Brain, Behavior, and Immunity 123 (2025) 164–176

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

The effects of childhood adversity on twenty-five disease biomarkers and twenty health conditions in adulthood: Differences by sex and stressor type

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ARTICLE INFO

Keywords:
Adverse childhood experiences
Early adversity
Stress
Inflammation
Latent class analysis
Mechanisms
Disease risk
Health

ABSTRACT

Background: Although early adversity is now recognized as a major public health concern, it remains unclear if the effects of early-life stressors on disease biology and health differ by sex or stressor type. Because childhood stressors often covary, examining whether such stressors typically occur together (e.g., cumulative adversity) or in distinct multivariate patterns is needed to determine if and how different life stressors uniquely affect disease biology and health.

Method: To investigate, we conducted latent class analyses (LCA) to identify clusters of adults experiencing multiple childhood stressors (N = 2,111, M_{age} = 53.04, 54.8% female) in the Midlife in the United States (MIDUS) Study. We then tested how latent stressor exposure groups, and individual stressors, related to 25 biomarkers of inflammation, metabolism, and stress, and 20 major health conditions. Multivariate effect sizes were estimated using Mahalanobis's D.

Results: Optimal LCA models yielded three female (Low-, Moderate-, and High-Stress) and two male (Low- and High-Stress) stressor exposure classes. The High-Stress classes had greater inflammation (male: D = 0.43; female: D = 0.59) and poorer metabolic health (male: D = 0.32–0.33; female: D = 0.32–0.47). They also had more cardiovascular (male: HR = 1.56 [1.17, 2.07]; female: HR = 1.97 [1.50, 2.58]), cancer (male: HR = 2.41 [1.52, 3.84]; female: HR = 2.51 [1.45, 4.35]), metabolic (male: HR = 1.54 [1.16, 2.03]; female: HR = 2.01 [1.43, 2.83]), thyroid (male: HR = 3.65 [1.87, 7.12]; female: HR = 2.25 [1.36, 3.74]), arthritis (male: HR = 1.81 [1.30, 2.54]; female: HR = 1.97 [1.41, 2.74]), and mental/behavioral health problems (male: HR = 2.62 [1.90, 3.62]; female; HR = 3.67 [2.72, 4.94]). Moreover, stressors were related to these outcomes in a sex- and stressor-specific manner.

Conclusions: Childhood adversity portends worse biological health and elevated risk for many major health problems in a sex- and stressor-specific manner. These findings advance stress theory, and may help inform precision interventions for managing stress and enhancing resilience.

1. Introduction

Prior to germ theory, the risk of dying from infectious diseases such as influenza and febrile illnesses was relatively high (Casanova and Abel, 2013). As medicine advanced and environments became more sanitary, people began living longer and are now more likely to die from chronic diseases of aging. According to the National Health Interview Survey, for example, 27.2% of all U.S. adults have multiple chronic conditions that shorten lifespan, including cancer, chronic obstructive pulmonary disease, coronary heart disease, diabetes, hepatitis, hypertension, stroke, and kidney disease (Boersma et al., 2020). Despite the sizeable burden of these conditions, we still know relatively little about their psychosocial drivers and mediating mechanisms, which has limited our ability to develop effective screening methods and personalized treatments.

Psychosocial stressors are a robust, but often underappreciated factor affecting chronic disease risk, and those occurring in childhood appear to be particularly impactful (Furman et al., 2019; Slavich, 2016). These stressors, sometimes called adverse childhood experiences (ACEs), encompass a wide range of adversities, with the ten canonical ACEs being emotional abuse, sexual abuse, physical abuse, emotional neglect, physical neglect, parental separation or divorce, witnessing domestic abuse or violence, household member alcohol or drug abuse, household

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https://doi.org/10.1016/j.bbi.2024.07.019
Received 26 March 2024; Received in revised form 11 July 2024; Accepted 15 July 2024
Available online 25 July 2024
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member mentally ill or suicidal, and household member imprisonment, all occurring before age 18. According to data from the Behavioral Risk Factor Surveillance System, which recently assessed eight of these ACEs across 34 U.S. states, an estimated 57.8% of Americans have experienced $\geq$ 1 ACE and 21.5% have experienced $\geq$ 3 ACEs during their lifetime (Giano et al., 2020). In turn, a large body of research has found that ACEs impact numerous psychological, neural, physiological, metabolic, and immune processes that promote chronic disease risk (Danese et al., 2009; Deighton et al., 2018; Hughes et al., 2017; Kalmakis and Chandler, 2015). Moreover, research has shown that the effects of ACEs on most clinical and behavioral endpoints are dose-dependent, with the poorer outcomes frequently being found for those experiencing the greatest adversity in a stepwise fashion (Dong et al., 2004; Felitti et al., 1998).

1.1. Sex and stressor-specific effects on health

Although the preponderance of research on early life stress has focused on ACEs, the ten canonical ACEs represent only a selection of childhood stressors that can impact health—namely, those occurring in the household. Moreover, it is important to note that different types of stressors can exert unique effects on health and physiology. For example, some research has found that abuse during childhood is more prognostic of later-life inflammation than neglect (Brown et al., 2021). Likewise, various types of abuse may affect different inflammatory markers (Baumeister et al., 2016). Individual-level factors, such as biological sex, may further influence if and how specific stressors affect health. Whereas some studies have found that the impact of certain forms of adversity on health is stronger for females (Brown et al., 2021; Kim et al., 2019), for example, others have reported that the immunocompromising effects of low childhood socioeconomic status are more pronounced for males (Gassen et al., 2021). Findings such as these have provided an unclear picture of how stressors affect health, highlighting the need for a more systematic approach to documenting how various types of early adversity impact disease biology, health, and well-being across the lifespan.

Identifying biological systems dysregulated by different forms of adversity (e.g., abuse, socioeconomic strain) is a critical first step toward developing more effective precision interventions. However, individual stressors rarely occur in isolation, and exposure to one form of childhood adversity greatly increases the risk of experiencing additional stressors (Dong et al., 2004; Felitti et al., 1998). Covariance between categories of stress presents practical limitations for assessing the independent effects of unique stressors in observational research (e.g., multicollinearity; uncertainty about causal paths between stressors) (Lähdepuro et al., 2019), and also raises questions about the ecological validity of doing so. Therefore, strategies for developing effective, precision-based strategies to mitigate the health consequences of specific stressors may benefit from a more holistic approach that considers whether different constellations of stressors emerge between individuals. For example, there may be clusters of individuals from materially wealthy families who have experienced low levels of childhood neglect, but high levels of abuse, whereas others may have experienced childhood poverty, but low levels of neglect and abuse. Many other permutations could exist with just these three stressors alone, thus highlighting the importance of considering overall multivariate patterns of adversity exposure when investigating how different stressors might interact to influence health.

1.2. Models of stress and health

One prevailing theory of how specific stressors impact health is the cumulative stress model (Evans et al., 2013; Felitti et al., 1998), which postulates that distinct forms of early adversity have an additive effect on health and development. Specifically, this perspective proposes that different forms of adversity are "created equal" with respect to their impact, and thus have similar consequences for human health and development. Research supporting this model has found greater negative outcomes in individuals exposed to different types of adversity in a dose-dependent manner (Atkinson et al., 2015; Danese and McEwen, 2012; Danese et al., 2009; Slopen et al., 2014). However, this model does not account for the fact that the effects of specific childhood stressors on key biological outcomes do appear to differ in magnitude (Baumeister et al., 2016; Brown et al., 2021). Accordingly, the cumulative stress framework does not lend insights into whether distinct categories (or clusters) of adversity differentially impact health, which is important for both better understanding disease physiology and developing precision health interventions.

In contrast, Ellis et al. (Ellis et al., 2022) proposed a framework of adversity that accounts for heterogeneity in the effects of specific stressors on health and development. Specifically, they posit that there are multiple dimensions of adversity that should all differentially affect human health, well-being, and development. The first dimension is environmental harshness, which is represented by mortality cues in the environment, such as neighborhood violence and socioeconomic adversity. The second dimension is threat, which is represented by experiences that more immediately threaten a child, such as emotional, physical, and sexual abuse. The third dimension is deprivation, which is when a child's basic needs are not met—that is, the resources needed for normative development are not available (e.g., neglect). Finally, the last dimension is unpredictability, which represents the predictability and reliability of the child's early life and the people within it. Unpredictability can be measured by experiences such as the number of parental transitions or times the child moved. Although there is growing evidence that all of these forms of adversity can impact development cognition and health (Afifi et al., 2016; Chen et al., 2002; Koss and Gunnar, 2018; Lam et al., 2022; Lambert et al., 2017; Luby et al., 2017; Maner et al., 2023; Miller et al., 2018; Noble et al., 2015; Roubinov et al., 2018; Rueness et al., 2020; Simpson et al., 2012; Spencer et al., 2013), we are not aware of any studies that have applied this framework to systematically investigate how different dimensions of early life adversity are related to a variety of specific biomarkers and health outcomes.

