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The association between adversity and hair cortisol levels in humans: A meta-analysis

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Abstract

Adverse life events are associated with a constellation of negative health outcomes. Theory and research suggest that the hypothalamic-pituitary-adrenal (HPA) axis acts as one mechanism connecting adverse experiences with negative health outcomes. However, this relation is complicated by the potential for adversity to be associated with both hyperactivity and hypoactivity of the HPA axis, as assessed in both animal and human studies. Over the past decade, methodological advances have enabled the sampling of cortisol stored in hair, which provides a marker of HPA axis activity over a several-month period. The present meta-analysis included 28 studies to assess the strength and direction of the relation between adverse experiences and hair cortisol levels. Analyses were conducted using multilevel modeling (MLM) to quantify the magnitude of effects and mixture modeling to identify distinct subgroups of studies. Results of MLM analyses indicated that the overall effect size was small but significant d=0.213, 95% CI [0.034, 0.397]. There was also significant between-study variance (τ=0.155, 95% CI [0.065, 0.367]). Mixture modeling to identify distinct classes of studies based on effect size and direction resulted in a 2-class model: The first class included four studies with an overall negative and moderate effect size (d=−0.478, 95% CI [−0.639, −0.318]), and the second class included the remaining 24 studies with an overall positive and significant, albeit small, effect size (d=0.141, 95% CI [0.084, 0.199]). Moderator analyses indicated that the strength and direction of the association between adversity and hair cortisol were moderated by features of the adversity exposure (e.g., type of adversity, timing of adversity), characteristics of the samples (e.g., clinical status, racial distribution), and features of the publication (e.g., publication type, geographic region of study). The findings refine our understanding of the long-term impact of adversity on dysregulation of the HPA axis, particularly as reflected in hair cortisol measures.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Keywords

Hair cortisol; Chronic stress; Adversity; Adverse experiences; Trauma; Meta-analysis

1. Introduction

Adverse life events are associated with a plethora of negative mental and physical health outcomes throughout the lifespan (Gallagher et al., 2009; Reynolds, 2013; Turner-Cobb, 2005). The hypothalamic-pituitary-adrenal (HPA) axis is a primary stress system that functions as a mechanism linking stressful life events and adverse health outcomes (e.g., Aguilera, 2011). The brain and body, as well as the stress systems that comprise them, are designed to adaptively respond to internal and external threats. The HPA axis does so by releasing cortisol in response to acute threat and down-regulating the cortisol response, through a negative feedback loop, when no longer under acute treat (Sapolsky et al., 2000). Deleterious health effects are caused by dysregulation of the HPA axis, which can include intense or chronic over-activation or under-activation (Chrousos, 2009), known as allostatic overload (McEwen, 1998).

Until recently, assessing chronic HPA activity was difficult, given that cortisol could only be assessed from saliva, blood serum, or urine, measures that indicate acute (i.e., serum, saliva) or short-term (i.e., 12–24 h; urine) cortisol alterations. Further, the aforementioned means of cortisol assessment are subject to great variability due to circadian rhythms (Spiga et al., 2014), individual differences in state arousal (Dickerson and Kemeny, 2004), and food consumption (Gibson et al., 1999). Recent methodological advances have enabled the sampling of cortisol in hair particles, providing a reliable retrospective measure of HPA axis activity over several months (Russell et al., 2012; Stalder and Kirschbaum, 2012). The average rate of hair growth rate is 1 cm/ month; thus, 3 cm of hair corresponds to hair grown over a three-month period (Wennig, 2000). The process of hair cortisol analyses involves cutting hair from the scalp, mincing the hair, extracting cortisol by methanol, and analyzing cortisol concentrations using either immune assays or liquid chromatography-mass spectrometry (LC/ MS) (Gow et al., 2010; Manenschijn et al., 2011). Although a relatively novel approach, hair cortisol has shown high test-retest reliability (Stalder and Kirschbaum, 2012) and has been validated against salivary (Xie et al., 2011) and urinary cortisol (Sauve et al., 2007). Moreover, the confounders noted above that influence saliva, blood serum, and urine measures do not affect hair cortisol.

The experience of adversity, including maltreatment (abuse and neglect), domestic violence, and exposure to traumatic events, such as accidents, war/combat, and natural disasters, can have an enduring impact on health. These adverse life experiences are associated with a range of negative mental and physical health outcomes, including depression, PTSD, suicide, non-suicidal self-injury, and cardiovascular disease (Chartier et al., 2010; Galea et al., 2005; Kaess et al., 2013; Steptoe and Kivimäki, 2013). Adverse experiences are also associated with atypical cortisol activity (Steudte-Schmiedgen et al., 2016). However, the direction of association between adversity and cortisol has varied, with some studies suggesting that those who have experienced adversity have higher salivary cortisol reactivity

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(Harkness et al., 2011), as well as higher diurnal salivary cortisol levels (Dozier et al., 2006), while other studies have reported lower salivary cortisol reactivity (Ouellet-Morin et al., 2011) and lower diurnal salivary cortisol levels (Alink et al., 2012).

Similarly, individuals who experience PTSD symptoms following exposure to a traumatic event have been shown to experience both elevated (Bremner et al., 2003; Elzinga et al., 2003) and blunted (Wessa et al., 2006) cortisol patterns. Meta-analytic findings confirm the variability in the direction of effects between PTSD and salivary, plasma, and urinary cortisol levels (Klaassens et al., 2012; Meewisse et al., 2007).

Similar to the adversity-cortisol research noted above, the broader stress literature suggests that chronic stress can cause both hyper- and hypo-activation of the HPA axis (e.g., Miller et al., 2007 for review). Several theories suggest that chronic stress can cause dysregulation in the HPA axis, known as allostatic overload, which can manifest as prolonged hyper-activation or hypo-activation (McEwen, 1998, 2007). Under ideal conditions when cortisol production reaches an optimal level, cortisol binds to glucocorticoid receptors to initiate a negative feedback loop, resulting in the halt of the hormone production (Sapolsky et al., 2000). However, under conditions of chronic or repeated stress, this negative feedback loop is altered, resulting in dysregulation of the HPA axis. Stressors cause an initial hyper-activation of the HPA axis, leading to periods of elevated cortisol that are not counteracted appropriately by the negative feedback loop (Guilliams and Edwards, 2010). Over the long-term, with exposure to prolonged or chronic stress, this hyper-activation causes a number of biological changes throughout the HPA axis (Fries et al., 2005), changes that can eventually result in an under-responsive, hypo-active system (Guilliams and Edwards, 2010). Therefore, the variable findings in the adversity-cortisol literature are consistent with basic research on the hyper- and hypo-activation of the HPA axis under conditions of chronic stress (Chrousos, 2009). Given the complexity in how the HPA axis responds to stress, the present meta-analysis seeks to understand the particular factors that impact whether adversity is associated with hyper-activity or hypo-activity as assessed by hair cortisol concentrations (HCC).

Both timing and type of adversity may be factors that influence whether the relation between adversity and cortisol levels is positive or negative. It is likely that different types of adversity, such as maltreatment, war, or natural disasters have a different impact on HPA activity. Further, many of these kinds of adversity, and in particular maltreatment, vary in nature (i.e., types of maltreatment), intensity, and pervasiveness (i.e., time of onset, duration and frequency of exposure) (Kalmakis and Chandler, 2014), which all have the potential to impact the HPA axis. Data suggest that severe physical neglect is associated with low morning cortisol levels, whereas severe emotional maltreatment is associated with high morning cortisol levels among children in foster care (Bruce et al., 2009). Therefore, in addition to the type of adversity, the subtype of maltreatment might have varying effects on HPA activity. Further, there is evidence that adversity-related changes in HPA activation can vary across development (Bosch et al., 2012; Trickett et al., 2010), with younger children showing elevated cortisol levels compared to adolescents and young adults, who show depressed cortisol levels. In addition, the time since the onset of the stressor can impact the direction of the cortisol response, such that cortisol activity tends to be elevated close to the

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onset of the stressor but reduces as time passes (Miller et al., 2007). It is noteworthy that the age of the sample, age of adversity, and time since adversity are often confounded in the literature. Taken together, in addition to type of adversity, the subtype of maltreatment (physical, emotional, sexual abuse, or neglect), the age of exposure to adversity, and time since exposure to adversity are important factors to consider.

Given the extensive interest in adversity and HPA activity, a burgeoning literature assessing HCC has emerged. In the hair cortisol literature, findings also vary as to whether adversity is related to increases or decreases in HCC. For example, in a community sample of children, lifetime exposure to trauma was associated with elevated HCC (Simmons et al., 2016). However, in another study, maltreated children exhibited lower HCC compared to non-maltreated children (White et al., 2017). Further, in combat-exposed soldiers, lower HCC predicted more severe PTSD symptoms following traumatic exposure (Steudte-Schmiedgen et al., 2015). Given these differing results, in the context of a number of potential methodological and sample-related contributors, a quantitative synthesis that includes a close examination of potential moderating factors suggested by the existing literature is warranted.

Meta-analysis is the gold-standard for quantitative synthesis. Stalder et al. (2017) recently completed the first meta-analysis of the hair cortisol literature, in which they reviewed studies on HCC to determine the relevant covariates and basic features of HCC. They also explored the relation between HCC and a range of chronic-stress-related measures, including self-reported perceived stress, chronic stress, and mental health problems (e.g., anxiety and mood disorders). Examples of chronic stress assessed included caregiving stress, unemployment, shift work, chronic pain, and surviving an earthquake. Stadler et al. showed that HCC differed by sex (with males having higher HCC), age (with older individuals having higher HCC), BMI (higher BMI associated with higher HCC), and proximal length of hair to scalp (less HCC after first proximal 3-cm hair segment). Regarding chronic and perceived stress, chronic stress was associated with elevated HCC; however, there was not a significant relationship between perceived stress and HCC.

