Childhood adversity and vagal regulation: A systematic review and meta-analysis

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\textbf{A B S T R A C T}

Childhood adversity (CA) is associated with increased risk for physical and mental health problems, with alterations in vagal regulation (an aspect of autonomic functioning indexed by vagally-mediated heart rate variability [vmHRV]) implicated as a mechanism. Three-level meta-analyses were conducted to synthesize research on the relationship between CA and 1) baseline vagal activity, and 2) vagal reactivity to challenges including stress tests, emotion-eliciting tasks and cognitive tasks. No significant overall association was found between CA and vagal activity ($r = -0.015; p = .11$) or vagal reactivity ($r = -0.017; p = .13$). However, analyses controlling for moderator interrelatedness revealed an association between CA and lower baseline vagal activity in samples including participants diagnosed with a psychiatric disorder, and for direct adversities such as maltreatment. For vagal reactivity, CA was associated with lower reactivity if the adversity was experienced less recently, and for studies operationalizing reactivity using task mean levels of vmHRV. These findings indicate that small alterations in vagal functioning occur for specific CA subtypes and subgroups of individuals.

1. Introduction

Childhood adversity, including exposure to abuse, neglect, poverty, and neighborhood violence, is among the most robust risk factors for the development of chronic health problems and psychopathology (Carr et al., 2013; Hughes et al., 2017; McLaughlin, 2016; Nemeroff, 2016; Oh et al., 2018). Extensive evidence suggests that exposure to childhood adversity is associated with alterations in the functioning of the autonomic nervous system (ANS; Leitzke et al., 2015; Oosterman et al., 2010; Propper and Holochwost, 2013; Voellmin et al., 2015), which may represent a key mechanism implicated in the pathway through which adversity increases risk for pathology (Koss and Gunnar, 2018; Young-Southward et al., 2020). The present study sought to determine whether childhood adversity relates to vagal regulation, a specific aspect of ANS functioning indexed by vagally-mediated heart rate variability (vmHRV). Two meta-analyses were performed, testing associations between childhood adversity and 1) baseline vagal activity and 2) task-induced vagal reactivity to challenges. As not all individuals who have experienced adversity develop negative health outcomes, we also investigated the role of potential moderators in this association. In addressing these questions, the present work aims to advance the understanding of how and under which circumstances childhood adversity leads to psychopathology. This knowledge may further inform prevention and treatment approaches. After describing conceptual frameworks for the study of vagal regulation in the context of childhood adversity and the available evidence, we discuss how adversity and study characteristics could moderate this association.

1.1. Vagal regulation

Besides regulating several involuntary physiological processes including digestion, respiration, body temperature, and sexual arousal,
the ANS is critically involved in cardiovascular functioning (Waxenbaum et al., 2019). Polyvagal Theory (Porges, 2003, 2007) describes how a specific aspect of ANS functioning—vagal regulation—promotes adaptive functioning in the context of changing environmental demands. Vagal regulation refers to parasympathetic influences on the heart via the tenth cranial nerve, the vagus nerve (Porges, 1995). At rest, the parasympathetic nervous system (PNS) exerts constant inhibitory control over the heart, reducing heart rate (Porges, 1995, 2007). This inhibition varies cyclically at a frequency corresponding to respiration, resulting in a pattern of heart rate decreases (during inhalation) and increases (during exhalation) which is known as respiratory sinus arrhythmia (RSA; Berntson et al., 1997). Under challenging conditions, vagal withdrawal enables increases in heart rate and arousal. In contrast, vagal augmentation (i.e., PNS activation) generally leads to a reduction in heart rate and arousal (Porges, 1995, 2007). Measures of resting vagal activity thus reflect an organism’s ability to maintain homeostasis and a general level of responsiveness during steady states, whereas measures of vagal reactivity represent the organism’s ability to flexibly engage with and disengage from the environment to meet changing situational demands (Appelhans and Luecken, 2006; Hamilton and Alloy, 2016). Generally speaking, higher levels of resting vagal activity and a moderate vagal withdrawal to challenge have been seen as reflecting adaptive and effective regulatory processes (Gentzler et al., 2009; Ottaviani et al., 2019).

1.2. Theoretical framework and evidence on the association between childhood adversity and vagal regulation

Childhood adversity has been defined as “experiences that are likely to require significant adaptation by an average child and that represent a deviation from the expectable environment” (McLaughlin, 2016, p. 363). Theories have been brought forward suggesting that prolonged exposure to adversity during sensitive developmental periods can modify the maturation of brain regions involved in stress regulation (Danese and McEwen, 2012; Gabard-Durnam and McLaughlin, 2019; Heim et al., 2019; Koenig, 2020; Lupien et al., 2009). In individuals exposed to childhood adversity, structural and functional alterations pertaining but not limited to the orbitofrontal cortex, ventromedial prefrontal cortex and the amygdala have repeatedly been identified (Kraaijenvanger et al., 2020; McCrory et al., 2010; Saarinen et al., 2021; Teicher et al., 2016). These structures are involved in the central autonomic network (CAN; Barrochet, 1993) that further comprises the anterior cingulate, the anterior and posterior insula, and the hypothalamus (among others; Thayer and Lane, 2000). As described in the Neurovisceral Integration Model (NVIM; R. Smith et al., 2017; Thayer et al., 2009; Thayer and Lane, 2000), the CAN integrates autonomic, neuroendocrine, and behavioral responses with emotion, attention, and cognition to support self-regulation and goal-directed behavior. The primary output of the CAN is mediated through sympathetic and parasympathetic nerves innervating the heart via the stellate ganglia and the vagus nerve, respectively (Thayer and Lane, 2000). The interplay of their inputs to the sinoatrial node (known as the “pacemaker” of the heart) gives rise to heart rate variability (HRV; Saul, 1990). Therefore, vmHRV is seen as an indicator of central-peripheral neural feedback as well as central and autonomic nervous system integration (Thayer and Lane, 2000).

As childhood adversity has been linked to alterations in structure and functioning of brain regions involved in vagal regulation (Teicher and Samson, 2016), it is likely that individuals with a history of adversity demonstrate alterations in vmHRV as a downstream marker of alterations in central functioning. In line with Polyvagal theory (Porges, 2003, 2007) and the NVIM (Thayer and Lane, 2000), atypical vagal regulation observed in the context of childhood adversity would reflect difficulties in self-regulation during social, emotional and cognitive challenges that impair adaptive functioning. While a number of studies show that experiences of childhood adversity are associated with alterations in baseline vagal activity and vagal reactivity to challenge, findings are mixed, revealing lower or higher (re-)activity or no significant association with childhood adversity (Busso et al., 2017; Dale et al., 2018; De Witte et al., 2016; Giuliano et al., 2018a; Hagan et al., 2020). Until now, only two meta-analyses (Lavi et al., 2019; Sigrist et al., 2021) have computed an overall effect between vagal functioning and childhood adversity, with both focusing on maltreatment. Based on 32 studies, Sigrist and colleagues (2021) concluded that child maltreatment was not associated with resting vagal activity per se, but that the relationship significantly varied as a function of both participants’ age and the presence of psychopathology. Within the framework of a larger meta-analysis, Lavi and colleagues (2019) found no association between maltreatment and childhood adversity based on five studies.

Given considerable heterogeneity in how childhood adversity has been defined and operationalized, and differences in study populations, inconsistent results on the association between childhood adversity and vagal regulation are not surprising. Further, childhood adversity has been shown to have little predictive specificity across psychiatric disorders (Kessler et al., 2010), highlighting the need to study moderators that influence pathways from adversity to health outcomes. In the following paragraphs, we discuss the role of adversity characteristics, individual characteristics, and methodological aspects in moderating the association between childhood adversity and vagal regulation.

1.3. Childhood adversity characteristics as potential moderators

1.3.1. Dimension of adversity

As childhood adversity is a rather broad construct, the nature of adversity may moderate the magnitude or direction of the association between childhood adversity and vagal regulation. As proposed in the dimensional model of adversity (Sheridan and McLaughlin, 2014), deprivation and threat may portray two orthogonal dimensions of early adverse experiences with distinct effects on the brain and biological systems. Deprivation reflects a lack of environmental inputs and a failure to meet a child’s needs (Hildyard and Wolfe, 2002), as is the case when children are emotionally and/or physically neglected by parents or raised in low-quality institutions. In contrast, threat encompasses exposures to interpersonal violence that involve harm to the child, such as physical and sexual abuse (Sheridan and McLaughlin, 2014). Differential associations for threat and deprivation have been shown for multiple outcomes, including functional threat reactivity (Hein et al., 2020; Puetz et al., 2020; Young et al., 2022), brain structure (Banihshemi et al., 2021; Colich et al., 2020), fear learning (Machlin et al., 2019), emotion regulation (Lambert et al., 2017; Milojevich et al., 2019), cognitive ability (Lambert et al., 2017; Machlin et al., 2019; Usacheva et al., 2022), as well as physical and mental health (A. B. Miller et al., 2017; Usacheva et al., 2022). As confirmed by studies on cortisol stress reactivity (Busso et al., 2017; Peckins et al., 2020), it is predicted in the dimensional model of adversity (Sheridan and McLaughlin, 2014) that early exposure to threat should result in disrupted physiological reactivity to novel stressors as it influences cortico-limbic circuits involved in fear learning and salience processing. In contrast, exposure to deprivation is thought unlikely to result in disrupted physiological reactivity when the co-occurrence of threat exposure is taken into account (Busso et al., 2017).

1.3.2. Proximity of adversity

The strength of the relation between childhood adversity and vagal regulation may also be influenced by the proximity of adversity. Adversities can exert an effect on an individual either directly (e.g., abuse or neglect) or indirectly through the living environment (e.g., poverty, neighborhood violence, or witnessing inter-parental aggression; Hughes et al., 2017). In contrast to the effects of direct adversities, the impact of an adverse environment can be buffered by parents, for example through sensitive and responsive caregiving (Chen et al., 2011; Depasquale and...
Gunnar, 2020; G. E. Miller et al., 2011). It is therefore possible that direct adversities exert more pronounced effects on stress physiology as compared to indirect adversities.

