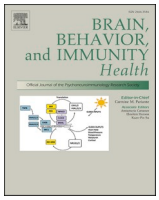
Brain, Behavior, & Immunity - Health 41 (2024) 100861

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



Stressful life events across the lifespan and inflammation: An integrative data analysis

Abby R. Hillmann [a,*], Roma Dhingra [b], Rebecca G. Reed [a]

[a] Department of Psychology, Dietrich School of Arts and Sciences, University of Pittsburgh, Pittsburgh, PA, USA
[b] Department of Biology, Georgetown College, Georgetown University, Washington, DC, USA

ARTICLE INFO

Keywords:
Psychological stress
Aging
Inflammation
Lifespan
Sensitive period

ABSTRACT

Experiencing more stressful life events has been linked to higher levels of inflammation, but this association may depend on when in the lifespan the stressors occur. To address this knowledge gap, we tested two lifespan theories, the accumulation of risks and sensitive period models, by assessing the association between the total number of stressful events and their life stage occurrence on later-life C-reactive protein (CRP). We harmonized data across two cohort studies, maximizing variation in stressors reported across the lifespan. Participants (N_{total} = 7,952, 57.7% female, M_{age} = 69) from the Health and Retirement Study (HRS: n = 5,136, M_{age} = 70.6) and the English Longitudinal Study of Aging (ELSA: n = 2,816, M_{age} = 66.1) completed retrospective surveys of stressful life events and indicated what year(s) each event occurred and had blood drawn ~4.5 years later. Stressful events were summed across the participants' lifespans (age 0 to current age) and within childhood (0–17 years), young adulthood (18–39), midlife (40–59), and late adulthood (60+). In main effects models, more cumulative stressors (γ = .05, SE = .02, p = .012) and stressors in young adulthood (γ = .06, SE = .03, p = .037) were associated with higher levels of CRP. In models with all life stages together among adults age 65+ (n = 4,972), experiencing more stressors in midlife significantly predicted higher levels of CRP (γ = .08, SE = .04, p = .038). Our findings replicate prior evidence of an association between cumulative stressors and inflammation and extend this work by identifying stressors in young adulthood and midlife as potentially unique sensitive periods that predict higher levels of later-life inflammation.

1. Introduction

Stressful life events, especially events that threaten an individual (e.g., physical assault, natural disaster, illness) or their close family (e.g., partner addiction, partner illness, loss of child), are commonly experienced (Kessler et al., 2017), may potentially be traumatic, and have been linked to greater morbidity and mortality risk (Kivimäki and Steptoe, 2018; Rutters et al., 2014). Various mechanisms may explain this increased risk, including activation of the physiological stress response (McEwen, 1998; Wheaton et al., 2013), which results in the release of hormones and inflammatory cytokines that, if sustained over time, can heighten risk for various chronic diseases and mortality (Berntson et al., 2017; Cohen et al., 2019; Hamer et al., 2008). Importantly, markers of systemic inflammation including C-reactive protein (CRP) may capture associations between stressful events and health decline before the onset of age-related chronic diseases (Furman et al., 2019). Despite much evidence linking stressful events to health risk, including inflammation, what remains understudied is how *the timing* of stressful events *across the lifespan* may affect inflammation. The current study tests both the accumulation of risks and sensitive period models to identify potential life stages when individuals may be at higher risk of physiological dysregulation following stressful events (Tursich et al., 2014).

The accumulation of risks model posits that the total number of stressful life events has a cumulative effect on health and increases risk of chronic disease (Cohen et al., 2019; McEwen, 2004). There is general support for the accumulation of risks model (but also see (Elliot et al., 2018; van Ockenburg et al., 2015)). Experiencing more retrospectively-reported stressful events across the lifespan was associated with higher levels of inflammation in midlife and older adults from nationally representative cohorts (Hostinar et al., 2015; Lin et al., 2016). Furthermore, prospective reports of stressful events predicted higher levels of inflammation in midlife (Bourassa et al., 2021).

The sensitive period model suggests that stressful events experienced during certain developmental stages may be stronger predictors of

* Corresponding author. 210 S. Bouquet St., University of Pittsburgh, Pittsburgh, PA 15260, USA.
E-mail address: arh151@pitt.edu (A.R. Hillmann).

https://doi.org/10.1016/j.bbih.2024.100861
Received 10 September 2024; Accepted 14 September 2024
Available online 16 September 2024

health (Miller et al., 2011). The majority of studies guided by this theory have focused on childhood as a sensitive period; empirical and meta-analytic evidence identified associations between various types of childhood stressors and higher levels of inflammation (Almuwaqqat et al., 2021; Chiang et al., 2022; Hartwell et al., 2013; Rooks et al., 2012). Importantly, however, studies focused on childhood do not often consider stressors that take place in adulthood, leaving it unknown whether the effects of childhood stressful events on inflammation persist above and beyond stressors experienced later in life. The few studies that have tested this provide support that stressors both in childhood (< age 18) and adulthood (age 18+) uniquely predict higher levels of inflammation, with slightly larger standardized effects reported for adulthood stress (Bourassa et al., 2021; Hostinar et al., 2015; Lin et al., 2016) (Weighted adulthood $\beta = .06$; Weighted childhood $\beta = .04$). However, these studies compared the effects of different stressful events in adulthood versus childhood; to fully test the sensitive period model, the *same* stressful events need to be compared across different life stages within the same study. Moreover, previous literature is limited by classifying any stressors that occur above the age of 18 as "adulthood" events, despite there being unique developmental stages, and potentially unique effects, within adulthood (Papalia et al., 2007).

The current study tested the accumulation of risks and sensitive period lifespan models to determine whether the total number of stressful life events and their life stages of occurrence associate with levels of CRP in older adults. We tested stressors experienced in four unique developmental stages: childhood (<18), young adulthood (18–39), midlife (40–59), and late adulthood (60+). These stages are developmentally informed and capture trends in social engagement, financial/resource availability, and goal prioritization across the lifespan that may buffer or exacerbate the effects of stressors on health (Scott et al., 2019; Stebbins et al., 2022). We hypothesized that the cumulative number of events would be associated with higher levels of CRP and based on findings from the only prospective cohort study to test major stressful events as a predictor of inflammation (Bourassa et al., 2021), we hypothesized that stressful events in childhood and young adulthood would have the largest effects. There was not enough prior evidence to make predictions about midlife and late adulthood stages. We used an Integrative Data Analytic approach (Curran and Hussong, 2009) to analyze raw data pooled from two cohorts, the *Health and Retirement Study* (HRS) and the *English Longitudinal Study of Aging* (ELSA), which offered advantages including a larger sample size and increased power, increased lifespan coverage, and variation in the reports of stressful events (Bainter and Curran, 2015). Conducting an integrative data analysis requires harmonization of predictors and outcomes across each cohort. Therefore, in primary analyses we utilized objective exposures to stressful events (e.g., natural disaster, physical attack) that were the same across cohorts, and CRP as the primary outcome because it was the only inflammatory marker measured in both cohorts.