Although Stalder et al. (2017) examined the impact of chronic and perceived stress on HCC, they did not comprehensively explore associations between a range of adverse experiences (e.g., maltreatment, domestic violence, natural disasters, accidents) and HCC. The present meta-analysis seeks to add to the existing literature by focusing specifically on the association between different types of adversity and HCC. To date, studies of adversity and HCC have included many types of adverse experiences. By examining associations between different types of adversity and HCC, as well as exploring relevant covariates and moderators, this meta-analysis seeks to address the variability in the literature regarding the magnitude and direction of effects between adversity and cortisol.

The first objective of the present meta-analysis was to systematically summarize and quantify the strength of the relation between adversity and HCC. A range of adversity types were examined, including maltreatment, domestic violence, and exposure to other traumas, such as accidents, war/combat, and natural disasters. Given the complexities inherent in how the HPA axis responds to chronic stress, our second objective was to examine whether there

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are differences in magnitude and direction of effect that identify distinct classes of studies assessing the relation between adversity and HCC (e.g., strong and positive relations between adversity and HCC, no relation, or a strong and negative relation). The third objective of this meta-analysis was to explore participant and methodological characteristics that may moderate the strength and direction of observed relations between adversity and HCC.

Potential moderators were chosen based on the extant literature. These moderators included type and timing of adversity, as well as sample characteristics, characteristics of HCC assessment, and publication characteristics. Regarding the type and timing of adversity, we tentatively hypothesized that the type of adversity would be a moderator in that those who were exposed to maltreatment, in particular, would experience blunted HCC levels compared to those who experienced other types of adversity, since maltreatment is often chronic. We also hypothesized that timing of adversity would also be a significant moderator, with those exposed to adversity in childhood showing a significant but negative effect on HCC levels, compared to those not exposed to adversity in childhood, because the potentially severe and persistent activation of the HPA axis in childhood might lead to hypoactivation over time. We hypothesized that more recent adult adversity is associated with elevated HCC levels, consistent with hyper-activation, due to the recency of the adversity. However, one might also predict that the effects of childhood adversity would ‘wash out’ over time, leading to smaller absolute effect sizes, while adult absolute effect sizes would be larger due to recency of the events. Given the aforementioned inconsistencies in the HCC literature, these moderator hypotheses are exploratory in nature.

Importantly, the effects of type and timing of adversity are confounded in the literature, in that all studies of adversity during childhood examine maltreatment, whereas there is more variability in types of adversity occurring during adolescence and adulthood. Therefore timing of adversity could not be separated conclusively from type of adversity. In addition, given the available literature, short duration of adversity could not be reliably differentiated from longer duration of adversity, so no hypotheses are offered regarding duration of adversity.

2. Methods

2.1. Literature search and study selection

A comprehensive search was conducted on several databases (PsycINFO, MEDLINE, Social Science Index, EMBASE, Dissertation Abstract International) to obtain published and unpublished research. The following search terms were used: “hair cortisol” *and* “maltreatment,” “neglect,” “abuse,” “adversity,” “early life stress,” “trauma,” “posttraumatic stress disorder,” “PTSD,” “stress,” “stressor,” “adverse events,” “negative events,” “negative life events,” “life events,” “violence,” “assault,” “rape,” or “accident.” This search included articles published prior to November 2017 that were published in English and used human participants. The literature search yielded 1576 articles, including 590 unique articles. Duplicate articles (e.g., dissertations that were later published) and articles that used the same sample were excluded. When multiple articles used the same sample, the article that included the most outcome data was included in the meta-analysis. In the event that two

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articles that used the same sample included identical outcome data, the article with the larger sample size was included. Duplicate studies and studies using the same sample were excluded because meta-analyses should have independent study-level effects (Rosenthal, 1991).

Studies were included if they 1) were an empirical study (i.e., not a literature review), 2) included a measure of hair cortisol, 3) included a measure of adversity or trauma (e.g., maltreatment, domestic violence, PTSD following traumatic exposure, non-specific lifetime trauma), and 4) provided outcome data that could be used to compute an effect size. See Fig. 1 for a flow chart of study inclusion. Fourteen studies met the first three requirements but did not provide relevant data to compute an effect size. The corresponding authors of these studies were contacted, and data were requested; five authors provide the requested data. In total, 28 articles were included in the present meta-analysis; 25 were published articles, 2 were dissertations, and 1 was a published abstract.

2.1.1. Reliability of study selection and coding study variables—The lead author reviewed all abstracts and full text articles for study inclusion and coded variables for all eligible studies. Two research staff completed reliability checks. First, a research staff reviewed all 590 abstracts/full-text articles for inclusion. There was 97% agreement between the lead author and staff member on which studies to include. Disagreements on 19 articles (3% of total articles) were discussed, and the final inclusion decisions reflect the consensus of both raters. A second staff member coded six (20%) randomly selected studies of the 28 studies that met inclusion criteria. Intraclass correlations across all coded continuous variables ranged from 0.85 to 1.00 (mean=0.96, SD=0.06), and kappas across all coded categorical variables ranged from 0.78 to 1.00 (mean=0.96, SD=0.08). Disagreements were discussed, and the final coding reflects the consensus of both coders.

2.2. Coding of study variables

Several methodological variables were coded to be assessed as potential moderators. These variables included factors associated with the article publication (e.g., publication year, publication status), sample characteristics, hair cortisol measurement, and assessment of adversity.

2.2.1. Article characteristics—As is routine practice for meta-analyses (e.g., Madigan et al., 2016), the geographical region where the study was conducted was coded (North America, Europe, Africa, China, Brazil). In addition, the year of publication and the publication status (peer reviewed article, dissertation) were coded for all studies.

2.2.2. Sample characteristics—Sample characteristics were coded based on the overall sample unless data were provided separately for subgroups within a sample (e.g., trauma-exposed and non-exposed groups). The following participant characteristics were coded: a) the number of individuals in the sample, b) the age category of the sample (i.e., child, adolescent, adult), c) the mean age of participants, d) the sex distribution (i.e., % male), e) the racial composition (i.e., % White), f) the percentage of the sample who smoked, g) the percentage of the sample taking medication, and h) the mean body mass

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index (BMI) of the sample. The clinical status (clinical diagnosis, no clinical diagnosis) of the sample was also coded. Specifically, studies were classified as including a clinical sample if the primary inclusion criterion for the sample was meeting diagnostic criteria for a psychological disorder (e.g., inpatients with Depressive Disorders) and/or the study provided outcome data for a clinical group compared to a healthy control group. In addition, samples were classified by PTSD diagnosis (PTSD diagnosis, non-PTSD) when relevant data were available.

In addition to the above sample characteristics, we attempted to code education level as a measure of socioeconomic status. However, education level, which was only reported in seven studies, was measured differently across studies. For example, some studies reported number of years of education and others reported the percentage of the sample falling into different educational categories (e.g., less than high school, some college, college, graduate). Given this inconsistent reporting, we were unable to statistically assess education level as a moderator.

2.2.3. Adversity measurement—Factors associated with the assessment of adversity were coded. These factors included the name of the specific questionnaire, the category of adversity (i.e., maltreatment, domestic violence, war/combat exposure, natural disaster, accident, lifetime trauma), the subtype of maltreatment (i.e., emotional, physical, sexual abuse, neglect), the type of measurement (i.e., questionnaire, interview, other), and the time period during which the adversity occurred (i.e., childhood, adulthood). The time period during which the adversity occurred differs from age of sample described above, given that several samples were adults retrospectively reporting experiences of maltreatment that occurred during childhood. We also dichotomized the category of adversity to explore whether maltreatment differed from other types of adversity (i.e., maltreatment vs other adversity). Among studies that assessed maltreatment, all but two (Boeckel et al., 2017; White et al., 2017) retrospectively assessed childhood maltreatment in adolescence or adulthood, in contrast Boeckel et al. (2017) included a sample of children who witnessed domestic violence and White et al. (2017) included a sample of maltreated children, classified based on the maternal report and child protection service records.

It should be noted that maltreatment was the only type of adversity that occurred in childhood (although studies assessed other types of adversity in adolescence). All studies that assessed other forms of adversity (e.g., domestic violence, natural disasters, combat exposure) included adolescent or adult samples only. Therefore, given the age and adversity distributions among studies, it was not possible to definitively separate timing of adversity from type of adversity. Because different types of maltreatment often occur in combination and because repeated experiences of adversity (e.g., maltreatment in childhood and subsequent trauma) likely have unique impact on HPA activity, we also explored the possibility of assessing repeated adversity as a moderator. However, only one study examined the impact of experiencing both maltreatment in childhood and subsequent interpersonal violence (Morris et al., 2017) on HCC; thus, we could not examine number of adversities (or single/multiple adversities) as a moderator. Similarly, we could not explore the age of onset of maltreatment or the duration of maltreatment as this information was not reported in a sufficient number of studies.

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2.2.4. Features of hair cortisol samples—Several features related to hair cortisol samples were coded. These features included the type of hair extraction procedure used (i.e., immunoassay [ImA]), liquid chromatography tandem mass spectrometry (LCMS), the length of the hair samples, the time period to which the sample corresponds (e.g., past 3 months), the mean number of times participants washed their hair per week, and information related to hair treatment and coloring.

2.3. Meta-analytic procedures

Individual studies varied in the way in which they presented out-come data. Data were presented as 1) Pearson correlation coefficients between adversity measures and HCC; 2) means and standard deviations of HCC for adversity and control groups, 3) *t*-tests describing the statistical difference in HCC between adversity and control groups, and 4) odds ratio and confidence limits for adversity and HCC. All outcome data were entered into Comprehensive Meta-Analysis Version 3.0 (CMA; Borenstein et al., 2005) and converted to a standardized point estimate effect size (Cohen's *d*), along with the corresponding effect size variance and confidence intervals (CI) (Hedges and Olkin, 1985). Effect sizes were weighted based on the sample sizes. Cohen (1988) classified standardized effect sizes into descriptive categories based on size: *d*=.20 (small), *d*= .50 (medium), and *d*=.80 (large) effects.