1.3.3. Severity of adversity

Another potential moderator is the severity of childhood adversity, which is a significant predictor of negative health outcomes (Evans et al., 2013; Hambrick et al., 2019; Lee et al., 2018; Muzik et al., 2017). Importantly, childhood adversities associated with maladaptive family functioning including family violence, physical abuse and neglect are associated with higher risk and persistence of psychopathology as compared to other adversities including parental death and family economic adversity (Kessler et al., 2010; McLaughlin et al., 2010). With regards to stress reactivity, extreme forms of adversity such as maltreatment have been more strongly associated with alterations in endocrine stress responses as compared to ‘milder’ forms including parental conflict or witnessing violence (Bunea et al., 2017). It is therefore possible that alterations in vagal regulation only emerge when adversity exceeds a certain threshold of severity.

1.3.4. Timing of exposure to adversity

Given sensitive periods during which brain regions undergoing maturation are particularly vulnerable to stressors (Boyce et al., 2021; Gabard-Durnam and McLaughlin, 2019; Gee, 2020; Lupien et al., 2009), the timing of exposure may be important to examine. Potential sensitive periods have been identified for brain regions involved in vagal regulation, including the amygdala and prefrontal cortex (Koenig, 2020; Teicher and Samson, 2016). Although there are no consistent cut-offs for these sensitive periods across studies, broadly speaking, the amygdala appears particularly sensitive to adversity during early childhood, whereas the prefrontal cortex is likely rather sensitive during adolescence (Andersen and Teicher, 2008; Gard et al., 2020; Humphreys et al., 2019; Pechtel et al., 2014).

The Bucharest Early Intervention Project has provided evidence on a potential sensitive period of socio-emotional development during the first two years of life: Youth from orphanages with very poor quality care improved more in cognitive and emotion regulatory functions if placed into foster care before they were two years old, as compared to those who were placed later (McLaughlin et al., 2015b). Some studies on mental health outcomes also implicate early childhood as a sensitive period (Dunn et al., 2020), whereas others point more to middle childhood or adolescence (Gerke et al., 2018; Schalinski et al., 2016; Yoon, 2020). Overall, childhood adversity likely impacts multiple developmental periods, rendering it unlikely that there is only one narrow window during which adversity affects psychobiological processes (Nelson and Gabard-Durnam, 2020).

Another line of research highlights the importance of the recency of exposure, indicating that more recent adversity exerts stronger effects on neurodevelopment (Greenough et al., 1987; Shanahan et al., 2011). Supporting evidence stems from a study of Dunn and colleagues (2018) who demonstrated that child psychopathology symptoms were primarily explained by recency effects, whereas evidence for sensitive periods was not strong. In contrast, another study of the same group found that the timing of adversity explained more variability in DNA methylation than the recency of exposure, rather supporting the sensitive period model (Dunn et al., 2019). Integrating these findings, it is likely that both the timing of exposure to adversity and the recency influence associations between adversity and developmental outcomes.

1.4. Individual characteristics as potential moderators

1.4.1. Sex

In line with findings that neural control of the heart may differ as a function of sex (Nugent et al., 2011), studies have shown that sex differences exist in resting vagal activity (Koenig et al., 2017; Koenig and Thayer, 2016) and vagal reactivity to challenge (Emery et al., 2018; Hamidovic et al., 2020; Li et al., 2009; Ordaz and Luna, 2012; T. W. Smith et al., 2009). Sex has further been observed to moderate associations between specific indexes of resting HRV and correlates of adversity including difficulties in emotion regulation (D. P. Williams, Tracy et al., 2019), depressive symptoms (Dietrich et al., 2011) and inflammation (D. P. Williams, Koenig et al., 2019). According to the Adaptive Calibration Model (Del Giudice et al., 2011), sex could influence the way physiological systems adapt to conditions of severe environmental stress: While females may more likely develop a vigilant pattern of responsivity characterized by low parasympathetic basal activity, low to moderate parasympathetic responsiveness, and high sympathetic basal activity and responsivity, males may more likely develop an unemotional pattern characterized by low sympathetic and parasympathetic basal activity and responsivity (Del Giudice et al., 2011). These predictions have so far received partial support in empirical studies (Del Giudice et al., 2012; Ellis et al., 2017).

1.4.2. Psychopathology

Previous research has established that individuals exposed to childhood adversity are at increased risk of developing psychopathology, particularly after being exposed to additional adversity in adulthood ('stress sensitization'; Bandoli et al., 2017; Hammen et al., 2000; Lin et al., 2022; Luo et al., 2021). An important difference between studies investigating the effects of childhood adversity is whether they involve participants with or without psychopathology (note that participants in “non-clinical samples” may also experience mental health problems not assessed in a study). Reduced levels of resting HRV are considered a core characteristic of mood and anxiety disorders (Brown et al., 2018; Chalmers et al., 2014; Koch et al., 2019; Koenig, Kemp, Beauchaine et al., 2016), and have further been observed in individuals diagnosed with schizophrenia (Clamor et al., 2016) or borderline personality disorder (Koenig, Kemp, Feeling et al., 2016). As shown in a recent meta-analysis on the association between resting vagal activity and maltreatment (Sigrist et al., 2021), it is possible that alterations in vagal regulation are more strongly associated with childhood adversity in clinical samples, as individuals who develop psychopathology may be the ones who experience more difficulties in coping with the stressful circumstances.

1.5. Methodological characteristics as potential moderators

1.5.1. Measurement of childhood adversity

The measurement of childhood adversity may also yield differences in observed effects of childhood adversity on vagal regulation. Childhood adversity can be quantified by self-, parent-, or teacher-report (e.g., through questionnaires or interviews), or by extracting information from official records (e.g., from Child Protective Services). Importantly, these methods may vary in how accurately they capture an individual’s experience and appraisal of adversity (Monroe, 2008). To illustrate, in a comparison study on adolescents who had been confirmed as victims of maltreatment prior to age 13, Pinto and Maia (2013) found low agreement (Kappa < .40) between official records and self-reports for most subtypes of childhood adversity. Only 17% of self-reports were consistent with official records. Emotional abuse and emotional neglect had the highest probabilities of being undocumented in official records, whereas physical neglect, physical abuse and domestic violence were more likely under-reported in self-reports, possibly because individuals have had experienced these as discipline or normal (Pinto and Maia, 2013). It is possible that risk pathways to mental illness differ depending on the method to assess adversity. For instance, a recent study
demonstrated that chronic inflammation—a correlate of vmHRV (D. P. Williams, Koenig et al., 2019)—was only predicted by maltreatment if assessed via official records but not via self-report (Osborn and Widom, 2020). An explanation could be that the maltreatment experiences that come to the attention of the authorities may be more severe compared to those that were retrospectively reported (Groeneveld and Giovannoni, 1977).

1.5.2. Index of vagally-mediated heart rate variability

Individual differences in vagal regulation are commonly assessed by time- or frequency-domain measures of vmHRV (Appelhans and Luecken, 2006; Shaffer and Ginsberg, 2017). Time-domain indices (also referred to as statistically-derived indices) quantify the amount of variability in interbeat intervals (IBIs) and yield numerical estimates of HRV in temporal units (e.g., milliseconds). The root mean of the square difference indices (RMSSD) is considered a primary index of vmHRV (T. W. Smith et al., 2020; Thayer et al., 2010; Williams, Koenig et al., 2019). Also RSA measured with the peak-valley method (Grossman et al., 1990) or Porges moving polynomial algorithm (Porges, 1986) are indexes of vagal activity (Grossman and Taylor, 2007). Within frequency-domain measures, power spectral analysis is employed to partition the variance of the IBIs into a spectrum of frequencies. The amount of variance within a given frequency range represents the amount of signal energy or “power” (Appelhans and Luecken, 2006).

The high-frequency component of HRV (HF-HRV), occurring at a respiratory frequency of .15–.40 Hz in adults, reflects vagal activity (Appelhans and Luecken, 2006; Shaffer and Ginsberg, 2017). Estimates of vmHRV derived from time-domain and frequency-domain analyses are highly correlated with one another (Goedhart et al., 2007; Lewis et al., 2012) and are similarly associated with top-down self-regulation (Holzman and Bridgett, 2017).

1.5.3. Type of challenge task

Although it has been proposed that vagal withdrawal indicates regulation across different contextual demands (Thayer and Lane, 2000), the association between childhood adversity and vagal reactivity may depend on the nature of the challenging task. Different tasks have been used to study vagal reactivity in the context of childhood adversity, varying in their extent to which they induce emotional arousal. While some studies have employed cognitive tasks (e.g., Stroop task, mental arithmetic task) representing rather affectively neutral (“cool”) contexts, other studies have used negative emotion-elicitng tasks (e.g., a film clip showing acts of violence) or stress tests (e.g., public speaking) that represent emotionally-loaded (“hot”) contexts (see Zelazo and Carlson, 2012). As childhood adversity is associated with poor emotion regulation (Gruhn and Compas, 2020; Raver et al., 2015), it is possible that alterations in vagal reactivity are more pronounced during tasks that require emotional regulatory processes as compared to relatively neutral cognitive tasks. Support for this hypothesis stems from a recent study testing 8- to 16-year-olds in which the severity of child abuse was associated with poor adaptation on an emotional Stroop task indicating difficulties with automatic emotion regulation, but was unrelated to cognitive control assessed in a similar task without emotional stimuli (Kim et al., 2021).

1.6. Date, qualitative and quantitative reviews show little agreement on whether alterations in vagal regulation are present in individuals exposed to childhood adversity (Lavi et al., 2019; Propper and Holochwost, 2013; Sigrist et al., 2021; Young-Southward et al., 2021). Importantly, meta-analytic evidence on the association between childhood adversity and vagal regulation has been limited to maltreatment, excluding other adversity types such as poverty or neighborhood violence which have also been linked to ANS alterations (Hill-Soderlund et al., 2015; Mellman et al., 2018). Further, only studies on resting vagal activity (Sigrist et al., 2021) or vagal emotion reactivity (Lavi et al., 2019) were included. Accordingly, the objective of the present meta-analysis was to quantify overall effect sizes for the association between childhood adversity and vagal regulation by adopting a broad conceptualization of childhood adversity (see Sheridan and McLaughlin, 2014), and by including both baseline vagal activity and task-induced vagal reactivity to different challenges (such as emotion-elicitng tasks, cognitive challenges, and stress tests). Given considerable heterogeneity in study designs and outcomes, we further investigated the role of potential moderators in these associations belonging to three broad categories: 1) childhood adversity characteristics, 2) individual characteristics, and 3) methodological characteristics.