In secondary analyses within the HRS sample, we also tested associations between stressful life events and two additional inflammatory markers, interleukin-6 (IL-6) and soluble tumor necrosis factor receptor-1 (sTNFR-1), and five DNA-methylation based measures of epigenetic age (epigenetic clocks: Horvath 1 (Horvath, 2013), Hannum (Hannum et al., 2013), PhenoAge (Levine et al., 2018), GrimAge (Lu et al., 2019), and Pace of Aging measure DunedinPoAm38 (Belsky et al., 2020)). IL-6 and the TNF-α receptor sTNFR-1 are involved in the acute inflammatory response and can stimulate production of acute phase proteins including CRP; cytokine dysregulation, captured by having prolonged high levels of each of these biomarkers, is associated with increased risk of morbidity, mortality, and age-related declines in physical and cognitive function (Justice et al., 2018). Changes in DNA methylation precede inflammatory dysregulation and measures of epigenetic age offer additional advantages including the ability to predict healthspan (Levine et al., 2018), time-to-death (Lu et al., 2019), and rate of deterioration across organ systems (Belsky et al., 2020). Experiencing a greater number of stressful events across the lifespan, (Katrinli et al., 2020; Skinner et al., 2024), in childhood (Joshi et al., 2023; Klopack et al., 2022), and in both childhood and adulthood (Suglia et al., 2024) have all been linked to older epigenetic ages in later life across various epigenetic clocks (Lim et al., 2022). In the current study, combined assessment of inflammation and epigenetic age allowed us to explore whether our hypotheses extend across primary (i.e., epigenetic) and integrative (i.e., inflammatory) hallmarks of biological aging (López-Otín et al., 2013).

2. Method

2.1. Participants and procedure

Participants were from the Health and Retirement Study (HRS) and the English Longitudinal Study of Aging (ELSA), each population-based cohort studies of adults aged 50 years or more residing in the United States and England respectively. HRS began data collection in 1992 with follow-up visits every four years for two separate cohorts, and ELSA began data collection in 2002/2003 with follow-up visits every two years for all participants. HRS participants completed retrospective life-history surveys in 2012/2010 or 2008/2006 (2012/2010 data were prioritized for analyses based on proximity to the blood draw) and CRP was measured at a venous blood (VB) draw in 2016. ELSA participants completed retrospective life-history surveys in 2007 and participated in a venous blood draw in 2009, 2013, and 2017 (the blood draw time point closest to the life-history survey was prioritized for analyses). Covariates were assessed at the time of blood draw. In HRS of the 13,896 individuals who reported at least one stressful life event (2012/2010: N = 9,740; 2006/2008: N = 4,156), 5,796 of them had CRP and covariate data, and 5,136 provided at least one year that corresponded with an endorsed event. In ELSA of the 4,907 individuals who reported at least one stressful life event, 3,050 of them had CRP and covariate data (2009: N = 2,747; 2013: N = 214; 2017: N = 89), and 2,816 provided at least one year that corresponded with an endorsed event.

2.2. Measures

2.2.1. Stressful life events (harmonized items)

HRS assessed the most recent occurrence of major stressful life events across 7 categories in the "Lifetime Traumas" questionnaire. ELSA assessed the earliest occurrence of 11 negative life events within the "Difficult Life Events" inventory. HRS and ELSA share 7 items that were harmonized (leaving only four items that could not be analyzed). The shared items included reporting experiencing (yes = 1 or no = 0): (1) has a child of yours ever died (this item was collected in the life history interview for ELSA), (2) a major fire, flood, earthquake, or other natural disaster, (3) combat experience, (4) having a partner or child addicted to drugs or alcohol, (5) being a victim of serious physical attack or assault, (6) a life threatening illness or accident (self), and (7) a life threatening illness or accident of a spouse, child, relative, or close friend. HRS and ELSA collected *what year* each endorsed event occurs; from this, we calculated the age per event. To facilitate retrospective recall, participants completed "Event History Calendars" or "Lifegrids" that make the accurate recalling of events, including those that took place in childhood, easier for older adults (Berney and Blane, 1997). The number of stressful life events was summed across one's lifespan (cumulative stressors) and summed within four different life stages: childhood (range (mean) = age 0–17 (10.5)), young adulthood (range (mean) = age 18–39 (27.7)), midlife (range (mean) = age 40–59 (49.6)), and late adulthood (range (mean) = age 60–91 (67.8)). We categorized the years 0–17 as "childhood" due to the fewer number of events reported in childhood and concerns about power; however, we recognize this encompasses several developmental stages within early life. In exploratory analyses we further probed more granular stages of childhood representing pre- and post-puberty onset (childhood pre-puberty range

(mean) = age 0–12 (7.4); childhood post-puberty range (mean) = age 13–17 (15.2)).

2.2.2. Childhood adversity

HRS and ELSA had two additional items that measured childhood adversities that were added to the childhood event sum for sensitivity analyses. These two items included (1) Did either of your parents' drink or use drugs so often that it caused problems in the family and (2) were your ever physically abused by either of your parents (yes = 1 or no = 0). Unlike the stressful life events in *2.2.1,* HRS participants did not report the year that these childhood adversities took place; rather, HRS defined childhood adversities as events that took place younger than age 18. ELSA defined childhood adversities as events that took place younger than age 16 and collected the age at which the event occurred.

2.2.3. Inflammation

HRS and ELSA collected a measure of high sensitivity CRP (hsCRP, mg/L), measured using a latex-particle enhanced immunoturbidimetric assay kit in HRS and the N latex CRP mono assay on the Dada Behring Nephelometer in ELSA (HRS: the lab inter-assay CV is 5.1% at a concentration of 1.05 mg/L and 6.7% at a concentration of 3.12 mg/L). We removed outliers ± 3 standard deviations (n = 134) and CRP values were log transformed for normality then harmonized using the proportion of maximum possible scores (POMP) technique, in line with prior integrative data analyses (Lam et al., 2021; Stawski et al., 2019). HRS assessed two additional markers of inflammation, which we examined in secondary analyses: interleukin-6 (IL-6, pg/mL) and soluble tumor necrosis factor receptor 1 (sTNFR-1, pg/mL), both measured using the ELISA technique (IL-6: the manufacturer inter-assay CV is 8.3% at a concentration of 41.5 pg/mL and 7.1% at a concentration of 1800 pg/mL; sTNFR-1: the manufacturer inter-assay CV is 11.8% at a concentration of 19.5 pg/mL and 10% at a concentration of 971 pg/mL).

2.2.4. Epigenetic clocks

HRS assayed whole blood samples for DNA methylation data using the Infinium Methylation EPIC BeadChip at the University of Minnesota. DNA methylation data were used to estimate epigenetic age from five epigenetic clocks, which we examined in secondary analyses: Horvath 1, Hannum, PhenoAge, and GrimAge, and the Pace of Aging measure, DunedinPoAm38 (Belsky et al., 2020; Crimmins et al., 2020; Hannum et al., 2013; Horvath, 2013; Levine et al., 2018; Lu et al., 2019).