All analyses were performed using M*Plus* version 8.1 (Muthén and Muthén, 2017). Analyses for Objectives 1 and 3 were performed using three-level multilevel models (MLM; Cheung, 2015; Van den Noortgate et al., 2013). Three-level MLM permits the inclusion of multiple effect sizes per study while adequately dealing with the non-independent nature of the data (i.e., effect sizes are nested within studies). Our analyses were performed using a random effect model that assumes that there is one population of effect sizes (i.e., with a mean and a variance that need to be estimated), and permits heterogeneity of effect sizes, which prevents effect size overestimation when heterogeneity in effects is present (Cooper and Hedges, 1994). In contrast with a more typical random effect model which models only the sampling variance of the observed effect size, the three-level MLM decomposes the variances of effect sizes into three components: sampling variance of the observed effect size, within-study variance (i.e., variance between effect sizes within a study), and between-study variance (i.e., variance in effect sizes between studies). In the case of the three-level model for the moderator analyses (Objective 3), the moderators were entered as predictors of variance in effect size. The moderators were either allowed to predict between-study variance (if their values varied across studies but not within studies) or both within-study and between-study variance (if their values varied across and within studies).

These models were estimated using Monte Carlo Markov Chain (MCMC) estimation, as we had few clusters (i.e., each study represents a cluster so that there were 28 clusters). Indeed, MCMC estimation can provide accurate parameter estimates for multilevel models with as few as 20 clusters (Hox et al., 2012). We report model estimates as well as their 95% Credible Interval[1] (95% CI) based on higher posterior density. Models were estimated with 50,000 iterations. Model convergence was estimated based on the potential scale reduction and by examining trace plots for irregularities (Hamra et al., 2013; Muthén, 2010).

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Analyses to identify subclasses of effects (Objective 2) were performed using fixed-effect meta-analytic mixture modeling (Cheung, 2015). Instead of assuming that there is only one population of heterogeneous effect sizes, the fixed effect meta-analytic mixture model assumes that effect sizes are from distinct but homogeneous subpopulations. Heterogeneity in effect sizes across studies is therefore explained by membership in different homogeneous populations, referred to as classes. The appropriate number of classes is identified by comparing models with an increasing number of classes and stopping when either the fit indices become statistically inferior or when classes are too small (Nylund et al., 2007). For the three following fit indices, lower numbers indicate better model fit: Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC), and sample size adjusted BIC (aBIC). The BIC is given priority given its good performance at identifying the correct number of classes (Nylund et al., 2007). A BIC difference of 10 is considered strong evidence in favor of the model with the lowest BIC (Nagin, 1999). We also report the Lo-Mendell-Rubin Likelihood Ratio Test (LMR) and the ad hoc adjusted LMR (aLMR), with a significant *p*-value indicating that a model with *k*-1 subgroups should be rejected in favor of the model with *k* classes (Tein et al., 2013). A final index is entropy, which indexes classification accuracy, with values above .80 indicating very good classification accuracy (Tein et al., 2013). These analyses were performed using the robust maximum likelihood estimator, and we report the estimates as well as their 95% Confidence Interval (95% CI). Since one cannot combine three-level models and mixture models in M*Plus*, we could only use a single effect size per study to examine Objective 2. In the event that a single study provided data for multiple outcomes of interest, these effect sizes were averaged so that there was only one weighted effect size for each individual study for mixture modeling analyses.

2.3.1. Data analytic plan—Analyses were performed in three steps. First, we used a three-level multilevel model to assess the overall magnitude of the association between adversity and hair cortisol, as well as the variance in effect sizes due to within-study and between-study variation (Van den Noortgate et al., 2013). Second, using mixture modeling (Cheung, 2015), we investigated whether there were multiple classes of studies with homogeneous effect sizes. Third, using multilevel modeling, analyses were performed to identify moderators associated with systematic variations in effect size. Moderator analyses were performed based on all effect sizes for which moderator data were present. For continuous moderators, we report the slope indexing the linear association between a moderator and variations in effect size. We also tested non-linear effects by including quadratic slopes. For categorical moderators, it is not possible to compute an omnibus test comparable to the Q statistic when using three-level models in M*Plus*. Instead, differences in effect sizes were investigated by creating new parameters capturing the difference between two estimates using the MODEL CONSTRAINT command (Muthén and Asparouhov, 2013). Two estimates were considered statistically different if the 95% CI for the new difference parameter did not include zero.

[1]When using MCMC, (Bayesian) credible intervals are reported instead of (frequentist) confidence intervals. With a large prior variance (as is the case here) and large samples, both approaches should lead to comparable results, but the former are more accurate in smaller samples (Muthén and Asparouhov, 2012)

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3. Results

3.1. Descriptive statistics

The 28 studies included in this meta-analysis consisted of a total of 3397 participants. Studies varied greatly in terms of sample composition. The average age of participants was 25.06 years old (*SD*=5.01). On average, samples consisted of 39.05% males and were 40.18% White race. See Table 1 for a description of sample and methodological characteristics of each study.

3.2. Overall effect of adversity on hair cortisol

In relation to our first aim, a three-level multi-level model was used to determine the magnitude of the mean effect of adversity on HCC. Here, we used a model without covariates to obtain an average estimate of the outcome (i.e., effect size), as well as its variation both within and across studies. Standardized mean effect sizes representing the impact of adversity on hair cortisol levels for each study are presented in Table 2. Taking into account all studies (k = 28), using all available effect sizes (n = 71), the estimated average effect size was 0.213, 95% CI [0.034, 0.397]. The model also showed that effect sizes were heterogeneous due to variations both within and between studies. The within-study variance (τ=0.034, 95% CI [0.003, 0.108]) was about five times smaller than the between-study variance (τ=0.155, 95% CI [0.065, 0.367]), with 82.7% of the total variance in effect size (0.155/ (0.034+0.155)=0.827). Given the significant heterogeneity in the magnitude and direction of the effects of adversity on HCC, we followed up these overall analyses, first, with mixture modelling to assess the presence of coherent classes of studies with similar effect sizes, and, second, with a series of moderator analyses.

3.3. Identifying coherent classes across studies

In relation to the second aim, we sought to determine whether there were distinct subpopulations of studies with homogeneous effect sizes. Fit indices of the mixture model with one to four classes are reported in Table 3. The AIC, BIC and aBIC showed substantial improvements when moving from one to two classes, comparatively smaller improvements when moving from two to three classes (i.e., the difference in BIC is less than 10), and showed worse fit when moving from three to four classes. The LMR and aLMR indicated that adding a second and a third class resulted in a significant improvement in fit, whereas this was not the case for the addition of a fourth class. Entropy was very good for the 2-class model and sufficiently good for the 3- and 4-class models. However, the lower entropy for the 3- and 4-class models indicated that the classes were less well separated in the 3- and 4-class models compared to the 2-class model. In other words, there was more uncertainty regarding the class to which each study belonged. In sum, while some indicators suggested that the 3-class model was a better fit than the 2- class model (LMR and LRT), the difference was small (according to the difference in BIC) and classes were less well separated (as indicated by the decrease in both BIC and entropy). Thus, the 2-class model was chosen as the most parsimonious fixed effects model.[2]

Results best indicated two classes of studies. One class of studies produced negative effects (i.e., more adversity was associated with lower hair cortisol), and the other class of studies

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produced positive effects (i.e., more adversity was associated with higher hair cortisol). Specifically, the first class included four studies with an overall negative direction of effect and a moderate effect size (d = −0.478, 95% CI [−0.639, −0.318]). The second class included the remaining 24 studies with an overall positive and significant, albeit small, effect size (d=0.141, 95% CI [0.084, 0.199]). These results are consistent with theories that adversity may lead to both hypo- and hyper-activation of the HPA axis (Chrousos, 2009).

The first class included four studies that together produced a medium-sized negative effect. These four studies (Hinkelmann et al., 2013; Melhem et al., 2017 Steudte et al., 2013; White et al., 2017) provided a total of nine effects, of which eight were significantly different from zero. Although there was some heterogeneity, these four studies all assessed forms of maltreatment, some through questionnaires (i.e., CTQ) and others through interviews (e.g., Maternal Maltreatment Classification Interview), providing some support for the hypothesis that maltreatment would be associated with cortisol hyporeactivity. Three of the four studies were based on adult samples retrospectively reporting maltreatment, while the fourth was based on a maltreated child sample (White et al., 2017). Further, the adult sample characteristics varied greatly, including samples of psychiatric patients and individuals with PTSD. The second class included 24 studies that produced a small but significant positive effect. These 24 studies produced a total of 66 effect sizes. Of importance, only 19 of these 66 effects (from 13 unique individual studies) were significantly different from zero ($p < .05$; Table 2). These studies varied greatly in terms of the types of adversity assessed (maltreatment, domestic violence, exposure to natural disaster) and in the characteristics of the sample (e.g., age, sex). Thus, maltreatment appeared in the group with small positive effects as well, indicating that maltreatment may be associated with significant blunting in some instances but not in others. In subsequent moderation analyses, we further explored whether study or sample characteristics explained the direction and magnitude of effects across all studies.

3.4. Moderators of the relation between adversity and HCC

In relation to the final aim of the meta-analysis, moderator analyses, using multilevel modeling, were performed to identify whether particular study variables explained variations in effect sizes relating adversity to HCC. Both linear effects and quadratic effects were tested. Only linear effects reached significance, so quadratic effects are not reported on further. Complete results of continuous and categorical moderator analyses are reported in Tables 4 and 5, respectively.