The following hypotheses and exploratory research questions were tested: In line with findings showing structural and functional alterations of brain regions related to vagal regulation (Teicher and Samson, 2014), and studies revealing self-regulatory difficulties in individuals exposed to adversity (Gruhn and Compas, 2020; Kim et al., 2021), we expected that higher levels of childhood adversity would be associated with lower baseline vagal activity and vagal reactivity (i.e., less vagal withdrawal in response to challenge). Based on the Adaptive Calibration Model (Del Giudice et al., 2011), we hypothesized sex differences to emerge in the association between adversity and vagal reactivity while no differences were expected for the association with baseline vagal activity. More specifically, the assumed effect of lower vagal reactivity in association with childhood adversity was thought to be more pronounced in males as compared to females. With regards to psychopathology, we hypothesized that effect sizes would be larger in studies including individuals with psychiatric diagnoses as compared to non-clinical samples (see Sigrist et al., 2021). Following predictions of the dimensional model of adversity (Sheridan and McLaughlin, 2014), we expected effect sizes to be larger on associations between vagal regulation with threat-related adversities as compared to deprivation-related adversities. Further, we assumed that direct adversities would be more strongly associated with vagal regulation as compared to indirect adversities. Given evidence on larger associations between more severe types of adversity and health outcomes (Hambrick et al., 2019), we expected effect sizes to be larger on associations between more severe types of adversity and health outcomes (Hambrick et al., 2019), we expected effect sizes to be larger on associations between vagal regulation and maltreatment as compared to other types of adversity. As existing studies provide inconsistent results with regards to the influence of sensitive periods and the recency of adversity on psychobiological and mental health outcomes (Dunn et al., 2018, 2019), we tested for these moderators in an exploratory way. Regarding the assessment type of childhood adversity, we expected studies based on official records to reveal larger effects as compared to studies based on questionnaires (Osborn and Widom, 2020). Further, we expected effect sizes to be larger on associations between vagal reactivity and childhood adversity when assessed in stress tests and emotion-elicitng tasks as compared to cognitive tasks. Last, we tested for a potential moderating role of the index of vmHRV (time- versus frequency-domain), the measurement of respiration, and the control of artifacts in an exploratory way.

2. Methods

2.1. Identification and selection of studies

Articles were identified by searching the electronic databases PsycINFO, Web of Science, and Medline on the 15th of September 2020. Keywords related to childhood adversity were combined with those related to vmHRV. No limits with regards to language, publication year or publication type were applied during the search phase. The protocol for the systematic search can be found in the Supplemental Material provided online. The search results were screened for duplicates with Zotero (for tutorial, see Staaks, 2020). We further examined the reference lists of reviews and meta-analyses on related topics (e.g., Bunea et al., 2017; Fogelman and Canli, 2018; Lavi et al., 2019;
Overview of Childhood Adversity Constructs Included and Excluded in this Meta-analysis.

<table>
<thead>
<tr>
<th>'Major' adversities → included</th>
<th>'Minor' adversities → excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maltreatment (physical abuse, sexual abuse, emotional abuse, physical neglect, emotional neglect)</td>
<td>'Normative' variations in parenting (e.g., parental sensitivity)</td>
</tr>
<tr>
<td>Adverse parenting (use of corporal punishment, harsh parenting, hostile-withdrawn parenting, coercion)</td>
<td>Inter-parental conflict (in terms of dissatisfaction, without verbal or physical aggression), marital dissatisfaction, separation / divorce of parents</td>
</tr>
<tr>
<td>Inter-parental aggression (including verbal or physical aggression)</td>
<td>Parental psychopathology (e.g., major depression, anxiety disorder, schizophrenia)</td>
</tr>
<tr>
<td>Parental psychopathology (e.g., major depression, anxiety disorder, schizophrenia)</td>
<td>Death of a parent (bereavement)</td>
</tr>
<tr>
<td>Parent incarceration</td>
<td>Changes in family composition</td>
</tr>
<tr>
<td>Poverty (i.e., income-to-needs ratio &lt; 1, family income below federal poverty line)</td>
<td>Changes in family finances, socio-economic status indicated by parental education or occupation, loss of job by parent</td>
</tr>
<tr>
<td>Household chaos / dysfunction</td>
<td>Relational / peer victimization</td>
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<tr>
<td>Relational / peer victimization</td>
<td>Witnessing a traumatic event according to DSM-V definition</td>
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<tr>
<td>Witnessing a traumatic event according to DSM-V definition</td>
<td>Neighborhood / community violence</td>
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<td>Neighborhood / community violence</td>
<td>Homelessness (street children)</td>
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<tr>
<td>Institutionalization</td>
<td>Institutionalization</td>
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</tbody>
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2.2. Data extraction and coding

A coding system was developed in SPSS by the first author in consultation with the co-authors based on guidelines of Lipsey and Wilson (2001) prior to conducting the systematic search. Coding categories were adapted in an iterative process during the coding of studies when necessary. The first author extracted the data from each study and computed the effect sizes. To assess inter-rater reliability, 20 studies were randomly selected and scored by the second author. Inter-rater reliability was determined by calculating the percentage of agreement for all study characteristics, Cohen’s Kappa for categorical variables and intraclass correlation for continuous variables. The inter-rater agreement for categorical variables proved to be moderate to almost perfect, with Kappa’s ranging from 0.77 (95% agreement) for artifact control to 1.00 (100% agreement) for type of report (journal article or dissertation), publication status and country of data collection. The inter-rater reliability for continuous variables was excellent, with intraclass correlations ranging from 0.94 (95% agreement) for the effect size value to 1.00 (100% agreement) for duration of HRV measurement at baseline.

2.2.1. Study characteristics

We coded the type of report (journal article or dissertation), publication status (published or unpublished), year of publication, country of data collection (categorized additionally into North-American countries vs. other countries), study design (correlational or group comparison study), and type of statistic to compute an effect size.

2.2.2. Sample characteristics

For each study, the sample size and the mean sample age, reflecting the age of participants at physiological assessments, were coded. For studies on school-aged children that only reported children’s grade, we estimated the sample’s mean age. We also coded the sample’s sex as the percentage of females, and the sample’s ethnicity as the percentage of minorities. As the association between childhood adversity and vagal regulation may differ between individuals with or without psychopathology, we further coded whether the sample included participants with a clinical diagnosis or not. Other sample characteristics coded were information on physical health (e.g., cardio-vascular diseases, medication intake, smoking), education and income of participants or their families.

2.2.3. Characteristics of childhood adversity

Subtypes of adversity were categorized into direct adversity (e.g., child abuse), indirect adversity (e.g., poverty), or mixed (i.e., exposure to direct and indirect forms of adversity; see Hughes et al., 2017), reflecting the proximity of adversity. Based on the dimensional model of adversity of Sheridan and McLaughlin (2014), we further categorized different forms of adversity into deprivation (e.g., child neglect), threat (e.g., harsh parenting), or mixed (i.e., exposure to both deprivation and threat). A categorization schema allocating the different adversity types to subcategories of proximity and dimension of adversity is integrated in the script for the statistical analyses available online. Following the approach of Bunea et al. (2017), we coded the severity of adversity as maltreatment (as a proxy for extreme severity) versus other forms of adversity. Further, we coded the recency of exposure to adversity in years which was calculated by subtracting the age at exposure to adversity from the age at vmHRV measurement. Finally, the assessment...
of adversity was categorized into questionnaires (including clinical interviews), official records (e.g., Child Protective Services’ records or neighborhood violence statistic), and other (e.g., experimenter examination such as through a checklist on household disorganization, or a naturalistic setting such as homelessness). The assessment of adversity was coded as mixed if a composite of these methods of childhood adversity was used. As only one study employed such a composite, the category ‘mixed’ was integrated into the category ‘other’.

2.2.4. Measurement of vagal regulation

We coded the index of vmHRV (RMSSD, RSA, or HF-HRV), the corresponding domain of analysis (time- or frequency-domain analysis), as well as the duration and condition of baseline measurement. The baseline condition was further categorized into ‘no task’ (including resting and relaxing), ‘rather passive task’ (including viewing neutral film clips or pictures, and listening to relaxing sounds or a neutral story), and ‘active task’ (including describing neutral pictures, reading aloud, paced breathing; for categorization schema, see analysis script in the Supplemental Material).

It was further assessed whether respiration was measured, and whether artifacts in the electrocardiogram signal were corrected. As only three studies in the meta-analysis on vagal reactivity did not report on artifact correction, this variable was not examined in the moderator analysis. For studies assessing vagal reactivity, we additionally coded the nature of the challenging task, categorized into cognitive task (without social evaluation), stress test, or negative emotion-eliciting task (for categorization schema, see analysis script in the Supplemental Material), the duration of this task, and the computation of reactivity scores (e.g., residualized change scores, difference scores subtracting the reactivity from the baseline condition, or task mean levels).

2.3. Effect size computation

The Pearson product-moment correlation coefficient $r$ was calculated as the common effect size for each reported association on childhood adversity and vagal regulation. Reported associations that were expressed in other forms than correlations were transformed using the converter of Wilson (www.campbellcollaboration.org) which is based on the formulas of Lipsey and Wilson (2001). For effect sizes on baseline vagal activity, a positive correlation coefficient reflected that higher levels of childhood adversity were associated with higher levels of baseline vmHRV. For studies on vagal reactivity, we inverted effect sizes as the common effect size for each reported association on childhood adversity and vagal reactivity to challenge. Given that several studies on artifact correction, this variable was not examined in the moderator analysis. Whether artifacts in the electrocardiogram signal were corrected. As only three studies in the meta-analysis on vagal reactivity did not report on artifact correction, this variable was not examined in the moderator analysis. For studies assessing vagal reactivity, we additionally coded the nature of the challenging task, categorized into cognitive task (without social evaluation), stress test, or negative emotion-eliciting task (for categorization schema, see analysis script in the Supplemental Material), the duration of this task, and the computation of reactivity scores (e.g., residualized change scores, difference scores subtracting the reactivity from the baseline condition, or task mean levels).

