revealed a non-significant pooled correlation between parenting and resting PNS activity ($r = .01$, 95% CI [-.01, .04]), between parenting and PNS reactivity ($r = -.01$, 95% CI [-.03, .02]), between parenting and resting SNS activity ($r = -.004$, 95% CI [-.06, .05]), and between parenting and SNS reactivity ($r = .01$, 95% CI [-.04, .06]). Tests of heterogeneity revealed substantial heterogeneity in the resting

SNS model (I^2 = .54), moderate heterogeneity in the resting PNS model (I^2 = .45) and the SNS reactivity model (I^2 = .39), but low heterogeneity in the PNS reactivity model (I^2 = .28).

Moderation Analysis

Resting PNS. The no-intercept model revealed that parenting was not significantly correlated with either resting HF-HRV (*r* = .02, 95% CI [-.01, .05]), resting RSA calculated using the peak-to-valley method (*r* = -.03, 95% CI [-.09, .02]), or resting RMSSD (*r* = -.01, 95% CI [-.16, .13]). In the full model, presented in Table 3.1, *experimental study* (*B* = .17, *SE* = .07, *p* = .01, 95% CI [.04, .3]) and *clinical sample* (*B* = .09, *SE* = .04, *p* = .047, 95% CI [.001, .18]) were significant moderators of the correlation between parenting and resting PNS activity. The positive correlation between positive parenting and resting PNS activity was greater among experimental studies (*r* = .22, 95% CI [.13, .30]), compared to correlational studies (*r* = .005, 95% CI [-.02, .03]). In addition, the positive correlation between positive parenting and resting PNS activity was greater among clinical samples (*r* = .14, 95% CI [.07, .21]), as compared to non-clinical samples (*r* = -.001, 95% CI [-.03, .03]). See Figure 3.3 for forest plots of experimental studies and clinical sample studies.

PNS Reactivity. The no-intercept model also revealed that parenting was not significantly correlated with HF-HRV reactivity overall (*r* = .001, 95% CI [-.03, .03]), RSA as derived from peak-to-valley method reactivity (*r* = -.04, 95% CI [-.09, .007]), or RMSSD reactivity (*r* = -.05, 95% CI [-.11, .008]). In the full model, there were no significant moderators of the relation between parenting and PNS reactivity (*p*'s > .37). See Table 3.2 for full results.

Resting SNS. The no-intercept model revealed that parenting was not significantly correlated with resting SCL (*r* = -.04, 95% CI [-.09, .01]), resting PEP (*r* = .02, 95% CI [-.24, .28]), or resting sAA (*r* = .05, 95% CI [-.14, .23]). In the full model, there were no significant

moderators of the correlation between parenting and resting SNS activity (*p*'s > .12). See Table 3.3 for full results.

SNS Reactivity. The no-intercept model revealed that parenting was not significantly correlated with resting SCL reactivity (*r* = .02, 95% CI [-.04, .09]), or resting PEP reactivity (*r* = -.01, 95% CI [-.08, .06]). In the full model, presented in Table 3.4, only *mean age* was a significant moderator of the relation between parenting and SNS reactivity (*B* = -.01, *SE* = .004, *p* = .03, 95% CI [-.02, -.002]). Visual inspection of the scatterplot between mean age and effect size, presented in Figure 3.4, revealed that as sample age increased from childhood to adolescence the correlation between positive parenting and SNS reactivity changed from positive to negative.

Exploratory Analyses

Exploratory analyses were conducted to further investigate which study-level and sample-level characteristics might explain variability in the effect sizes observed. For exploratory analysis, additional moderators were individually added to the no-intercept RVE models (including dummy variables for each biomarker), but to conserve statistical power only moderators previously observed to be significant in the primary analysis were retained in the model as covariates.

Relationship Measures. The moderating effects of attachment and relationship measures was tested by including two dummy coded variables representing *attachment* measures, and *relationship quality* measures, as compared to parenting measures. In the resting PNS model, *attachment measure*, as compared to parenting measure, was a significant moderator (*B* = -.08, *SE* = .03, *p* = .001, 95% CI [-.13, -.03]), such that effect sizes from attachment measures (*r* = -.08, 95% CI [-.13, -.04]) were significantly smaller (more negative) than those from parenting

measures (r = .02, 95% CI [-.01, .05]). The moderating effect of attachment measure in the resting PNS model is presented in Figure 3.5. The moderating effect of *attachment* measure was also significant in the PNS reactivity model (B = .07, SE = .04, p = .046, 95% CI [.002, .14]), such that effect sizes from attachment measures (r = .04, 95% CI [-.04, .13]) were larger (more positive) than effect sizes from parenting measures (r = -.01, 95% CI [-.04, .02]). No other moderating effect of attachment measure nor relationship quality measure were observed across models (p's > .56). The moderating effect of attachment measure in the PNS reactivity model is presented in Figure 3.6.

Parenting Measure Type. Within parenting measures, specific type of parenting measure was tested as a moderator by first removing effect sizes for relationship measures, then adding two dummy coded variables representing the moderating effect of *emotion socialization* measures, and *control or discipline* measures to the models. The resulting effect represents the difference in effect size between each of these measures in comparison to measures reflecting either sensitivity and warmth, or harshness and aggression. Parenting measure type was not a significant moderator in any of the models (p's > .09).

Type of Report. In order to provide information for future researchers regarding differences in report type among correlational studies, we compared parent-reported, child-reported, observed, and composite (e.g., observed and parent-reports combined) parenting measures. First, we removed studies that used either (1) experimental designs, or (2) documented history (i.e., abuse). In addition, only two studies used composite measures in SNS models; composite measure was therefore not tested in those models. In the resting PNS model, effect sizes that used child-reported measures were significantly larger (i.e., more positive), compared to those using parent-reported measures (B = .08, SE = .03, p = .002, 95% CI [.03, .13]).

Specifically, the correlation between positive parenting and resting PNS activity was positive when parenting was child-reported (r = .03, 95% CI [-.02, .09]), and negative when parent-reported (r = -.03, 95% CI [-.07, .01]). The moderating effect of report type is presented in Figure 3.5. No other moderating effect of report type was observed across models (p's > .09).

Country of Sample and Percent Minority. Country of sample was not a significant moderator in any model (p's > .37). Percent minority was also not a significant moderator in any model (p's > .17).

Non-challenging Task. Non-challenging task was a significant moderator of the relation between parenting and PNS reactivity (B = -.17, SE = .06, p = .004, 95% CI [-.29, -.06]). Positive parenting was correlated with lower PNS reactivity during non-challenging tasks (r = -.16, 95% CI [-.27, -.05]), but not during challenging tasks (r = -.002, 95% CI [-.03, .02]). The moderating effect of non-challenging task is presented in Figure 3.6. Non-challenging task was not tested as a moderator of the relation between parenting and SNS reactivity because only one SNS reactivity study used a non-challenging task.

Full Resting PNS Moderation Model. Given the large number of significant moderators observed in the resting PNS model, a full moderation model was tested that included all significant moderators (*experimental study*, *clinical sample, report type, relationship measure*). Results from this full resting PNS model, presented in Table 3.5, revealed that all moderators remained significant (p's < .04), suggesting independent moderating effects.

Sensitivity Analysis

Sensitivity analysis was conducted to test the robustness of findings to: (1) the exclusion of an outlier in the resting PNS model, (2) exclusion of sAA effect sizes in the resting SNS model, (3) the use of alternative methods for handling missing data in the moderator *percent*

female, and (4) the exclusion of imputed non-significant effect sizes. The removal of a single outlier with a small sample size in the resting PNS model did not change results. The exclusion of sAA effect sizes did not change study results. When *percent female* was removed from the primary analysis meta-regression models, all primary results and inferences remained the same. When *percent female* was not imputed and list-wise deletion was instead used, resulting in the loss of $k = 3$ resting PNS studies ($n = 7$ effects), the moderating effect of *clinical sample* in the resting PNS model was no longer significant ($p = .15$). When imputed effect sizes were excluded from analysis no study results changed.

Discussion

In the current meta-analysis we tested the strength of the correlation between parenting and child ANS physiology. In contrast to expectations, we observed non-significant pooled associations between parenting and child parasympathetic and sympathetic nervous system activity. These non-significant associations were observed across biomarkers used for measuring PNS and SNS physiology, for both resting and reactivity measures. The autonomic nervous system has been proposed as a biological mediator between parenting experienced in early life and later child health and behavioral outcomes (Propper & Moore, 2006; Repetti et al., 2002). Results from the current meta-analysis suggest that overall parenting during early life is not strongly associated with child ANS functioning, providing weak evidence for this conceptual model.

Importantly, given the comprehensive scope of the current meta-analysis, substantial heterogeneity in both study methods and participant sample were observed in the literature. Mirroring this qualitative characteristic, between-study heterogeneity in effect sizes was also observed, warranting investigation of potential moderators such as aspects of the study design

and sample that might explain variability in the correlations between parenting and child ANS physiology. Several significant moderators were observed. First, within the resting PNS model, effect sizes were larger for studies that used experimental designs, specifically parenting intervention studies, as compared to correlational designs, though it must be noted that fewer studies used experimental designs than correlational. The positive pooled effect size observed among these studies suggests that interventions designed to improve parenting and facilitate the development of a secure attachment between parent and child lead to higher resting PNS activity in children.

The interventions identified were diverse, including programs aimed at increasing sensitivity (Hastings, Kahle, et al., 2019; Tabachnick 2019; 2020) and emotion coaching in parents (Katz et al., 2020), as well as programs designed to foster stronger emotional bonds between parent and child (Porges et al., 2019; Welch et al., 2020). The effect of these interventions on resting PNS activity is consistent with parent socialization and attachment theory. Developmentally appropriate protection, sensitive responding, and coaching of emotional understanding by parents, as well as secure bonds that facilitate trust between child and caregiver, may influence neural-autonomic systems implicated in self and affect-regulation (Propper & Moore, 2006; Thompson, 2015).

The finding that effects were stronger among intervention studies suggests that accurate approximations of parenting effects on child ANS physiology may be difficult to obtain using correlational data, where we could expect high levels of noise and confounding from unmeasured variables (e.g., physical exercise level, larger family context). In addition, correlational results are complicated by the bidirectional relation between child physiology and parenting. Physiological profiles associated with poorer emotion regulation skills (e.g., low resting HRV)

may lead to less supportive, or more overcontrolling, parenting (Hastings, Grady, & Barrieau, 2019; Kennedy et al., 2004). Alternatively, children with poorer emotion regulation abilities may sometimes evoke *more* support during moments of challenge because parents anticipate them requiring it (Planalp et al., 2019). The principle of "goodness-of-fit" parenting (Chess & Thomas, 1999) adds further complexity to correlational findings, as certain temperamental or physiological characteristics may influence the magnitude or direction of parent socialization effects (Rubin et al., 2002). In their seminal paper, Collins and colleagues suggested that parenting intervention studies can provide the most convincing evidence for or against parenting influences on child development (Collins et al., 2000). Our results support this claim and further suggest that future developmental researchers should increase efforts to utilize experimental, over correlational, designs whenever possible.