A first step in testing this framework involves identifying the extent to which different dimensions of adversity are inter-correlated. This is important because if most individuals who experience harshness *also* experience threat (for example), an argument could be made that the cumulative risk model is most practically useful because, in reality, individuals rarely experience only one stressor dimension. Alternatively, evidence indicating that individuals often experience select dimensions of stress may suggest that a multi-dimensional stressor framework better represents peoples' early-life environment.

1.3. Present study

With these insights in mind, we had four aims: (a) identify how individuals cluster together based on their exposure to various forms of early-life adversity; (b) test whether these clusters better reflect the cumulative stress model or the dimensions of adversity theory; (c) examine how these clusters differ across the biological sexes; and (d) investigate the extent to which various adversity clusters, as well as individual stressors, are associated with twenty-five different stress and disease biomarkers, and twenty major health conditions. To accomplish these aims, we first conducted latent class analyses to identify latent stressor exposure groups. We used multiple measures of various types of early adversity that map onto some of the dimensions described by Ellis et al. (Ellis et al., 2022)—namely, harshness (i.e., financial distress); threat (i.e., emotional, physical, and sexual abuse); deprivation (i.e., emotional and physical neglect); and unpredictability (i.e., frequency of moving and living away from their biological parents). This enabled us to test whether the childhood stressors assessed in our sample better reflected the cumulative stress model or multi-dimensional stressor framework (Ellis et al., 2022) and, in addition, whether these clusters were similar for men vs. women. Next, we estimated associations

between the different stressor exposure clusters and (a) twenty-five well-known biomarkers of inflammation (i.e., serum pro- and anti-inflammatory cytokines), metabolic function (i.e., anthropometric measures, glucose metabolism, and lipid levels), and stress (i.e., blood pressure, and urinary glucocorticoids and catecholamines), and (b) twenty major health conditions. Finally, we examined multivariate effect sizes for associations between individual adversity dimensions, biomarker categories, and disease risk.

To permit a high-quality, systematic approach to examining associations between early adversity and specific health outcomes (Kuhlman et al., 2018), as well as multiple biomarkers of stress and health (Friedman et al., 2015), we used data from Midlife in the United States (MIDUS): A National Longitudinal Study of Health and Well-being. The present analysis extends prior work on this cohort by (a) using all available cross-sectional biomarker data; (b) using the full range of childhood measures, and examining their multivariate architecture both within and between the biological sexes; and (c) pairing the biomarker data with twenty major health conditions. Considered together, these analyses represent one of the most comprehensive examinations of the biological and clinical consequences of ACEs of which we are aware.

2. Method

2.1. Participants

A full description of the study methodology is in Supplemental Materials 1. In brief, we obtained data from 2,111 participants (54.8% female, $M_{age} = 53.04$, $SD_{age} = 12.57$) who completed either MIDUS 2 and the corresponding Biomarker study ($n = 1{,}250$) or the MIDUS Refresher and Biomarker Study ($n = 861$). All participants provided informed consent prior to participation, and institutional review board approval for the MIDUS study covers secondary research using these data. There were no exclusions other than for missing data, which was minimal (see Data Analysis section below).

2.2. Measures

Childhood adversity. Descriptive statistics for the childhood stressors experienced by participants are shown in Table S1. Participants reported several sources of childhood adversity, including (a) financial distress; (b) being on welfare; (c) emotional, physical, and sexual abuse; (d) emotional and physical neglect; (e) frequency of moving; and (f) living away from their biological parents. Questions pertaining to financial distress and welfare status were derived from commonly used, individual items in MIDUS. Specifically, financial distress was measured with the question: "When you were growing up, was your family better off or worse off financially than the average family was at that time?" responded to using a 7-point scale, including 1 (*a lot better off*), 4 (*same as average family*), and 7 (*a lot worse off*). Welfare status, in turn, was measured with the question: "During your childhood and adolescence, was there ever a period of six months or more when your family was on welfare or ADC [Aid for Dependent Children]?" (dichotomous). Abuse and neglect were measured using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994). For each construct on the CTQ, participants responded to five items using a 5-point scale, including 1 (*never true*), 3 (*sometimes true*), and 5 (*very often true*). Composites were then computed by summing across items for which there were no missing data (Cronbach's α: 0.68–0.95). Times moved was measured by asking participants to report (as a whole number) how many times they moved to a new town or neighborhood during their childhood. Finally, cohabitation with biological parents was measured with the question: "Did you live with both of your biological parents up until you were 16?" (dichotomous).

Biomarker data. Descriptive statistics for the biomarker data are presented in Table S2. Biological assay data for the MIDUS biomarker studies have been previously described (University of Wisconsin I of A, 2018), and the assay methods, reference ranges, and other details are available online (see https://midus.wisc.edu/). In brief, serum assays were conducted using fasting blood samples, and urine assays were conducted using 12-hour overnight urine collection samples. Serum inflammatory markers of interest for the present analysis included levels of the pro-inflammatory cytokines interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNF-α), and the anti-inflammatory markers IL-10, soluble IL-6 receptor (sIL-6r), C-reactive protein (CRP), fibrinogen, E-selectin, and intercellular adhesion molecule 1 (I-CAM). Metabolic markers included anthropometric measures [body mass index (BMI), waist-to-hips ratio (WHR)], markers of glucose metabolism [serum glucose and insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), hemoglobin A1C (HbA1c)], and serum lipid levels [high- and low-density lipoproteins (HDL, LDL), triglycerides]. We also analyzed data for several stress biomarkers, including blood pressure (systolic and diastolic; average of second and third measurements), urinary glucocorticoid levels (cortisol, cortisone), and urinary catecholamine levels (norepinephrine, epinephrine, and dopamine), each adjusted for urinary creatinine levels. Biomarker variables that were positively skewed were log-transformed to limit heteroscedasticity and reduce the influence of outlying, but otherwise biologically plausible values.

Participants indicated whether they had ever been diagnosed with twenty major health conditions, the frequencies of which are presented in Table S3. All models were tested a second time while adjusting for clinically relevant covariates, including age, race, current household income, use of steroidal or non-steroidal anti-inflammatory, central nervous system, anti-coagulant, cardiovascular, or respiratory medications, smoking status, history of alcohol or drug abuse (excluding when drug abuse/alcoholism was an outcome), and hours fasting prior to biomarker collection.

2.3. Data analysis

Full details about the data analysis and missing data approach are in Supplemental Materials 1, and the statistical code for all analyses is in Supplemental Materials 2 and 3. Analyses were conducted using MPlus (Muthén and Muthén, 2017) and R (R Core Team, 2021), and all p-values were two-tailed and considered statistically significant at $p < 0.05$. Latent class analysis (Oberski, 2016; Sinha et al., 2021) was used to identify unobserved groups of individuals that clustered together based on the distributions of their exposure to childhood stressors, controlling for the effects of age and sex on class membership probability. These covariates were included to reduce the possibility of generational (age) or sex differences in childhood environments that could confound associations between latent classes and health outcomes (Fingerman et al., 2012; Tolin and Foa, 2006). Optimal k-class solutions were determined collectively based on model fit statistics, entropy, likelihood ratio tests, and class size (see Table S4 for model comparison). Model non-invariance was tested across both MIDUS waves and sex.

To estimate the impact of latent class membership on biomarker levels, the 3-step method was applied (Asparouhov and Muthén, 2014; Lanza et al., 2013), which involved including class membership as a nominal indicator of the latent class variable with measurement error fixed to that obtained from the initial latent class analysis. This procedure allows for error in class assignment to be accounted for when examining associations between latent classes and distal outcomes. Mean biomarker levels between classes were compared using Wald tests with variances allowed to differ across classes. Cox proportional hazards models (Therneau, 2023) were used to test proportional hazards assumptions and examine associations between latent class membership and hazard rates for 20 diseases and health conditions. To adjust for class assignment error in survival analyses, probabilities of membership in a participants' assigned classes were included as weights in all models. Multivariate effect sizes were computed for each biomarker using Mahalanobis distances (Del Giudice, 2019). Harmonic mean p

analyses were used to control familywise error and false discovery rate in the context of dependent hypothesis tests (see Supplemental Materials 1 and 3) (Wilson, 2019).

Finally, associations between individual childhood stressors and health outcomes were tested in a series of follow-up models. For each biomarker category, multivariate effect sizes were computed as Mahalanobis distances between levels of binary predictors (e.g., welfare status) and one standard deviation above and below the mean of continuous predictors (e.g., abuse). Cox proportional hazard models were used to examine the effects of individual childhood stressors on risk for each disease category.

3. Results

3.1. Childhood stressor latent class analysis

The latent class analysis including both sexes yielded an optimal 4-class solution for childhood stressors. However, log-likelihood difference testing revealed that this class structure differed across the sexes ($p < 0.001$). Separate latent class analyses were thus conducted for males and females, yielding a 2-class solution for males and 3-class solution for females, neither of which differed across the MIDUS waves (male: $p = 0.71$, female: $p = 0.32$). As is shown in Fig. 1, males were defined by low childhood stressor exposure (i.e., Low Stress; $n = 791$) and high childhood stressor exposure (High Stress; $n = 163$). In contrast, female latent classes were characterized by low (Low Stress; $n = 643$), moderate (Moderate Stress; $n = 358$), and high (High Stress; $n = 156$) childhood stressor exposure.