2.4. Statistical analysis

Two separate meta-analyses were conducted to assess the association between childhood adversity and baseline vagal activity, and childhood adversity and vagal reactivity to challenge. Given that several studies reported on multiple forms of childhood adversity or used more than one method to assess childhood adversity, it was possible to extract multiple effect sizes per study for 54.4% of all baseline studies, and 69.1% of all reactivity studies. As effect sizes from the same study may be more alike than effect sizes from different studies, the assumption of independent effect sizes required by traditional meta-analytic approaches was violated (see Cooper, 2010; Lipsey & Wilson, 2001). In order to deal with effect size dependency, a multi-level approach was applied to the current meta-analysis (Assink & Wibbelink, 2016; Cheung, 2015; Cooper, 2010; Van den Noortgate et al., 2013, 2014). Effect sizes were pooled in a three-level random effects model, in which three levels of variance were modeled: variation in effect sizes due to random sampling of effect sizes (Level 1), variation in effect sizes due to differences within a single study (Level 2), and variation in effect sizes between different studies (Level 3; Assink & Wibbelink, 2016). The overall strength of association between childhood adversity and both indicators of vagal activity was assessed by building separate three-level meta-analytic models without predictors (i.e., intercept-only models). In these models, the estimated intercept values represented the effect of childhood adversity on baseline vagal activity and vagal reactivity.

In order to determine whether heterogeneity in effect sizes was present within each meta-analysis, the significance of the variance at Levels 2 and 3 was assessed through two separate one-tailed log-likelihood-ratio tests. In these tests, the deviance of the full model was compared to the deviance of the model excluding one of the variance parameters (Assink & Wibbelink, 2016). In case that significant variance was detected at Level 2 and/or 3, moderator analyses were conducted to test whether differences between effect sizes may be explained by various study characteristics. Categorical moderator analyses were restricted to cases where each category included at least five studies. Dummy variables were created for each discrete variable, and each continuous variable was centered around its mean. Each potential moderator was then examined in a separate three-level meta-analytic model in which the moderator was added as a covariate. Given that the REstricted Maximum Likelihood (REML) method was used for estimating parameters of the meta-analytic model, omnibus tests were conducted to determine whether a variable had a significant moderating effect (Assink & Wibbelink, 2016).

All analyses were conducted in R (version 3.6.1; R Core Team, 2019) using the metafor package (Viechtbauer, 2010). The syntax was based on the tutorial of Assink and Wibbelink (2016) written for three-level random effects meta-analyses. A significance level of $p < 0.05$ was used in all analyses. A summary forest plot was created following the guidelines of Fernández-Castilla et al. (2020) which accounts for the existence of multiple effect sizes within primary studies. In contrast to traditional forest plots, each black line no longer portrays an individual effect size, but the results of meta-analyses of outcomes within each study. In addition, caterpillar plots were created based on the syntax provided by Fernández-Castilla et al. (2020). The complete dataset and the R syntax employed for the analyses can be found in the Supplemental Material available online.

2.5. Risk of bias assessment

In order to assess whether a publication or subjective reporting bias was present within our set of included studies, various analyses were performed in R using the metafor package (Viechtbauer, 2010) and code adapted from Fernández-Castilla et al. (2021). We used a multi-level extension of Egger’s test (Egger et al., 1997) from Fernández-Castilla et al. (2021) in which effect sizes were regressed on the inverse of standard errors while accounting for effect size dependency. Further, we computed a multi-level extension of the Funnel Plot test (Fernández-Castilla et al., 2021) in which sample sizes were used as predictors of the effect sizes. In both tests, a significant regression coefficient would indicate potential bias. In addition, we conducted the Trim and Fill method (Duval and Tweedie, 2000a, 2000b; Fernández-Castilla et al., 2021) in which funnel plot asymmetry stemming from potential bias is detected and corrected by adding the estimated hypothetical “missing” effect sizes. The presence of bias was evaluated by comparing the value of the estimator $L_2$ with cutoffs proposed by Fernández-Castilla et al. (2021) which depended on the pooled effect size and the number of effect sizes included in each meta-analysis.
For visualization purposes, we created two funnel plots using the ggplot2 package (Wickham, 2016) in R, following guidelines on funnel plots for multi-level meta-analyses (Fernández-Castilla et al., 2020). In the first funnel plot, all effect sizes were plotted against their standard errors. If no selection bias exists, studies based on large samples should be closer to the pooled effect compared to studies with lower samples which are expected to distribute more widely along both sides of the pooled effect at the base of the graph, yielding a symmetrical inverted funnel shape. In the second funnel plot, the study effects estimated through separate random-effects meta-analyses to each study were plotted against their meta-analytic standard errors. In this study-funnel plot, the precision of each study not only depends on the sample size as in funnel plots of all effects, but further depends on the number of effect sizes reported and on their variability. Based on visual inspection of the funnel plots, selection bias could exist if part of the funnel of all effect sizes is empty or if the distribution of study-specific effects is asymmetrical.

3. Results meta-analysis 1: association between childhood adversity and baseline vagal activity

3.1. Study selection and characteristics

A flow diagram for the identification of articles appears in Fig. 1. The search process yielded a total of 3009 potentially relevant records, from which 1852 remained after removing duplications. After the screening based on title and abstract, 279 reports remained for the screening based on the full-text. The meta-analysis on baseline vagal activity included 115 articles reporting on 90 independent studies (k) and comprising 250 effect sizes (#ES). The publication year of the included studies ranged from 2000 to 2020 (median = 2015). Studies were predominantly conducted in North America (n = 74), followed by Europe (n = 12), Asia (n = 2), Africa (n = 1) and Australia (n = 1). The overall sample size was N = 18,716 unique participants, with study sample sizes ranging from N = 36 (Garland et al., 2019) to N = 3362 participants (Bakema et al., 2020). The mean age of the participants was 12.85 years (SD = 9.96 years). Within 11.1% of the studies, a mean of 40.0% (SD = 29.6%) of participants were diagnosed with a psychiatric disorder. The mean number of extracted effect sizes per study was 2.58 (SD = 3.0). With regards to the childhood adversity type, the majority of effect sizes related to maltreatment (n = 92), followed by interparental aggression (n = 45), parental psychopathology (n = 28), poverty (n = 20), composites of different adversity types (n = 19), adverse parenting (n = 17), peer victimization (n = 14), neighborhood violence (n = 7), and other (n = 8). In the Supplemental Material, several characteristics of the included studies are summarized in a spreadsheet.

3.2. Overall association

No significant association was found between childhood adversity and baseline vagal activity (r = –0.015; 95% CI [–0.033, 0.003; p = .109; see Table 2). Fig. 2 shows the summary forest plot representing the results of meta-analyses of outcomes within each study. In Fig. 3A, we have plotted the caterpillar plot with all effect sizes and their confidence intervals, ordered by their magnitude. In Fig. 3B, we have plotted the study-caterpillar plot, in which effect sizes within studies are synthesized (as in the forest plot).

3.3. Moderator analyses

3.3.1. Heterogeneity in effect sizes

We tested whether differences in effect sizes could be attributed to random sampling error (Level 1), within-study variance (Level 2), or between-study variance (Level 3). For the association between childhood adversity and baseline vagal activity, significant variation was present in effect sizes within studies (τ² = .001, χ²(1) = 8.96, p = .001; one-sided) and in effect sizes between studies (τ² = .003, χ²(1) = 8.05, p = .002; one-sided). With regards to the distribution of variances, 52.44% of the total variance was accounted for by variation in effect sizes between studies, 16.18% within studies, and 31.38% by random sampling variance.

3.3.2. Moderator effects

As significant heterogeneity within and between studies was present in the dataset, we tested whether moderators could potentially explain part of the variation in effect sizes. An overview of all moderator variables and results of the moderator analyses are presented in Table 3, in which the potential moderators are classified into characteristics of the study, sample, childhood adversity, and vmHRV measurement. In total, we identified four moderating variables of which one was part of the sample characteristics, and three were part of the childhood adversity characteristics.

First, a significant moderating effect was found for the presence of psychopathology in the sample. More specifically, childhood adversity was more strongly associated with baseline vagal activity in samples in which part of the participants had a psychiatric diagnosis (r = –.106, p < .001) than in non-clinical samples (r = –.005, p = .586). Second, the severity of adversity was a significant moderator. Stronger relations between childhood adversity and baseline vagal activity were found for studies on maltreatment (r = –.058, p < .001) as compared to studies on other forms of adversity (r = .004, p = .736). Third, the dimension of adversity moderated the association between childhood adversity and baseline vagal activity. Exposure to deprivation as well as exposure to both deprivation and threat (mixed) showed stronger associations with vmHRV (r = –.044, p = .036; r = –.029, p = .041, respectively) than exposure to threat with vmHRV (r = –.002, p = .859). Fourth, the proximity of adversity was a significant moderator. Stronger associations between childhood adversity and baseline vagal activity were found for exposure to direct adversity (r = –.037, p = .002) as compared to exposure to indirect adversity (r = –.001, p = .950) or exposure to both direct and indirect adversity (mixed; r = .039, p = .108). All other characteristics (including year of publication, country of data collection, study design, number of participants, age of participants, percentage females, percentage minorities, assessment of adversity, recency of adversity, vmHRV index, duration of vmHRV baseline measurement, baseline condition, measurement of respiration and artifact correction) were not significant moderators in the association between childhood adversity and baseline vagal activity.

3.3.3. Multiple moderator analysis

As moderators may be interrelated, possibly leading to multicollinearity in the analyses, we followed the recommendation by Hox (2010) and tested the unique effect of the variables that were previously identified as significant moderators combined in a single model. To this end, we extended the meta-analytic model by adding the variables psychopathology, severity, dimension and proximity of adversity simultaneously. The results of this model are presented in Table 4. The omnibus test showed significant results, F(6|243) = 5.52, p < .001, suggesting that at least one of the regression coefficients of the moderators significantly deviated from zero. Results revealed that psychopathology and the proximity of adversity had a unique moderating effect on other forms of adversity. Consistent with results from the univariate moderator analyses, childhood adversity was associated with lower baseline vagal activity in

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1 A sensitivity analysis was performed by excluding studies in which participants experienced prenatal adversity or adulthood adversity in addition to childhood adversity (k = 3, ES = 9). The overall association between childhood adversity and baseline vagal activity remained non-significant, r = –.014; 95% CI [–.033, .003], p = .145.
studies in which part of the participants had a psychiatric diagnosis and in those in which direct adversities were investigated.