2.2.5. Covariates

Covariates were collected at the time of blood draw and included chronological age, sex (male = 0, female = 1: to account for men typically having higher inflammation than women (Bernardi et al., 2020)), cohort (HRS = 0, ELSA = 1: to account for variation across countries and study design differences), body mass index (BMI), smoking status at the time of blood draw (0 = no, 1 = yes), and time elapsed between life-history survey and blood draw in years (calculated as: date of blood draw– date of life history survey). Secondary covariates in sensitivity analyses included race (0 = White, 1 = Non-white), education (0–14+ years of education), and a comorbidity index (i.e., the total number of physician-diagnosed chronic diseases: hypertension, diabetes, cancer, chronic lung disease, heart disease, and stroke). The HRS comorbidity index was extracted from the RAND cooperation longitudinal data set. Corresponding items were extracted from the ELSA core data files capturing whether the participant endorsed having been diagnosed previously or currently having any of the same conditions collected in the HRS comorbidity index.

3. Data analysis

In primary analyses predicting CRP, data from HRS and ELSA cohorts were combined. We used multilevel models to account for individuals (level 1) nested within households (level 2) at the time of survey completion. Data were analyzed using the lmer (linear mixed effects) function from the lmer library (1.1.35.1) in R (version 4.3.1). Models were estimated using Restricted Maximum Likelihood Estimation (REML) and included a random intercept for household, but adding a random slope did not improve model fit as only a small proportion of the total variance was accounted for by household clustering (ICC = 8.6%). All models controlled for primary covariates (section 2.2.5) including chronological age, sex, cohort, BMI, smoking status, and time elapsed between survey completion and the blood draw. Standardized effects (β) for primary models are reported in supplemental materials (Hoffman, 2015).

To address Aim 1 (cumulative model), we tested the total number of stressful life events as a predictor of CRP. To address Aim 2, we first tested stressful life events from each of the four life stages (i.e., childhood, young adulthood, midlife, late adulthood) as separate predictors of CRP in individual main effects models. Main effects models were corrected for multiple comparisons to account for the four life stages tested (Benjamini and Hochberg, 1995). Then, in independent effects models, stressors in the different life stages were included in the same model together predicting CRP to compare the effects of the life stages above and beyond each other. Independent effects models were tested using a sub-sample of individuals who were old enough to experience stressors in the first three life stages (age 45+: n = 7,928) and old enough to experience stressors in all life stages (age 65+: n = 4,972).

In secondary analyses, we tested both aims using additional biological aging outcomes, IL-6, sTNFR-1, and epigenetic clocks, which were present only in the HRS cohort. We conducted linear regression models using the lm (linear model) function from the stats (version 4.3.1) package in R because there were no dependent observations in this subsample. We used a similar model building approach as we did for CRP to test each additional outcome; we first tested the cumulative effect of stressful life events, then the main effects of stressors in each life stage (correcting for multiple comparisons across four life stages). If any main effects were statistically significant, we further probed independent effects by including life stages together in the same model. All secondary analyses include primary covariates (age, sex, cohort, body mass index, smoking status at the time of blood draw, and time elapsed between life-history survey and the blood draw). In addition to the primary covariates, models testing epigenetic outcomes further controlled for cell type distributions ($CD4^+$ total, $CD8^+$ total, B cells, NK cells, and monocytes).

4. Results

Characteristics of the combined sample (N = 7,952; 5,136 from HRS and 2,816 from ELSA) are presented in Table 1 and bivariate correlations among study variables are in Table S1. Participants were on average 69 years old at the time of blood draw (SD = 9.97, range = 36–107), 42% male, 85% White, and 66% completed at least 12 years of education (see Table 1). To allow for comparisons across cumulative and life stage analyses, participants included in this study had to have experienced at least one stressful life event in their lifetime; this encompassed the majority of individuals (65% of the full sample), which aligns with surveys from the World Mental Health organization demonstrating 70% of individuals experience a major stressful event in their lifetime (Kessler et al., 2017). Participants who reported one or more events did not differ significantly from those who did not report any stressful events on sex, age, body mass index (BMI) or CRP. However, our sample was less likely to smoke (% non-smokers: 1 or more events = 89.3% vs no events = 90.4%, $X^2 = 2329$, $p < .001$), was comprised of more ELSA participants (% ELSA: 1 or more events = 35.4% vs no events = 21.3%, $X^2 = 6.98$, $p = .008$), and had fewer years between survey completion and the blood draw (mean (SD) time lapsed: 1 or more events = 4.57 (2.33) vs no events = 5.03 (2.23) $t = 10.66$, $p < .001$). Participants experienced an average of 1.7 events across the lifespan (range: 1–6). Fig. 1 displays the frequency of, and highlights the

Table 1
Sample descriptives for analyses.

	ELSA (N = 2816)		HRS (N = 5136)		Combined Sample (N = 7952)	
	Mean (SD), %	range	Mean (SD), %	range	Mean (SD), %	range
Sex						
Male	1290 (45.8%)		2071 (40.3%)		3361 (42.3%)	
Female	1526 (54.2%)		3065 (59.7%)		4591 (57.7%)	
Age (years)						
Mean (SD)	66.1 (9.40)	[37.0, 99.0]	70.6 (9.91)	[36.0, 107]	69.0 (9.97)	[36.0, 107]
Currently Smoking						
No	2481 (88.1%)		4618 (89.9%)		7099 (89.3%)	
Yes	335 (11.9%)		518 (10.1%)		853 (10.7%)	
Body Mass Index (BMI) (kg/m^2)						
Mean (SD)	28.0 (4.96)	[15.7, 71.1]	28.9 (6.18)	[14.4, 68.0]	28.6 (5.79)	[14.4, 71.1]
Time Elapsed (blood draw year– life history survey year)						
Mean (SD)	2.52 (1.74)	[2.00, 11.0]	5.69 (1.77)	[4.00, 10.0]	4.57 (2.33)	[2.00, 11.0]
Race						
White	2730 (96.9%)		4001 (77.9%)		6731 (84.6%)	
Non-White	37 (1.3%)		1108 (21.6%)		1145 (14.4%)	
Missing	49 (1.7%)		27 (.5%)		76 (1%)	
Education						
Less than 12 years	1779 (63.2%)		826 (16.1%)		2605 (32.7%)	
More than 12 years	988 (35.1%)		4283 (83.4%)		5271 (66.3%)	
Missing	49 (1.7%)		27 (.5%)		76 (1%)	
Comorbidity Index						
Mean (SD)	.64 (.82)	[0, 4]	1.67 (1.23)	[0, 6]	1.3 (1.21)	[0, 6]
Missing	0 (0%)		48 (.9%)		48 (.6%)	
Total Events Continuous						
Mean (SD)	1.56 (.763)	[1.00, 6.00]	1.82 (.993)	[1.00, 6.00]	1.73 (.926)	[1.00, 6.00]
Reported Childhood Event						
Yes	943 (33.5%)		587 (11.4%)		1530 (19.2%)	
Reported Young Adulthood Event						
Yes	1255 (44.6%)		2200 (42.8%)		3455 (43.4%)	
Reported Midlife Event						
Yes	1039 (36.9%)		2599 (50.6%)		3638 (45.7%)	
Reported Late Adulthood Event						
Yes	397 (14.1%)		1506 (29.3%)		1903 (23.9%)	
log CRP						
Mean (SD)	.585 (1.07)	[-2.30, 3.34]	.871 (.968)	[-1.77, 3.68]	.770 (1.01)	[-2.30, 3.68]
CRP POMP						
Mean (SD)	5.11 (1.89)	[0, 10.0]	4.85 (1.78)	[0, 10.0]	4.94 (1.82)	[0, 10.0]
Raw CRP (mg/L)						
Mean (SD)	3.11 (3.73)	[.100, 28.3]	3.88 (4.72)	[.170, 39.7]	3.60 (4.41)	[.100, 39.7]