3.2. Childhood stressor-based differences in biomarker levels

Associations between the latent childhood stressor classes and individuals' biomarker levels are shown in Table 1, and multivariate effect sizes are depicted in Fig. 2. Standardized effect sizes (Cohen's *d*) for each biomarker are presented in Table S5, and Mahalanobis's *D* estimates and corresponding confidence intervals are available in Table S6.

Inflammation biomarkers. Compared with Low-Stress males, High-Stress males had higher serum levels of IL-6 (unadjusted: $p = 0.03$, adjusted: $p = 0.02$, Cohen's $d = 0.20$), CRP (unadjusted: $p = 0.007$, adjusted: $p = 0.004$, Cohen's $d = 0.25$), and I-CAM (unadjusted: $p < 0.001$, adjusted: $p = 0.01$, Cohen's $d = 0.26$). For females, there were no consistent differences between Low- and Moderate-Stress individuals with respect to inflammation. However, High-Stress females had higher serum levels of IL-6 (unadjusted: $p < 0.001$, adjusted: $p = 0.004$, Cohen's $d = 0.32$), CRP (unadjusted: $p < 0.001$, adjusted: $p = 0.004$, Cohen's $d = 0.39$), and fibrinogen (unadjusted: $p < 0.001$, adjusted: $p < 0.001$, Cohen's $d = 0.26$) than Low-Stress females.

Metabolic biomarkers. Compared to Low-Stress males, High-Stress males had higher BMI (unadjusted: $p = 0.01$, adjusted: $p = 0.003$, Cohen's $d = 0.28$), insulin levels (unadjusted: $p < 0.001$, adjusted: $p = 0.001$, Cohen's $d = 0.33$), insulin resistance (unadjusted: $p = 0.004$, adjusted: $p = 0.002$, Cohen's $d = 0.31$), triglycerides (unadjusted: $p = 0.002$, adjusted: $p = 0.01$, Cohen's $d = 0.25$), and LDL (unadjusted: $p = 0.03$, adjusted: $p = 0.048$, Cohen's $d = 0.19$), as well as lower HDL (unadjusted: $p = 0.03$, adjusted: $p = 0.02$, Cohen's $d = 0.26$). Although there were no significant differences in metabolic markers for Low- vs. Moderate-Stress females, High-Stress females had higher BMI (unadjusted: $p < 0.001$, adjusted: $p = 0.005$, Cohen's $d = 0.39$), insulin levels (unadjusted: $p < 0.001$, adjusted: $p = 0.001$, Cohen's $d = 0.35$), insulin resistance (unadjusted: $p = 0.001$, adjusted: $p = 0.007$, Cohen's $d = 0.33$), and triglycerides (unadjusted: $p = 0.005$, adjusted: $p = 0.005$, Cohen's $d = 0.25$) than Low-Stress females.

Stress biomarkers. Low- and High-Stress males did not differ in terms of their individual stress biomarker levels. However, High-Stress females had lower urinary cortisol levels than Low-Stress females (unadjusted: $p = 0.006$, adjusted: $p = 0.04$, Cohen's $d = 0.25$) and, to a lesser extent, Moderate-Stress females (unadjusted: $p = 0.04$, adjusted: $p = 0.16$, Cohen's $d = 0.20$).

3.3. Childhood stressor-based differences in health conditions

Next, we examined associations between childhood stressor exposure and participants' health conditions. The complete statistics are shown in Table 2, and the hazard ratios by disease category are depicted in Fig. 3. Compared with Low-Stress males, High-Stress males exhibited greater risk for numerous health problems, including high blood pressure (unadjusted HR: 1.67 [1.27, 2.20]; adjusted HR: 1.71 [1.25, 2.32]), circulation problems (unadjusted HR: 2.18 [1.24, 3.83]; adjusted HR: 2.61 [1.40, 4.86]), cholesterol problems (unadjusted HR: 1.42 [1.08, 1.86]; adjusted HR: 1.52 [1.13, 2.05]), thyroid disease (unadjusted HR: 3.04 [1.60, 5.75]; adjusted HR: 3.65 [1.87, 7.12]), cancer (unadjusted HR: 2.02 [1.29, 3.15]; adjusted HR: 2.41 [1.52, 3.83]), arthritis (unadjusted HR: 1.75 [1.31, 2.33]; adjusted HR: 1.81 [1.30, 2.53]), and depression (unadjusted HR: 3.15 [2.35, 4.21]; adjusted HR: 3.09 [2.22, 4.31]).

Compared with Low-Stress females, Moderate-Stress females had greater risk of cholesterol problems (unadjusted HR: 1.32 [1.07, 1.62]; adjusted HR: 1.31 [1.05, 1.64]), thyroid disease (unadjusted HR: 1.57 [1.17, 2.11]; adjusted HR: 1.73 [1.26, 2.38]), and depression (unadjusted HR: 1.60 [1.27, 2.03]; adjusted HR: 1.56 [1.20, 2.02]). Moreover, compared to Low-Stress females, High-Stress females were at greater risk for experiencing 18 of the 20 health conditions assessed (unadjusted HRs: 1.60–13.04; adjusted HRs: 1.51–9.28), except for blood clots and glaucoma.

3.4. Associations between specific childhood stressors, stress and disease biomarkers, and health conditions

Finally, we examined how participants' exposure to specific childhood stressors related to twenty-five stress and disease biomarkers, and twenty major health conditions. Inter-correlations between the childhood stressors are shown in Table S7.[2]

Stress and disease biomarkers. Regarding the stress and disease biomarkers assessed (Fig. 2, Panel B; Fig. 4), the effects of welfare status during childhood were most prominently reflected in elevated inflammatory activity. Both males and females who reported being on welfare exhibited higher inflammation, but the effect sizes were larger for males. Although the magnitudes of the effects were smaller than for inflammation for both sexes, associations between welfare status and both catecholamine levels and lipid levels were stronger for males than females, whereas the opposite was true for glucocorticoids and anthropometric measurements. The effects of welfare status on markers of glucose metabolism and blood pressure, in turn, were similar for males and females. For the other measure of socioeconomic standing during childhood—namely, financial distress—associations with biomarker levels were stronger for stress markers (i.e., glucocorticoids, catecholamines, and blood pressure) among males, but more evident in elevated inflammation and glucose levels among females. The effects of financial distress on lipids and anthropometrics, in turn, were generally smaller than for the other biomarkers and similar between the sexes.

Among the three types of abuse measured (i.e., emotional, physical, and sexual), the effects of emotional abuse were generally modest and

[2] Because these analyses generated 810 effects (times two if comparing adjusted and unadjusted models), we report only the effect sizes in Figs. 2–3 (multivariate and aggregate effect sizes for biomarker/disease categories) and Figs. 4–5 (effect sizes for individual biomarkers and health conditions), and interpret the general patterns of findings in section 3.4. Accordingly, it is important to consider that the differences in effect sizes between the stress groups and sexes that are displayed in Figs. 2–5 do not necessarily reflect statistically significant differences.

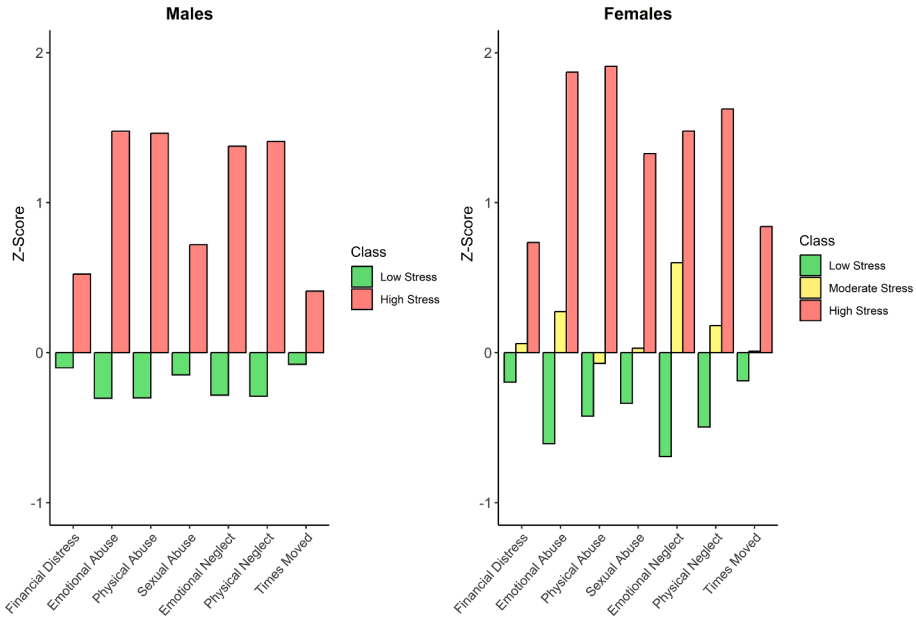

Fig. 1. Latent class differences in childhood stressors. Depicted are standardized differences (z-scores) between latent classes in each childhood stressor. The y-axis reflects standard deviations from the sex-specific mean for each variable on the x-axis.

overall stronger for males compared to females, especially for elevated levels of glucocorticoids and higher diastolic blood pressure. Emotional abuse was also associated with certain inflammatory markers (e.g., IL-8, CRP, ICAM-1) and, to a lesser extent, lipid levels, with slightly larger effect sizes for males in some cases and females in other cases. In most biomarker domains, effect sizes for physical abuse were larger than for emotional abuse and, for the most part, similar for males and females. However, high levels of physical abuse did tend to be associated with higher markers of glucose metabolism and larger anthropometric measurements for females, but less so for males. For sexual abuse, effects on inflammation, lipids, and blood pressure were similar between the sexes, but were overall stronger for catecholamines among males, and stronger for glucose metabolism and anthropometrics for females. The magnitude of the effect of sexual abuse on catecholamine levels, in turn, was relatively small for both males and females.