For PNS reactivity, no moderating effect of *experimental study* was observed. Notably, only two studies were identified that tested parenting intervention effects on PNS reactivity, and they differed greatly in the length of follow-up. Parenting intervention resulted in reduced PNS withdrawal among toddlers measured 6 months after treatment (Hastings, Kahle, et al., 2019), but did not influence PNS withdrawal among children tested 9 years after treatment (Tabachnick et al., 2019). This suggests that parenting intervention effects on PNS reactivity may diminish over time. Future researchers should aim to continue testing parenting intervention effects on child ANS functioning, stressing the need for additional studies on PNS reactivity, as well as studies on SNS activity. In addition, further attention should be paid to investigate the effect of follow-up interventions, whereby parental sensitivity training refreshers could be provided, analogous to vaccine booster shots.

We also found that the positive correlation between parenting and resting PNS activity was greater among studies with a clinical sample. The types of clinical samples identified varied greatly, including samples with behavioral and mood disorders (e.g., attention deficit hyperactivity disorder, internalizing problems), as well as samples at elevated developmental risk (e.g., premature birth). Stronger positive associations between parenting and resting PNS activity among clinical samples may reflect stronger influences of parenting on children's ANS physiology among these more at-risk youth. Potentially, children who are at greater risk of psychopathology or developmental delay may rely more on positive parent socialization efforts, which can directly buffer against, or help entrain positive coping abilities to independently manage the higher levels of adversity this group may be exposed to (Blair & Raver, 2012; Hostinar et al., 2014). These effects observed were almost entirely correlational, so strong causal inferences should be avoided. Nevertheless, future researchers interested in parent socialization of child ANS physiology could benefit from focusing on clinical samples, or other samples of children at elevated risk of psychopathology (e.g., children living in poverty).

We also found some evidence that the use of child-reports may lead to larger correlations between parenting and child resting PNS activity, as compared to parent-reports. There is substantial literature describing the often-divergent reporting of parenting behavior between parents and children (Korelitz & Garber, 2016), and some evidence that associations with child outcomes may be stronger when parenting is child-reported. In a meta-analysis of the relation between parenting and child delinquency, Hoeve et al. similarly found larger effects when parenting was child-reported as compared to parent-reported (2009). Pinquart also observed stronger effects if parenting was child-reported in a meta-analysis of parenting and child internalizing symptoms (2017). One possible explanation of this could be parents' minimizing or

underreporting of their own negative parenting behaviors (Leung & Shek, 2014). Indeed, meta-analytic findings suggest parents tend to rate their parenting as more positive compared to their children (Korelitz & Garber, 2016).

Effects from child-reports may also be stronger because the way a child's perception of their parent's behavior and attitudes towards them may become incorporated into their beliefs about themselves and the world (Conway, 2011). This would mean that a child's perception and report may carry additional relevance over and above objective, observable behaviors. Alternatively, the larger effect from child-reports may come from confounding by child characteristics. For example, children with high resting HRV may be more agreeable and as such rate their parents as more positive (Oveis et al., 2009). However, it should be noted that resting HRV is only inconsistently linked to indices of well-being and personality (Sloan et al., 2017). Furthermore, the developmental literature is increasingly viewing disagreements in how children and parents report on parenting behavior as an important aspect of the parent-child dyad worth exploring, rather than a matter of reporting error (Hastings, 2018; Korelitz & Garber, 2016). With that in mind, more research involving multi-method assessments of parenting is needed to better understand the link between parenting and child ANS physiology.

The correlation between parenting and resting PNS activity was also moderated by whether a parenting or attachment measure was utilized. Surprisingly, we observed negative relations between attachment security and resting PNS activity. This is in contrast to findings with parenting measures, and expectations that secure attachment would be linked to higher levels of resting PNS activity. It should be noted that the identified studies that investigated attachment and child ANS physiology exhibited substantial variability. Attachment measures used in primary source studies included observed behavioral (ABC-D classification), narrative,

and child-report measures. Unfortunately, due to the limited number of attachment studies identified we were unable to test more nuanced moderation analysis regarding type of attachment measure used. In addition, opposing emotion regulation linked behavioral reactions to interpersonal challenge (e.g., separation) differentiate insecure-avoidant from insecure-resistant attachment (Cassidy, 1994). It is therefore unlikely that different styles of insecure attachment, or even different methods for measuring attachment insecurity, would relate to physiological systems of affect and stress regulation in a similar manner. The exploratory nature of these results, in addition to the relatively small number of attachment studies, must be taken into consideration. Nevertheless, future research is needed to clarify why attachment security, which is linked to sensitive parenting (Cassidy, 1994), may exhibit differential associations with resting PNS activity as compared to characteristics of parenting.

We also found some preliminary evidence that type of task may influence the association between parenting and ANS reactivity. Positive parenting was negatively associated with PNS withdrawal during non-challenging tasks, but during challenging tasks effect sizes varied greatly from negative to positive, with an average effect size that was not significantly different from zero. This finding is consistent with the context-dependent nature of the appropriateness of PNS withdrawal. Specifically, it has been proposed that, under threat, higher levels of HRV withdrawal reflect adaptive responding to and engagement with the task (Beauchaine, 2001). Conversely, high levels of withdrawal during tasks that should not be threatening or challenging could reflect an overactivation (Hastings et al., 2014). Importantly, determining what is overactivation versus an appropriate level of activation will depend not only on the task, but also on the range of levels within the sample. Moderate levels of reactivity during challenge may be what is most adaptive (J. G. Miller, 2018). This could lead to mixed results from tests of simple

linear relations (e.g., correlation): if the range of change scores extend from low to moderate reactivity, then we might expect higher values within the sample to be more adaptive; if scores range from moderate to high, then relatively lower values could be more adaptive.

The lack of a significant pooled effect among challenging tasks may therefore be due to (1) the high heterogeneity in type of challenging task, and (2) the non-linear relation between reactivity to challenge and adaptability. Associations between parenting and PNS reactivity may be more easily identified among the non-challenging tasks, where low reactivity is consistently the normative or expected outcome. Given their exploratory nature, these findings should be interpreted with caution. However, in general this finding agrees with suggestions from experts that context must be taken into consideration when interpreting PNS reactivity (Beauchaine et al., 2007; Hastings et al., 2014). More research is needed measuring child ANS physiology during multiple, standardized tasks, to better tease apart these complex results.

Lastly, the correlation between parenting and SNS reactivity was moderated by mean age of the sample. As mean age of the sample increased from early childhood to late adolescence, the correlation between positive parenting and SNS reactivity appeared to change from positive to negative. Longitudinal or age-comparison studies of SNS reactivity to challenge have tended to show increases in SNS reactivity from early childhood to adolescence (Hinnant et al., 2011; Quigley & Stifter, 2006). Positive parenting being associated with less reactivity in adolescence may mean that positive parenting leads to more moderate levels of reactivity at an age when reactivity is on average higher. Alternatively, given the lack of a significant pooled estimate, it is possible that the relation between positive parenting and SNS reactivity is always negative, but simply becomes stronger later in youth. Again, these results highlight further complexity of ANS

reactivity measures, which are dependent on (1) context, (2) range of levels within the sample, and (3) period of development.

Surprisingly, given the large variability in parenting measures, we did not observe any moderating effect of type of parenting measure. Across models, effect sizes did not differ between measures of sensitivity or harshness, measures of emotion socialization, or measures of control or discipline. This could reflect high correlation among these different parenting domains (i.e., parents who are more sensitive tend to also engage in more emotion coaching). It could also reflect that all of these aspects of parenting are similarly important in shaping physiological mechanisms of emotion and self-regulation (Propper & Moore, 2006; Repetti et al., 2002). Conversely, considering the non-significant pooled correlation between parenting and ANS physiology, this could be explained by a generally minimal effect of normative variation in parenting on the development of the ANS. However, given the significant causal evidence observed within parent-intervention studies, this is not a likely explanation. Instead, the difficulty of identifying associations between parenting and child ANS physiology using correlational designs might be similar between different types of parenting measures.

Study Limitations and Future Directions

There are several strengths of this study, as the first quantitative synthesis of the literature on parenting and child ANS physiology. First, the study was rather comprehensive. We included a diverse range of parenting and parental socialization measures theorized to influence development through physiological systems of affect and self-regulation. In addition, we assessed well validated single-branch measures of both the PNS and the SNS and included both resting and reactivity measures. Among the ANS physiology literature, substantial heterogeneity of methods exists, posing challenges for the synthesis of evidence (Laborde et al., 2017). Our

moderation analysis contributes important information for guiding future researchers interested in parenting and ANS physiology. Lastly, we found no evidence of publication bias, an important finding considering we restricted our analysis to peer-reviewed journal articles.

Despite these strengths, several limitations should be mentioned to help clarify findings and guide future research. First, relatively fewer studies were identified that looked at SNS activity, as compared to PNS activity. This may explain why most significant moderators were found among PNS studies. Second, the study data available were not appropriate for testing moderating effects of child gender. Gender influences on parent socialization have been documented (e.g., Klimes-Dougan et al., 2007). In fact, differential associations between parenting and PNS activity (resting HF-HRV) between boys and girls have been found (Van der Graaff et al., 2016). However, primary source studies identified included half female and half male participants on average, with very little variability. Testing sample percent female as a moderator was therefore unable to reveal any effect. Many studies did not report effect sizes separately for boys and girls, but future efforts to gather separate effect sizes for boys and girls could facilitate testing gender as a moderator. Similarly, we were unable to properly test parent gender as a moderator. This is mainly because of a lack of male parent participants in most primary source studies. Despite the increasing call for addressing the lack of father participation in developmental research, evidence suggests no significant improvements over the past decade (Parent et al., 2017). Future efforts to recruit more fathers, or to test relations between parenting and child ANS physiology separately, could help address this limitation. Results may also be limited due to a lack of balance in some categorical moderators. Fewer studies were experimental, as compared to correlational, and fewer studies had clinical samples, as compared to non-clinical samples. This may be due to increased difficulty in conducting research with

experimental designs or clinical samples. Future efforts to conduct experimental research and research with clinical samples could help address this limitation.

Our use of ANS reactivity change scores may also be a limitation. Measuring resting, reactivity, and recovery ANS physiology (referred to as the 3 R's) provides a more comprehensive assessment of ANS functioning (Laborde et al., 2017). Too few studies provided recovery measures to facilitate a meta-analysis of the relation between parenting and ANS recovery. Increased attention to recovery measures is an important future direction, as this has the potential to clarify the heterogeneous findings with ANS reactivity to challenge. Potentially, parent socialization of stress and affect regulation may emerge more in how a child recovers following threat, as compared to how much the child reacts initially (J. G. Miller et al., 2013). Developmental psychophysiology researchers have recommended the use of more statistically advanced methods for quantifying change (e.g., growth curve modeling), over the traditional change score (J. G. Miller, 2018). However, results using these advanced statistical methods are not easily integrated into a meta-analysis, given that growth curve modeling may differ across studies depending on timing or frequency of measurement, as well as different time-varying covariates. Lastly, the focus on the activity of single branches of the ANS may limit the ability to detect associations, if parenting shapes the overall balance of sympathetic versus parasympathetic activity (Quigley & Moore, 2018). We could not identify any studies that used indices of autonomic balance, but measures of autonomic balance (e.g., cardiac autonomic balance) have been implicated in both behavioral (Alen et al., 2021) and health-related outcomes (Alen, Deer, & Hostinar, 2020; Bernston et al., 2008; Thayer et al., 2010). A clearer understanding of the relation between parenting and autonomic balance is an important future

direction for research into the biological underpinnings of parental socialization of affect and self-regulation in children (Quigley & Moore, 2018).