Note. Covariates age, sex, BMI, smoking status, race, education, and comorbidities are reported at the time of blood draw.

substantial variability in, the events reported in each of the four life stages (childhood (<18), young adulthood (18–39), midlife (40–59), and late adulthood (60+). Close to half of the sample experienced events during midlife (45%) or young adulthood (43%) but events in childhood and late adulthood were still common and reported in approximately 1 in every 5 participants. The most reported stressors were illness of a close other, illness of self, and natural disaster (Fig. S1).

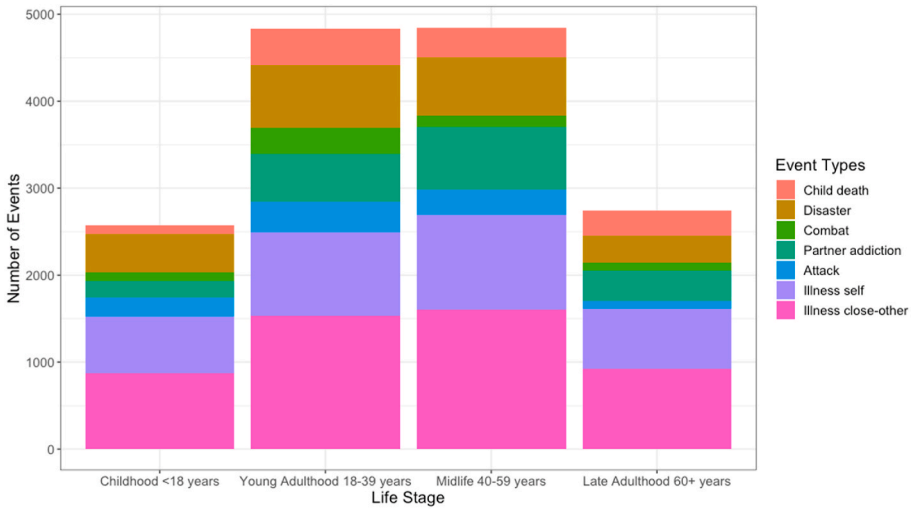
Results from models testing the (1) cumulative effect of stressful life events and the (2) main and (3) independent effects of stressful life events within each life stage on CRP are shown in Fig. 2. Results are depicted from primary analyses (Fig. 2, Model 1) that controlled for main covariates (age, sex, cohort, body mass index [BMI], smoking status, and time elapsed between the stressor survey and blood draw in years) and from six sets of sensitivity analyses (Fig. 2, Models 2–7). Sensitivity analyses: 1) Further controlled for race and education (Model 2), because individuals with higher socioeconomic status may have resources that buffer the effects of some stressors; 2) Removed BMI as a covariate (Model 3), based on evidence suggesting that it may operate as a substantive mediator (and not covariate) in the long-term relationships between stress and inflammation (Schrepf et al., 2014); 3) Removed the self-illness stressful event from the event count (Model 4), to ensure that individual illness was not directly related to heightened inflammation (Bourassa et al., 2021); 4) Removed individuals with raw CRP levels above 10 mg/L (Model 5), to ensure acute illness at the time of blood draw was not a confound (Pearson et al., 2003); 5) Further controlled for a comorbidity index at the time of blood draw to ensure the presence of chronic illnesses that may have associations with inflammation (i.e., hypertension, diabetes, cancer, chronic lung disease, heart disease, and stroke) was not a confound (Pawelec et al., 2014) (Model 6); and 6) Included additional childhood specific adversities (section *2.2.2*) to our event count (Model 7), to ensure that there was an equal likelihood of stressful life events taking place across the lifespan because some of the events in primary analyses were less likely to occur before age 18 (e.g., combat experience). Results are reported as unstandardized coefficients.

4.1. Cumulative effect of stressors on CRP

Cumulative models tested the effect of the total number of life stressors summed across all life stages on CRP. In primary models adjusted for main covariates, experiencing more stressful events across the lifespan was associated with higher levels of CRP ($\gamma = .051$, SE = .020, $p = .012$). This finding remained similar across all sensitivity analyses (see Fig. 2 and Table S2), with one exception: Removing individuals with CRP levels greater than 10 mg/L (n = 563), who may have acute illness, did not change the direction of the association but did attenuate the significance ($\gamma = .037$, SE = .019, $p = .052$). We further probed this association in Fig. S2 and concluded the individuals with high CRP were not driving the observed association (i.e., they did not have a stronger positive association between the total number of events and CRP than the rest of the sample) and therefore this attenuation was likely due to decreased power.

4.2. Main effects of stressors experienced in individual life stages on CRP

Main effects models tested each life stage separately as a predictor of CRP. Primary models were adjusted for main covariates and corrected for multiple comparisons across four life stages using the Benjamini Hochberg correction method (Q = .05) (Benjamini and Hochberg, 1995). Experiencing more stressors in young adulthood (ages 18–39) was associated with higher levels of CRP ($\gamma = .056$, SE = .026, $p = .037$), but this association did not withstand correction for multiple comparisons (BH threshold = .013). This young adulthood finding was generally consistent and survived correction for comparison across three out of the six sensitivity analyses (see Fig. 2 and Table S4). When BMI was removed as a covariate, a new association emerged between experiencing events in midlife (ages 40–59) and higher CRP, which survived correction (midlife: $\gamma = .084$, SE = .029, $p = .004$; Table S5). In primary analyses, there were no statistically significant associations between experiencing stressors in childhood (ages 0–17), midlife (40–59), or late adulthood (60+) and CRP (Tables S3, S5, and S6).



Note. Figure demonstrates the variation in the different stressful life events experienced in each of the four life stages.

Fig. 1. Histogram of the frequency of different stressful life events experienced in each life stage
Note. Figure demonstrates the variation in the different stressful life events experienced in each of the four life stages.