3.4. Risk of bias assessment

For the meta-analysis on childhood adversity and baseline vagal activity, the non-significant regression coefficients from the adapted Egger's test ($\beta = -0.014, SE = 0.026, p = .582$) and the adapted Funnel plot test ($\beta = -0.013, SE = 0.019, p = .207$) yielded no evidence of publication bias. However, the Trim and Fill method indicated potential bias. The estimator $L_0$ was 8.03 and thereby larger than the cutoff of 3 which was chosen given that the baseline meta-analysis revealed a non-significant pooled effect size of $r = -.015$ with 250 effect sizes being included (see Fernández-Castilla et al., 2021). A visual representation of the funnel plots can be found in Fig. 4.

4. Results meta-analysis 2: association between childhood adversity and vagal reactivity

4.1. Study selection and characteristics

The screening based on title and abstract was the same as in the meta-analysis on baseline vagal activity (see Fig. 1). The meta-analysis on vagal reactivity included 75 articles reporting on 55 independent studies ($k$), comprising 190 effect sizes (#ES). The publication year of the included studies ranged from 2001 to 2020 (median = 2014). Studies were predominantly conducted in North America ($n = 49$), followed by Europe ($n = 4$), Asia ($n = 1$), and Australia ($n = 1$). The overall sample size was $N = 8741$ unique participants, with study sample sizes ranging from $N = 36$ (Garland et al., 2019) to $N = 1047$ participants (Conradt et al., 2016). The mean age of the participants was 12.80 years ($SD = 9.24$ years). Within 10.9% of the studies, a mean of 27.8% ($SD = 26.3$%) of participants were diagnosed with a psychiatric disorder. The mean number of extracted effect sizes per study was 3.45 ($SD = 3.89$). With regards to the childhood adversity type, the majority of effect sizes related to maltreatment ($n = 56$), followed by interparental aggression ($n = 25$), parental psychopathology ($n = 23$), (neighborhood) violence exposure ($n = 19$), poverty ($n = 12$), composites of different adversity types ($n = 20$), adverse parenting ($n = 15$), peer victimization ($n = 10$), and other ($n = 10$). With regards to the challenge task, the majority of effect sizes pertained to emotion-eliciting tasks ($n = 93$), followed by stress tasks ($n = 33$) and cognitive tasks ($n = 33$). The mean duration of task recording was 5.34 min ($SD = 3.94$). In the Supplemental Material, several characteristics of the included studies are summarized in a spreadsheet.

<table>
<thead>
<tr>
<th>Association</th>
<th>$#k$</th>
<th>#ES</th>
<th>N</th>
<th>$Z_r$ (SE)</th>
<th>$r_r$ (SE)</th>
<th>95% CI ($r$)</th>
<th>$t(df)$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood adversity – baseline vagal activity</td>
<td>90</td>
<td>250</td>
<td>18716</td>
<td>-.015 (.009)</td>
<td>-.015 (.009)</td>
<td>[.033,.003]</td>
<td>-1.61 (249)</td>
<td>.109</td>
</tr>
<tr>
<td>Childhood adversity – vagal reactivity</td>
<td>55</td>
<td>190</td>
<td>8741</td>
<td>-.017 (.011)</td>
<td>-.017 (.011)</td>
<td>[.039,.005]</td>
<td>-1.53 (189)</td>
<td>.127</td>
</tr>
</tbody>
</table>

Note. $#k =$ number of studies; #ES = number of effect sizes; $N =$ total number of unique participants; $Z_r =$ Fisher’s $Z$ correlation; $SE =$ standard error; $r_r =$ Pearson’s correlation coefficient $r$; 95% CI = 95% confidence intervals of Pearson’s $r$; $df =$ degrees of freedom.
Fig. 2. Summary forest plot showing the results of the meta-analysis on childhood adversity and baseline vagal activity. The thickness of the grey confidence intervals is proportional to the number of effect sizes reported within studies. Effect sizes of studies marked with an asterisk (*) were further reported in other publications based on the same data set. Effect sizes related to Buisman et al. (2018) also apply to Buisman et al. (2019); Cipriano (2011); Cipriano et al. (2011), Creaven et al. (2014); Connell et al. (2011); Connell et al. (2015); Conrada et al. (2014a); Conrada et al. (2014b); Conrada et al. (2014c); Duprey et al. (2020); Oshri et al. (2020); El-Sheikh et al. (2001); El-Sheikh et al. (2005); El-Sheikh et al. (2009) – study 2: El-Sheikh et al., (2011, 2013), Hinnant et al. (2015), Philbrook et al. (2018), Wetter and El-Sheikh (2012); Fletcher et al. (2017); Benito-Gomez et al. (2019a); b); Keller et al. (2014); El-Sheikh et al. (2015); McLaughlin et al. (2014); Basso et al. (2017), McLaughlin et al. (2015a); Obradović et al. (2010); Obradović et al. (2011); Oshri et al. (2018); Liu et al. (2020); Shenk et al. (2010); Shenk et al., (2012, 2014); Skowron et al. (2014); Giuliano et al., (2015, 2018b).

Fig. 3. Caterpillar plots of the meta-analysis on childhood adversity and baseline vagal activity. (A) Caterpillar plot with all effect sizes and their 95% confidence intervals and (B) study-caterpillar plot.
and vagal reactivity to challenge \((p < .05; **p < .01; ***p < .001)\). The overall association between childhood adversity and vagal reactivity remained non-significant, \(r = -.018; 95\% CI [-.041, .005], p = .130\).

### 4.2. Overall association

No significant association was found between childhood adversity and vagal reactivity to challenge \((r = -.017; 95\% CI [-.039, 0.005]; p = .127)\). Fig. 5 shows the summary forest plot representing the results of meta-analyses of outcomes within each study. In Fig. 6A, we have plotted the caterpillar plot with all effect sizes and their confidence intervals, ordered by their magnitude. In Fig. 6B, we have plotted the study-caterpillar plot, in which effect sizes within studies are synthesized (as in the forest plot).

### 4.3. Moderator analyses

#### 4.3.1. Heterogeneity in effect sizes

For the association between childhood adversity and vagal reactivity, significant variation was present in effect sizes between studies \(\left(\chi^2(1) = 27.08, p < .001; \text{one-sided}\right)\) but not in effect sizes of meta-analyses of outcomes within each study. In Fig. 6A, we have plotted the caterpillar plot with all effect sizes and their confidence intervals, ordered by their magnitude. In Fig. 6B, we have plotted the study-caterpillar plot, in which effect sizes within studies are synthesized (as in the forest plot).
In Fig. 4 B, the size of the dots is proportional to the number of effect sizes included in those studies. Fig. 4. Childhood Adversity and Baseline Vagal Activity: Results for the Multiple Moderator Model. Results revealed that the recency of adversity and the reactivity computation method were unique moderators of the relationship between childhood adversity and vagal reactivity, F(4184) = 7.98, p < .001, see Table 6. To specify, childhood adversity was associated with lower vagal reactivity for studies in which individuals had experienced adversity less recently, and for studies in which reactivity was operationalized through task mean levels of vmHRV.

Table 4 Childhood Adversity and Baseline Vagal Activity: Results for the Multiple Moderator Model.

<table>
<thead>
<tr>
<th>Moderator</th>
<th>β (SE)</th>
<th>95% CI</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>.137 (.032)</td>
<td>[-.200; -.075]</td>
<td>-4.331</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Psychopathology: no clinical diagnoses reported</td>
<td>.083 (.029)</td>
<td>[.025; .140]</td>
<td>2.817</td>
<td>.005***</td>
</tr>
<tr>
<td>Severity: other forms of adversity (vs. maltreatment)</td>
<td>.025 (.023)</td>
<td>[-.021; .071]</td>
<td>1.067</td>
<td>.287</td>
</tr>
<tr>
<td>Dimension: threat (vs. deprivation)</td>
<td>.029 (.017)</td>
<td>[.005; .063]</td>
<td>1.706</td>
<td>.089</td>
</tr>
<tr>
<td>Dimension: mixed (vs. deprivation)</td>
<td>-.011 (.023)</td>
<td>[-.057; .034]</td>
<td>-0.488</td>
<td>.626</td>
</tr>
<tr>
<td>Proximity: indirect adversity (vs. direct adversity)</td>
<td>.027 (.021)</td>
<td>[.014; .068]</td>
<td>1.303</td>
<td>.194</td>
</tr>
<tr>
<td>Proximity: mixed (vs. direct adversity)</td>
<td>.065 (.029)</td>
<td>[.008; .122]</td>
<td>1.234</td>
<td>.26*</td>
</tr>
</tbody>
</table>

* p < .1; * p < .05; *** p < .001

within studies (\(\sigma^2 = .001, \chi^2(1) = 1.98, p = .080\); one-sided). With regards to the distribution of variances, 62.21% of the total variance was accounted for by variation in effect sizes between studies, 7.96% within studies, and 29.83% by random sampling variance.

4.3.2. Moderator effects

As significant heterogeneity between studies was present in the dataset, we tested whether moderators could potentially explain part of the variation in effect sizes. An overview of all moderator variables and results of the moderator analyses are presented in Table 5, in which the potential moderators are classified into characteristics of the study, sample, childhood adversity, and vmHRV measurement. In total, we identified three moderating variables: age of participants, recency of exposure to adversity, and vagal reactivity computation method.

First, as the sample’s mean age increased, the overall strength of association between childhood adversity and vagal reactivity significantly increased. Thus, childhood adversity was associated with less vagal withdrawal in older-aged samples. Second, as childhood adversity occurred less recently, the overall strength of association increased. In other words, childhood adversity was associated with less vagal withdrawal in individuals who had experienced adversity longer ago. Third, while there was a significant negative association between childhood adversity and vagal reactivity for studies in which reactivity was operationalized through task mean levels of vmHRV (\(r = -.079, p < .001\), there was no significant association for studies in which reactivity was computed as a difference score (\(r = .007, p = .608\)) or residualized change score (\(r = .013, p = .488\)).