Conclusion

The current meta-analysis of the association between parenting and child ANS physiology revealed vast variability in both methods and results. The synthesis of these heterogenous studies resulted in an overall lack of evidence for a strong association between parenting and child ANS physiology. However, dissection of this complex literature revealed that the general non-significant results masked some important takeaways. First, experimental manipulation of parenting, through positive parenting intervention, leads to higher resting parasympathetic activity in children. Second, positive parenting is more strongly associated with higher resting PNS activity among clinical samples of youth. Higher resting HRV is consistently associated with better health outcomes across the lifespan and may predict better psychosocial functioning (Beauchaine, 2001; Thayer et al., 2010). Results from this study highlight the ANS as a potential biological mechanism through which positive parenting interventions, particularly among those most at risk, can improve health and well-being. Lastly, this study revealed differential results based on how parenting was measured (informant) and how ANS reactivity was measured (type of task), that future research should consider. Large-scale studies that employ multi-method designs for measuring parenting, and that include multiple, standardized reactivity tasks, can help provide a better understanding of how parenting is associated with child ANS functioning.

CHAPTER 5: GENERAL DISCUSSION

Childhood parental experiences help shape our patterns of affect and stress reactivity and regulation (Hastings et al., 2014; Propper & Moore, 2006; Thompson, 2014a). This has substantial implications for lifelong health. Parenting that is harsh, abusive or neglectful, has been associated with poorer health (Repetti et al., 2002). Conversely, sensitive parenting is associated with better health (Chen et al., 2017). This dissertation serves as a multi-method investigation into the role of the autonomic nervous system (ANS) in the link between parenting and health. This final chapter presents a brief integration of the main takeaways from these three studies.

Takeaway 1: ***Parenting influences offspring autonomic nervous system physiology, but effects may be small and primarily detectable through intervention studies*****.**

In Study 1 we tested the longitudinal association between retrospectively-reported parental warmth and resting high frequency heart rate variability (HF-HRV) in midlife using a large sample of adults. We observed a significant, though small, positive association between childhood parental warmth and resting HF-HRV, after controlling for a host of theoretically related covariates. This finding is strengthened by the large, nationally representative sample, and the longitudinal design. However, the use of retrospective reporting of parental warmth raises questions about the validity of the parenting measure. In addition, the correlational design precludes causal inferences.

The literature on parenting and child ANS physiology is complex and presents findings using heterogeneous methods that are difficult to integrate. Study 3 was specifically designed out of concerns for both (1) the limitations of Study 1, and (2) the complexity and inconsistency observed in the literature. In Study 3 we tested the strength of the association between parenting

and child ANS physiology using meta-analytic methods. What we observed was a non-significant pooled correlation between parenting and child ANS physiology. To a degree, this is consistent with Study 1 results: the correlation between parenting and ANS physiology may be small, and therefore easier to detect in large samples. However, some important moderating effects emerged from Study 3: (1) among experimental studies, exposure to interventions designed to increase positive parenting resulted in higher resting PNS activity in offspring, and (2) the relation between parenting and child resting PNS activity was greater among more at-risk youth. This provides causal evidence for an effect of parenting on child ANS physiology. In addition, it suggests that positive parenting may be more influential on physiological functioning among children who are at elevated risk of psychopathology.

Takeaway 2: ***The activity of the autonomic nervous system predicts health outcomes.***

In Study 1, we also tested longitudinal relations between resting PNS activity and health and mortality. We found that, controlling for concurrent cardiovascular health, higher resting HF-HRV predicted better cardiovascular health 9 years later. We also found that higher HF-HRV was associated with reduced odds of mortality up to 9 years later. Of course, these findings are correlational in nature. However, they are consistent with substantial literature documenting links between parasympathetic activity and both health and longevity (Thayer et al., 2010). In Study 2, we engaged in basic science research, expanding upon the literature on ANS-inflammation links to investigate the relation between cardiac autonomic balance and changes in inflammation during psychosocial challenge. We found that children who exhibited relatively greater parasympathetic and lower sympathetic modulation of the heart were less likely to show increases in inflammation in response to challenge. Given robust evidence implicating

inflammation in the etiology of chronic diseases such as coronary heart disease (Libby, 2002), this evidence suggests ANS activity may be a useful target for intervention.

Together these findings suggest that ANS physiology may be a valuable marker and predictor of both (1) practical outcome measures of health and well-being, and (2) individual differences in psychoneuroimmunology implicated in the manifestation of disease (Miller & Chen, 2010). The robust association between ANS physiology and health may result from individual differences in psychosocial functioning or *wear and tear* on physiology (Thayer et al., 2010). However, considering the role of inflammation in disease manifestation (Libby, 2002), the likely importance of neural-immune communication in this process is hard to deny.

Takeaway 3: ***The autonomic nervous system may partially mediate the link between parenting and health.***

In Study 1, we directly tested the conceptual model that ANS physiology may mediate the association between parenting and health. What we found was a small indirect effect of childhood parental warmth, through resting HF-HRV, on cardiovascular health. Specifically, warmer parenting predicted higher resting HF-HRV, which predicted better cardiovascular health. It is important to keep in mind that mediation is a complex concept. Drawing valid inferences from a mediation analysis requires that several assumptions are met (e.g., single direction of effect, no confounding covariates or unmeasured alternative mediators; Hayes, 2009; Rucker et al., 2011). This means that without experimental, longitudinal designs, that control for all plausible confounders on the mediator (i.e., alternative mediators), careful and critical evaluation of the study limitations is necessary. Experimental designs are difficult, and not always feasible or ethical to conduct in humans; and longitudinal assessments from childhood into old age would require an investment of time and resources that is not always possible. We

therefore must evaluate results within the larger body of evidence and consider how it fits into established or emerging theoretical models.

Through three studies, we found converging evidence that positive parenting is associated with higher resting PNS activity, which is itself associated with better health outcomes and longevity, and a profile of reduced inflammatory response to challenge. Importantly, this dissertation used diverse data and methods, and produced results that are consistent with conceptual models proposed by developmental researchers (Calkins et al., 2013; Propper & Moore, 2006). Considering the small effect size, and vast evidence for mediating roles of psychosocial functioning, health behaviors, as well as other biological systems (e.g., endocrine, immune; Chen et al., 2017; Miller et al., 2011; Repetti et al., 2002; Uchino & Way, 2017), it is highly unlikely that ANS physiology fully mediates the relation between parenting and offspring health. Instead, the ANS likely plays a partial role, in combination or interaction with other biological, behavioral, and cognitive processes, in explaining why children who experience more positive parenting during early life exhibit better health.

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Table 1.1. *Major Variable Descriptives and Sample Characteristics*

Variable	*N*	*M*	*SD*	Range
HF-HRV	1,148	4.92	1.28	0.90–9.66
Heart Rate	1,148	72.84	10.85	44.4–109.8
aHF-HRV	1,148	0.97	1.45	-3.84–5.95
Parental Warmth	1,223	2.92	0.66	0.96–3.96
Number of CV Problems	938	0.79	0.90	0–5
Number of CV Problems (MIDUS 2)	1,227	0.79	0.97	0–6
Self-Evaluated Health[a]	943	2.54	1.02	0–4
Self-Evaluated Health[b] (MIDUS 2)	1,010	7.84	3.08	0–10
Age (years)	1,255	57.32	11.55	35–86
Childhood SES[c]	1,217	5.82	2.86	1–12
	N	Level	Frequency	Percent
Cardiovascular Problems	938	At least one	524	55.9
		None	414	44.1
Cardiovascular Problems (MIDUS 2)	1,244	At least one	647	52.0
		None	597	48.0
Deceased	1,255	Yes	84	6.7
		No	1171	93.3
Sex	1,255	Female	713	56.8
		Male	542	43.2
Race	1,251	Caucasian	985	78.5
		African American	215	17.2
		Native American	17	1.4
		Asian	3	0.2
		Other	31	2.5
Engages in Regular Exercise	1,255	Yes	960	76.5
Current Smoker	1,255	Yes	187	14.9
Medication that Increases HF-HRV	1,255	Yes	186	14.8
Medication that Decreases HF-HRV	1,255	Yes	195	15.5
Menopause Status	1,255	Post	248	19.8

Note. HF-HRV = high-frequency heart rate variability. aHF-HRV = HF-HRV adjusted for heart rate. CV = cardiovascular. [a] Self-evaluated Health during MIDUS 3 ranged from: 0 = *poor* to 4 = *excellent*. [b] Self-Evaluated Health during MIDUS 2 ranged from: 0 = *worst* to 10 = *best*. [c] Childhood SES was indexed through highest parental education level, and ranged from: 1 = no school/some grade school to 12 = doctoral degree.

Table 1.2. *Bivariate Correlations Between Study Variables and Covariates*

	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. HF-HRV	.06*	-.13**	-.13**	.02	-.09*	-.28**	.07*	.18**	.00	.00	.14**	-.01	-.09**	-.04	-.06*	-.06*	.00	-.47**	.98**
2. Parental Warmth	–	.04	.01	.11**	.01	.04	-.11**	.16**	-.01	.04	-.01	.02	-.06*	-.03	.02	.03	.14**	-.07*	.07*
3. CV Problem (MIDUS 3)		–	.93**	-.32**	.05	.28**	-.04	.04	-.08*	-.08*	.00	.31**	.05	-.01	.56**	.57**	-.20**	-.01	-.10**
4. Sum of CV Problems (MIDUS 3)			–	-.35**	.06	.28**	-.03	.04	-.11**	-.12**	.02	.36**	.08*	-.01	.56**	.60**	-.23**	-.04	-.09**
5. Self-Evaluated Health (MIDUS 3)				–	-.08*	.01	.00	-.13**	.11**	.15**	-.15**	-.16**	-.13**	.07*	-.22**	-.25**	.40**	.00	.17
6. Deceased by MIDUS 3					–	.23**	-.05	-.04	-.09*	-.05	.00	.10**	.11**	-.01	.16**	.18**	-.06	.04	-.09**
7. Age						–	-.03	-.16**	-.19**	-.03	-.17**	.23**	.07*	.26**	.29**	.33**	.07*	-.14**	-.21**
8. Sex (female)							–	.08**	.02	-.03	-.04	-.02	.11**	.43**	.05	.05	.04	.17**	.03
9. Race (non-Caucasian)								–	-.19**	-.15**	.18**	-.01	-.05	-.01	.09**	.09**	-.04	.04	.15**
10. Childhood SES									–	.11**	-.11**	-.08**	-.02	-.01	-.11**	-.14**	.07*	.04	.00
11. Exercise										–	-.07**	-.11**	-.07**	-.02	-.10**	-.12**	.02	-.05	.00
12. Smoking											–	-.04	.02	-.06*	-.03	-.02	-.11**	-.03	.13**
13. Medications that Increase HF-HRV												–	.07*	.00	.35**	.39**	-.08	-.26**	.06*
14. Medications that Decrease HF-HRV													–	-.01	.13**	.15**	-.08**	.01	-.08**
15. Menopause Status (post)														–	.03	.03	.02	.03	-.04
16. CV Problem (MIDUS 2)															¬¬–	.94**	-.16**	-.02	-.04
17. Sum of CV Problems (MIDUS 2)																–	-.18**	-.06	-.04
18. Self-Evaluated Health (MIDUS 2)																	–	-.02	.00
19. Heart Rate																		–	-.65**
20. aHF-HRV																			–

Note. HF-HRV = high frequency-heart rate variability. CV = cardiovascular. aHF-HRV = HF-HRV adjusted for heart rate. Correlations calculated using Spearman's rho.
*$p < .05$, **$p < .01$.