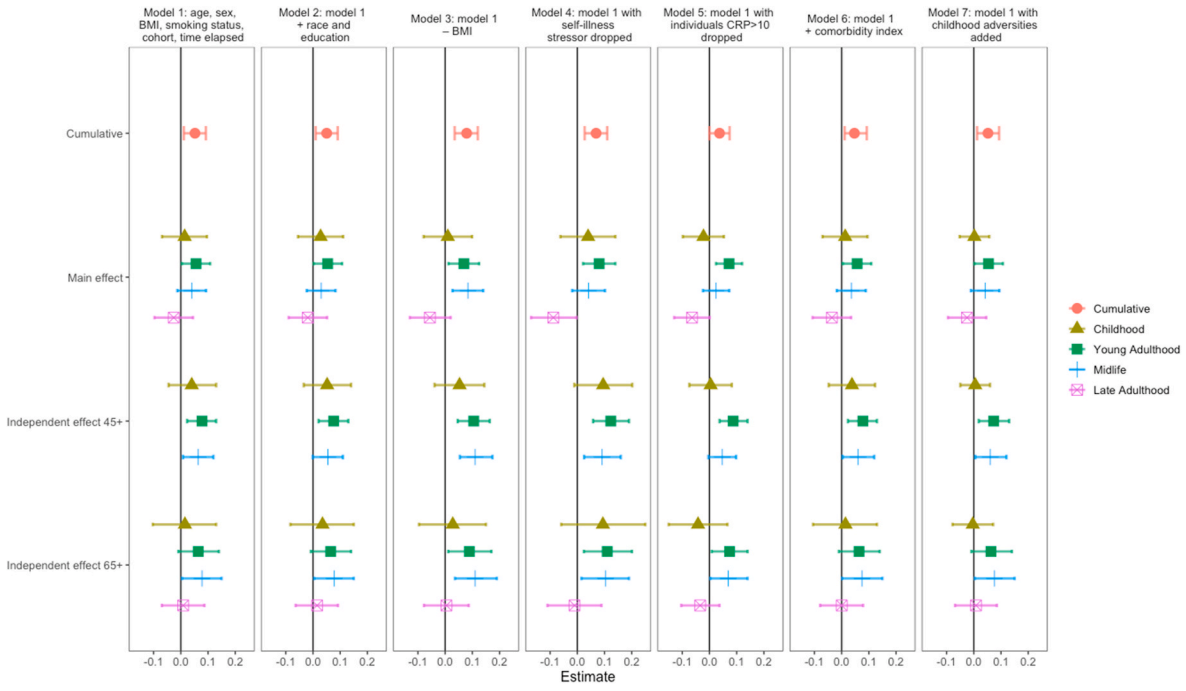


Fig. 2. Model estimates for primary and sensitivity analyses for each stage of model building
Note. Unstandardized γ coefficients and 95% confidence intervals for primary (Model 1, N = 7,952) and sensitivity (Models 2–7) analyses of stressors experienced across the lifespan (cumulative) and in childhood (<18 years), young adulthood (18–39 years), midlife (40–59 years), and late adulthood (60+ years) in main effects models (life stages tested separately) and independent effects models (life stages tested together) in sub-samples aged 45+ (n = 7,928) and 65+ years old (n = 4,972). Tables with estimates can be found in supporting materials. All analyses control for age, sex, smoking status, cohort, and the time elapsed between survey completion and blood draw.

4.3. Independent effects of stressors in life stages on CRP in sample aged 45+

Independent effects models tested the effects of stressors experienced in the first three life stages (i.e., childhood, young adulthood, and midlife) above and beyond each other when entered in the same model. To ensure individuals had an equal opportunity of experiencing events in all three life stages, we conducted these analyses in participants aged 45 years and older (n = 7,928; i.e., the youngest age was a minimum of 5 years into the midlife stage). Experiencing more stressors in young adulthood and midlife were associated with higher CRP levels, above and beyond each other and childhood (young adulthood: γ = .078, SE = .028, p = .005; midlife: γ = .064, SE = .029, p = .024). The association between young adulthood events and CRP was consistent across all sensitivity analyses (see Fig. 2 and Table S7). The association between midlife events and CRP was similar across all sensitivity analyses but was attenuated slightly and no longer statistically significant when adjusting for race and education and when individuals with CRP levels greater than 10 mg/L were removed (Fig. 2 and Table S7).

4.4. Independent effects of stressors in life stages on CRP in sample aged 65+

Independent effects models tested the effects of stressors experienced in up to all four life stages (i.e., childhood, young adulthood, midlife, and late adulthood) above and beyond each other when entered in the same model. To ensure individuals had an equal opportunity of experiencing events in all four life stages, we conducted these analyses in participants aged 65 years and older (n = 4,972; i.e., the youngest age was a minimum of 5 years into the late adulthood stage). Experiencing more stressors in midlife was associated with higher CRP above and beyond the other life stages (midlife: $\gamma = .078$, SE = .038, $p = .038$). This finding remained consistent across all sensitivity analyses (see Fig. 2 and Table S8). In addition, a new association between stressful events in young adulthood and higher CRP emerged in sensitivity analyses that removed BMI as a covariate (young adulthood: $\gamma = .088$, SE = .039, $p = .024$), dropped the self-illness stressor from the event count (young adulthood: $\gamma = .11$, SE = .045, $p = .013$), and removed individuals with CRP levels greater than 10 mg/L (young adulthood: $\gamma = .074$, SE = .034, $p = .028$) (Table S8).

4.5. Secondary analyses with additional biomarkers of aging

We conducted secondary analyses within the HRS sample to test additional inflammatory markers (IL-6 and sTNFR-1) and epigenetic age (see full results in supporting materials). We found a similar pattern of results across the additional biomarkers; the cumulative number of stressful life events was associated with higher levels of IL-6 and sTNFR-1 and a faster Pace of Aging (IL-6: $b = .008$, SE = .002, $p < .001$; sTNFR-1: $b = .012$, SE = .005, $p = .017$; Pace: $b = .005$, SE = .002, $p = .007$). In main effects models that withstood correction for multiple comparison, experiencing more events in young adulthood was associated with higher IL-6 ($b = .012$, SE = .003, $p < .001$) and more events in late adulthood was associated with higher sTNFR-1 ($b = .026$, SE = .009, $p = .002$).

4.6. Exploratory analyses

We conducted exploratory analyses testing sex as a moderator in the association between total number of life stressors/stressors in each life stage and CRP, based on prior evidence that men and women may experience different stressor types and have different negative affective and physiological responses to stress especially across the lifespan (Davis et al., 2011). There were no statistically significant interactions between the total number of stressors nor any of the life stages and sex on CRP (p's $> .49$). We also created more fine-grained childhood stages (pre- and post-puberty) to capture some of the social and biological changes that take place *within* childhood that may be relevant for stress responses. There were no statistically significant associations between pre-puberty childhood stressors or post-puberty childhood stressors and CRP (p's $> .69$).

5. Discussion

The current study examined the association between the cumulative number of stressful life events, and the life stages in which stressful events occur, and systemic inflammation in a cross-country sample of almost 8,000 older adults pooled across two cohort studies. The results supported a cumulative effect of the total number of stressors on inflammation and identified young adulthood and midlife as potential sensitive periods where stressors have the largest effect on inflammation. These results were independent of chronological age, sex, BMI, smoking status, time elapsed between survey completion and the blood draw, and cohort. Additionally, the patterns of results were largely robust across multiple sensitivity analyses that controlled for race and education, removed BMI as a covariate, dropped the self-illness stressor, removed individuals with high CRP (greater than 10 mg/L), controlled for chronic conditions, and included additional childhood adversities (i.e., parental drug/alcohol use, abuse). The effect sizes of stressful events were modest, for both cumulative and young adulthood/midlife effects, but the standardized effects (see Supporting Tables) were about one-third the size of other predictors of inflammation, including chronological age and smoking status.