All other characteristics (year of publication, country of data collection, study design, number of participants, percentage females, percentage minorities, psychopathology, severity, dimension, proximity, assessment, timing and recency of adversity, vmHRV index, duration of vagal reactivity measurement, challenge task, and measurement of respiration) were not significant moderators in the association between childhood adversity and vagal reactivity.

4.3.3. Multiple moderator analysis

In order to test the unique effect of the variables that were previously identified as significant moderators combined in a single model, we extended the meta-analytic model by adding the variables participant age, recency of adversity and reactivity computation method simultaneously. Results revealed that the recency of adversity and the reactivity computation method were unique moderators of the relationship between childhood adversity and vagal reactivity, \(F(4184) = 7.98, p < .001\) see Table 6. To specify, childhood adversity was associated with lower vagal reactivity for studies in which individuals had experienced adversity less recently, and for studies in which reactivity was operationalized through task mean levels of vmHRV.

4.4. Risk of bias assessment

For the meta-analysis on childhood adversity and vagal reactivity, no indication of bias was detected through Egger’s test (\(\hat{b} = .037, SE = .035, p = .290\)) or the Funnel Plot test (\(\hat{b} = -.024, SE = .015, p = .105\)). Also the Trim and Fill method yielded no indication of bias, as \(L_h = 0 < 3\) (the cutoff chosen based on recommendations from Fernández-Castilla et al. (2021); given a pooled effect size of \(r = -.017\) and 190 included effect sizes). A visual representation of the funnel plots can be found in Fig. 7.

5. Discussion

This meta-analysis examined the association between childhood adversity and vagal regulation as indexed by baseline vagal activity and vagal reactivity to various challenges, including cognitive tasks, negative emotion-eliciting tasks and stress tests. In contrast to our hypotheses, no significant overall association was present between childhood adversity and both indexes of vagal regulation. However, significant moderators were found in both meta-analyses after controlling for their potential interrelatedness. Specifically, childhood adversity was associated with lower baseline vagal activity in samples in which part of the

![Fig. 4. Funnel plots of the meta-analysis on childhood adversity and baseline vagal activity. (A) Funnel plot of all effect sizes and (B) study-funnel plot that includes the number of outcomes reported in each study. In Fig. 4B, the size of the dots is proportional to the number of effect sizes included in those studies.](image-url)
participants were diagnosed with a psychiatric disorder, and direct adversities such as maltreatment were associated with lower baseline vagal activity. Further, childhood adversity was associated with lower vagal reactivity for studies in which individuals had experienced adversity less recently, and for studies in which reactivity was operationalized through task mean levels of vmHRV.

5.1. Overall association between childhood adversity and vagal regulation

The finding of no overall association suggests that childhood adversity does not lead to alterations in vagal regulation per se, indicating that this physiological system generally maintains its functional integrity in the context of adversity. This finding was unexpected, as structural and functional alterations in brain regions implicated in vagal regulation have been demonstrated in individuals exposed to adversity (Koenig, 2020; Teicher and Samson, 2016). However, a significant overall association between childhood adversity and the functioning of stress regulatory systems such as the hypothalamic-pituitary-adrenal (HPA) axis was also not found in other meta-analyses (see e.g., Bernard et al., 2017; Fogelman and Canli, 2018). In line with the model of 'stress sensitization' (Hammen et al., 2000), it is possible that alterations in vagal regulation are more likely to develop in individuals with a history of childhood adversity when exposed to additional adversity in adulthood. In accordance with this hypothesis, a recent study showed that patients with major depressive disorder who experienced both childhood and adulthood adversity had higher rates of suicidal ideation, whereas neither childhood nor adulthood adversity alone had a predictive value (Lin et al., 2022). Along the same lines, recent regulation have been demonstrated in individuals exposed to adversity (Koenig, 2020; Teicher and Samson, 2016). However, a significant overall association between childhood adversity and the functioning of stress regulatory systems such as the hypothalamic-pituitary-adrenal (HPA) axis was also not found in other meta-analyses (see e.g., Bernard et al., 2017; Fogelman and Canli, 2018). In line with the model of 'stress sensitization' (Hammen et al., 2000), it is possible that alterations in vagal regulation are more likely to develop in individuals with a history of childhood adversity when exposed to additional adversity in adulthood. In accordance with this hypothesis, a recent study showed that patients with major depressive disorder who experienced both childhood and adulthood adversity had higher rates of suicidal ideation, whereas neither childhood nor adulthood adversity alone had a predictive value (Lin et al., 2022). Along the same lines, recent
interpersonal stressful events were found to predict smaller hippocampal volumes in adults over and above childhood maltreatment (Lawson et al., 2017). As only one study in both meta-analyses included individuals with additional adulthood adversity, we were unable to further test for this potential sensitization effect.

5.2. Moderating effects in the association between childhood adversity and baseline vagal activity

As suggested by our moderator findings, adversity-related alterations in vagal regulation may arise under specific circumstances such as when studies included participants with a psychiatric diagnosis in their sample. In line with our hypotheses, a small significant association between childhood adversity and lower baseline vagal activity was observed in clinical samples. This finding is consistent with evidence from a recent meta-analysis showing that resting-state HRV was more reduced in individuals exposed to early-life maltreatment as compared to non-exposed controls in clinical samples in contrast to general population samples (Sigrist et al., 2021). One possible interpretation of these findings would be that adversity-related alterations in vagal activity only develop in those who are more strongly affected by the negative effects of adversity and consequently develop psychopathology, but not in others who maintain normative functioning in the long run. As studies included in the meta-analysis commonly assessed participant characteristics such as the presence of psychopathology concurrently to the measurement of vagal regulation, no conclusions can be drawn on the temporal order of alterations in vagal activity and the onset of psychopathology. A possibility could be that psychopathology is an independent (moderating) factor determining vulnerability to adversity-related alterations in vagal regulation. However, this option is rather unlikely given longitudinal studies suggesting that vagal dysregulation often precedes the onset of psychopathology (Carnevali et al., 2018; Huang et al., 2018; Jandackova et al., 2016; Wekenborg et al., 2019). Considering that reduced levels of resting HRV are a core characteristic of various psychiatric disorders (Brown et al., 2018; Chalmers et al., 2014; Clamor et al., 2016; Koch et al., 2019; Koenig, Kemp, Beauchaine et al., 2016; Koenig, Kemp Feeling et al., 2016) and their temporal precedence over clinical symptoms, another possibility would be that alterations in vagal regulation mediate the association between childhood adversity and psychopathology. In turn, other factors are likely involved that render an individual vulnerable to both alterations in vagal functioning and the development of psychopathology in the face of adversity. Several individual and environmental factors not limited to the ones addressed in this meta-analysis (e.g., genetic predisposition, attachment security, social support throughout development) and potential interactions between such factors could play an important role along the pathway from adversity to pathology (see e.g., Allegrini et al., 2017; Back et al., 2022; Moscardino et al., 2021; Scrimin et al., 2018; Somers and Luecken, 2021).

Intriguingly, research suggests that vagal functioning at the time of exposure to adversity may represent a marker of an individual’s susceptibility to the negative effects of adversity, with general agreement that low resting vagal activity portrays a marker of increased risk and relatively high resting vagal activity a protective factor (Carnevali et al., 2018; Curtis et al., 2017; Duprey et al., 2018; Koenig, 2020; McLaughlin et al., 2014; Patron et al., 2021). Similarly, vagal reactivity has been identified as a moderator in the association of adversity to pathology, with inconsistent findings on whether heightened or buffered reactivity acts as a protective factor (Daches et al., 2019; Hagan et al., 2017; Liu et al., 2020; McLaughlin et al., 2014; Oshri et al., 2018; Vaughn-Coxum et al., 2020). Integrating these findings with our meta-analytic results, it is possible that vagal functioning at the time of exposure to adversity reflects an individual’s ability to cope with stress. Individuals with the high-risk endophenotype of low resting vagal activity would more likely develop alterations in vagal functioning over time, which are preceded or paralleled by alterations in brain structure and function. In turn, alterations in vagal functioning would confer vulnerability to psychopathology. So far, several studies were unable to provide evidence for a mediating role of vagal regulation (Busso et al., 2017; Fagan et al., 2017; Hagan et al., 2017; Jankovic et al., 2021). However, this may be related to the fact that assessments of vagal regulation and psychopathology were commonly conducted at the same time or with only a short time interval in between. While it seems plausible that alterations in vagal functioning and symptoms of psychopathology reinforce each other recursively over time, longitudinal studies spanning different developmental periods are needed to shed light on the complex developmental cascade leading from adversity to negative health outcomes.

As expected, direct adversities were more strongly associated with lower baseline vagal activity than indirect adversities or a combination of direct and indirect adversities (as applies to composite scores of adversity). There are different reasons that could explain these findings. First, although indirect adversities such as poverty and neighborhood violence likely portray a significant challenge for the developing child, the detrimental effects of these adversities can be buffered through sensitive and responsive caregiving (Depasquale and Gunnar, 2020; Tarsha & Narvaez, 2022). To exemplify, adults who grew up in low socio-economic status households whose mothers expressed high warmth toward them exhibited lower levels of inflammation as compared to those who experienced low maternal warmth (Chen et al., 2011). Second, direct adversities may be more strongly associated with vagal activity as they include more severe adversity types such as maltreatment. Indeed, inherent to the operationalization of direct adversity, 71.3% of direct adversities in our baseline meta-analysis related to maltreatment, whereas the rest comprised other types such as...
association between maltreatment and resting vagal activity. These contrasts findings of Sigrist et al. (2021) who did not find an overall severity of adversity was identified as a significant moderator, which severe types that directly affect the child can influence vagal that besides severe adversity types such as maltreatment, also other less integration of variance anymore. Integrating these findings, it seems plausible moderator model, the severity did not significantly add to an explana-

Table 5
Childhood Adversity and Vagal Reactivity: Estimated Results (Fisher’s Z, Regression Coefficients, Omnibus-Test) for Continuous and Categorical Moderator Variables.