Table 1.3. *Multiple Linear Regression Predicting Resting HF-HRV*

Predictor	Step 1			Step 2		
	B	*SE*	β	*B*	*SE*	β
Constant	4.53	.18		6.04	.30	
Parental Warmth	.12	.06	.06*	.14	.06	.07*
Age				-.03	.004	-.27**
Sex (female)				.17	.08	.06*
Race (non-Caucasian)				.34	.10	.11**
Childhood SES				-.01	.01	-.02
Exercise				.04	.09	.01
Smoking				.25	.11	.07*
Medication that Increases HF-HRV				.25	.11	.07*
Medication that Decreases HF-HRV				-.28	.10	-.08**
Menopause Status				.01	.11	.002

Note. HF-HRV = high-frequency heart rate variability.

* $p < .05$, ** $p < .01$.

Table 1.4. *Generalized Linear Model Predicting Total Sum of Cardiovascular Health Problems*

	Step 1			Step 2			Step 3		
Predictor	*B*	*SE*	95% CI	*B*	*SE*	95% CI	*B*	*SE*	95% CI
Constant	0.28	.16		-0.28	.17		0.28	.43	
HF-HRV	-.12**	.03	[-.19, -.06]	-.10**	.03	[-.17, -.04]	-.10**	.04	[-.17, -.03]
CV Problems (MIDUS 2)				.52**	.03	[.45, .59]	.44**	.04	[.36, .52]
Age							.01	.004	[-.002, .01]
Sex (female)							.08	.09	[-.11, .26]
Race (non-Caucasian)							-.27	.14	[-.55, .01]
Childhood SES							-.01	.02	[-.04, .02]
Exercise							.10	.10	[-.09, .29]
Smoking							-.20	.12	[-.45, .04]
Medication that Increases HF-HRV							-.45**	.10	[-.65, -.25]
Medication that Decreases HF-HRV							-.05	.11	[-.27, .16]
Menopause Status							-.02	.12	[-.25, .21]

Note. HF-HRV = high-frequency heart rate variability. CV = cardiovascular. 95% CI = [lower limit, upper limit] of 95% Wald confidence interval of *B*.

* $p < .05$, ** $p < .01$.

Table 1.5. *Binary Logistic Regression Predicting Mortality by the MIDUS 3 assessment*

Predictor	Step 1			Step 2		
	B	*SE*	*OR*	*B*	*SE*	*OR*
Constant	-1.20	.48		-6.36	1.24	
HF-HRV	-.36**	.11	.70	-.23*	.11	.79
Age				.08**	.01	1.08
Sex (female)				-.53	.34	.59
Race (non-Caucasian)				.44	.38	1.55
Childhood SES				-.04	.06	.96
Exercise				-.11	.32	.90
Smoking				.54	.41	1.71
Medication that Increases HF-HRV				.43	.33	1.54
Medication that Decreases HF-HRV				1.06**	.32	2.88
Menopause Status				.05	.43	1.05

Note. HF-HRV = high-frequency heart rate variability. *OR* = odds ratio.

* $p < .05$, ** $p < .01$.

Table 2.1. *Sample Characteristics.*

	M	*SD*	Range
CAB	-0.12	1.48	-3.81–3.43
RSA	6.52	1.20	3.83–9.33
PEP	79.31	11.07	42.67–105.20
HR	86.84	11.39	65.09–113.86
IL6 (pg/ml) Time 1	1.30	0.75	0.26–3.93
IL6 (pg/ml) Time 2	1.46	1.06	0.20–5.57
IL6 Change	0.16	0.77	-1.36–3.45
IL8 (pg/ml) Time 1	7.17	2.00	3.63–14.02
IL8 (pg/ml) Time 2	6.95	1.90	3.19–12.34
IL8 Change	-0.23	0.91	-3.13–1.49
IL10 (pg/ml) Time 1	2.45	1.14	1.13–7.99
IL10 (pg/ml) Time 2	2.40	1.04	0.90–6.10
IL10 Change	-0.05	0.45	-1.89–1.06
TNFa (pg/ml) Time 1	6.18	1.32	3.59–9.84
TNFa (pg/ml) Time 2	6.14	1.46	2.45–11.04
TNFa Change	-0.04	1.04	-3.38–2.28
Age	9.93	0.57	9.12–11.10
BMI	17.89	3.16	12.92–28.90
	Level	*N*	%
Sex	Male	51	53.1
	Female	45	46.9
Parental Education	Less than high school	1	1.0
	High school or GED	11	11.5
	2-year or vocational degree	12	12.5
	4-year degree	30	31.3
	Masters level degree	31	32.2
	Doctoral level degree	11	11.5

Note. CAB = cardiac autonomic balance. RSA = respiratory sinus arrhythmia. PEP = pre-ejection period. HR = heart rate. IL6 = interleukin-6. IL8 = interleukin-8. IL10 = interleukin-10. TNFa = tumor necrosis factor-alpha. BMI = body mass index. Parental education is the highest education level among parents.

Table 2.2. *Bivariate Correlation Matrix.*

	2	3	4	5	6	7	8	9	10	11	12
1. CAB	.71***	.75***	-.62***	-.25*	-.22*	-.30**	-.21†	.00	-.20†	.03	.12
2. RSA	–	.07	-.79***	-.22*	-.18†	-.21*	-.19†	.02	-.22*	.05	-.13
3. PEP		–	-.16	-.13	-.10	-.24*	-.09	.02	-.07	-.01	.19†
4. HR			–	.30**	.13	.11	.14	.02	.23*	-.08	.15
5. IL6 Change				–	.23*	.08	.29**	-.12	.04	.03	.01
6. IL8 Change					–	.42***	.29**	-.03	.23*	-.06	.02
7. IL10 Change						–	.24*	.05	-.01	.12	-.09
8. TNFa Change							–	-.07	.08	.03	-.05
9. Age								–	.00	-.07	.07
10. Sex (female)									–	-.03	.10
11. Parental Education										–	-.11
12. BMI											–

Note. CAB = cardiac autonomic balance. RSA = respiratory sinus arrhythmia. PEP = pre-ejection period. HR = heart rate. IL6 = interleukin-6. IL8 = interleukin-8. IL10 = interleukin-10. TNFa = tumor necrosis factor-alpha. BMI = body mass index. Inflammatory change scores calculated by subtracting Time 1 from Time 2. Parental education is the highest education level among parents, coded as the following: *less than highschool* = 0, *highschool or GED* = 1, *2-year or vocational degree* = 2, *4-year degree* = 3, *master's level degree* = 4, *doctoral level degree* = 5.
†$p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

Table 2.3. *Linear Regression Results Predicting Cytokine Change.*

	Model Dependent Variable											
	IL6 Change			IL8 Change			IL10 Change			TNFa Change		
Predictor	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
CAB	**-.14**[a]	.06	.015	-.11	.07	.09	**-.09**[a]	.03	.005	-.14	.08	.09
Age	-.09	.14	.52	-.02	.17	.90	.07	.08	.38	-.13	.20	.54
Sex	.01	.17	.94	.33	.20	.10	-.03	.10	.76	.18	.23	.44
Parental Education	.02	.07	.79	-.05	.08	.53	.05	.04	.18	.04	.10	.66
BMI	.02	.03	.49	.01	.03	.67	-.01	.02	.45	-.00	.04	.98
Alone Condition	-.31	.20	.12	.06	.24	.80	-.19	.12	.10	-.38	.28	.19
Parent Condition	.16	.19	.41	.20	.23	.40	-.05	.11	.65	-.16	.27	.56

Note. IL6 = interleukin-6. IL8 = interleukin-8. IL10 = interleukin-10. TNFa = tumor necrosis factor-alpha. CAB = cardiac autonomic balance. BMI = body mass index. Parental education is the highest education level among parents, coded as the following: *less than high school* = 0, *high school or GED* = 1, *2-year degree* = 2, *4-year degree* = 3, *master's level degree* = 4, *doctoral level degree* = 5.

[a] estimate *p*-value significant after Benjamini-Hochberg correction for multiple comparisons (i.e., 4 models).

Table 2.4. *Benjamini-Hochberg Correction for 4-model Comparisons*

Cytokine Predicted	*p*	Rank	*q* = (Rank/4)*.05	*significant
IL10	.003	1	.0125	*
IL6	.012	2	.025	*
TNFa	.06	3	.0375	*ns*
IL8	.12	4	.05	*ns*

Note. IL10 = interleukin-10. IL6 = interleukin-6. TNFa = tumor necrosis factor-alpha. IL8 = interleukin-8. *ns* = non-significant.
*Estimate is significant if the obtained *p*-value is smaller than the corresponding *q*-value.

Table 3.1. *Meta-regression of Parenting and Resting PNS Activity.*

K = 72 studies, *n* = 174 effects							I^2 = 42.7%
	B	*SE*	*t*-value	df	*p*	LL	UL
HF-HRV Intercept[a]	-.005	.02	-0.25	62	.81	-.04	.03
Peak-to-Valley Intercept[a]	**-.06**	.03	-2.23	62	.03	-.12	-.01
RMSSD Intercept[a]	-.02	.07	-0.24	62	.81	-.16	.13
Positive Measure = 1	.03	.03	1.06	62	.30	-.02	.08
Parent Absent = 1	.00	.04	0.00	62	.99	-.09	.09
Intervention = 1	**.17**	.07	2.64	62	.01	.04	.30
Longitudinal = 1	-.02	.03	-0.71	62	.48	-.07	.03
Clinical Sample = 1	**.09**	.04	2.03	62	.047	.001	.18
Mean Age	-.002	.004	-0.42	62	.68	-.01	.01
Percent Female	-.05	.26	-0.19	62	.85	-.58	.47

Note. PNS = parasympathetic nervous system. HF-HRV = high-frequency heart rate variability. RMSSD = root mean squared successive differences. LL = 95% confidence interval lower limit. UL = 95% confidence interval upper limit. [a]Intercept estimates reflect the pooled effect size estimate for each biomarker when all moderators are set to zero. Mean age and percent female are mean centered. Bolded coefficients are significant at the $p < .05$ alpha level.

Table 3.2. *Meta-regression of Parenting and PNS reactivity.*

K = 50 studies, *n* = 137 effects							I^2 = 34.4%
	B	*SE*	t-value	df	*p*	LL	UL
HF-HRV Intercept[a]	.03	.03	0.99	39	.33	-.03	.09
Peak-to-Valley Intercept[a]	-.001	.04	-0.03	39	.98	-.09	.09
RMSSD Intercept[a]	-.03	.05	-0.51	39	.61	-.13	.07
Positive Measure = 1	-.02	.03	-0.92	39	.37	-.08	.03
Parent Absent = 1	-.03	.03	-0.83	39	.41	-.09	.04
Intervention = 1	.01	.14	0.08	39	.94	-.26	.28
Longitudinal = 1	-.01	.03	-0.41	39	.69	-.08	.05
Residualized = 1	-.00	.04	-0.00	39	.99	-.08	.08
Clinical Sample = 1	-.04	.07	-0.51	39	.62	-.18	.11
Mean Age	-.00	.004	0.11	39	.92	-.01	.01
Percent Female	.02	.24	0.10	39	.92	-.45	.50

Note. PNS = parasympathetic nervous system. HF-HRV = high-frequency heart rate variability. RMSSD = root mean squared successive differences. LL = 95% confidence interval lower limit. UL = 95% confidence interval upper limit. Mean age and percent female are mean centered. [a]Intercept estimates reflect the pooled effect size estimate for each biomarker when all moderators are set to zero. Bolded coefficients are significant at the $p <$ .05 alpha level.