The effects of emotional neglect on most biomarkers were of similar size, with the exception of slightly stronger associations with elevated inflammation, and there were few differences between males and females. However, high levels of emotional neglect were more strongly related to catecholamine levels for males than females, and the effect on glucocorticoids was slightly larger for females. For physical neglect, the effects on inflammation, glucocorticoids, and catecholamines were modest and of similar magnitude for males and females. However, associations between physical neglect and lipids, glucose metabolism, and anthropometrics were stronger for females than males, and stronger for blood pressure among males vs. females.

For the remaining childhood stressors, not living with one's parents during childhood appeared to have minimal effects on most biomarkers, with the exception of higher glucose metabolism and, to a lesser extent, lipid levels for females. The effect sizes for this predictor were otherwise small and similar between the sexes. The effects of times moved during childhood were generally larger for females than males, particularly for anthropometric measurements, glucose biomarkers, and lipid levels. Minimal effects of movement during childhood were found for the remaining biomarkers, and these results were similar for males and females.

Health conditions. In terms of health conditions (Fig. 3, Panel B; Fig. 5), results revealed that, for most conditions, welfare status during childhood was more prognostic of health problems for females than males, including thyroid, metabolic, cardiovascular, digestive, joint, and respiratory issues, as well as glaucoma (Fig. 3, Panel B). Risks of blood disorders and mental/behavioral issues were slightly higher for males (vs. females) who were on welfare, but overall hazard ratios for the effects of welfare status were modest relative to those associated with abuse and neglect. Hazard ratios for financial distress, on the other hand, hovered around 1 for all conditions (representing null effects) for both males and females.

Consistent with what we found for the stress and disease biomarkers assessed, emotional abuse was more strongly related to several health conditions for males vs. females, and this was particularly true for thyroid conditions, mental/behavioral issues, blood disorders, and glaucoma. However, hazard ratios for mental/behavioral issues among females who reported high levels of emotional abuse were still large. Both males and females who experienced emotional abuse during childhood also exhibited higher risk of cancer and respiratory issues, with hazard ratios being of similar size between the sexes. We found a similar pattern for physical abuse, although the sex differences were less pronounced. Specifically, physical abuse was associated with higher risk of all health conditions for both sexes, but the hazard ratios were larger among males for thyroid issues, joint problems, and glaucoma. Hazard ratios for sexual abuse were overall smaller than for other forms of abuse and alike between males and females, with the exception of greater risk for thyroid disorders for males, and slightly higher risk for cardiovascular and blood disorders for females.

Similar to emotional abuse, emotional neglect was also more strongly associated with thyroid problems, blood disorders, and glaucoma for males and, to a lesser extent, mental/behavioral issues. Nevertheless, females who experienced high levels of emotional neglect were also at a greater risk for thyroid and mental/behavioral problems, as well as metabolic disorders and cancer, with the hazard ratios for these latter two conditions being similar between the sexes. Associations between physical neglect and most health conditions were weak for females, with the exception of higher risk for cancer (more so than males) and mental/behavioral health problems (similar in magnitude to males). Males reporting high levels of physical neglect were at higher risk than females for thyroid issues, blood disorders, and glaucoma. Finally, neither living away from parents nor times moved during childhood were consistently related to most health conditions for males or females. There was, however, a small effect of living away from parents on risk of glaucoma for both sexes.

Table 1
Wald tests of differences in biomarker levels between the latent stressor classes.

Biomarker	Males				Females											
	Low Stress v. High Stress				Low Stress v. Moderate Stress				Low Stress v. High Stress				Moderate Stress v. High Stress			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	W [1]	*p*	*W* [1]	*p*	*W* [1]	*p*	*W* [1]	*p*	*W* [1]	*p*	*W* [1]	*p*	*W* [1]	*p*	*W* [1]	*p*
Inflammation																
IL-6	4.98	0.03	5.33	0.02	0.77	0.38	1.93	0.17	12.50	0.0004	8.42	0.004	7.44	0.006	3.51	0.06
IL-8	1.22	0.27	0.34	0.56	0.18	0.67	0.05	0.83	8.39	0.004	1.68	0.20	6.02	0.01	1.84	0.18
IL-10	0.05	0.82	0.19	0.66	3.97	0.05	0.64	0.43	0.31	0.58	0.56	0.46	1.40	0.24	0.01	0.94
CRP	7.33	0.007	8.37	0.004	0.0001	0.99	0.02	0.90	20.56	< 0.0001	8.50	0.004	16.87	< 0.0001	6.84	0.009
TNF-α	1.49	0.22	3.11	0.08	0.42	0.52	0.02	0.89	0.17	0.68	0.02	0.89	0.003	0.96	0.05	0.83
sIL6r	0.003	0.96	0.28	0.60	0.05	0.83	0.50	0.48	1.37	0.24	0.10	0.75	1.54	0.22	0.58	0.45
Fibrinogen	0.10	0.76	0.74	0.39	0.29	0.59	0.06	0.80	10.13	0.002	9.55	0.002	6.44	0.01	9.85	0.002
E-selectin	3.15	0.08	0.79	0.37	4.41	0.04	2.79	0.09	8.43	0.004	3.23	0.07	16.59	< 0.0001	8.80	0.003
I-CAM	12.48	0.0004	6.64	0.01	1.18	0.28	0.12	0.73	5.26	0.02	2.28	0.13	2.18	0.14	2.77	0.10
Anthropometric																
BMI	6.72	0.01	8.77	0.003	0.91	0.34	0.01	0.91	15.87	0.0001	7.96	0.005	9.24	0.002	6.82	0.009
WHR	0.37	0.55	0.02	0.90	1.25	0.26	2.57	0.11	7.64	0.006	1.66	0.20	3.87	0.049	0.09	0.76
Glucose																
Glucose	9.96	0.002	1.08	0.30	1.53	0.22	0.06	0.81	1.11	0.29	3.38	0.07	3.60	0.06	3.61	0.06
Insulin	16.24	0.0001	11.58	0.001	0.87	0.35	1.31	0.25	13.04	0.0003	6.81	0.001	15.79	0.0001	10.35	0.001
HbA1c	0.42	0.52	0.01	0.94	9.75	0.002	2.85	0.09	0.003	0.96	0.28	0.60	3.35	0.07	2.14	0.14
HOMA-IR	8.29	0.004	9.50	0.002	0.79	0.38	1.01	0.31	11.82	0.001	7.37	0.007	14.48	0.0001	10.35	0.001
Lipid Levels																
LDL	4.55	0.03	3.92	0.048	0.02	0.89	0.73	0.39	0.0001	0.99	0.30	0.59	0.01	0.92	1.13	0.29
HDL	9.11	0.003	7.45	0.006	0.84	0.36	0.25	0.62	7.52	0.006	1.69	0.19	3.84	0.05	0.80	0.37
Triglycerides	9.32	0.002	6.70	0.01	1.17	0.28	0.50	0.48	8.01	0.005	8.00	0.005	3.71	0.05	4.73	0.03
Blood Pressure																
Systolic BP	0.37	0.55	0.18	0.67	0.06	0.80	0.44	0.51	1.58	0.21	0.004	0.95	0.96	0.33	0.16	0.69
Diastolic BP	7.71	0.006	1.22	0.27	2.17	0.14	1.04	0.31	0.93	0.33	0.04	0.84	0.01	0.91	0.71	0.40
Glucocorticoids																
Cortisol	3.30	0.07	2.79	0.09	0.38	0.54	0.79	0.37	7.57	0.006	4.42	0.04	4.43	0.04	2.00	0.16
Cortisone	2.98	0.08	1.41	0.24	1.25	0.26	0.07	0.80	2.92	0.09	0.001	0.98	6.56	0.01	0.04	0.84
Catecholamines																
Norepinephrine	0.002	0.96	0.04	0.84	4.94	0.03	0.66	0.42	3.64	0.06	0.25	0.62	0.03	0.86	0.01	0.94
Epinephrine	0.06	0.81	0.03	0.87	0.02	0.89	0.04	0.85	0.43	0.51	0.14	0.71	0.26	0.61	0.22	0.64
Dopamine	1.69	0.19	0.003	0.96	0.0001	0.99	0.07	0.79	0.50	0.48	0.09	0.76	0.44	0.51	0.01	0.92

Abbreviations: IL = interleukin, CRP = C-reactive protein, TNF-α = tumor necrosis factor-α, sIL6r = soluble interleukin-6 receptor, I-CAM = intercellular adhesion molecule 1, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance, HBA1c = hemoglobin A1C, LDL = low-density lipoprotein, HDL = high-density lipoprotein, BP = blood pressure.