3.4.1. Study characteristics—While no specific hypotheses were offered related to geographical region, there were two significant moderator effects for the geographical region in which the study was conducted. Studies conducted in Europe had significantly smaller effect sizes than studies from China (difference estimate = −0.808, 95% CI [−1.397, −0.260]) or from Brazil (difference estimate = −0.641, 95% CI [−1.235, −0.049]). Only studies conducted in China, North America, and Brazil produced effects that were

[2]The 3-class model separated the positive class into two: a larger class with a small and positive effect size (n = 15, d = .109, 95% CI [0.068, 0.149]) and a smaller class with a larger effect size (n = 15, d = .706, 95% CI [0.473, 0.940]). One additional study (Morris et al., 2017) was also included in the negative class.

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significantly different from zero (Table 5). There was also one significant difference as a function of publication type. Effect sizes taken from published abstracts (d=1.760, k =1), were significantly larger than effect sizes from published articles (d=0.169, k=25; difference estimate=1.587, 95% CI [0.334, 2.920]). The year of publication did not significantly moderate the strength of the observed effect (b=0.063, 95% CI [−2.506, 3.918]).

3.4.2. Participant characteristics—No specific hypotheses were offered regarding participant race. However, racial distribution (i.e., % of sample participants who were White) was a significant moderator (b = −0.006, 95% CI [−0.012, −0.001]), such that samples with fewer White participants produced larger positive effects of adversity on HCC. In addition, the clinical status of the sample was a significant moderator, such that non-clinical samples (d = 0.317, k =19) had significantly different effect sizes compared to clinical samples (d = −0.049, k = 9; difference estimate = 0.365, 95% CI [0.046, 0.692]. Only studies that included non-clinical samples produced effects that were significantly different from zero (Table 4). Other sample characteristics, including overall mean age (years) of the participants, age classification (i.e., child, adolescent, adult), sex distribution (% males), percentage of the sample who smoked, percentage taking medication, PTSD diagnostic status, and BMI were not significant moderators (see Tables 4 and 5). It is important to note that the age of the participants in each sample differs from the age of experienced adversity, as examined below, because in a majority of studies adult participants reported adversity experienced in childhood.

3.4.3. Adversity characteristics and adversity measurement—Several adversity-related variables were also explored as potential moderators. First, the type of adversity was hypothesized to impact the direction of effect, such that those who were exposed to maltreatment, in particular, would experience blunted HCC levels compared to those who experienced other types of adversity. This hypothesis received mixed support from the mixture modelling above. When the different categories of adversity were examined as moderators (i.e., natural disaster, accident, war/combat, domestic violence, maltreatment, life-time trauma), only natural disaster effects were significantly different from zero (Table 5). In addition, there were two significant differences within the category of adversity. Samples exposed to natural disasters (d=0.777, k =2) had a significantly larger positive effect size compared both to samples exposed to maltreatment (d=0.132, k =20; difference estimate=0.646, 95% CI [0.053, 1.122]) and to samples exposed to lifetime unspecified trauma (d = −0.069, k = 3; difference estimate=0.852, 95% CI [0.160, 1.494]). However, note that these analyses compute the mean effect size across positive and negative effects, while mixture modelling results above indicated that maltreatment studies fell into two distinct classes, one characterized by moderate negative effects and one by small positive effects.

In addition, we dichotomized adversity as ‘maltreatment’ or ‘all other adversity’ in order to increase the power of this moderator analysis and explore whether maltreatment significantly differed from all other types of adversity. Only ‘other adversity’ effects were significantly different from zero; however, the effects were not significantly different from

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one another, i.e., maltreatment effects were not significantly smaller than ‘other adversity’ effects.

Moderating effects of subtypes of maltreatment were also examined, including physical, emotional, and sexual abuse, as well as physical and emotional neglect. No maltreatment subtype was significantly associated with hair cortisol and, when the five types of abuse were compared to one another, no differences among maltreatment types were observed.

We also tentatively hypothesized that adversity that occurred in childhood would show a significant but negative relation to HCC levels, compared to those not exposed to adversity in childhood. More recent adult adversity was hypothesized to be associated with significantly higher HCC levels. The time period during which the adversity occurred (i.e., childhood, adulthood, lifetime/unspecified) emerged as a significant moderator. Samples exposed to adversity in adulthood (d = 0.596, k = 6) had a significantly different effect size compared both to samples exposed in childhood (d=0.169, k =22; difference estimate= 0.430, 95% CI [0.028, 0.851]) and to samples with lifetime/ unspecified timing of trauma (d = −0.042, k =4; difference estimate= 0.640, 95% CI [0.093, 1.189]). Further, only samples exposed to adversity in adulthood had effects significantly different from zero (Table 5). There were no differences as a function of the specific adversity measure used (i.e., the specific questionnaires used to measure adversity; see Table 5) or the format of measurement (i.e., interview, questionnaire, other).

3.4.4. Features of hair samples—Several features of the hair cortisol sampling were examined as potential moderators of the adversity-HCC relation, though no specific hypotheses were advanced. The length of hair samples did not moderate results (b=0.022, 95% CI [−0.132, 0.174]). Thus, there were no significant differences by the time period covered by the hair cortisol assessment (1–2 months, 3 months,>3 months; Table 5). However, of these three time periods, only samples that corresponded to greater than 3 months of hair sampled were significantly different from zero (d=0.495).

Based on the eight studies that provided data on hair washing frequency (per week) and hair treatment, neither hair washing frequency (b=0.174, 95% CI [−0.095, 0.458]) nor hair treatment (b = −0.005, 95% CI [−0.025, 0.014]) significantly moderated the relation between adversity and HCC. In addition, no difference was observed as a function of the type of hair extraction procedure used (i.e., ImA or LCMS; Table 5).

4. Discussion

Although hair cortisol is a relatively new measure, a burgeoning literature associating adversity and HCC has emerged over the past decade. Prior research suggests that adversity may be significantly associated with both hyper- and hypo-activity of the HPA axis. In order to evaluate how adversity is related to HCC, this meta-analysis used a wide-ranging definition of adversity, including maltreatment (abuse and neglect), domestic violence, and exposure to other traumatic events, including accidents, war/combat, and natural disasters. The analysis aggregated findings from 28 studies that included 3397 participants from childhood to adulthood and from non-clinical and clinical samples.

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The first objective of this meta-analysis was to quantify the magnitude of the effect of adversity on HCC. The first MLM analysis, in which all study effects were included, resulted in a small, albeit significant, positive association between adversity and HCC (d = 0.213, 95% CI [0.034, 0.397]). However, there was significant and large between-study and within-study heterogeneity, indicating significant sources of difference between effect sizes. Given that adversity may be linked to both hyper- and hypo-activity of the HPA axis, potentially resulting in elevated and lowered HCC levels, respectively, pooling negative and positive effects across studies risks yielding a null effect, when in fact there may be two important processes operating with different directions of effect.

Therefore, in relation to the second objective of the study, mixture modeling was used to test whether there were distinct categories of relations between adversity and HCC, that is, subgroups of studies with homogeneous effect sizes. The results of mixture modeling differentiated two coherent classes of effects. The first class included four studies with an overall negative and moderate effect size (d = −0.478), and the second class included the remaining 24 studies with an overall positive, though small, effect size (d=0.141). This finding is consistent with prior research, as well as with theories positing both HPA hypo- and hyper-activity following adversity. For example, adversity is thought to alter the HPA axis, resulting in dysregulation in the form of hyper-activation in the short-term hypo-activation in the long-term (Guilliams and Edwards, 2010).

Characteristics of the studies in the two classes were consistent with this broad prediction in that the four studies with negative effects on HCC all included measures of maltreatment beginning in childhood (three retrospective reports from adulthood, one current protective service involvement/parent report in childhood). Conversely, studies of adult experiences of trauma were clustered among the studies with positive effects on HCC. However, 16 studies of childhood maltreatment were also included in the class of 24 studies with small positive effects. Thus, it will be important to identify additional factors associated with childhood maltreatment that differentiate maltreated individuals with hypo- versus hyper-reactivity. For example, the chronicity and severity of maltreatment may contribute to variability (Gunnar et al., 2001). A prior meta-analysis found that in agency-referred samples, child maltreatment was associated with blunted wake-up salivary cortisol levels (Bernard et al., 2017), but no associations were found when maltreatment was self-reported, suggesting a measure- specific or severity-specific finding. Other factors such as the perpetrator of maltreatment (e.g., caregiver or stranger) and compensating environmental supports (e.g., positive family environment; peer relationships) might contribute to the HPA axis response to maltreatment (McCrory et al., 2010). Many of these factors were not reported frequently enough in the HCC literature to include in the current analyses and should be considered in future work.

To address the significant heterogeneity in effect sizes and the distinct positive and negative effect size classes, we evaluated several factors that might moderate the relation between adversity and HCC in a series of moderator analyses (Objective 3).

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4.1. Features of adversity as moderator

The age at which adversity occurred moderated the relation between adversity and HCC, such that adversity that occurred in adulthood produced significantly different effects than adversity experienced during childhood/adolescence or adversity that occurred during a non-specific time frame. This finding is in line with the results of the mixture modelling indicating that the studies of childhood maltreatment fell into two distinct classes, with one characterized by a small overall positive effect and the other by a robust negative effect. While the moderation effect alone might indicate simply that more recent adversity produces larger elevations in cortisol, the mixture modelling further indicates that the age at which adversity is experienced does not produce a single linear attenuation process based on time elapsed since the adversity. Instead, age of adversity appears to be associated with the occurrence of two distinct processes with opposite directions of effect. Thus, results suggest that adversity is best understood as associated with diverging effect sizes, which include both positive and negative effects.

In regard to variation based on adversity type, results indicated that the specific type of adversity impacted the magnitude of effects. Studies of natural disasters produced different effects compared both to studies of maltreatment and studies of unspecified types of trauma (see Table 5). However, when maltreatment was compared to all other types of adversity (i.e., a dichotomous comparison), maltreatment did not differ significantly from other forms of adversity. Again, as noted above, in a subgroup of studies maltreatment was associated with lower hair cortisol levels (i.e., studies that comprise the first class from the mixture modeling), which might act to reduce the mean effect size associated with maltreatment in these moderation analyses.