<table>
<thead>
<tr>
<th>Moderator</th>
<th>#k</th>
<th>#ES</th>
<th>Z (SE)</th>
<th>β1 (SE)</th>
<th>F (df1, df2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of publication</td>
<td>55</td>
<td>190</td>
<td>-0.017 (.011)</td>
<td>-0.000 (.003)</td>
<td>F(1, 188) = 0.02</td>
<td>.891</td>
</tr>
<tr>
<td>Country of data collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(1, 188) = 0.01</td>
<td>.922</td>
</tr>
<tr>
<td>U.S. or Canada (North-America; RC)</td>
<td>49</td>
<td>160</td>
<td>-0.017 (.012)</td>
<td></td>
<td></td>
<td>1.42</td>
</tr>
<tr>
<td>Other countries outside North-America</td>
<td>6</td>
<td>30</td>
<td>-0.020 (.031)</td>
<td>-0.003 (.034)</td>
<td></td>
<td>1.54</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(1, 188) = 0.29</td>
<td>.590</td>
</tr>
<tr>
<td>Correlational (RC)</td>
<td>44</td>
<td>149</td>
<td>-0.014 (.012)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Group comparison</td>
<td>14</td>
<td>41</td>
<td>-0.029 (.020)</td>
<td>-0.012 (.022)</td>
<td></td>
<td>1.58</td>
</tr>
<tr>
<td>Sample Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of participants</td>
<td>55</td>
<td>190</td>
<td>-0.018 (.011)</td>
<td>0.000 (.000)</td>
<td>F(1, 188) = 0.49</td>
<td>.486</td>
</tr>
<tr>
<td>Age (in years)</td>
<td>55</td>
<td>190</td>
<td>-0.016 (.011)</td>
<td>0.003 (.001)</td>
<td>F(1, 188) = 5.34</td>
<td>.022*</td>
</tr>
<tr>
<td>Sex (%) females</td>
<td>53</td>
<td>181</td>
<td>-0.016 (.012)</td>
<td>0.000 (.001)</td>
<td>F(1, 179) = 0.01</td>
<td>.907</td>
</tr>
<tr>
<td>Ethnicity (%) Minorities</td>
<td>53</td>
<td>186</td>
<td>-0.020 (.012)</td>
<td>0.000 (.000)</td>
<td>F(1, 184) = 0.53</td>
<td>.468</td>
</tr>
<tr>
<td>Psychopathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(1, 188) = 0.31</td>
<td>.577</td>
</tr>
<tr>
<td>Clinical diagnoses reported (RC)</td>
<td>6</td>
<td>10</td>
<td>-0.004 (.040)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>No clinical diagnoses reported</td>
<td>50</td>
<td>180</td>
<td>-0.018 (.012)</td>
<td>-0.023 (.041)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Childhood adversity characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of adversity</td>
<td>27</td>
<td>70</td>
<td>-0.023 (.012)</td>
<td>-0.026 (.019)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Other forms of adversity</td>
<td>46</td>
<td>134</td>
<td>-0.023 (.012)</td>
<td>-0.026 (.019)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Dimension of adversity</td>
<td>5</td>
<td>13</td>
<td>0.010 (.032)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Deprivation (RC)</td>
<td>23</td>
<td>67</td>
<td>-0.008 (.013)</td>
<td>-0.018 (.032)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Mixed (deprivation &amp; threat)</td>
<td>32</td>
<td>101</td>
<td>-0.001 (.016)</td>
<td>-0.048 (.035)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Proximity of adversity</td>
<td>27</td>
<td>70</td>
<td>-0.004 (.014)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Direct adversity (RC)</td>
<td>9</td>
<td>19</td>
<td>0.023 (.015)</td>
<td>-0.019 (.017)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Indirect adversity</td>
<td>55</td>
<td>181</td>
<td>-0.016 (.011)</td>
<td>0.002 (.002)</td>
<td>F(1, 187) = 0.82</td>
<td>.367</td>
</tr>
<tr>
<td>Mixed (direct &amp; indirect adversity)</td>
<td>55</td>
<td>181</td>
<td>-0.018 (.010)</td>
<td>0.005 (.002)</td>
<td>F(1, 187) = 7.28</td>
<td>.008***</td>
</tr>
<tr>
<td>Assessment of adversity: Informant</td>
<td>24</td>
<td>71</td>
<td>-0.007 (.017)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Self-report (RC)</td>
<td>39</td>
<td>119</td>
<td>-0.022 (.013)</td>
<td>-0.014 (.019)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Assessment of adversity: Type</td>
<td>47</td>
<td>166</td>
<td>-0.013 (.012)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Questionnaires (RC)</td>
<td>5</td>
<td>13</td>
<td>-0.052 (.036)</td>
<td>-0.039 (.038)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Official records</td>
<td>6</td>
<td>11</td>
<td>-0.022 (.037)</td>
<td>-0.009 (.039)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Timing of exposure to adversity</td>
<td>55</td>
<td>181</td>
<td>-0.016 (.011)</td>
<td>0.002 (.002)</td>
<td>F(1, 187) = 0.82</td>
<td>.367</td>
</tr>
<tr>
<td>Recency of exposure to adversity</td>
<td>55</td>
<td>181</td>
<td>-0.018 (.010)</td>
<td>0.005 (.002)</td>
<td>F(1, 187) = 7.28</td>
<td>.008***</td>
</tr>
<tr>
<td>vmHRV characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vmHRV Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time-Domain (RC)</td>
<td>27</td>
<td>79</td>
<td>0.000 (.015)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Frequency-Domain</td>
<td>28</td>
<td>108</td>
<td>-0.028 (.014)</td>
<td>-0.028 (.020)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Task duration included in analysis</td>
<td>53</td>
<td>170</td>
<td>-0.012 (.011)</td>
<td>-0.001 (.003)</td>
<td>F(1, 168) = 0.20</td>
<td>.652</td>
</tr>
<tr>
<td>Challenge task</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(2187) = 0.34</td>
<td>.715</td>
</tr>
<tr>
<td>Cognitive task (RC)</td>
<td>10</td>
<td>33</td>
<td>-0.004 (.023)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Emotion-eliciting task</td>
<td>41</td>
<td>93</td>
<td>-0.016 (.014)</td>
<td>-0.012 (.025)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Stress test</td>
<td>16</td>
<td>64</td>
<td>-0.028 (.019)</td>
<td>-0.024 (.029)</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Reactivity computation</td>
<td>17</td>
<td>73</td>
<td>-0.079 (.018)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Task mean levels (RC)</td>
<td>31</td>
<td>78</td>
<td>-0.007 (.014)</td>
<td>-0.086 (.024)**</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Difference score</td>
<td>12</td>
<td>37</td>
<td>-0.013 (.019)</td>
<td>-0.092 (.021)**</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Residualized change score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement of respiration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No respiration measurement reported</td>
<td>28</td>
<td>89</td>
<td>-0.004 (.016)</td>
<td></td>
<td></td>
<td>1.36</td>
</tr>
</tbody>
</table>
| Note. #k = number of studies; #ES = number of effect sizes; Z = Fisher’s Z correlation; SE = standard error; β1 = estimated regression coefficient; df = degrees of freedom; RC = reference category; vmHRV = vagally-mediated HRV  a For categorical moderators, a study can be represented in more than one moderator category if the effect sizes reported relate to different moderator categories. Thus, the sum of the number of studies (k) included in distinct categories belonging to the same moderator can exceed 55 (the total number of unique studies); b Omnibus test of all regression coefficients in the model; c continuous variable; d as effect sizes on task mean levels were inverted to ensure that all reactivity effect sizes were in the same direction, a negative coefficient Zr implies that higher levels of childhood adversity are related to higher task mean levels of vmHRV. + p < .1; * p < .05; ** p < .01; *** p < .001

as adverse parenting and peer victimization. As hypothesized, the severity of adversity was identified as a significant moderator, which contrasts findings of Sigrist et al. (2021) who did not find an overall association between maltreatment and resting vagal activity. These inconsistent findings may have arisen due to differences in the employed meta-analytical method and sample composition. However, when we included both proximity and severity of adversity in our multiple moderator model, the severity did not significantly add to an explanation of variance anymore. Integrating these findings, it seems plausible that besides severe adversity types such as maltreatment, also other less severe types that directly affect the child can influence vagal functioning.

Although the dimension of adversity was a significant moderator in the univariate model—showing that deprivation was associated with lower vagal activity than threat—it became non-significant after adjusting for the other moderators in multivariate analyses. As emphasized in previous studies examining the dimensional model of adversity, it is important to control for the exposure to threat in investigating the effects of deprivation (and vice versa), as both dimensions often co-occur (Busso et al., 2017). However, as we included only raw correlations in the meta-analysis, and most studies did not adjust for the co-occurrence in adversity dimensions, we were unable to investigate
adjusted associations. With regards to the categorization into dimensions of adversity, it further needs to be remarked that deprivation and threat may not always be clearly distinguishable, as for instance being neglected portrays a major threat to an infant’s life. Given that no moderation effect of the dimension of adversity was further found for vagal reactivity, we could not confirm that both dimensions of adversity differentially relate to vagal functioning. However, this may have been related to methodological aspects of the present meta-analysis and the studies included, and more research is needed to shed light on whether deprivation and threat affect vagal functioning in distinct ways.

5.3. Moderating effects in the association between childhood adversity and vagal reactivity to challenge

In the meta-analysis on vagal reactivity to challenge, we found that childhood adversity was more strongly associated with vagal reactivity in older individuals and if adversity had occurred less recently. These findings were in line with evidence from a recent meta-analysis showing that greater reductions in resting-state HRV in association with more severe exposure to maltreatment appeared in studies including older-aged samples as compared to younger samples (Sigrist et al., 2021).

As in our meta-analysis, the recency of adversity was operationalized by subtracting the age at exposure to adversity from the age at vagal reactivity measurement, and 60.6% of studies assessed these measures concurrently, both moderator variables were highly interrelated ($r = .91, p < .01$). This dependency of moderators may explain why the variable age did not withstand the multiple moderator model. Integrating these findings, the recency of adversity as compared to the mere age of participants seems to more strongly influence whether adversity-related alterations in vagal reactivity arise; however, a larger time in between exposure to adversity and assessments of vagal reactivity naturally implies that individuals are older. Therefore, our findings suggest that childhood adversity can set in motion a detrimental developmental cascade in which alterations in physiological system functioning become more apparent in the long run.