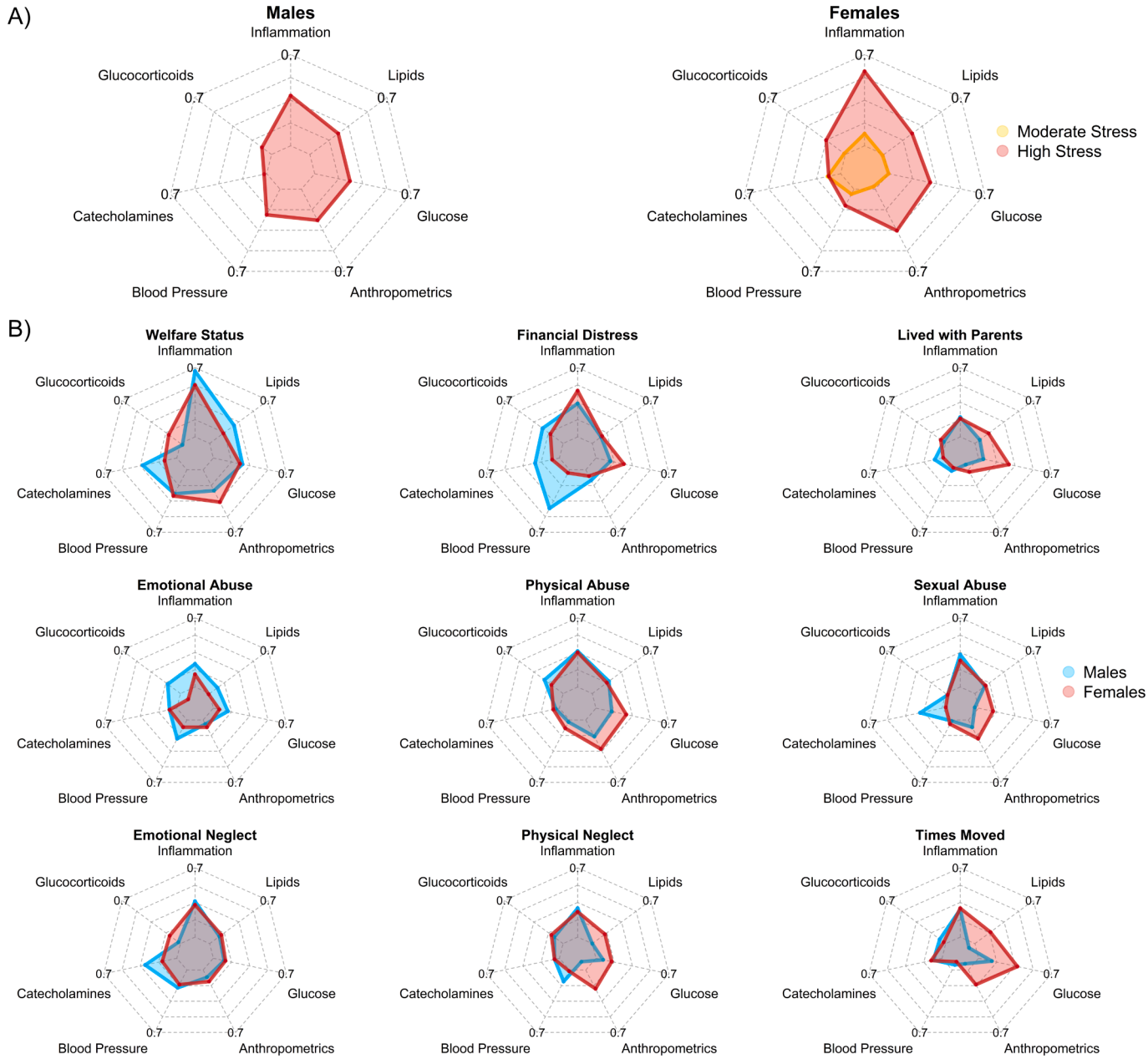

Fig. 2. Multivariate effect sizes between childhood stressors and the stress- and disease-related biomarkers. Shown are radar plots of Mahalanobis distances within each biomarker category between the latent classes (Panel A) and either levels of individual binary predictors or one standard deviation above and below the mean of individual continuous predictors (Panel B). The center of each heptagon represents no difference from low childhood adversity, with standardized effect sizes increasing as points approach the exterior.

In sum, these results indicate that different childhood stressors have wide-ranging effects on biomarkers and health, and that these effects differ by sex. Even for stressors that comprise the same higher-order construct (e.g., physical, emotional, sexual abuse), different stressor types appear to have distinct consequences for health, especially when also considering moderation by sex. Despite the heterogeneity of these results, some consistent patterns are evident. For example, the effects of childhood stressors on metabolic biomarkers were generally larger for females than males. Furthermore, emotional abuse and neglect tended to exert more pronounced effects in males than females for several biomarkers and health conditions, particularly thyroid issues, blood disorders, and mental/behavioral health problems (see Figs. 2 and 3).

3.5. Robustness checks

Finally, we examined the robustness of these effects using harmonic mean *p* analyses. The results indicated that the effects of childhood stressors on participants' stress- and disease-related biomarkers, as well as health outcomes were largely robust while adjusting for multiple comparisons (see Supplementary Files 1 and 3). For the twenty-five biomarkers assessed, in fact, only blood pressure, glucocorticoids, and catecholamines (3 of 25 biomarkers) did not reach statistical significance while adjusting for multiple comparisons. Similarly, all omnibus tests with health conditions as the outcome survived adjustment for multiple comparisons, except for glaucoma. Together, these results reveal highly robust associations between latent childhood stressor

Table 2
Hazard ratios for health conditions by latent stressor class.