Although we conducted separate analyses for the conceptually distinct effects of age and type of adversity, it should be noted that age of adversity and type of adversity were highly confounded in the existing literature. Of the 22 studies classified as assessing adversity during childhood/adolescence, 20 assessed effects of childhood maltreatment and only two assessed effects of a natural disaster (experienced in adolescence). In contrast, all studies of adversity experienced during adulthood assessed effects of other forms of adversity (domestic violence, natural disaster, etc.). Therefore, given the distributions of sample age, timing, and types of adversity in the existing literature, the moderator results can only reliably assess the distinction between maltreatment occurring in childhood/adolescence and other forms of trauma occurring in adulthood.

Due to the paucity of studies, we could not assess reliably whether other types of adversity in childhood (e.g., exposure to natural disasters, accidents) yield significant effects on HCC. In addition, in 17 of 19 studies of childhood maltreatment, maltreatment was assessed through adult retrospective report encompassing all of childhood. Only two studies assessed childhood maltreatment *during* childhood, through parent report and protective service involvement. Thus, we also do not have enough data to evaluate whether maltreatment assessed in childhood would yield the same pattern of effects as that yielded here by cumulative childhood maltreatment reported in adulthood.

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Some prior evidence also suggests that the impact of adversity on the HPA axis varies based on stage of development at exposure (Bosch et al., 2012; Trickett et al., 2010). However, except for the two child samples included, the studies that explored adversity in relation to HCC in child samples either did not include relevant data in the manuscript or used a broader definition of adversity (e.g., parental separation, bullying) and thus were not included here. Further studies are needed assessing HCC in childhood, both in relation to experiences of maltreatment and in relation to other forms of adversity, to better differentiate age of occurrence from type of adversity and to elucidate developmental effects.

Prior research has also shown differences among maltreatment subtypes on *salivary* cortisol (e.g., Cicchetti and Rogosch, 2001), such that emotional maltreatment is associated with high morning cortisol levels whereas physical neglect is associated with low morning cortisol levels (Bruce et al., 2009). Many of these studies of salivary cortisol were conducted in childhood. Among studies on HCC included in the present analyses, seven studies provided outcome data for separate types of maltreatment (see Table 2), but all seven studies were adolescent or adult samples retrospectively reporting childhood maltreatment. In the current analyses that compared effects of abuse, neglect, and witnessing domestic violence on HCC, none of the maltreatment subtypes differed. Thus, cortisol effects associated with different types of maltreatment may be more evident when assessed in childhood compared to adolescence/adulthood (as done here), or effects may be more evident in salivary than hair measures. Longitudinal research is needed to assess subtypes of maltreatment across childhood and adolescence in association with both hair and salivary cortisol to further examine how types of maltreatment impact regulation of the HPA axis.

Notably, in all the above analyses of childhood maltreatment, there are potential issues of validity related to adult retrospective reporting of childhood adversity. Although a review of the literature concluded that false positive reports are rare, there are substantial false negative reports (i.e., non-reporting of abuse) (Hardt and Rutter, 2004). Thus, adult retrospective reports of maltreatment may underrepresent adversity and should be interpreted with caution, particularly when recalling very early experiences or experiences that are heavily reliant on interpretation (Hardt and Rutter, 2004).

4.2. Sample characteristics

As stated by Russell et al. (2012), “there is a dearth of knowledge on the effect of factors such as ethnicity, age, [and] sex…on hair cortisol content” (p. 598). Given other recent meta-analytic work on this issue (Stalder et al., 2017), it was not our aim to examine *main effects* of sample characteristics on HCC. Instead, we explored whether sample characteristics *moderated* associations between adversity and HCC. First, we found that the clinical status of the sample moderated results, such that clinical samples had significantly smaller effects compared to non-clinical samples, and only non-clinical samples produced effects that were significantly different from zero (Table 5). We did not find that samples with a PTSD diagnosis differed from samples without a PTSD diagnosis.

While the moderator analyses tell us that the overall mean effects were smaller among clinical groups, they do not tell us whether effects in clinical samples were more likely to yield significant negative effects, suggesting hypo-reactivity of the HPA axis. Notably, the

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mixture modelling did place three clinical samples within the class with a moderate negative effect on HCC (all also reported childhood maltreatment). This indicates that adversity in clinical samples (similar to maltreated samples) might be more likely to manifest as hypo-reactivity of the HPA axis. However, this interpretation is tentative, given that several clinical samples were also classified in the small positive effect-size class. In addition, given the overlap in studies using clinical samples and assessing maltreatment, it is difficult to disentangle the extent to which psychopathology, maltreatment, or an interaction between psychopathology and maltreatment were contributing to HPA hypo-reactivity.

In relation to this point, in prior studies using salivary cortisol, there is evidence that different mental health disorders are associated with different forms of dysregulation in HPA axis functioning (e.g., depression with elevated cortisol and PTSD with lowered cortisol; Knorr et al., 2010; Wahbeh and Oken, 2013). Prior research has also found interacting effects of abuse and depression on HPA-axis activity (Heim et al., 2001). In response to a CRH (corticotropin releasing hormone) challenge, women with a history of abuse but no depression had relatively higher ACTH responses whereas women with depression (with or without abuse history) had relatively lower ACTH responses, and those with depression and abuse had the most blunted cortisol responses. This suggests that although abuse may lead to HPA alterations, the nature of these alterations may change in interaction with psychiatric symptoms. Thus, the clinical composition of studies should be considered when interpreting HCC results. Unfortunately, current literature does not allow exploration of how particular kinds of psychopathology, with or without abuse, relate to HCC. More studies are needed to compare effects of psychopathology, maltreatment, and their additive and interactive effects on HCC.

We also found that race moderated findings, such that samples with more non-White participants produced a larger positive relation between adversity and HCC. Prior studies have documented variation in HCC by race/ethnicity. For example, in a study of pregnant women, Black women were found to have higher HCC than White women across all trimesters of pregnancy, and Hispanic women were found to have higher HCC than non-Hispanic White women in the second and third trimesters of pregnancy (Schreier et al., 2015). Some researchers (see Brunst et al., 2014) have proposed that different races may respond differentially to stress exposures via a variety of possible mechanisms, including genetic, lifestyle, and social differences. However, it is also possible that in the present analyses race may be confounded by a third unmeasured variable, such as cumulative environmental risk (e.g., income, education, refugee status, etc.). Future research is needed to explore further how race relates to an array of other risk variables in moderating associations between adversity and HCC.

We also explored whether participant age at the time of study participation (i.e., child, adolescent, adult) moderated results and did not find evidence of moderation. Importantly, as noted earlier, age of participant differed from age of experienced adversity (child/adolescent, adult, not specified) because in 18 studies adolescent or adult participants reported on adversity experienced in childhood. Thus, these findings should be interpreted cautiously.

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There were several other sample characteristics that did not moderate adversity-HCC associations, including sex, medication use, smoking status, and BMI. One limitation of comparing these participant factors across studies is that studies varied greatly in their reporting of such factors. In fact, a number of sample characteristics (i.e., % White, % medication, % smokers, BMI) were reported in fewer than 20 studies. Given that this literature is in its infancy, despite the nonsignificant associations found here, future research should continue to explore how sample characteristics are associated with HCC and whether such characteristics moderate the relation between adversity and HCC.

4.3. Features of hair samples

We also explored whether the association between adversity and HCC varied based on qualities of the hair samples. Prior meta-analytic findings showed that HCC declines by almost 30% from the first proximal 3-cm hair segment to the second most proximal 3-cm hair segment (Stalder et al., 2017). The length of hair samples and corresponding time period assessed by hair samples (i.e., 1 to 2 months, 3 months, > 3 months) are overlapping variables. However, given that length is a continuous variable and time period is a categorical variable, they were not entirely overlapping. First, we found that only hair samples corresponding to > 3 months produced moderator effect sizes significantly different from zero (d=0.495; Table 5). However, moderator effects were not significant when comparing the three different time periods of hair sampling (i.e., 1 to 2 months, 3 months,>3 months) or when examining hair length as a continuous moderator (Table 4). Thus, it is unclear whether hair length or the time period indexed by the hair sample moderates the link between adversity and HCC, and future research should continue to explore hair length and corresponding time period as potential moderators of HCC effects.

We also did not find that hair washing frequency or hair treatment moderated effects of adversity on HCC. In contrast, prior meta-analytic work (Stalder et al., 2017) found that hair-washing frequency was negatively associated with HCC. It is possible that the nonsignificant effect here is related to the limited power in these moderation analyses, as only eight studies provided information regarding hair washing. However, to date, no mechanism has been advanced to explain why hair washing might affect HCC or the relation between HCC and adversity. It is also possible that other sample characteristics that are associated with hair washing frequency, such as race, culture, or country, may be confounding these findings. Taken together, results suggest that hair washing frequency and hair treatment might be associated with HCC levels but do not specifically impact the association between adversity and HCC.

4.4. Theoretical considerations related to HPA activation

The results from both the multi-level mixture analyses and the moderator analyses can be understood in the context of theories of HPA activation. The two classes of effect sizes that emerged from the mixture modelling suggest that adversity may be associated with both HPA axis hyper-activation and hypo-activation. Hyper-activation may be due to sensitization of the HPA axis following stress, resulting in a more reactive stress system. For example, heightened activity of the amygdala results in increased stimulation of the paraventricular nucleus of the hypothalamus (McEwen, 2007), contributing to greater HPA activity.

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Heightened activation of the HPA axis can lead to depletion of neurochemicals responsible for cortisol production (e.g., CRH receptor down-regulation; Heim et al., 2000), leading to HPA hypo-activity over time (Guilliams and Edwards, 2010).