As a methodological moderator, the computation method of reactivity scores determined the strength of association between childhood adversity and vagal reactivity. A small significant association between childhood adversity and vagal reactivity was only present in studies which assessed reactivity through task mean levels as compared to studies which computed difference scores or residualized change scores from baseline to task. Childhood adversity was associated with higher mean levels of vmHRV during the challenge task, which reflects less arousal in the face of challenge. Integrating this finding with meta-analytic results showing no adversity-related differences in baseline vagal activity, it is conceivable that individuals with a history of adversity tend to demonstrate a rather blunted response to challenge, indicated by a lack of vagal withdrawal. However, this hypothesis is difficult to reconcile with the finding that no association between childhood adversity and vagal reactivity was present when reactivity scores included the baseline, which would rather suggest a similar extent of vagal arousal in adversity-exposed and non-exposed individuals.

5.4. Strengths and limitations of the meta-analysis

This study has several strengths. Based on two separate meta-analyses, we examined associations between childhood adversity with both vagal activity under baseline conditions and vagal reactivity in response to challenge, providing a quantitative summary of a complex literature with heterogeneous findings. In order to include unpublished effect sizes that may therefore more likely represent ‘null results’, we sent data requests to authors of studies in which the relevant measures of childhood adversity and vagal regulation were assessed. Indeed, many of the provided correlations were non-significant and inclusion of these

<table>
<thead>
<tr>
<th>Moderator</th>
<th>$\beta$ (SE)</th>
<th>95% CI</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-.082 (.017)</td>
<td>[-.115; -.049]</td>
<td>-4.954</td>
<td>&lt; .001***</td>
</tr>
<tr>
<td>Age</td>
<td>-.000 (.002)</td>
<td>[-.004; .003]</td>
<td>-0.969</td>
<td>.373</td>
</tr>
<tr>
<td>Recency of adversity</td>
<td>.006 (.003)</td>
<td>[.000; .011]</td>
<td>2.152</td>
<td>.033*</td>
</tr>
<tr>
<td>Reactivity computation: difference score (vs. mean levels)</td>
<td>.091 (.020)</td>
<td>[.052; .131]</td>
<td>4.549</td>
<td>&lt; .001***</td>
</tr>
<tr>
<td>Reactivity computation: residualized change score (vs. mean levels)</td>
<td>.088 (.023)</td>
<td>[.043; .133]</td>
<td>3.837</td>
<td>&lt; .001***</td>
</tr>
</tbody>
</table>

$+p < .1; * p < .05; *** p < .001$

*Fig. 7.* Funnel plots of the meta-analysis on childhood adversity and vagal reactivity. (A) Funnel plot of all effect sizes and (B) study-funnel plot that includes the number of outcomes reported in each study. In Fig. 7B, the size of the dots is proportional to the number of effect sizes included in those studies.
was likely to contribute to the overall lack of association in both meta-
analyses. Given the reliance on a three-level meta-analytic model, we
were able to include multiple effect sizes per study, thereby allowing for
the examination of different adversity types that can vary within studies.
Further, researchers interested in conducting more nuanced analyses
such as comparing different abuse subtypes or testing for moderators
within specific adversity types are referred to the Supplemental Material
in which the data set and script for statistical analyses are provided.
Another strength portrays the rigorous testing of the significance of in-
dividual moderators by combining them in a unique moderator model.

The present work has several limitations as well. First, we focused on
only one specific aspect of ANS functioning, while other indices
reflecting the functioning of the parasympathetic and sympathetic
branch (or a combination of both) may be uniquely influenced by
childhood adversity, including the ratio between low- and high-
frequency power (LF/HF), blood pressure, skin conductance, and heart
rate (Appleton et al., 2017; Miski et al., 2015; Tell et al., 2021; Voell-
min et al., 2015; Wilshire et al., 2022). Second, we did not include effect
sizes on the association between childhood adversity and vagal recovery
after challenge. While poor cardiovascular recovery following stress
may be more relevant for the interpretation of pathology than stress
reactivity itself (Panait et al., 2015), not many studies have specifically
investigated recovery (for an exception, see e.g., McLaughlin et al.,
2014). Third, we did not account for factors that can influence vagal
functioning, including smoking, alcohol consumption, meal intake,
physical training, and daytime (Laborde et al., 2017). While several
studies implemented specific instructions in the study protocol for
handling these issues, others statistically corrected for potential con-
founds or did not report on it. Given these different approaches, we
relied on raw correlations between childhood adversity and vagal
regulation to avoid potential variability in methodology. Last, a major
drawback that specifically applies to the reactivity meta-analysis was
that effect sizes based on correlations between adversity and vagal
reactivity failed to do justice to the fact that adversity-related alterations
may pertain to both vagal augmentation and vagal withdrawal. Put
simply, while some individuals exposed to adversity may react to chal-
lenge with excessive vagal withdrawal, others may demonstrate
excessive vagal augmentation, and approaches such as group compar-
sions or correlations would conceal these more specific alterations in
vagal reactivity. As an alternative, a pattern-based approach to vagal
reactivity may be more suitable to capture heterogeneity in
adversity-related alterations in vagal reactivity. Applying such an
approach, Cui et al. (2019) found that neighborhood violence was
positively associated with aggressive behavior only in those adolescents
who showed RSA augmentation to a film clip portraying bullying but not
in those who showed RSA suppression.

5.5. Recommendations for future studies

To date, meta-analyses on psychobiological correlates of childhood
adversity have commonly focused on a single biological system such as
the PNS (Sigrist et al., 2021), the HPA axis (Bernard et al., 2018; Bunea
et al., 2017; Fogelman and Canli, 2018), or the immune system (Kuhl-
man et al., 2020). However, it is possible that alterations only become
apparent at the level of interaction between multiple biological systems.
To exemplify, it has been proposed that the degree of covariation be-
 tween psychological arousal, the HPA axis, and inflammation may
become apparent at the level of interaction between multiple biological systems.

The present work has several limitations as well. First, we focused on
only one specific aspect of ANS functioning, while other indices
reflecting the functioning of the parasympathetic and sympathetic
branch (or a combination of both) may be uniquely influenced by
childhood adversity, including the ratio between low- and high-
frequency power (LF/HF), blood pressure, skin conductance, and heart
rate (Appleton et al., 2017; Miski et al., 2015; Tell et al., 2021; Voell-
min et al., 2015; Wilshire et al., 2022). Second, we did not include effect
sizes on the association between childhood adversity and vagal recovery
after challenge. While poor cardiovascular recovery following stress
may be more relevant for the interpretation of pathology than stress
reactivity itself (Panait et al., 2015), not many studies have specifically
investigated recovery (for an exception, see e.g., McLaughlin et al.,
2014). Third, we did not account for factors that can influence vagal
functioning, including smoking, alcohol consumption, meal intake,
physical training, and daytime (Laborde et al., 2017). While several
studies implemented specific instructions in the study protocol for
handling these issues, others statistically corrected for potential con-
founds or did not report on it. Given these different approaches, we
relied on raw correlations between childhood adversity and vagal
regulation to avoid potential variability in methodology. Last, a major
drawback that specifically applies to the reactivity meta-analysis was
that effect sizes based on correlations between adversity and vagal
reactivity failed to do justice to the fact that adversity-related alterations
may pertain to both vagal augmentation and vagal withdrawal. Put
simply, while some individuals exposed to adversity may react to chal-
lenge with excessive vagal withdrawal, others may demonstrate
excessive vagal augmentation, and approaches such as group compar-
sions or correlations would conceal these more specific alterations in
vagal reactivity. As an alternative, a pattern-based approach to vagal
reactivity may be more suitable to capture heterogeneity in
adversity-related alterations in vagal reactivity. Applying such an
approach, Cui et al. (2019) found that neighborhood violence was
positively associated with aggressive behavior only in those adolescents
who showed RSA augmentation to a film clip portraying bullying but not
in those who showed RSA suppression.

5.5. Recommendations for future studies

To date, meta-analyses on psychobiological correlates of childhood
adversity have commonly focused on a single biological system such as
the PNS (Sigrist et al., 2021), the HPA axis (Bernard et al., 2018; Bunea
et al., 2017; Fogelman and Canli, 2018), or the immune system (Kuhl-
man et al., 2020). However, it is possible that alterations only become
apparent at the level of interaction between multiple biological systems.
To exemplify, it has been proposed that the degree of covariation be-
 tween psychological arousal, the HPA axis, and inflammation may
predict long-term health outcomes after adversity (Kuhlman et al.,
2017). More studies are needed that incorporate the measurement of
multiple systems in the same sample to advance the understanding of
how childhood adversity increases risk for later (psycho)pathology (see
for example, Goulter et al., 2021; Rudd et al., 2021). Given common reliance on
time- and frequency domain (linear) measures of vagal regulation, the
inclusion of nonlinear measures of HRV that would capture potential
alterations in the structure or complexity of the IBI time series is an
important issue for future research (Kleiger et al., 2005). As many of the

5.6. Conclusions

In conclusion, although meta-analytic results did not reveal a sig-
ificant association between childhood adversity and vagal regulation,
such an association may be present under certain circumstances. More
specifically, lower levels of baseline vagal activity were found in asso-
ciation with childhood adversity in samples including participants with
clinical diagnoses and in association with direct adversity (including
maltreatment, adverse parenting and peer victimization). Further, the
association between childhood adversity and lower levels of vagal
reactivity was stronger when adversity had occurred longer ago and
when reactivity scores were operationalized through task mean levels.
More research is needed to gain an integrated understanding of bio-
logical mechanisms underlying the association between childhood
adversity and (psycho)pathology, factors of vulnerability and resilience
along this pathway, and the malleability of physiological systems
following intervention.

Other information

This meta-analysis was pre-registered on the 15th of September 2020
through a web-based protocol on the International Prospective Register
of Systematic Reviews (PROSPERO; Booth et al., 2012) before study
selection (registration number: CRD42020198115). Amendments to
information provided at registration are reported in the online Supple-
mental Material. Further, data sets and scripts for statistical analyses can
be found online (link for peer review).

Declaration of Competing Interest

The authors declare that they have no competing financial interests.

Data Availability

The datasets used in both meta-analyses and corresponding scripts
for statistical analyses are available online (https://osf.io/cyumb/).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104920.

References

References with an asterisk (*) were included in the meta-analysis.