Our cumulative findings support the accumulation of risks model and align with previous studies linking retrospective reports of more stressful life events experienced across the lifespan to higher levels of inflammation (Hostinar et al., 2015; Lin et al., 2016). Higher levels of CRP have clinical relevance and have been shown to prospectively predict all-cause, cancer, and cardiovascular disease mortality risk (Barron et al., 2015). Although CRP is often regarded as being more stable and reliable biomarker than other inflammatory markers, we further replicated our cumulative findings across two additional inflammatory markers (IL-6 and sTNFR-1) and the third-generation epigenetic clock Pace of Aging. These findings validate the cumulative effect of stress on multiple biomarkers of aging and highlight the potential for repeated exposure to stressful events across the lifespan to increase risk for poorer health outcomes including morbidity, mortality, and age related declines in physical and cognitive functioning (Furman et al., 2019; Justice et al., 2018). The only contradictory finding across all six cumulative sensitivity analyses was the attenuated association when dropping individuals (n = 563) with high levels of CRP ($p = .052$). We concluded this was due to reduced power and not driven by current illness. We maintain that the models with the full range of CRP values are most generalizable because in older adult samples higher CRP values may represent important variation in health status as opposed to acute illness (Giollabhui et al., 2020); for instance, in our sample having CRP levels greater than 10 was linked to having significantly higher BMI (mean BMI = 32.13) compared to individuals with CRP levels below 10 (mean BMI = 28.33, $t = -11.4$, $p < .001$).

Our life stage findings extend the current literature by identifying stressful events in young adulthood and midlife as most consistently predictive of inflammation, above and beyond events in childhood and late adulthood. Specifically, in the independent effects models in the 45+ sample where we compared events in childhood, young adulthood, and midlife within the same model, both stressful events in young adulthood and midlife were significant predictors of higher CRP with the same standardized effect size ($\beta = .03$). However, in the independent effects models in the 65+ sample where all life stages were compared to each other, only midlife remained a significant predictor. In the exclusively older adult (65+) sample it is possible that the association between young adulthood stressors and CRP was weakened because this sub-set of participants included fewer people who reported young adulthood stressors. Importantly, when the health-related stressor was removed from analyses, the independent effects in the 65+ sample mirrored those in the 45+ sample, suggesting that proximal health related stressors in midlife may be responsible for some of the findings observed in the 65+ sample.

The associations with young adulthood and midlife stress align with previous work that most consistently links stressful events between ages 18–30 and 31–64 years to self-rated health, acute/chronic conditions, and functional disability above and beyond stressors in childhood and late adulthood (Krause et al., 2004). It is possible that young and middle-aged adults are most vulnerable to major stressful events because they may hold more social roles (e.g., being both a parent and caregiver to older parents) and so in stressful circumstances (e.g., death of a loved one, natural disaster) they may serve as primary support providers for both their children and parents and receive less support than they give (Fingerman et al., 2011; Wang and Gruenewald, 2019; Wrzus et al., 2013). Another explanation we considered was whether the financial stress that accompanies some of these events was putting strain on young and midlife adults who are financially responsible for dependents. Previous work has shown low socioeconomic status (SES) is

associated with stressful experiences (John-Henderson et al., 2016; Tschanz et al., 2013). To address this possibility, we included education as a covariate in sensitivity analyses; education is relatively stable across the lifespan and should more accurately reflect the individual's socioeconomic status at the time the stressor occurred as compared to other measures of SES that may fluctuate over time (i.e., income, occupation). In the 45+ independent effects analyses, the addition of education did not attenuate the young adulthood association with CRP, and moderately attenuated the midlife association with CRP ($p = .056$). The addition of race and education explained only an additional .5% of the total variance in CRP, suggesting other factors beyond sociodemographics may explain the health significance of stressors in these life stages. Aside from this attenuation, the young adulthood and midlife associations were largely consistent across sensitivity analyses (see Fig. 2) and emerged as both significant main effects and independent effects predictors of additional biomarkers of aging. For example, when we tested additional biomarkers, young adulthood stressors emerged as a significant predictor in main effects models (predicting IL-6) and in independent effects models (predicting IL-6). Midlife stressors also emerged as a significant predictor in independent effects models (predicting IL-6, PhenoAge, and Pace of Aging) (see supporting materials Secondary Analyses).

Based on prior work (Chiang et al., 2022) it was surprising that we did not find an association between childhood stressors and inflammation, but this could be because previous studies have not often controlled for adulthood stress in the model. There was variability in the number and type of stressors experienced during each life stage, including childhood, suggesting a floor effect was not a likely explanation for our null childhood associations. To further ensure there was an equal opportunity of experiencing stressful life events during each life stage, in sensitivity analyses we included additional childhood adversity items, and our results remained unchanged. Despite the addition of two childhood specific adversities, it should be noted that we still did not have data on various childhood experiences that are often assessed, such as childhood sexual and emotional abuse. It is also possible we may have failed to detect a statistically significant childhood effect because our definition of childhood was too broad (0–17 years), but when we tested more granular childhood developmental stages (pre-puberty 0–12 and post-puberty 13–17) our results remained the same. Furthermore, there were fewer childhood stressors reported compared to the other life stages, and failure to detect results, especially when further dividing this group into more granular stages, could be due to reduced power. Testing additional childhood developmental stages with a more comprehensive measure of childhood adversity is an important area to explore in future lifespan research. Additionally, to determine if our findings replicate, future studies should continue to test the sensitive period model by using large samples with sufficient variation in events reported across the lifespan and by comparing the life stages within the same model.

The current study has notable strengths including the integrative data analysis approach, large sample size, generalizability of results across two countries, assessment of multiple biomarkers relevant for healthy aging, and incorporation of a lifespan approach to test two relevant lifespan models. This is the first study with sufficient characterization of and variation in stressful events across the lifespan to test the associations between stressors in multiple well-defined developmental stages and systemic inflammation, whereas previous studies have only compared childhood (<18 years) to adulthood stressors (18+) (Bourassa et al., 2021; Lin et al., 2016).