Table 3.3. *Meta-regression of Parenting and Resting SNS Activity.*

K = 23 studies, *n* = 47 effects							I^2 = 51.3%
	B	*SE*	t-value	df[b]	*p*	LL	UL
SCL Intercept[a]	-.05	.05	-0.83	4.8	.44	-.18	.09
PEP Intercept[a]	.02	.10	0.19	4.5	.86	-.24	.27
sAA Intercept[a]	.04	.06	0.65	2.8	.56	-.15	.22
Positive Measure = 1	-.01	.05	-0.27	15.1	.79	-.13	.10
Parent Absent = 1	.05	.06	0.73	7.2	.49	-.11	.20
Longitudinal = 1	-.13	.06	-2.01	3.6	.12	-.31	.06
Mean Age	-.01	.01	-0.63	7.9	.55	-.03	.02
Percent Female	.59	.50	1.19	5.9	.28	-.63	1.81

Note. SCL = skin conductance level. PEP = pre-ejection period (reverse coded). sAA = salivary alpha amylase. LL = 95% confidence interval lower limit. UL = 95% confidence interval upper limit. Mean age and percent female are mean centered. [a]Intercept estimates reflect the pooled effect size estimate for each biomarker when all moderators are set to zero. [b]Degrees of freedom are calculated using small sample bias correction. Bolded coefficients are significant at the $p < .05$ alpha level.

Table 3.4. *Meta-regression of Parenting and SNS Reactivity.*

K = 24 studies, *n* = 57 effects							I^2 = 35.4%
	B	*SE*	t	df[b]	*p*	LL	UL
SCL Intercept[a]	.05	.06	0.94	9.3	.38	-.07	.18
PEP Intercept[a]	.003	.04	0.07	6.5	.95	-.10	.10
Positive Measure = 1	-.00	.04	-0.02	16.1	.99	-.09	.09
Parent Absent = 1	-.02	.04	-0.39	14.6	.70	-.11	.08
Clinical Sample = 1	-.16	.07	-2.20	2.6	.13	-.42	.10
Mean Age	**-.01**	.004	-3.05	5.5	.03	-.03	-.002
Percent Female	-.59	.36	-1.63	6.3	.15	-1.46	.28

Note. SCL = skin conductance level. PEP = pre-ejection period (reverse coded). LL = 95% confidence interval lower limit. UL = 95% confidence interval upper limit. Mean age and percent female are mean centered. [a]Intercept estimates reflect the pooled effect size estimate for each biomarker when all moderators are set to zero. [b]Degrees of freedom were calculated using small sample bias correction. Bolded coefficients are significant at the $p < .05$ alpha level.

Table 3.5. *Full Meta-regression: Parenting and Resting PNS Activity.*

K = 72 studies, *n* = 174 effects							I^2 = 38.1%
	B	*SE*	*t*-value	df	*p*-value	LL	UL
HF-HRV Intercept[a]	-.02	.02	-1.09	62	.28	-.07	.02
Peak-to-Valley Intercept[a]	**-.08**	.03	-2.83	62	.01	-.14	-.02
RMSSD Intercept[a]	-.02	.08	-0.26	62	.79	-.18	.14
Intervention = 1	**.20**	.06	3.24	62	.002	.08	.33
Clinical Sample = 1	**.09**	.04	2.10	62	.04	.004	.17
Child-report = 1	**.08**	.03	3.27	62	.002	.03	.13
Observed Measure = 1	.05	.03	1.57	62	.12	-.01	.11
Composite Measure = 1	.04	.04	1.14	62	.26	-.03	.12
Attachment Measure = 1	**-.10**	.03	-3.56	62	.001	-.16	-.04
Relationship Quality Measure = 1	.00	.02	0.11	62	.91	-.03	.03

Note. PNS = parasympathetic nervous system. HF-HRV = high-frequency heart rate variability. RMSSD = root mean squared successive differences. LL = 95% confidence interval lower limit. UL = 95% confidence interval upper limit. Attachment and relationship quality measure estimates are in comparison to parenting measures. Child-report and observed measure estimates are in comparison to parent-report measures. [a]Intercept estimates reflect the pooled effect size estimate for each biomarker when all moderators are set to zero. Bolded coefficients are significant at the $p < .05$ alpha level.

FIGURES

Figure 1.1. Scatterplot showing the relation between childhood parental warmth and resting high-frequency heart rate variability (HF-HRV) in midlife.

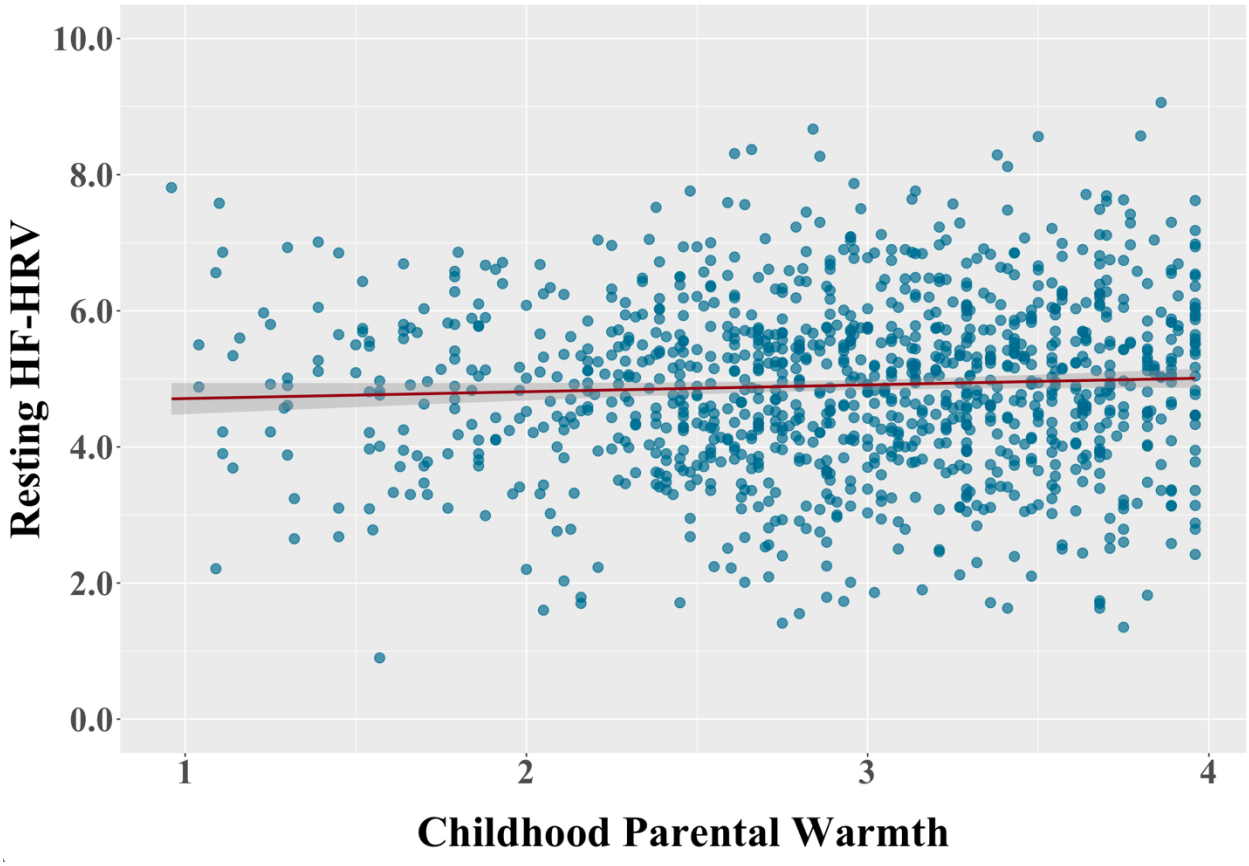


Figure 1.2. Scatterplot showing the relation between high-frequency heart rate variability (HF-HRV) and number of cardiovascular health problems.

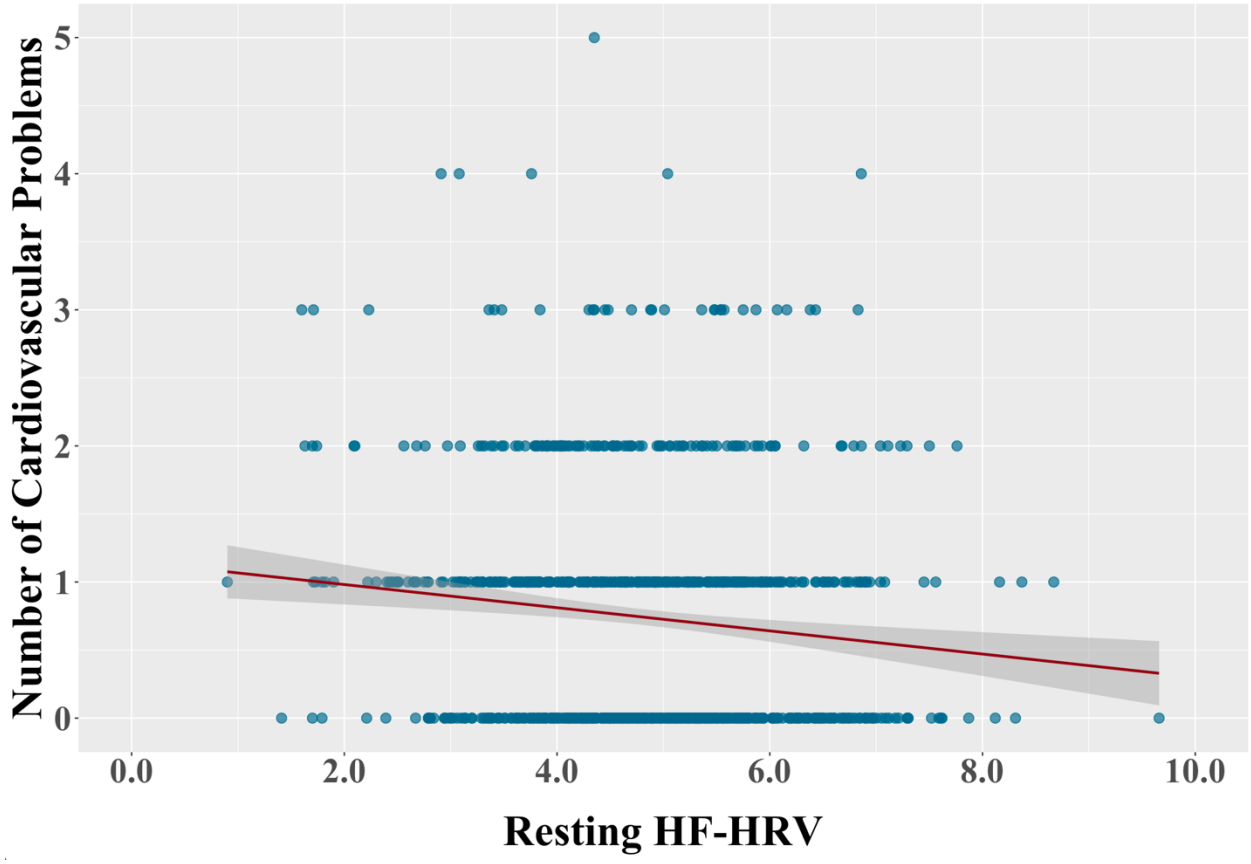
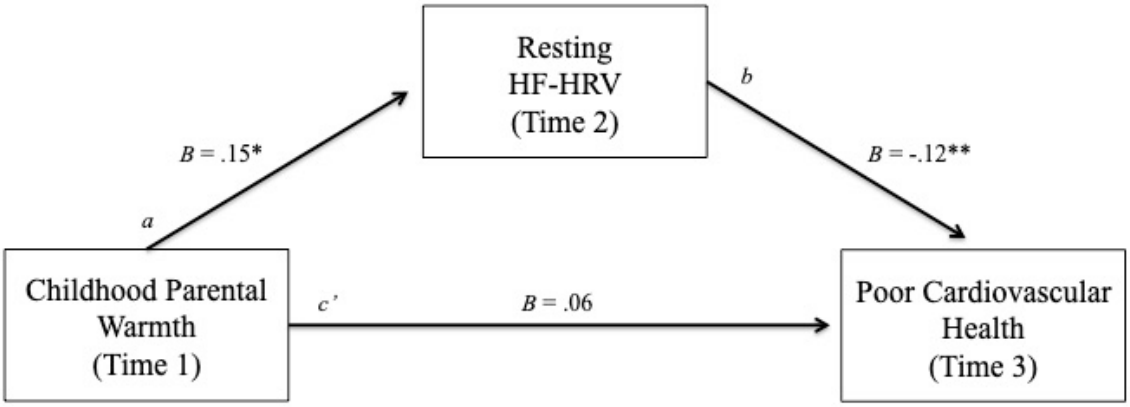