Condition	Males		Females						Category[a]
	Low Stress v. High Stress		Low Stress v. Moderate Stress		Low Stress v. High Stress		Moderate Stress v. High Stress		
	Unadjusted HR [95% CI]	Adjusted HR [95% CI]	Unadjusted HR [95% CI]	Adjusted HR [95% CI]	Unadjusted HR [95% CI]	Adjusted HR [95% CI]	Unadjusted HR [95% CI]	Adjusted HR [95% CI]	
Heart Disease	1.52 [0.90, 2.58] $p = 0.113$	1.61 [0.86, 2.98] $p = 0.129$	0.77 [0.46, 1.30] $p = 0.344$	0.78 [0.43, 1.41] $p = 0.415$	2.78 [1.58, 4.90] $p < 0.001$	3.24 [1.63, 6.42] $p = 0.001$	3.58 [1.84, 6.95] $p < 0.001$	4.14 [1.89, 9.03] $p < 0.001$	Cardiovascular
High BP	1.67 [1.27, 2.20] $p < 0.001$	1.71 [1.25, 2.32] $p = 0.001$	1.03 [0.84, 1.28] $p = 0.727$	0.99 [0.77, 1.27] $p = 0.950$	1.98 [1.46, 2.69] $p < 0.001$	1.63 [1.12, 2.36] $p = 0.010$	1.91 [1.38, 2.64] $p < 0.001$	1.64 [1.10, 2.44] $p = 0.014$	Cardiovascular
Circulation Problems	2.18 [1.24, 3.83] $p = 0.006$	2.61 [1.40, 4.86] $p = 0.002$	1.48 [1.01, 2.17] $p = 0.044$	1.40 [0.90, 2.16] $p = 0.132$	3.14 [1.98, 4.96] $p < 0.001$	2.74 [1.53, 4.92] $p = 0.001$	2.11 [1.29, 3.45] $p = 0.003$	1.96 [1.07, 3.58] $p = 0.028$	Cardiovascular
Blood Clots	1.36 [0.58, 3.17] $p = 0.474$	1.20 [0.41, 3.48] $p = 0.728$	1.50 [0.87, 2.60] $p = 0.142$	1.67 [0.93, 2.99] $p = 0.081$	1.98 [0.88, 4.46] $p = 0.098$	1.51 [0.57, 3.99] $p = 0.396$	1.31 [0.56, 3.07] $p = 0.526$	0.90 [0.34, 2.39] $p = 0.842$	Cardiovascular
Heart Murmur	1.08 [0.62, 1.89] $p = 0.777$	1.07 [0.57, 2.02] $p = 0.820$	1.15 [0.82, 1.62] $p = 0.398$	1.23 [0.84, 1.79] $p = 0.278$	2.06 [1.35, 3.16] $p = 0.001$	2.31 [1.42, 3.76] $p = 0.001$	1.78 [1.12, 2.83] $p = 0.014$	1.87 [1.13, 3.11] $p = 0.015$	Cardiovascular
Stroke	0.94 [0.29, 3.01] $p = 0.920$	1.27 [0.35, 4.52] $p = 0.710$	1.09 [0.54, 2.17] $p = 0.804$	1.13 [0.53, 2.41] $p = 0.742$	4.29 [2.03, 9.05] $p < 0.001$	3.09 [1.14, 8.38] $p = 0.026$	3.93 [1.70, 9.09] $p = 0.001$	2.72 [0.94, 7.82] $p = 0.062$	Cardiovascular
Anemia/ Blood Diseases	1.84 [0.92, 3.66] $p = 0.081$	2.02 [0.96, 4.27] $p = 0.064$	1.19 [0.93, 1.52] $p = 0.151$	1.34 [1.01, 1.78] $p = 0.036$	1.93 [1.41, 2.64] $p < 0.001$	1.88 [1.28, 2.75] $p = 0.001$	1.61 [1.15, 2.25] $p = 0.005$	1.39 [0.94, 2.06] $p = 0.095$	Blood
Cholesterol	1.42 [1.08, 1.86] $p = 0.010$	1.52 [1.13, 2.05] $p = 0.005$	1.32 [1.07, 1.62] $p = 0.008$	1.31 [1.05, 1.64] $p = 0.015$	2.02 [1.44, 2.83] $p < 0.001$	2.16 [1.50, 3.12] $p < 0.001$	1.53 [1.08, 2.15] $p = 0.014$	1.64 [1.13, 2.37] $p = 0.008$	Metabolic
Diabetes	1.60 [0.99, 2.60] $p = 0.054$	1.40 [0.76, 2.59] $p = 0.270$	1.06 [0.72, 1.56] $p = 0.749$	1.01 [0.60, 1.68] $p = 0.963$	1.84 [1.11, 3.05] $p = 0.018$	2.11 [1.13, 3.94] $p = 0.018$	1.73 [1.00, 2.99] $p = 0.048$	2.09 [1.10, 3.96] $p = 0.023$	Metabolic
Asthma	1.27 [0.75, 2.17] $p = 0.361$	1.05 [0.54, 2.04] $p = 0.865$	1.21 [0.88, 1.66] $p = 0.236$	1.26 [0.87, 1.82] $p = 0.215$	2.64 [1.84, 3.77] $p < 0.001$	2.63 [1.68, 4.11] $p < 0.001$	2.17 [1.48, 3.20] $p < 0.001$	2.08 [1.30, 3.31] $p = 0.002$	Respiratory
Emphysema/COPD	2.20 [0.91, 5.29] $p = 0.078$	1.99 [0.63, 6.31] $p = 0.239$	0.78 [0.31, 1.91] $p = 0.588$	0.66 [0.21, 2.00] $p = 0.464$	3.97 [1.79, 8.79] $p = 0.001$	4.01 [1.56, 10.20] $p = 0.004$	5.09 [1.89, 13.74] $p = 0.001$	6.08 [1.78, 20.74] $p = 0.004$	Respiratory
Thyroid Disease	3.04 [1.60, 5.75] $p = 0.001$	3.65 [1.87, 7.12] $p < 0.001$	1.57 [1.17, 2.11] $p = 0.003$	1.73 [1.26, 2.38] $p = 0.001$	1.75 [1.12, 2.72] $p = 0.013$	2.25 [1.35, 3.74] $p = 0.002$	1.11 [0.70, 1.75] $p = 0.641$	1.29 [0.78, 2.14] $p = 0.317$	Thyroid
Peptic Ulcers	1.16 [0.48, 2.78] $p = 0.731$	1.00 [0.39, 2.51] $p = 0.998$	1.12 [0.62, 2.03] $p = 0.690$	0.88 [0.43, 1.81] $p = 0.744$	3.89 [2.18, 6.93] $p < 0.001$	3.61 [1.85, 7.04] $p < 0.001$	3.45 [1.74, 6.83] $p < 0.001$	4.07 [1.74, 9.47] $p = 0.001$	Digestive
Colon Polyp	0.94 [0.61, 1.43] $p = 0.780$	0.97 [0.61, 1.55] $p = 0.925$	1.18 [0.88, 1.58] $p = 0.259$	1.26 [0.92, 1.74] $p = 0.142$	1.60 [1.01, 2.52] $p = 0.044$	1.60 [0.94, 2.71] $p = 0.077$	1.35 [0.83, 2.19] $p = 0.218$	1.26 [0.73, 2.17] $p = 0.393$	Digestive
Cirrhosis/Liver Disease	1.10 [0.24, 5.00] $p = 0.899$	1.53 [0.33, 6.99] $p = 0.579$	1.68 [0.55, 5.09] $p = 0.355$	1.98 [0.70, 5.55] $p = 0.195$	4.85 [1.51, 15.50] $p = 0.008$	2.79 [0.98, 7.93] $p = 0.054$	2.88 [0.90, 9.20] $p = 0.074$	1.40 [0.49, 4.00] $p = 0.520$	Digestive
Cancer	2.02 [1.29, 3.15] $p = 0.002$	2.41 [1.52, 3.83] $p < 0.001$	1.35 [0.97, 1.88] $p = 0.075$	1.40 [0.98, 2.01] $p = 0.060$	2.15 [1.32, 3.50] $p = 0.002$	2.51 [1.45, 4.34] $p = 0.001$	1.59 [0.96, 2.65] $p = 0.071$	1.78 [1.02, 3.10] $p = 0.042$	Cancer
Arthritis	1.75 [1.31, 2.33] $p < 0.001$	1.81 [1.30, 2.53] $p < 0.001$	1.20 [0.99, 1.47] $p = 0.057$	1.20 [0.95, 1.50] $p = 0.112$	2.03 [1.52, 2.72] $p < 0.001$	1.96 [1.41, 2.73] $p < 0.001$	1.68 [1.24, 2.28] $p = 0.001$	1.63 [1.15, 2.31] $p = 0.005$	Joint
Glaucoma	0.47 [0.12, 1.82] $p = 0.276$	0.69 [0.16, 2.92] $p = 0.617$	1.17 [0.59, 2.34] $p = 0.644$	0.66 [0.24, 1.86] $p = 0.442$	1.67 [0.58, 4.74] $p = 0.334$	2.03 [0.56, 7.25] $p = 0.275$	1.42 [0.46, 4.30] $p = 0.534$	3.03 [0.70, 13.03] $p = 0.135$	Glaucoma
Alcoholism	2.08 [1.09, 3.99] $p = 0.026$	2.24 [0.99, 5.09] $p = 0.053$	1.51 [0.48, 4.76] $p = 0.477$	1.57 [0.43, 5.76] $p = 0.490$	13.04 [5.37, 31.60] $p < 0.001$	9.28 [3.05, 28.20] $p < 0.001$	8.60 [3.01, 24.58] $p < 0.001$	5.88 [1.65, 20.91] $p = 0.006$	Mental/ Behavioral
Depression	3.15 [2.35, 4.21] $p < 0.001$	3.09 [2.22, 4.31] $p < 0.001$	1.60 [1.27, 2.03] $p < 0.001$	1.56 [1.20, 2.02] $p = 0.001$	3.89 [3.01, 5.03] $p < 0.001$	3.59 [2.65, 4.88] $p < 0.001$	2.42 [1.85, 3.15] $p < 0.001$	2.30 [1.68, 3.15] $p < 0.001$	Mental/ Behavioral

Abbreviations: HR = hazard ratio, BP = blood pressure, COPD = chronic obstructive pulmonary disease.
[a] Category refers to which conditions were grouped together for plotting.