The current study also has a number of limitations, including the retrospective reporting of stressful events. However, the HRS and ELSA samples took additional consideration to ensure accurate retrospective reporting, including utilizing an "Event History Calendar" or "Lifegrid" where participants construct personal timelines and reference landmark events that are recalled with high accuracy (e.g., births, deaths) and historical events relevant to the cohort (e.g., death of Queen Victoria, JFK assassination). Participants generally report that the Lifegrid makes recall easier (Pascale and McGee, 2008), and in a small sample of older adults ($N = 57$) 80% of individuals were able to accurately recall details about their childhood home environment compared to archival data (Berney and Blane, 1997). Furthermore, exploration of the factors that may explain the associations between young adulthood and midlife stressors and health was limited by the available stress data collected in HRS and ELSA. For example, we have no measure of the perceived severity of the events, leaving it unclear if *and to what extent* the events were traumatic or if they led to symptoms of PTSD, which would further increase risk of heightened inflammation (Bourassa and Sbarra, 2024; Tursich et al., 2014). In addition, the available measure of stressful events does not have sufficient variation in event types to determine if categories of stressors (e.g., social threats, physical threats) have differential impacts on inflammation. For example, based on previous theoretical and empirical research, we would expect that the presence of social threats would have particularly substantial influences on inflammation, but we were unable to test this hypothesis (e.g., Slavich et al., 2023); these data may be collected more easily prospectively and could be considered in future work. An additional consideration is that this analysis focused on the effect of stressful events among individuals who experienced at least one stressful event, which permitted comparison across our cumulative and life stage analyses. Our analytic sample largely did not differ from the individuals who did not report any stressful events on the primary covariates (i.e., BMI, sex, age) or levels of CRP, but there may be other differences on unmeasured variables that could have biased response rates. For this reason, we caution the over generalization of our findings. Last, although our sample combined people across countries, it was not racially diverse and due to data privacy restrictions, our race categorization specificity was limited (i.e., White vs. non-White); race and ethnicity can have important implications for how individuals are exposed to and respond to stress (Slopen et al., 2010).

In conclusion, our findings support prior evidence that over time stressors have a cumulative wear and tear effect on our physiology. In addition, stressful events that occur during sensitive periods of adult development, specifically young adulthood and midlife, may have the largest negative effects on chronic inflammation. Therefore, implementing strategies to ameliorate the negative health effects of some of these stressful life events may be most beneficial if implemented as early as young adulthood. Future concurrent research is needed to investigate protective factors (e.g., social support) that may be most effective in buffering the negative effects of stress during these life stages.

Funding

The Health and Retirement Study (HRS) is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan. ELSA is funded by the National Institute on Aging (R01AG017644), and by UK Government Departments coordinated by the National Institute for Health and Care Research (NIHR). Support was provided by grants from the National Heart, Lung, and Blood Institute (T32HL007560), the National Institutes of Health (R24AG048024; U24AG072699), and the National Institute on Aging (AG056635). A.R.H acknowledges training received from the University of Michigan Genomics for Social Scientists Workshop (NIA R25 AG053227).

CRediT authorship contribution statement

Abby R. Hillmann: Conceptualization, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. **Roma Dhingra:** Formal analysis, Writing – review & editing. **Rebecca G. Reed:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

HRS and ELSA data are publicly available

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100861.

References

Almuwaqqat, Z., Wittbrodt, M., Young, A., Lima, B.B., Hammadah, M., Garcia, M., Elon, L., Pearce, B., Hu, Y., Sullivan, S., 2021. Association of early-life trauma and risk of adverse cardiovascular outcomes in young and middle-aged individuals with a history of myocardial infarction. JAMA Cardiology 6 (3), 336–340.

Bainter, S.A., Curran, P.J., 2015. Advantages of integrative data analysis for developmental research. J. Cognit. Dev. 16 (1), 1–10. https://doi.org/10.1080/15248372.2013.871721.

Barron, E., Lara, J., White, M., Mathers, J.C., 2015. Blood-borne biomarkers of mortality risk: systematic review of cohort studies. PLoS One 10 (6), e0127550. https://doi.org/10.1371/journal.pone.0127550.

Belsky, D.W., Caspi, A., Arseneault, L., Baccarelli, A., Corcoran, D.L., Gao, X., Hannon, E., Harrington, H.L., Rasmussen, L.J., Houts, R., 2020. Quantification of the pace of biological aging in humans through a blood test, the DunedinPoAm DNA methylation algorithm. Elife 9, e54870.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc. B 57 (1), 289–300.

Bernardi, S., Toffoli, B., Tonon, F., Francica, M., Campagnolo, E., Ferretti, T., Comar, S., Giudici, F., Stenner, E., Fabris, B., 2020. Sex differences in proatherogenic cytokine levels. Int. J. Mol. Sci. 21 (11), 3861. https://doi.org/10.3390/ijms21113861.

Berney, L.R., Blane, D.B., 1997. Collecting retrospective data: accuracy of recall after 50 years judged against historical records. Soc. Sci. Med. 45 (10), 1519–1525.

Berntson, J., Patel, J.S., Stewart, J.C., 2017. Number of recent stressful life events and incident cardiovascular disease: moderation by lifetime depressive disorder. J. Psychosom. Res. 99, 149–154.

Bourassa, K.J., Rasmussen, L.J., Danese, A., Eugen-Olsen, J., Harrington, H., Houts, R., Poulton, R., Ramrakha, S., Sugden, K., Williams, B., 2021. Linking stressful life events and chronic inflammation using suPAR (soluble urokinase plasminogen activator receptor). Brain Behav. Immun. 97, 79–88.

Bourassa, K.J., Sbarra, D.A., 2024. Trauma, adversity, and biological aging: behavioral mechanisms relevant to treatment and theory. Transl. Psychiatry 14 (1), 285. https://doi.org/10.1038/s41398-024-03004-9.

Chiang, J.J., Lam, P.H., Chen, E., Miller, G.E., 2022. Psychological stress during childhood and adolescence and its association with inflammation across the lifespan: a critical review and meta-analysis. Psychol. Bull. 148 (1–2), 27–66.

Cohen, S., Murphy, M.L., Prather, A.A., 2019. Ten surprising facts about stressful life events and disease risk. Annu. Rev. Psychol. 70, 577–579.

Crimmins, E., Kim, J., Fisher, J., Faul, J., 2020. HRS Epigenetic Clocks. Release 1.

Curran, P.J., Hussong, A.M., 2009. Integrative data analysis: the simultaneous analysis of multiple data sets. Psychol. Methods 14 (2), 81.

Davis, M.C., Burleson, M.H., Kruszewski, D.M., 2011. Gender: Its relationship to stressor exposure, cognitive appraisal/coping processes, stress responses, and health outcomes. *The handbook of stress science: Biology, psychology, and health*, pp. 247–261.

Elliot, A.J., Heffner, K.L., Mooney, C.J., Moynihan, J.A., Chapman, B.P., 2018. Social relationships and inflammatory markers in the MIDUS cohort: the role of age and gender differences. J. Aging Health 30 (6), 904–923.

Fingerman, K.L., Pitzer, L.M., Chan, W., Birditt, K., Franks, M.M., Zarit, S., 2011. Who gets what and why? Help middle-aged adults provide to parents and grown children. J. Gerontol. B Psychol. Sci. Soc. Sci. 66 (1), 87–98.

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D.W., Fasano, A., Miller, G.W., Miller, A.H., Mantovani, A., Weyand, C.M., Barzilai, N., Goronzy, J.J., Rando, T.A., Effros, R.B., Lucia, A., Kleinstreuer, N., Slavich, G.M., 2019. Chronic inflammation in the etiology of disease across the life span. Nat. Med. 25 (12), 1822–1832. https://doi.org/10.1038/s41591-019-0675-0.