In addition, the moderation results related to the time period in which adversity occurred and the type of adversity experienced can also be understood in the context of HPA axis development and allostatic load. Prior research suggests that adversity experienced during sensitive periods of development can produce unique alterations to the allostatic systems and resulting HPA axis activity (Danese and McEween, 2012). For example, childhood adversity can result in biological embedding that leads to enduring modifications in the maturation and responsiveness of allostatic systems (Danese and McEwen, 2012). Adversity during stress-sensitive periods when brain plasticity is high may have a particularly large impact on allostatic load (Ganzel and Morris, 2011). The time period of adversity may also influence the direction of effects on HPA activity (Ganzel and Morris, 2011). For example, one study found that CRH was higher in adult women who experienced childhood abuse after the age of 6 compared to those who experienced abuse before the age of 6 (Heim et al., 2008). Therefore, age at the time of adversity might impact the direction of effects on subsequent HPA axis development. As noted earlier, research is needed to separate effects of timing of adversity from type of adversity, as both might have a unique impact on allostatic changes.

4.5. Strengths and limitations

This meta-analysis has many strengths, including the range of adversity assessed (i.e., maltreatment, domestic violence, war/combat, natural disaster, accident), the breadth of assessment measures captured (i.e., a range of interviews and questionnaires), and the examination of several adversity, hair, and participant moderators. Despite its many strengths, this meta-analysis has some limitations.

First, this meta-analysis is constrained by the methodological variability of the studies included. Because studies varied greatly in the measures utilized and the metrics used to examine similar moderators, comparing variables across studies was challenging. For example, although many studies provided the racial/ethnic distribution of the sample, the way in which the distributions were reported varied greatly (e.g., % White, % minority). We chose to report the percentage of the sample who were White because this was the most frequently used indicator of race/ethnicity. However, it is an estimate that does not capture the richness of the possible racial distributions within each sample.

Second, there are other factors that are theoretically important to the observed effect, but which we were not able to assess given that those factors were not assessed in enough individual studies. For example, the time elapsed since an adverse event occurred likely influences both the strength and direction of effects. However, such timing information was not reported in many individual studies. In addition, timing may be difficult to ascertain given that many types of adversity may be chronic, intermittent, or ongoing. In addition, prior research suggests that the developmental timing of maltreatment has unique implications for the development of the HPA axis (Gunnar and Hostinar, 2015; Hostinar et al., 2015). However, there were not enough studies available to allow us to test whether the developmental timing of maltreatment (e.g., early childhood versus adolescence) influences

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the direction and magnitude of effects on HCC. Further, it is likely that timing of adversity experience and time lapse since adversity occurred were confounding each other given that many samples were adolescents/adults retrospectively reporting adversity that occurred during childhood. Future research that includes samples across the lifespan who vary in amounts of time since exposure are needed to elucidate the potentially separable effects of developmental stage at occurrence of adversity and time lapsed since adversity. Finally, examining the joint impact of childhood adversity and subsequent adversity on HCC may have revealed important insights. However, only one study included data for groups who experienced both childhood trauma and subsequent interpersonal violence (Morris et al., 2017). We urge future researchers to assess the impact of multiple forms of adversity on HCC to uncover the potential impact of repeated adversity on the HPA axis.

In addition, we were not able to determine whether specific kinds of psychopathology differentially moderated effects because few studies provided data for separate types of psychopathology. In the developmental context, only White et al. (2017) provided descriptive statistics for a sample with distinct internalizing/externalizing problems. We encourage future researchers to provide data on psychopathology in their samples to permit the examination of multiple forms of psychopathology as moderators of the effect of adversity on HCC.

Also, data for some of the moderators assessed (% White, % taking medication, % smokers, BMI, hair treatment, hair washing frequency) were provided in a limited number of studies. Based on MCMC estimation guidelines, moderators should include 20 or more clusters. Thus, these moderator analyses should be interpreted with caution.

It should also be noted that the current meta-analysis included two studies (*Groer et al., 2015; *Pacella et al., 2017) that derived their effects from the number of PTSD symptoms in association with HCC. Importantly, effects derived from PTSD symptom measures were not significantly different from effects derived from other kinds of adversity measures (difference estimate=0.475, CI [−0.364, 1.258]). These two studies were included to maximize the number and representativeness of the studies contributing to the analyses. However, the inclusion of these two studies should be considered when interpreting results.

Finally, while we comprehensively explored the impact of individual factors as moderators of the relation between HCC and adversity, we were unable to examine the interactions among moderators. Given the complex profiles of individuals who have experienced adversity, future research is needed to examine more complex moderation models. Future studies should also explore potential protective factors and their interactions with risk factors as possible moderators of adversity-HCC associations.

5. Conclusion

The present meta-analysis demonstrates that adversity is significantly related to hair cortisol levels. Results point to coherent classes of effects in the literature, with one class indexing a significant, albeit small, increase in HPA activity consistent with hyperactivity, and another indexing a robust and significant negative effect on HPA activity, consistent with

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hypoactivity in response to adversity. Notably, all studies with significant negative effects of adversity on HCC included a measure of childhood maltreatment. These findings underscore a particular need for studies across development in order to map how the HPA system responds to different forms of adversity during different periods of development.

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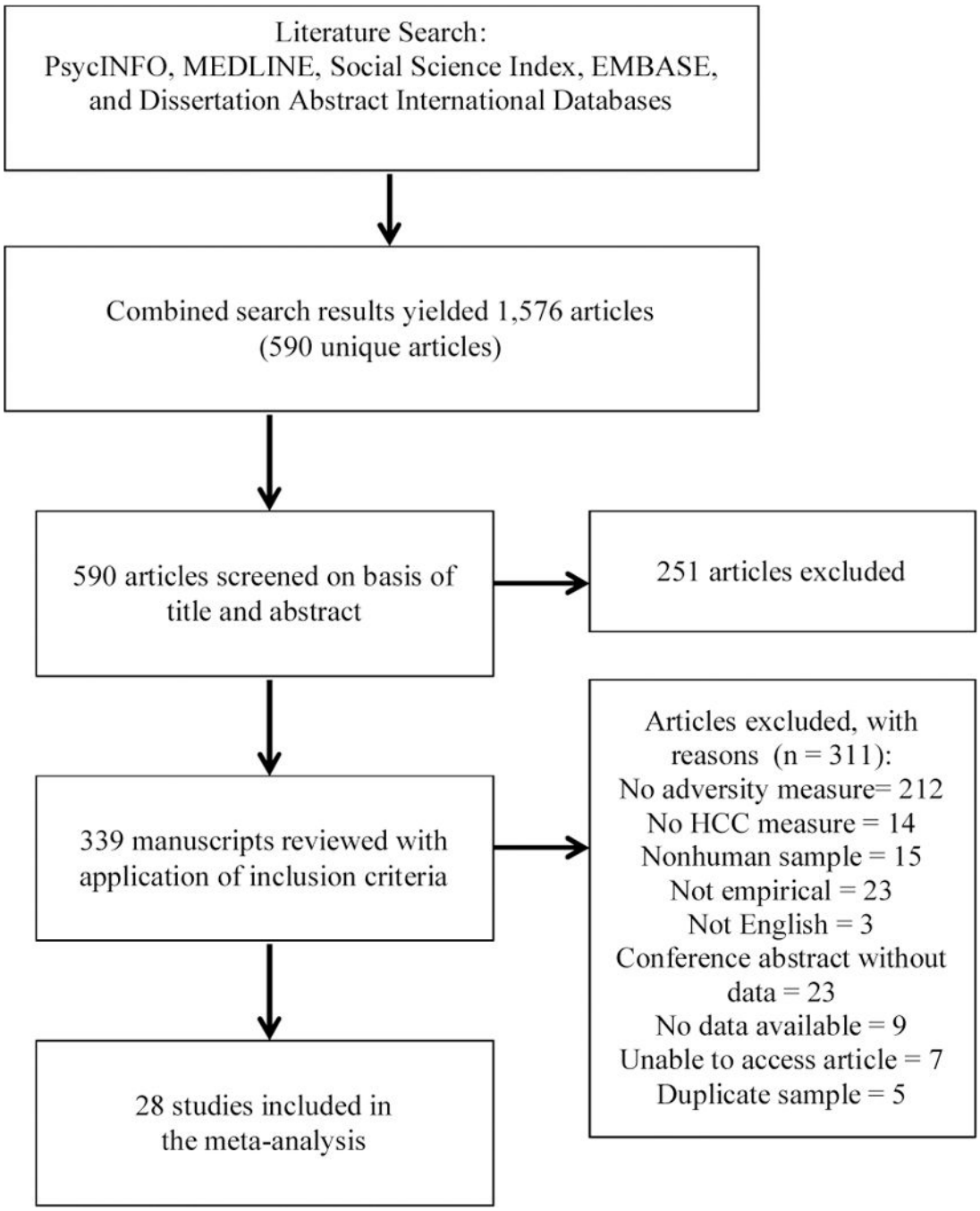

Fig. 1.
Flow chart for studies included in the meta-analysis. HCC=h air cortisol concentration.

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Table 1

Reviewed studies, sample characteristics, methods of adversity assessment, and methods of hair extraction for all studies included in the meta-analysis.