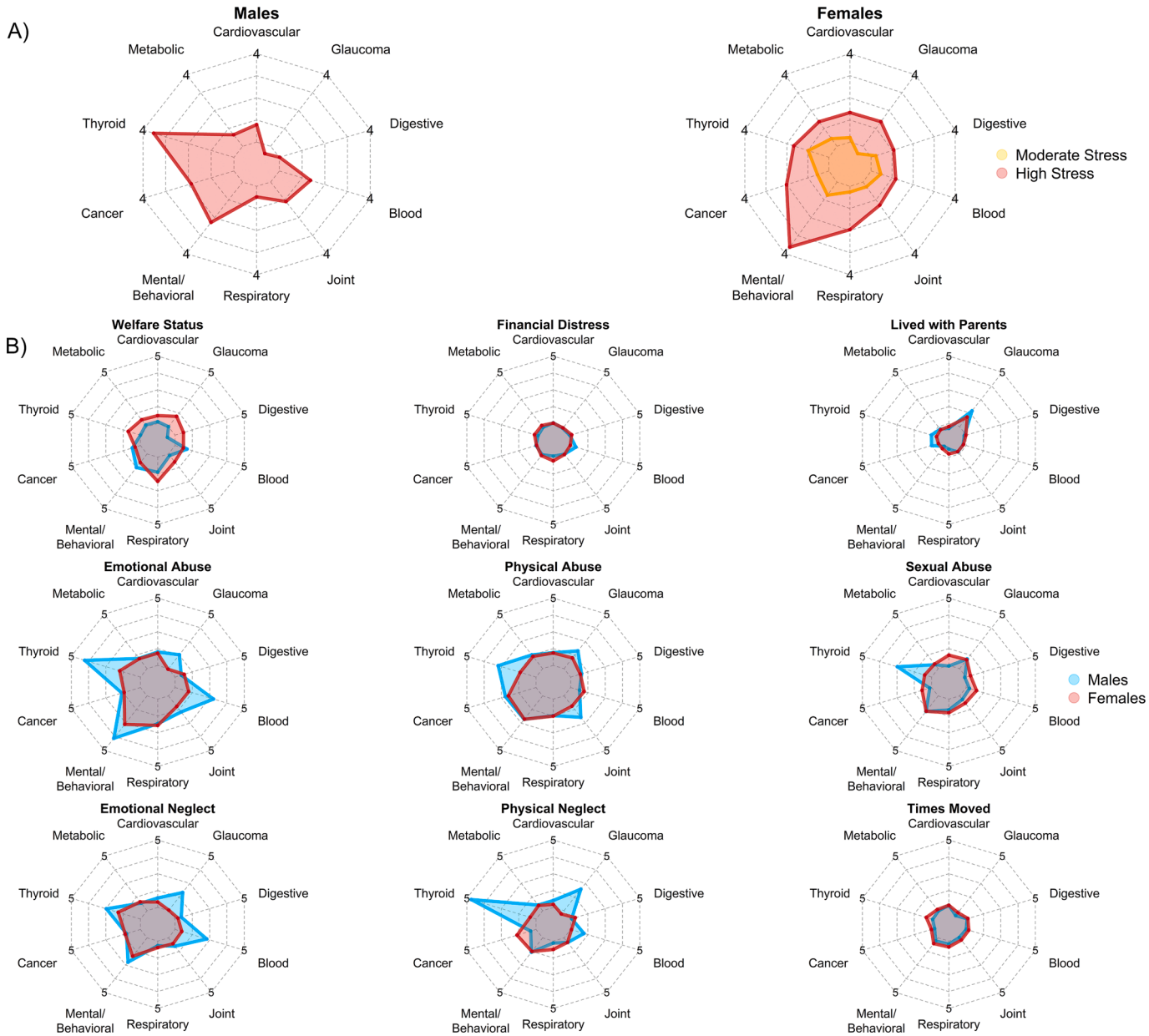

Fig. 3. Hazard ratios for associations between childhood stressors and health conditions. Radar plots of hazard ratios for the effects of latent class membership (Panel A) and individual childhood stressors (Panel B) on risk of each health outcome. The center of each decagon represents a hazard ratio of 1 (i.e., no effect), with effects increasing in size as points approach the exterior.

classes and multiple biological and health outcomes, the patterning of which differs based on both participants' sex and the specific types of stressors experienced.

4. Discussion

Although the literature on life stress and health is sizable, much of this work suffers from a lack of specificity regarding possible stressor → health associations, as the assessment of biomarkers and health in this context is often limited to a very short list of outcomes with no attention paid to how different stressors might exert differential effects (Slavich, 2019). We sought to address this critical issue by providing the most comprehensive picture that we know of linking different types of childhood adversity with biological function and health status across a wide variety of twenty-five different stress- and disease-related biomarkers, and twenty different mental and physical health outcomes. As expected, we found that experiencing more childhood adversity was consistently related to dysregulated biological functioning and higher risk for numerous serious health problems. Moreover, these associations were largely robust to adjustment for multiple comparisons and they differed across the sexes, latent adversity classes identified, and specific stressors that participants experienced.

Although we did find evidence of stressor-specific effects, the results of our latent class analyses suggested that individuals tended to cluster more so based on the severity of the adversities they experienced than on the dimensions of those stressors. Using this latent cluster analysis approach in turn revealed the presence of different latent childhood stressor classes for males vs. females, with individuals having these profiles exhibiting distinct patterns of biological dysregulation. Specifically, whereas both males and females in the High Stress class had the greatest inflammation and poorest metabolic health, for female participants, there were few differences between those in the Low and Moderate Stress classes for most biomarkers. With respect to the twenty health conditions examined, we found that associations between

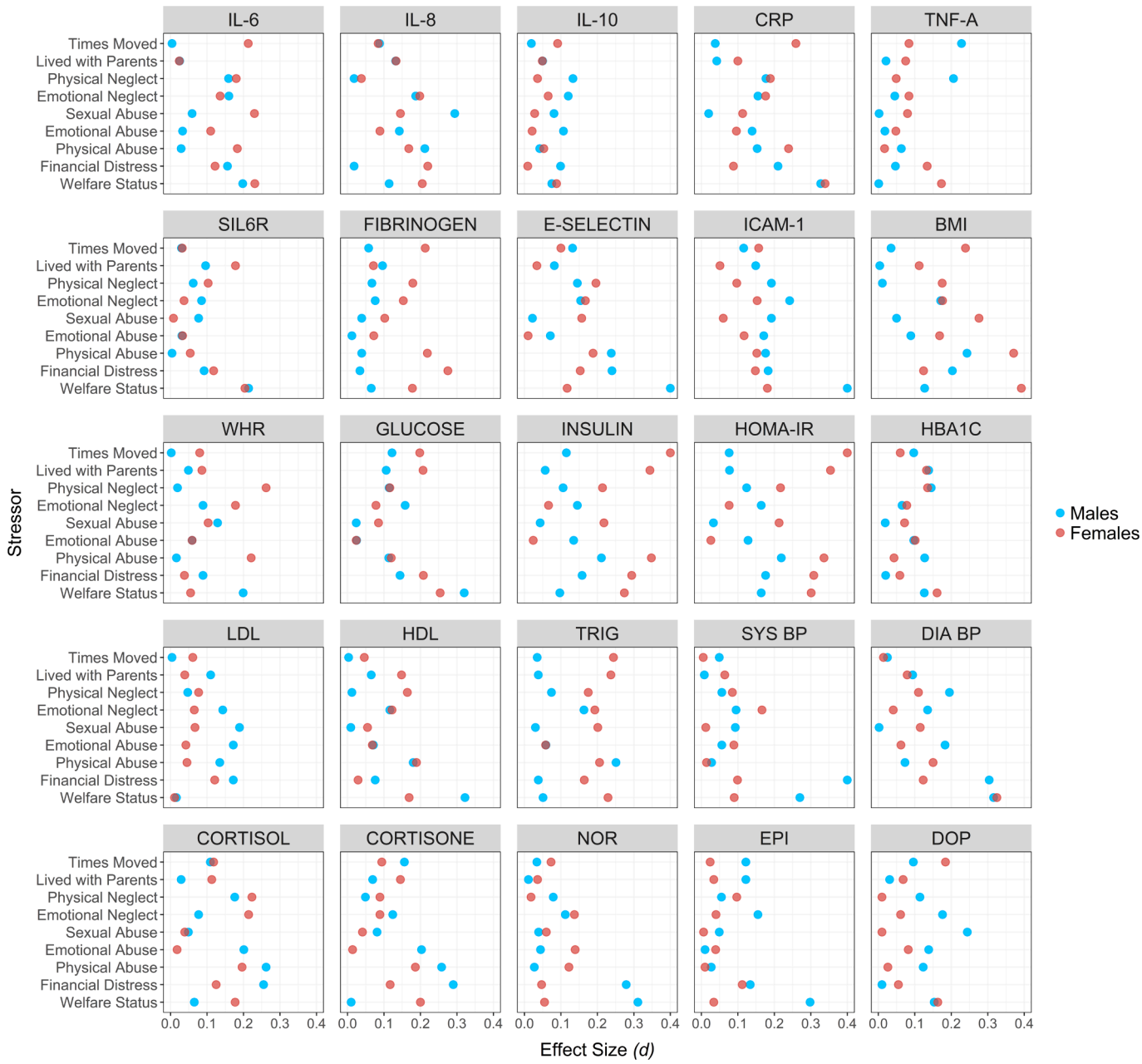

Fig. 4. Univariate effects sizes between each childhood stressor and the stress- and disease-related biomarkers. Shown are Cohen's *d* values between levels of individual binary predictors or one standard deviation above and below the mean of individual continuous predictors. For plotting, Cohen's *d* values were capped at 0.4 (maximum observed: 0.47). IL = interleukin, CRP = C-reactive protein, TNF-A = tumor necrosis factor-α, SIL6R = soluble IL-6 receptor, ICAM-1 = intercellular adhesion molecule 1, BMI = body mass index, WHR = waist to hips ratio, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance, HBA1C = hemoglobin A1C, LDL = low-density lipoprotein, HDL = high-density lipoprotein, TRIG = triglycerides, SYS = systolic, DIA = diastolic, BP = blood pressure, NOR = urinary norepinephrine, EPI = urinary epinephrine, DOP = urinary dopamine.

childhood adversity and disease risk were largely dose dependent for almost all outcomes, with the Low Stress group exhibiting the fewest major health problems, followed by the Moderate Stress group and then the High Stress group. Again, these associations differed for males and females, highlighting important sex differences in associations between childhood adversity and health, and underscoring the importance of testing for such differences in biomedical stress research.