Figure 1.3. Model of resting high-frequency heart rate variability (HF-HRV) as a mediator between parental warmth and presence of a cardiovascular health disorder.

*$p < .05$. **$p < .01$.



Total effect (*c*): *B* = .04, *SE* = .08, *p* = .58
Indirect effect (*a***b*): *B* = -.02, *SE* = .01, 95% Bootstrapped CI [-.043, -.003]

Figure 2.1. Bar plot showing serum interleukin-6 (IL6) levels at Time 1 and Time 2, grouped by experimental condition. Error bars represent +/- 1 standard error.

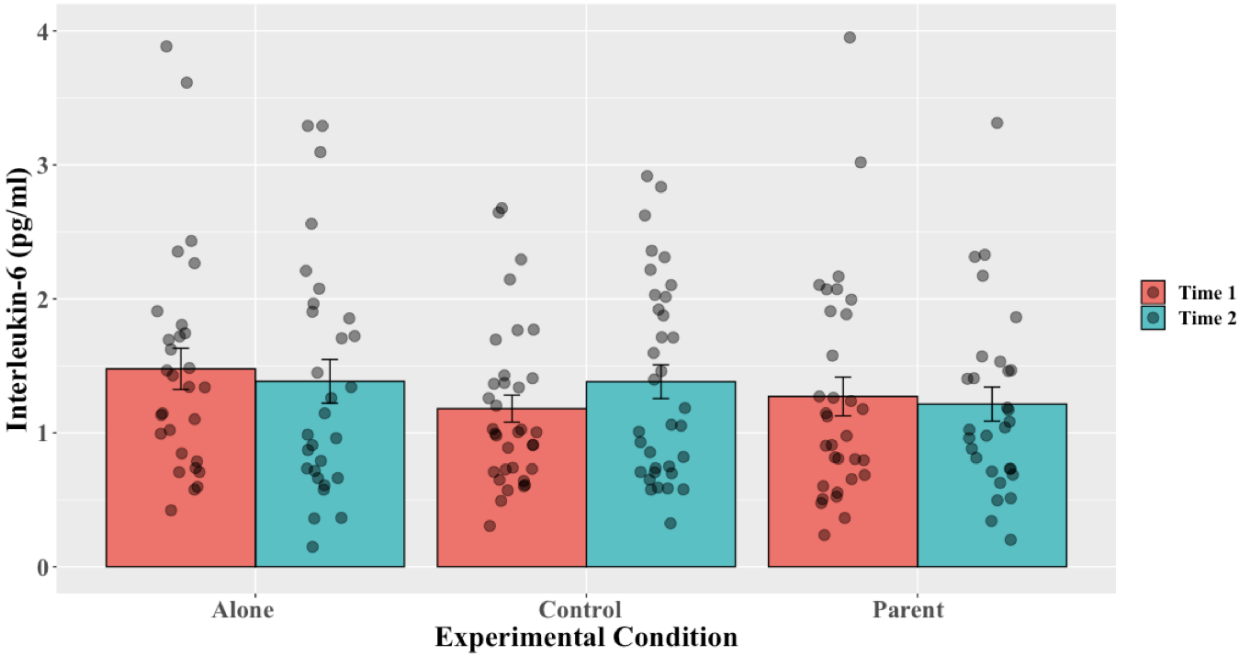


Figure 2.2. Scatterplots of the relations between cardiac autonomic balance (CAB) and (A) interleukin-6 (IL6) change, (B) interleukin-8 (IL8) change, (C) interleukin-10 (IL10) change, and (D) tumor necrosis factor-alpha (TNFa) change. Change scores were calculated such that higher scores represent greater increases in cytokine levels from Time 1 to Time 2. Shaded area represents the 95% confidence interval.

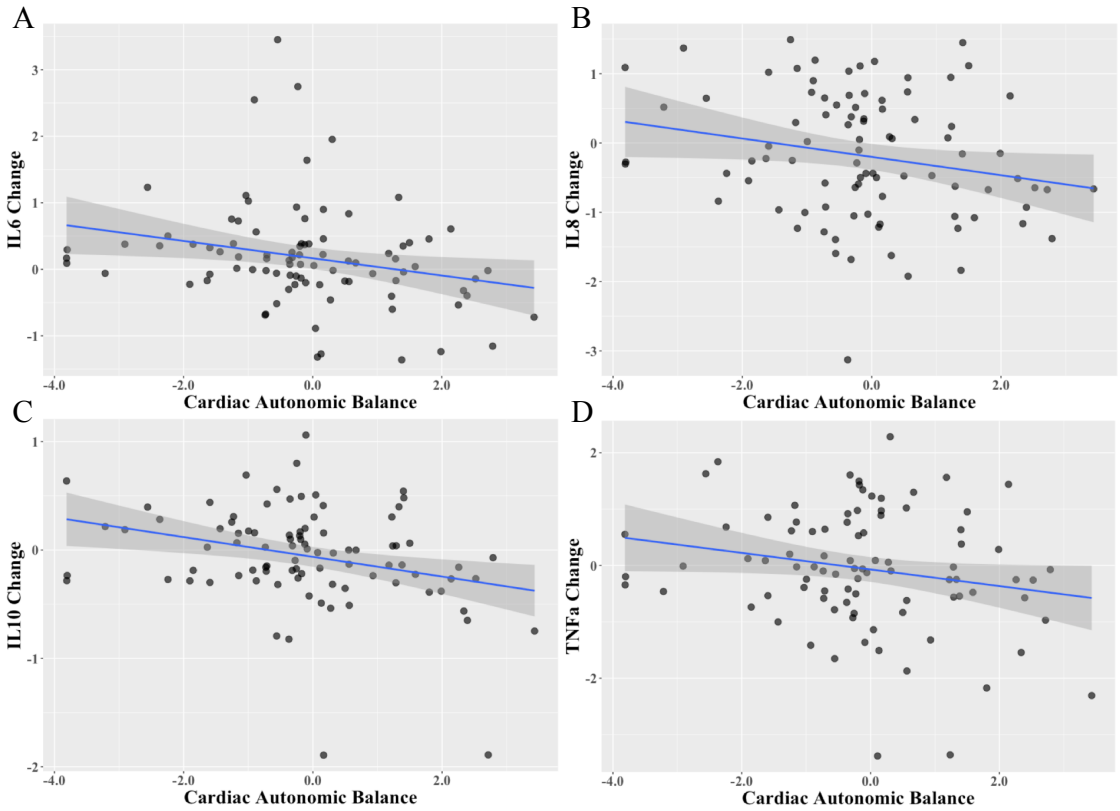


Figure 3.1. PRISMA flow chart.