	Study	N	Sample Description	Age M (SD)	Sex (% male)	BMI M (SD)	Adversity Indicator	Adversity Classification	Hair Extraction & Length
1	Boeckel et al. (2017)	59	Mothers and children exposed to interpersonal violence	35.1 (7.4)	0%	n/a	Revised Conflict Tactic Scale	Domestic Violence	ImA; 1cm
2	do Prado et al., 2017	57	Adolescents	15.3 (1.4)	42%	24.6 (2.8)	Childhood Trauma Questionnaire	Child Maltreatment	ImA; 3cm
3	Etwel et al. (2014)	39	Women exposed to the Libyan war	23.8 (6.2)	0%	23.1 (4.8)	Libyan War	War Exposure	ImA; 3cm
4	Fischer et al. (2016)	139	Community sample	50.6 (14.6)	28%	27.5 (6.0)	Childhood Trauma Questionnaire	Child Maltreatment	ImA; 3cm
5	Ford et al. (2016)	578	Adolescents	14.6 (1.8)	50%	n/a	Adverse Childhood Experiences	Child Maltreatment	ImA; 3cm
6	Gao et al. (2014)	92	Adult and adolescent earthquake survivors	30.0 (7.1)	80%	n/a	Earth Quake	Natural Disaster	LCMS; 3cm
7	Groer et al. (2015)	52	Soldiers	25.0	98%	n/a (n/a)	PTSD Symptom Checklist	War Exposure	ImA; 3cm
8	Heinze et al. (2016)	58	Clinical sample and healthy controls	20.5 (2.7)	10%	22.7	Childhood Trauma Questionnaire	Child Maltreatment	ImA; 3cm
9	Hinkelmann et al. (2013)	84	Depressed sample and healthy controls	41.5 (11.0)	37%	n/a	Childhood Trauma Questionnaire	Child Maltreatment	ImA; 3cm
10	Hoffman et al. (2017)	33	Pregnant women	n/a	n/a	n/a	Adverse Childhood Experiences	Child Maltreatment	n/a
11	Kaess et al. (2017)	36	Clinical sample (youth with Internet Gaming Disorder)	19.0 (3.4)	100%	22.65 (n/a)	Childhood Trauma Questionnaire	Child Maltreatment	ImA; n/a
12	Kalmakis et al. (2015)	55	Undergraduate sample	19.5 (1.6)	24%		Adverse Childhood Experiences	Child Maltreatment	ImA; 3cm
13	Keenan-Devlin (2015)	88	Low-SES youth	15.2 (2.0)	50%	24.0 (6.1)	Adverse Childhood Experiences	Child Maltreatment	ImA; 1cm
14	Luo et al. (2012)	84	Earth quake survivors (half with PTSD) and healthy controls	14.0 (1.2)	0%	n/a	Chinese version of the Children's Revised Impact of Event Scale Structured Clinical Interview for DSM-IV Axis I Disorders	Natural Disaster	LCMS; 3cm
15	Mayer (2017)	74	Medical interns	27.41 (2.4)	44%	23.02 (3.5)	Childhood Trauma Questionnaire	Child Maltreatment	ImA; 4cm
16	Melhem et al. (2017)	115	Psychiatric inpatients and healthy controls	22.7 (3.0)	55%	23.8 (3.8)	Childhood Trauma Questionnaire	Child Maltreatment	ImA; 3cm
17	Morris et al. (2017)	34	Women exposed to interpersonal violence or child trauma	24.0 (3.1)	0%	n/a	Childhood Trauma Questionnaire	Child Maltreatment	ImA; 3cm
18	Pacella et al. (2017)	35	Adults with physical injury	n/a	n/a	n/a	PTSD Symptom Checklist	Physical Injury	ImA; 3cm

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	Study	N	Sample Description	Age M (SD)	Sex (% male)	BMI M (SD)	Adversity Indicator	Adversity Classification	Hair Extraction & Length
19	Reichl et al. (2016)	52	Adolescents engaging in NSSI and healthy controls	16.3 (1.2)	8%	n/a	Childhood Experiences of Care and Abuse Interview	Child Maltreatment	ImA; 3cm
20	Schalinski et al. (2015)	43	Clinical outpatients and healthy controls	34.9 (10.3)	0%	26.4 (5.7)	Event checklist Early Trauma Inventory	Lifetime Trauma	ImA; 3cm
21	Schreier et al. (2015)	180	Pregnant women	31.0 (5.4)	0%	25.8 (5.4)	Childhood Trauma Questionnaire	Child Maltreatment	LCMS; 3cm
22	Schury et al. (2017)	94	Mothers of newborns	32.5 (5.4)	0%	24.5 (4.8)	Childhood Trauma Questionnaire	Child Maltreatment	LCMS; 3cm
23	Steudte et al. (2011)	27	PTSD patients and healthy controls	19.7 (4.5)	52%	21.9 (2.1)	Lifetime traumatic events	Lifetime Trauma	ImA; < 3cm
24	Steudte et al. (2013)	78	PTSD patients and healthy controls	38.7 (12.5)	8%	23.7 (3.4)	Childhood Trauma Questionnaire Trauma History Questionnaire Munich Composite International Diagnostic Interview	Child Maltreatment Lifetime Trauma	LCMS; 3cm
25	Steudte-Schmiedgen et al. (2015)	90	Soldiers	27.68 (6.1)	100%	25.45(2.7)	Childhood Trauma Questionnaire Traumatic events	Child Maltreatment Lifetime Trauma	LCMS; 2cm
26	Trautmann et al. (2018)	618	Soldiers	28.8 (6.2)	100%	24.8 (2.7)	Childhood Trauma Questionnaire	Child Maltreatment	ImA; 2cm
27	Wells et al. (2014)	217	Community sample	n/a	28%	n/a	Intimate Partner Physical Aggression	Domestic Violence	ImA; 2cm
28	White et al. (2017)	286	Maltreated children compared to non-maltreated controls	9.9 (3.1)	50%	50.1 (30.1)	Maternal Maltreatment Classification Interview	Child Maltreatment	ImA; 3cm

Note: Descriptive information (age, sex, BMI) is provided for the entire sample. If studies provided separate demographic information for subsamples, data were averaged across subsamples. BMI=Body Mass Index; ImA=Immunoassay; LCMS=liquid chromatography tandem mass spectrometry; NSSI=non-suicidal self-injury.

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Table 2

Effect sizes for the association between adversity and hair cortisol concentrations by study and subsample.

	Study	Description of separate effects (e.g., subsample/ adversity subtype/ time points)	Effect Size (Cohen's d)			
			Estimate	SE	95% CI	*p*-value
1	Boeckel et al. (2017)	Mothers	0.659	0.268	[0.133, 1.185]	.014
		Children	0.294	0.263	[−0.221, 0.809]	.263
2	do Prado et al. (2017)	T1	0.690	0.273	[0.155, 1.225]	.012
		T2	0.219	0.266	[−0.302, 0.741]	.410
		T3	1.23	0.289	[0.661, 1.794]	< .001
3	Etwel et al. (2014)	T1- prewar	0.034	0.093	[−0.150, 0.217]	.720
		T2 - postwar	0.311	0.178	[−0.038, 0.660]	.081
4	Fischer et al. (2016)	Emotional neglect	−0.065	0.242	[−0.539, 0.410]	.789
		Physical neglect	−0.221	0.292	[−0.793, 0.351]	.449
		Emotional abuse	0.010	0.266	[−0.512, 0.531]	.971
		Physical abuse	0.045	0.315	[−0.572, 0.662]	.887
		Sexual abuse	0.165	0.238	[−0.301, 0.630]	.489
5	Ford et al. (2016)	Witnessing violence	0.081	0.083	[−0.083, 0.244]	.334
		Victim DV	0.129	0.084	[−0.035, 0.292]	.124
		Foster care	−0.055	0.083	[−0.219, 0.109]	.510
6	Gao et al. (2014)	Adults	1.78	0.361	[1.072, 2.49]	< .001
		T1-adolescents	0.893	0.304	[0.296, 1.49]	.003
		T2-adolescents	0.639	0.298	[0.055, 1.22]	.032
		T3-adolescents	0.422	0.294	[−0.153, 1.00]	.150
7	Groer et al. (2015)		0.797	0.308	[0.194, 1.40]	.010
8	Heinze et al. (2016)	Emotional abuse	−0.486	0.412	[−1.29, 0.321]	.238
		Physical abuse	−0.122	0.393	[−0.892, 0.648]	.756
		Emotional neglect	−0.425	0.409	[−1.23, 0.376]	.298
		Physical neglect	0.391	0.392	[−0.377, 1.16]	.318
		Sexual abuse	0.268	0.396	[−0.507, 1.04]	.498
		Total maltreatment	−0.451	0.437	[−1.31, 0.406]	.302
9	Hinkelmann et al. (2013)		−1.64	0.693	[−2.99, −0.278]	.018

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	Study	Description of separate effects (e.g., subsample/ adversity subtype/ time points)	Effect Size (Cohen's d)			
			Estimate	SE	95% CI	*p*-value
10	Hoffman et al. (2017)		1.76	0.486	[0.804, 2.71]	< .001
11	Kaess et al. (2017)	Emotional abuse	0.288	0.352	[−0.401, 0.977]	.413
		Physical abuse	0.261	0.351	[−0.427, 0.949]	.457
		Sexual abuse	0.157	0.349	[−0.528, 0.841]	.653
		Emotional neglect	0.275	0.351	[−0.414, 0.964]	.434
		Physical neglect	0.009	0.348	[−0.673, 0.692]	.978
		Total maltreatment	0.279	0.352	[−0.410, 0.968]	.428
12	Kalmakis et al. (2015)		0.566	0.283	[0.011, 1.121]	.046
13	Keenan-Devlin (2015)	Girls	0.904	0.343	[0.233, 1.58]	.006
		Boys	−0.169	0.330	[−0.815, 0.478]	.609
14	Luo et al. (2012)	T1- PTSD & HC	−0.471	0.289	[−1.037, 0.095]	.103
		T2- PTSD & HC	0.623	0.292	[0.052, 1.20]	.033
		T3- PTSD & HC	1.16	0.307	[0.562, 1.77]	< .001
		T1- non-PTSD & HC	0.241	0.286	[−0.319, 0.802]	.399
		T2- non−PTSD & HC	1.24	0.310	[0.634, 1.85]	< .001
		T3- non-PTSD & HC	1.29	0.312	[0.679, 1.90]	< .001
15	Mayer (2017)	T1- pre-internship	0.673	0.250	[0.182, 1.16]	.007
		T2- internship	0.100	0.238	[−0.366, 0.566]	.674
16	Melhem et al. (2017)		−0.430	0.193	[−0.808, −0.051]	.026
17	Morris et al. (2017)	Child trauma & IPV	−0.341	0.390	[−1.105, 0.424]	.383
		Child trauma only	−0.480	0.463	[−1.39, 0.429]	.301
18	Pacella et al. (2017)		0.516	0.365	[−0.199, 1.23]	.157
19	Reichl et al. (2016)	Neglect	0.231	0.297	[−0.351, 0.814]	.436
		Physical abuse	0.302	0.300	[−0.285, 0.889]	.313
		Sexual abuse	0.010	0.296	[−0.570, 0.590]	.973
		Psychological abuse	0.181	0.349	[−0.504, 0.866]	.554
		Total maltreatment	0.180	0.297	[−0.402, 0.762]	.544
20	Schalinski et al. (2015)	Hair segment 1	0.025	0.327	[−0.615, 0.665]	.939
		Hair segment 2	0.974	0.339	[0.309, 1.64]	.004
21	Schreier et al. (2015)	Physical abuse	0.400	0.153	[0.097, 0.700]	.009