4.1. Scientific and clinical implications

These results have both scientific and clinical implications. Scientifically, although a large body of research has shown that early adversity can have long-lasting effects on biology, few studies have taken a systems biology approach and tested for differential stressor effects across multiple health-relevant biological systems or health outcomes in the same sample. Doing so in the present study revealed not only stressor-specific effects, but also effects that systematically differed for males and females, thus highlighting mechanistic pathways that may link early-life stressor exposure with sex-specific differences in risk for inflammation-related and metabolic disorders (Mengelkoch, 2024; Slavich and Sacher, 2019).

These results may also help advance theories of stress and health, which have historically been based on relatively simplistic assessments of stressor exposure and biology (Ellis et al., 2022; Slavich, 2020;

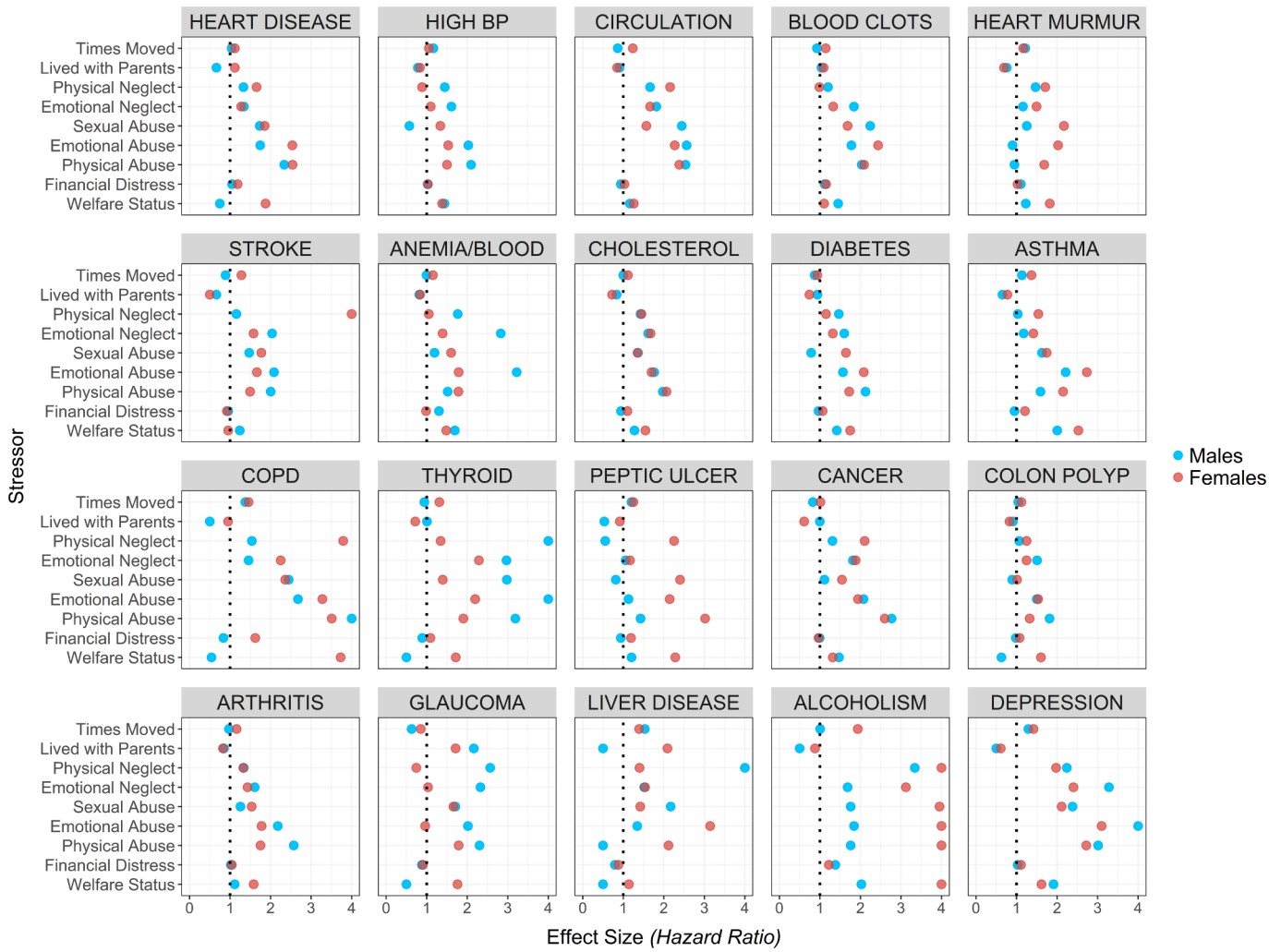

Fig. 5. Hazard ratios for associations between childhood stressors and each health condition. Hazard ratios were capped at 0.5 (minimum) and 4 (maximum) for plotting; these values were within the confidence intervals of effects for variables that were censored. The dotted vertical line denotes a hazard ratio of 1, denoting a null effect. BP = blood pressure, COPD = chronic obstructive pulmonary disease.

Slavich, 2022; Slavich et al., 2023). Specifically, we found that the latent stressor exposure classes better reflect the cumulative risk hypothesis (Evans et al., 2013; Felitti et al., 1998) than the specific dimensions proposed by Ellis et al. (Ellis et al., 2022). Critically, our analysis does not indicate that these dimensions do not exist or that they do not have unique implications for health in adulthood. Instead, the data merely suggest that because of high covariance between exposure to different stressors, it may be difficult to estimate the independent effects of different stressor categories. Research using larger sample sizes and assessments that are specifically tailored to capture key constructs such as harshness, threat, deprivation, and unpredictability may find that individuals' experiences do vary along these dimensions. In the present study, for example, we used financial distress as a proxy for harshness, when, in fact, neighborhood quality or local mortality rates would have been better indices. Therefore, additional research is needed to test the cumulative and multi-dimensional stress models described herein.

In terms of clinical implications, present approaches in healthcare do not involve systematically screening patients' stress levels or tailoring adjunctive stress management programs to focus on the specific biological pathways that are maximally disrupted across individuals (Malat et al., 2017; McBain et al., 2023; Princip et al., 2022; Valderhaug and Slavich, 2020; Wulsin et al., 2022). Rather, patients are given non-specific interventions (e.g., exercise) to reduce their stress, if anything at all. The present data are informative in this regard as they can help providers identify what adjunctive stress management interventions may be indicated based on each patient's biological sex and specific childhood adversity profile. This approach would move the field away from a one-size-fits-all approach to treating stress-related health conditions and toward a precision medicine-based approach that could greatly improve patients' lives by providing them with the exact therapeutic(s) they need most (Gilgoff et al., 2024; Kim et al., 2024; Mengelkoch et al., 2023; Mengelkoch et al., 2024).

4.2. Strengths and limitations

This study has several strengths, including its assessment of many different types of childhood stressors, inclusion of twenty-five different stress- and disease-related biomarkers, and focus on twenty major health conditions thought to be driven, at least in part, by stress. In addition, the sample was well-characterized and the data were analyzed using gold-standard modeling approaches.

At the same time, several limitations should be noted. First, the MIDUS biomarker samples are not nationally representative; therefore, additional research is needed to investigate the generalizability of these results. Second, it is possible that a larger or different sample, or that adding protective factors, could have yielded different latent class assignments; consequently, the present data analytic approach should be replicated in other contexts. Third, retrospectively measuring childhood

adversity is not without bias. Specifically, there is research suggesting that subjective vs. objective experiences of childhood adversities are only moderately correlated (Francis et al., 2023). Although this research does suggest that subjective reports of adversity are more predictive of psychopathology than objective reports (Francis et al., 2023), and thus not a critical limitation in work focused on health outcomes, future studies should aim to address this limitation. Finally, the present data are correlational and the study design was not longitudinal. Therefore, causality and directionality cannot be assumed, and additional research is needed to investigate the temporal nature of the effects described herein.

4.3. Conclusion

Notwithstanding these limitations, the present data provide important new insight into how childhood adversity relates to disease biology and health conditions that cause substantial morbidity and mortality in adulthood. The results also add specificity to our understanding of how stressor → health associations differ for males and females, and as a function of exposure to different types of childhood stressors. Finally, these findings underscore the importance of screening for early-life stressors as a first step toward reducing disease risk in clinical settings.

Funding

J.A. and G.M.S. were supported by grant #OPR21101 from the California Governor's Office of Planning and Research/California Initiative to Advance Precision Medicine. The findings and conclusions in this article are those of the authors and do not necessarily represent the views or opinions of these organizations, which had no role in designing or planning this study; in collecting, analyzing, or interpreting the data; in writing the article; or in deciding to submit this article for publication.

CRediT authorship contribution statement

Jenna Alley: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Jeffrey Gassen:** Writing – review & editing, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **George M. Slavich:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data availability

The data are publicly available.

Acknowledgement

We thank the excellent reviewers who helped to greatly improve this work.

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Appendix A. Supplementary data

Supplementary data for this article can be found online at https://doi.org/10.1016/j.bbi.2024.07.019.

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