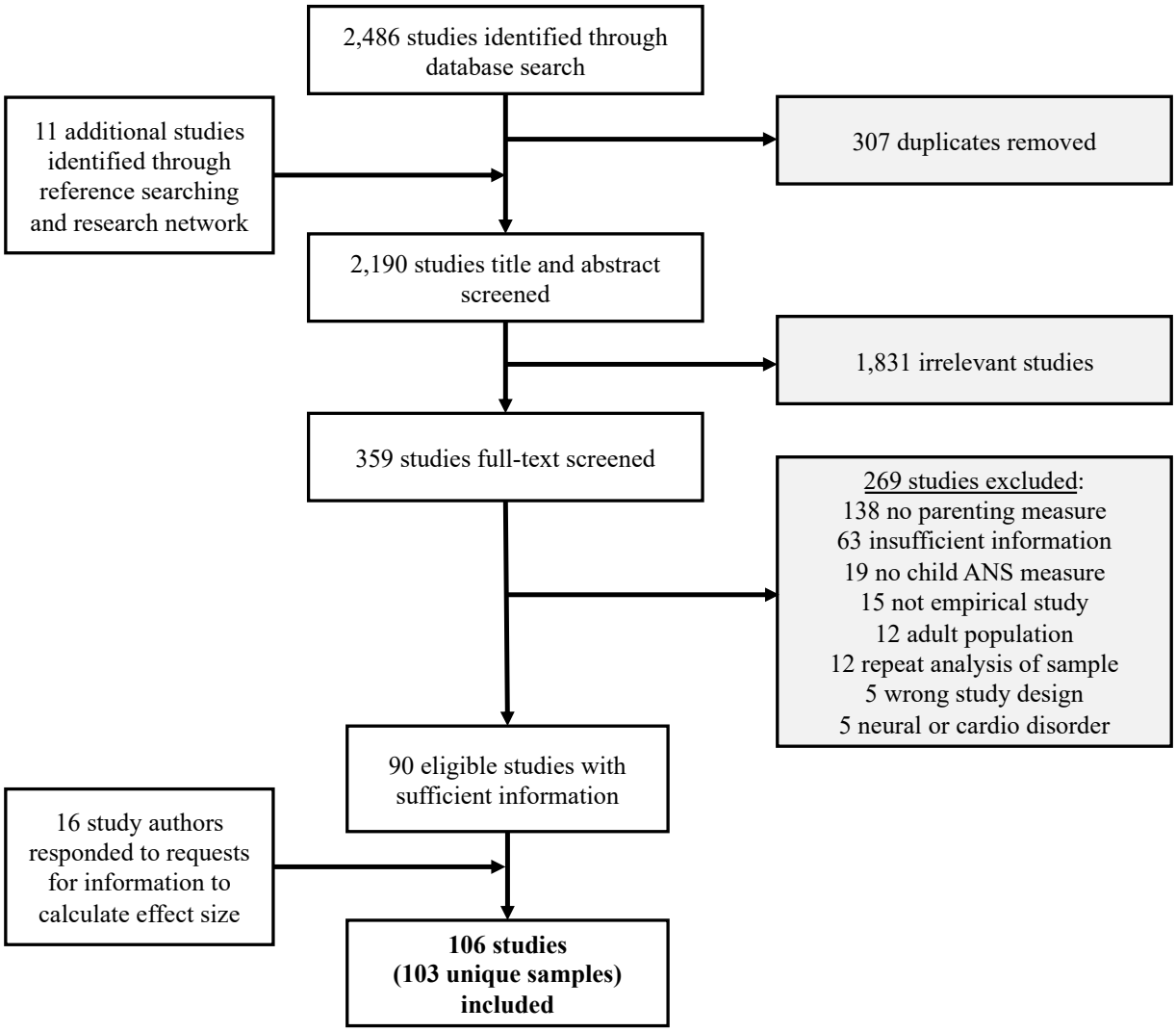


Figure 3.2. Funnel plots for visual inspection of publication bias in the included studies on parenting and (A) resting parasympathetic nervous system (PNS) activity, (B) PNS reactivity, (C) resting sympathetic nervous system (SNS) activity, and (D) SNS reactivity. White region represents 95% CI. The dashed vertical line represents the average effect size.

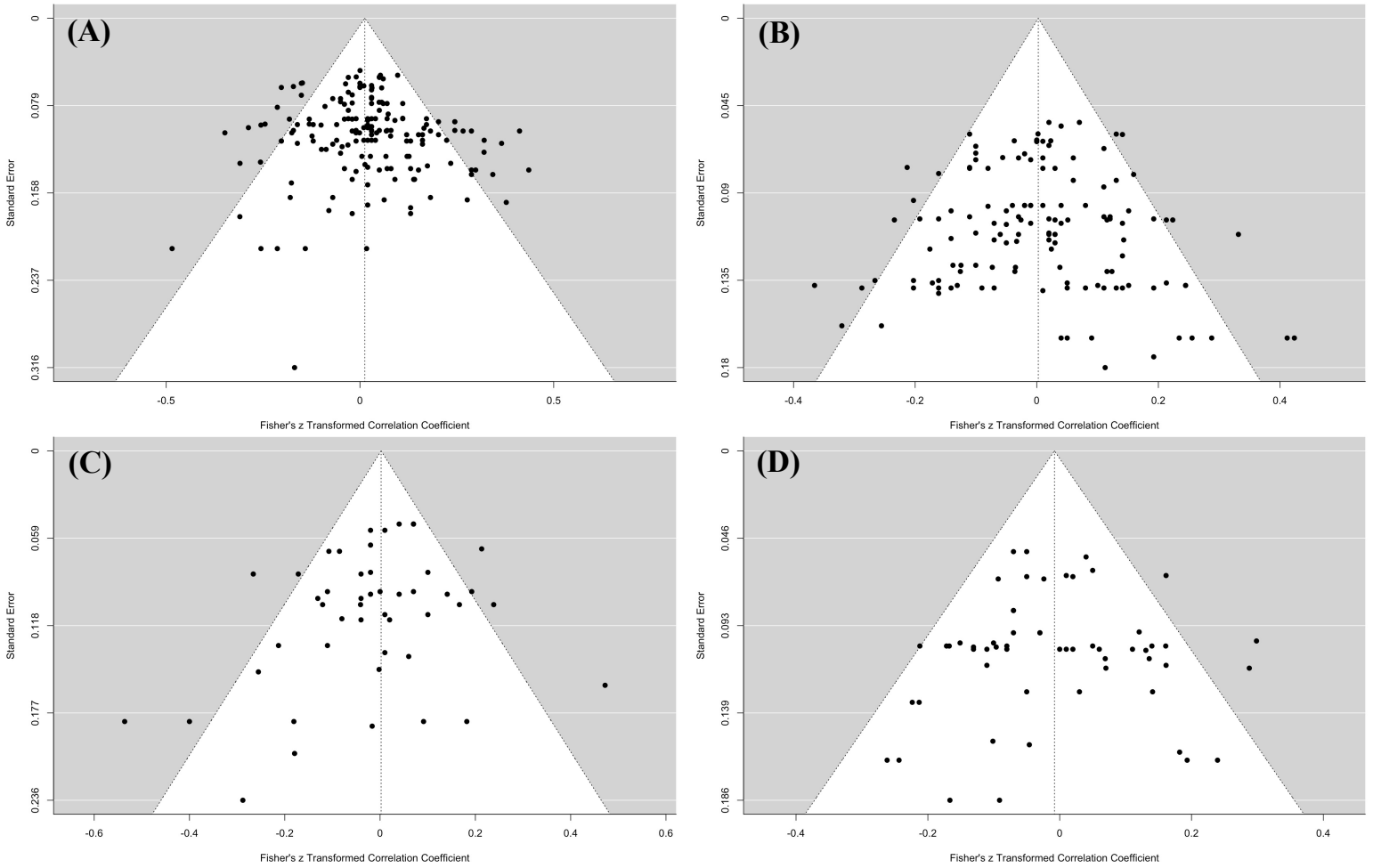


Figure 3.3. Effect sizes (Fisher's Z) for relation between parenting and resting PNS activity in (A) intervention studies, and (B) studies with clinical samples. HF-HRV = high frequency heart rate variability. Size of squares reflects relative weight of effect. Error bars represent 95% CI. Diamond and dashed line represent weighted mean effect size. * Effect sizes from negative valanced measures were reverse scored.

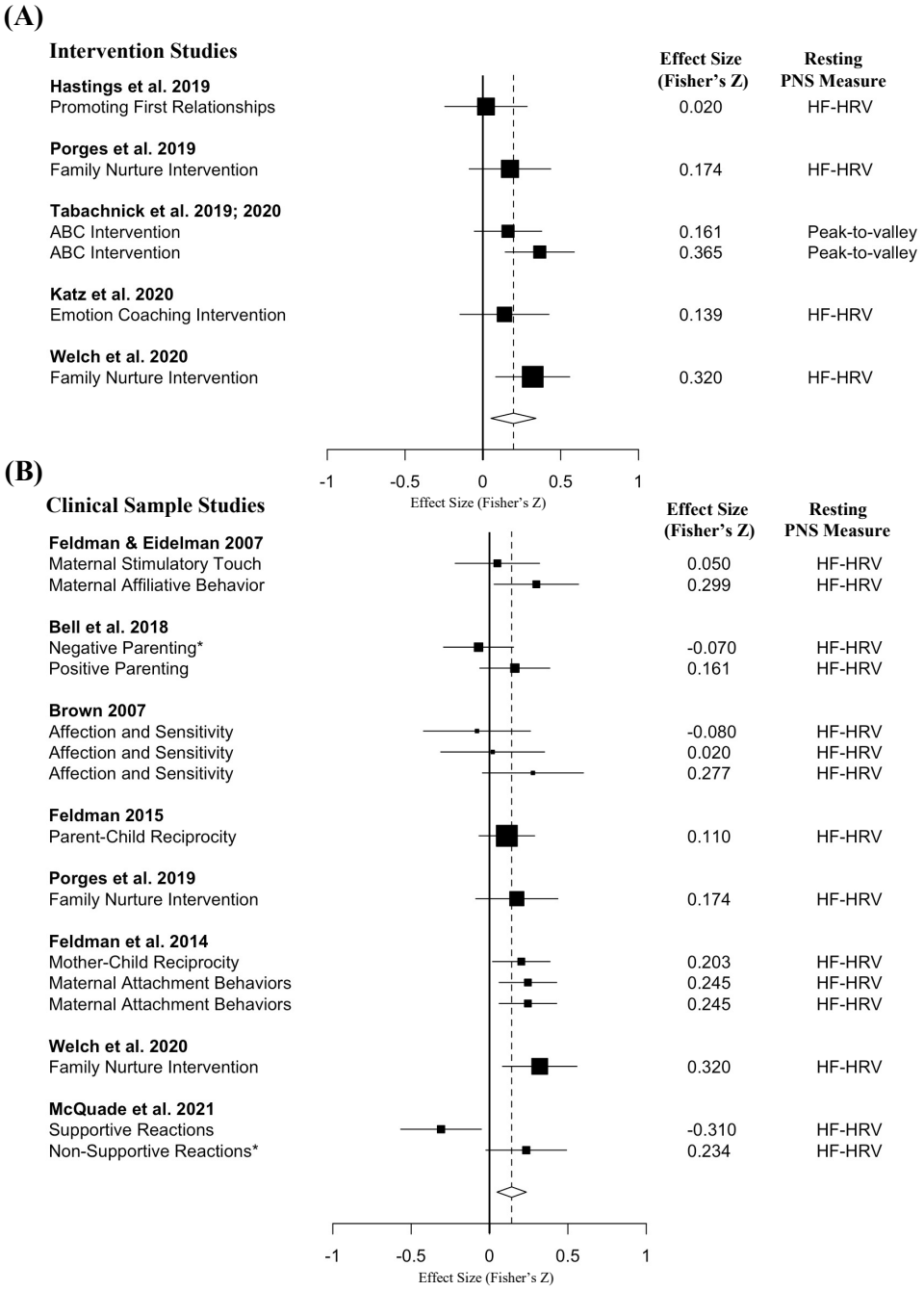


Figure 3.4. Moderating effect of sample mean age on relation between parenting and sympathetic nervous system (SNS) reactivity. Negative effect sizes reflect negative relation between positive parenting and increases in SNS (i.e., reactivity). Size of data points reflects relative weight given to each effect size in analysis. Shaded area represents 95% CI.