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	Study	Description of separate effects (e.g., subsample/ adversity subtype/ time points)	Effect Size (Cohen's d)			
			Estimate	SE	95% CI	*p*-value
		Emotional abuse	0.084	0.151	[−0.211, 0.379]	.577
22	Schury et al. (2017)		0.151	0.211	[−0.263, 0.565]	.475
23	Steudte et al. (2011)		0.899	0.448	[0.022, 1.78]	.045
24	Steudte et al. (2013)	PTSD & HC, hair 1	−0.739	0.284	[−1.30, −0.182]	.009
		PTSD & HC, hair 2	−0.838	0.287	[−1.401, −0.276]	.003
		No-PTSD & HC, hair 1	−0.634	0.282	[−1.186, −0.081]	.025
		No-PTSD & HC, hair 2	−0.697	0.283	[−1.252, −0.141]	.014
		Total maltreatment	−0.291	0.233	[−0.748, 0.166]	.212
		Traumatic events	−0.583	0.241	[−1.055, −0.112]	.015
25	Steudte-Schmiedgen et al. (2015)	Total maltreatment	−0.012	0.214	[−0.432, 0.408]	.955
		Traumatic events	−0.163	0.215	[−0.584, 0.259]	.450
26	Trautmann et al. (2018)	Emotional abuse	0.140	0.081	[−0.018, 0.299]	.083
		Physical abuse	0.201	0.081	[0.042, 0.360]	.013
		Emotional neglect	0.020	0.081	[−0.138, 0.178]	.804
		Physical neglect	0.120	0.081	[−0.038, 0.279]	.137
		Total maltreatment	0.140	0.081	[−0.018, 0.299]	.083
27	Wells et al. (2014)		0.219	0.138	[−0.050, 0.489]	.111
28	White et al. (2017)		−0.345	0.120	[−0.580, −0.110]	.004

Notes: ES = effect size; PTSD = Posttraumatic stress disorder, HC = healthy control; IVP = Interpersonal violence; t = time point.

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Table 3

Fit indices of the latent profile analysis with a varying number of classes.

	AIC	BIC	aBIC	Entropy	LMR	aLMR	Class Sizes
1-class	177.743	179.075	175.966	n/a	n/a	n/a	28
2-class	136.344	140.340	131.013	.881	.0000	.0000	24, 4
3-class	129.351	136.012	120.467	.709	.0002	.0007	15, 8, 5
4-class	133.249	142.575	120.811	.750	.6412	.6536	15, 8, 5, 0

Notes: AIC = Akaike's Information Criteria; BIC = Bayesian Information Criteria; aBIC = adjusted BIC; LMR = Lo-Mendell-Rubin Likelihood Ratio Test; aLMR = adjusted LMR.

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Table 4

Continuous moderators of associations between adversity and hair cortisol.

Continuous Moderator	k (n)	Slope [95% CI]
Age (years)	27 (70)	0.002 [−0.014, 0.018]
Sex (% male)	27 (70)	−0.002 [−0.007, 0.003]
Race (% White)	15 (37)	−0.006* [−0.012, −0.001]
Medication usage (% on medication)	15 (38)	−0.006 [−0.017, 0.005]
Smoking status (% smokers)	13 (33)	−0.006 [−0.021, 0.009]
BMI	15 (39)	−0.019 [−0.050, 0.021]
Length of hair	26 (65)	0.022 [−0.132, 0.174]
Hair treatment	9 (26)	−0.005 [−0.025, 0.014]
Hair washes	8 (24)	0.174 [−0.095, 0.458]
Year of publication	28 (71)	0.063 [−2.506, 3.918]

Note. k = number of studies; n = number of effect sizes; CI = credible interval; BMI = Body Mass Index.

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Table 5

Categorical moderators of associations between adversity and hair cortisol.

Categorical Moderator	k (n)	d [95% CI]	Significant differences between effect sizes
Age Classification	28 (71)		None
Adult	19 (46)	0.253* [0.024, 0.487]	
Adolescent	7 (23)	0.188 [−0.197, 0.544]	
Child	2 (2)	−0.120 [−0.745, 0.513]	
Clinical Sample	28 (71)		
Clinical	9 (28)	−0.049 [−0.334, 0.246]	1) Clinical vs Non-clinical
Non-clinical	19 (43)	0.317* [0.122, 0.521]	
PTSD Sample	28 (71)		
PTSD sample	3 (9)	−0.117 [−0.550, 0.296]	None
Non-PTSD sample	25 (62)	0.243* [0.062, 0.427]	
Adversity Category	28 (71)		
Natural disaster	2 (10)	0.777* [0.226, 1.335]	1) Natural disaster vs Lifetime
Accident	1 (1)	0.534 [−0.572, 1.647]	2) Natural disaster vs Maltreatment
War/combat	2 (3)	0.382 [−0.273, 1.012]	
Domestic violence	2 (2)	0.405 [−0.176, 1.016]	
Child maltreatment	19 (46)	0.132 [−0.058, 0.335]	
Lifetime trauma	4 (9)	−0.069 [−0.459, 0.323]	
Maltreatment vs other adversity	28 (71)		
Maltreatment	17 (46)	0.174 [−0.029, 0.389]	None
Other	11 (25)	0.283* [0.018, 0.554]	
Maltreatment Sub-Classification			
Physical abuse	10 (31)	0.214 [−0.039, 0.450]	None
Emotional abuse		0.085 [−0.164, 0.322]	
Sexual abuse		0.152 [−0.200, 0.506]	
Emotional neglect		−0.004 [−0.279, 0.269]	
Physical neglect		0.094 [−0.163, 0.370]	
Witness DV		0.144 [−0.168, 0.522]	
Adversity Timing	28 (71)		

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Categorical Moderator	k (n)	d [95% CI]	Significant differences between effect sizes
Childhood/adolescence	22 (55)	0.169 [−0.028, 0.368]	1) Adult vs Childhood/Adolescence
Adulthood	6 (7)	0.596* [0.216, 0.996]	2) Adult vs Lifetime
Lifetime/unspecified time	4 (9)	−0.042 [−0.440, 0.345]	
Adversity Measure	26 (65)		
PTSD Checklist	2 (2)	0.649 [−0.225, 1.538]	None
CTS-2	2 (3)	0.334 [−0.394, 1.083]	
ACE	4 (7)	0.509 [−0.048, 1.105]	
CECA	1 (4)	0.193 [−0.865, 1.260]	
Lifetime trauma	2 (2)	0.147 [−0.523, 0.828]	
CTQ	13 (33)	0.093 [−0.202, 0.391]	
THC	1 (1)	−0.107 [−0.883, 0.678]	
Event Checklist	1 (2)	0.511 [−0.576, 1.620]	
Maltreatment Inventory	1 (1)	−0.343 [−1.402, 0.682]	
PTSD Diagnostic Interview	2 (10)	−0.132 [−0.688, 0.393]	
Adversity Measure Type	28 (71)		
Questionnaire	22 (48)	0.224* [0.023, 0.435]	None
Interview	5 (17)	0.045 [−0.311, 0.396]	
Other	2 (6)	0.495 [−0.154, 1.116]	
Hair Timing	26 (65)		
1 to 2 months	9 (18)	0.197 [−0.099, 0.479]	None
3 months	17 (39)	0.126 [−0.105, 0.351]	
> 3 months	4 (8)	0.495* [0.092, 0.902]	
Hair Extraction Method	27 (70)		
ImA	21 (60)	0.273 [−0.086, 0.622]	None
LCMS	6 (20)	0.154 [−0.044, 0.361]	
Publication Type	28 (71)		
Published Abstract	25 (66)	1.760* [0.461, 3.028]	1) Article vs abstract
Dissertation	2 (4)	0.364 [−0.299, 0.985]	
Published Article	1 (1)	0.169 [−0.015, 0.348]	
Geographic Region	28 (71)		
North America	11 (17)	0.264* [0.014, 0.678]	1) Europe vs China

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Categorical Moderator	k (n)	d [95% CI]	Significant differences between effect sizes
Europe	11 (36)	−0.049 [−0.288, 0.182]	2) Europe vs Brazil
Africa	2 (3)	0.337 [−0.267, 0.968]	
China	2 (10)	0.760* [0.264, 1.289]	
Brazil	2 (5)	0.592* [0.046, 1.136]	

Note. k = number of studies; *n* = number of effect sizes; CI = credible interval; *d* = standardized difference in mean; *d* [95% CI] = indicates if effect size is statistically different from zero; statistical difference between effects=indicates if different categories of each moderator have statistically different effect sizes; ACE=Adverse Childhood Experiences Questionnaire; CTQ=Childhood Trauma Questionnaire; CECA=Childhood Experiences of Care and Abuse Interview; CTS-2 = Conflict Tactic Scale; PTSD=Posttraumatic Stress Disorder; Maltreatment Interview=Maternal Maltreatment Classification Interview; THC=Trauma History Questionnaire; ImA=immunoassay; LCMS=liquid chromatography tandem mass spectrometry.