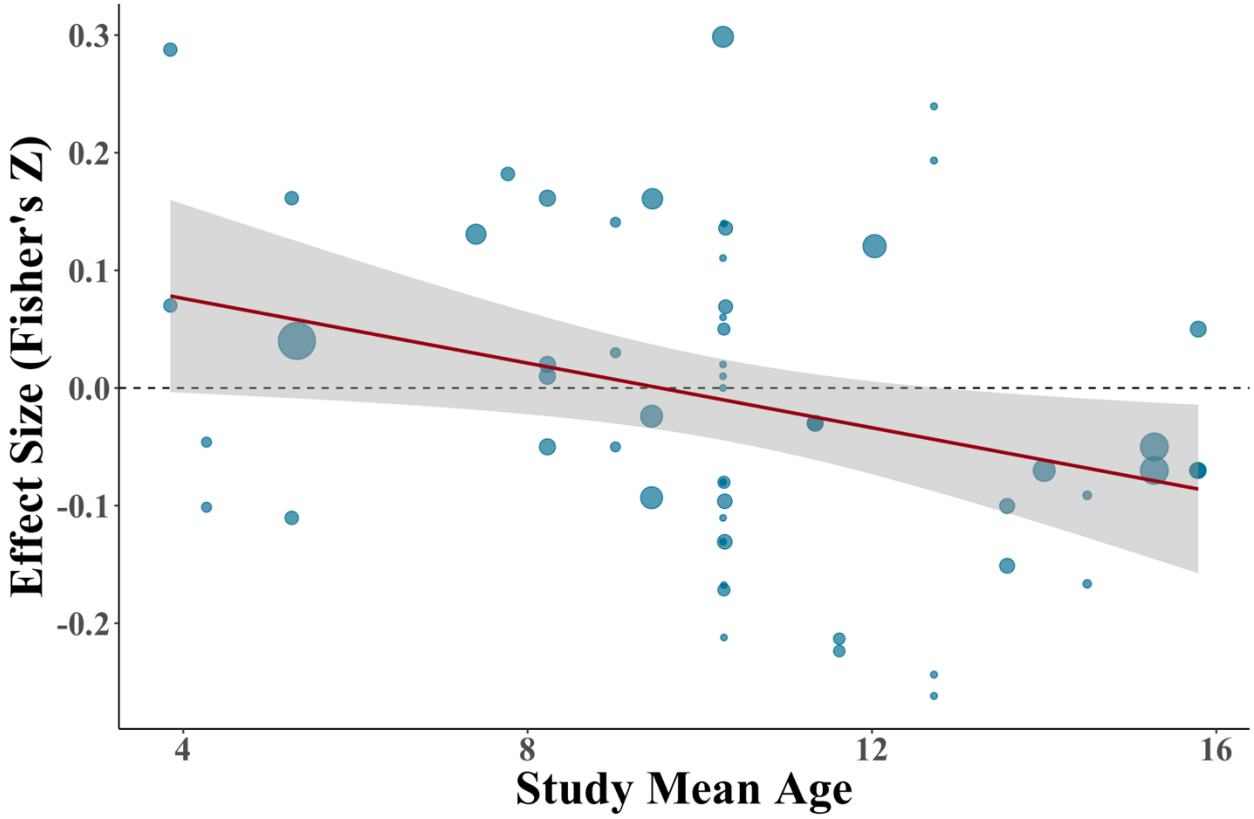


Figure 3.5. Moderating effects of (A) attachment measure and (B) child-reported measure on the relation between parenting and resting parasympathetic nervous system (PNS) activity. Diamonds represent weighted mean effect size in each subgroup. Size of data points represent relative weight used in calculating mean effect size. Error bars represent 95% CI. * $p < .05$. ** $p < .01$.

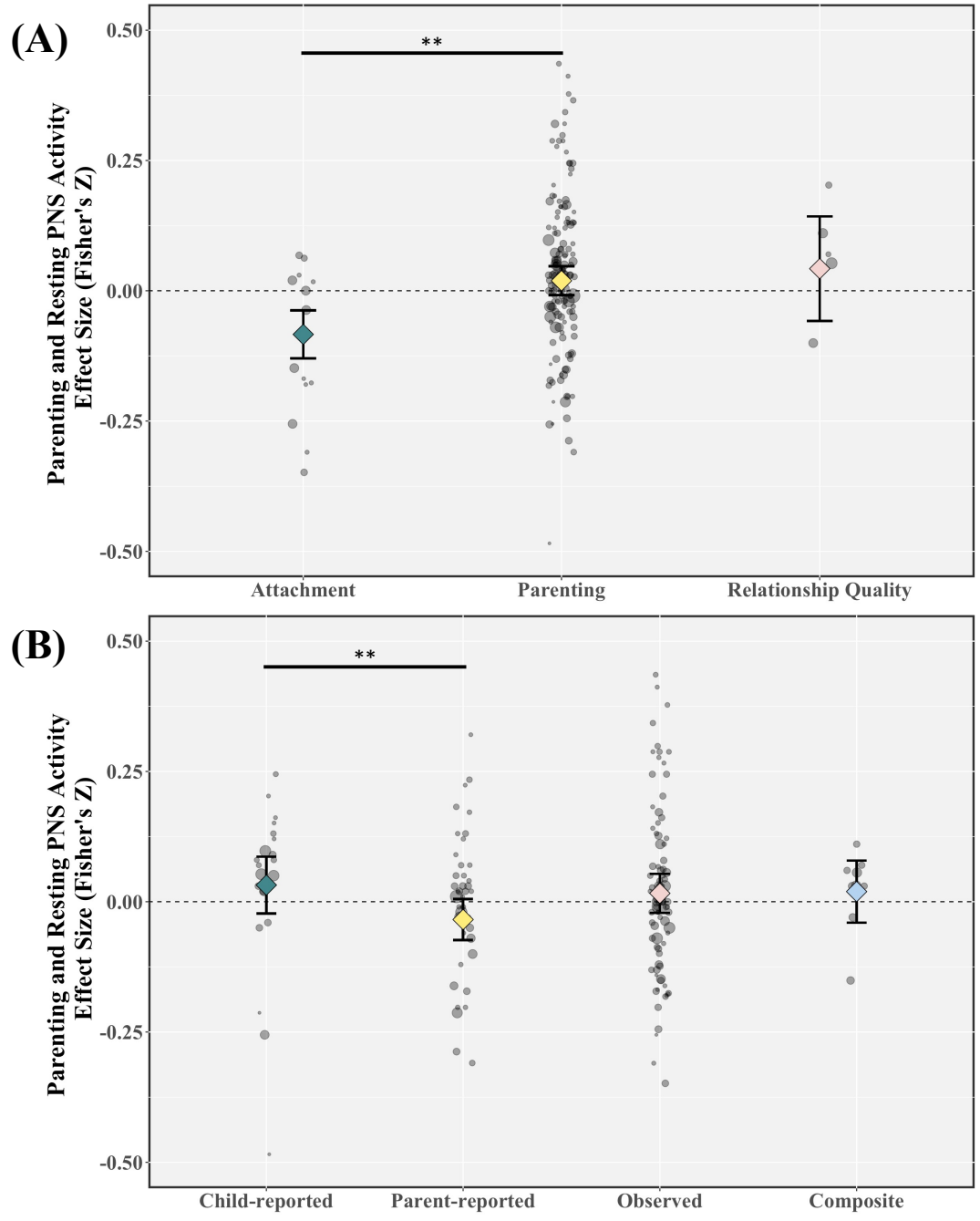
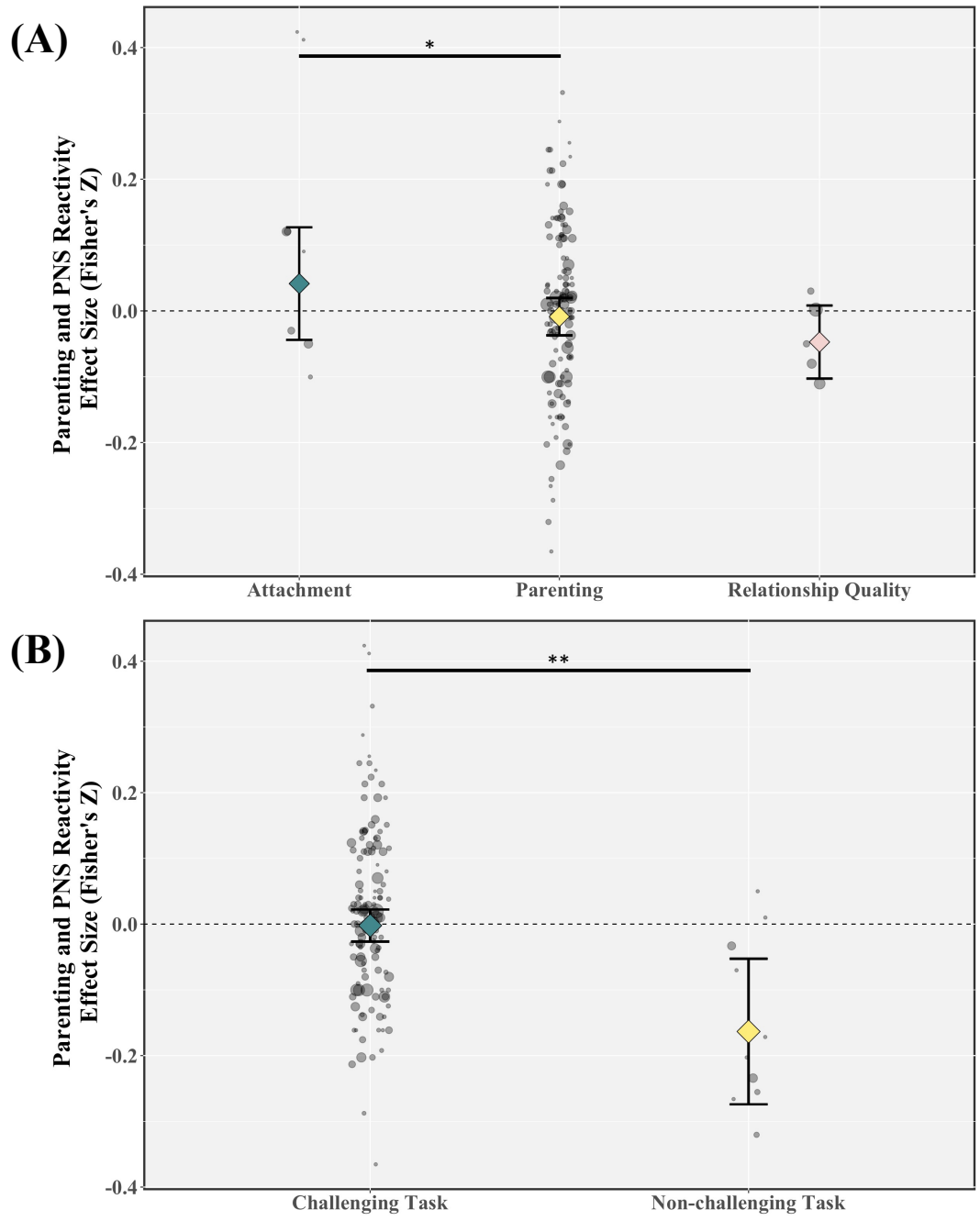


Figure 3.6. Moderating effects of (A) attachment measure and (B) non-challenging task on the relation between parenting and parasympathetic nervous system (PNS) reactivity. Diamonds represent weighted mean effect size in each subgroup. Size of data points represent relative weight used in calculating mean effect size. Error bars represent 95% CI. * $p < .05$. ** $p < .01$.



Appendix

Effect Size Coding Scheme for Study 3:

Baseline ANS measures: positive coefficients reflect positive relation between positive parenting and higher baseline levels of ANS measure (i.e., a significant positive pooled effect suggests that more positive parenting is associated with higher baseline levels).

Reactivity ANS measures: positive coefficients reflect positive relation between positive parenting and reactivity.

Note: in addition to this coding scheme, all PEP effect sizes are reverse coded, and then all SNS reactivity measures are reverse coded, as described in text.

Parenting Valence	ANS measure value type	Adjustments required
Positive	Baseline	none
Negative	Baseline	reverse
Positive	Change neg. (Baseline – Task)	none
Negative	Change neg. (Baseline – Task)	reverse
Positive	Change pos. (Task – Baseline)	reverse
Negative	Change pos. (Task – Baseline)	none
Positive	Residualized change score	reverse
Negative	Residualized change score	none
Positive	Reverse residualized change score	none
Negative	Reverse residualized change score	reverse