Giollabhui, N., Ellman, L.M., Coe, C.L., Byrne, M.L., Abramson, L.Y., Alloy, L.B., 2020. To exclude or not to exclude: considerations and recommendations for C-reactive protein values higher than 10 mg/L. Brain Behav. Immun. 87, 898–900. https://doi.org/10.1016/j.bbi.2020.01.023.

Hamer, M., Molloy, G.J., Stamatakis, E., 2008. Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms. J. Am. Coll. Cardiol. 52 (25), 2156–2162.

Hannum, G., Guinney, J., Zhao, L., Zhang, L.I., Hughes, G., Sadda, S., Klotzle, B., Bibikova, M., Fan, J.-B., Gao, Y., 2013. Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol. Cell 49 (2), 359–367.

Hartwell, K.J., Moran-Santa Maria, M.M., Twal, W.O., Shaftman, S., DeSantis, S.M., McRae-Clark, A.L., Brady, K.T., 2013. Association of elevated cytokines with childhood adversity in a sample of healthy adults. J. Psychiatr. Res. 47 (5), 604–610.

Hoffman, L., 2015. Longitudinal Analysis: Modeling Within-Person Fluctuation and Change. Routledge.

Horvath, S., 2013. DNA methylation age of human tissues and cell types. Genome Biol. 14 (10), 1–20.

Hostinar, C.E., Lachman, M.E., Mroczek, D.K., Seeman, T.E., Miller, G.E., 2015. Additive contributions of childhood adversity and recent stressors to inflammation at midlife: findings from the MIDUS study. Dev. Psychol. 51 (11), 1630.

John-Henderson, N.A., Marsland, A.L., Kamarck, T.W., Muldoon, M.F., Manuck, S.B., 2016. Childhood SES and the occurrence of recent negative life events as predictors of circulating and stimulated levels of Interleukin-6. Psychosom. Med. 78 (1), 91–101.

Joshi, D., Gonzalez, A., Lin, D., Raina, P., 2023. The association between adverse childhood experiences and epigenetic age acceleration in the Canadian longitudinal study on aging. Aging Cell 22 (2), e13779. https://doi.org/10.1111/acel.13779.

Justice, J.N., Ferrucci, L., Newman, A.B., Aroda, V.R., Bahnson, J.L., Divers, J., Espeland, M.A., Marcovina, S., Pollak, M.N., Kritchevsky, S.B., 2018. A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup. Geroscience 40 (5), 419–436.

Katrinli, S., Stevens, J., Wani, A.H., Lori, A., Kilaru, V., Van Rooij, S.J.H., Hinrichs, R., Powers, A., Gillespie, C.F., Michopoulos, V., Gautam, A., Jett, M., Hammamieh, R., Yang, R., Wildman, D., Qu, A., Koenen, K., Aiello, A.E., Jovanovic, T., et al., 2020. Evaluating the impact of trauma and PTSD on epigenetic prediction of lifespan and neural integrity. Neuropsychopharmacology 45 (10), 1609–1616. https://doi.org/10.1038/s41386-020-0700-5.

Kessler, R.C., Aguilar-Gaxiola, S., Alonso, J., Benjet, C., Bromet, E.J., Cardoso, G., Degenhardt, L., de Girolamo, G., Dinolova, R.V., Ferry, F., 2017. Trauma and PTSD in the WHO world mental health surveys. Eur. J. Psychotraumatol. 8 (Suppl. 5), 1353383.

Kivimäki, M., Steptoe, A., 2018. Effects of stress on the development and progression of cardiovascular disease. Nat. Rev. Cardiol. 15 (4), 215–229.

Klopack, E.T., Crimmins, E.M., Cole, S.W., Seeman, T.E., Carroll, J.E., 2022. Accelerated epigenetic aging mediates link between adverse childhood experiences and depressive symptoms in older adults: results from the Health and Retirement Study. SSM-Population Health 17, 101071.

Krause, N., Shaw, B.A., Cairney, J., 2004. A descriptive epidemiology of lifetime trauma and the physical health status of older adults. Psychol. Aging 19 (4), 637–648.

Lam, P.H., Chiang, J.J., Chen, E., Miller, G.E., 2021. Race, socioeconomic status, and low-grade inflammatory biomarkers across the lifecourse: a pooled analysis of seven studies. Psychoneuroendocrinology 123, 104917.

Levine, M.E., Lu, A.T., Quach, A., Chen, B.H., Assimes, T.L., Bandinelli, S., Hou, L., Baccarelli, A.A., Stewart, J.D., Li, Y., 2018. An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany NY) 10 (4), 573.

Lim, S., Nzegwu, D., Wright, M.L., 2022. The impact of psychosocial stress from life trauma and racial discrimination on epigenetic aging—a systematic review. Biol. Res. Nurs. 24 (2), 202–215. https://doi.org/10.1177/10998004211060561.

Lin, J.E., Neylan, T.C., Epel, E., O'Donovan, A., 2016. Associations of childhood adversity and adulthood trauma with C-reactive protein: a cross-sectional population-based study. Brain Behav. Immun. 53, 105–112.

López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153 (6), 1194–1217.

Lu, A.T., Quach, A., Wilson, J.G., Reiner, A.P., Aviv, A., Raj, K., Hou, L., Baccarelli, A.A., Li, Y., Stewart, J.D., 2019. DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging (Albany NY) 11 (2), 303.

McEwen, B.S., 1998. Stress, adaptation, and disease: allostasis and allostatic load. Ann. N. Y. Acad. Sci. 840 (1), 33–44.

McEwen, B.S., 2004. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann. N. Y. Acad. Sci. 1032 (1), 1–7.

Miller, G.E., Chen, E., Parker, K.J., 2011. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol. Bull. 137 (6), 959–997.

Papalia, D.E., Sterns, H.L., Feldman, R.D., Camp, C.J., 2007. Adult Development and Aging. McGraw-Hill.

Pascale, J., McGee, A., 2008. A multi-method evaluation of the use of an event history calendar. Surv. Methodol. 2.

Pawelec, G., Goldeck, D., Derhovanessian, E., 2014. Inflammation, ageing and chronic disease. Curr. Opin. Immunol. 29, 23–28.

Pearson, T.A., Mensah, G.A., Alexander, R.W., Anderson, J.L., Cannon III, R.O., Criqui, M., Fadl, Y.Y., Fortmann, S.P., Hong, Y., Myers, G.L., 2003. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107 (3), 499–511.

Rooks, C., Veledar, E., Goldberg, J., Bremner, J.D., Vaccarino, V., 2012. Early trauma and inflammation: role of familial factors in a study of twins. Psychosom. Med. 74 (2), 146–152.

Rutters, F., Pilz, S., Koopman, A.D., Rauh, S.P., Te Velde, S.J., Stehouwer, C.D., Elders, P. J., Nijpels, G., Dekker, J.M., 2014. The association between psychosocial stress and mortality is mediated by lifestyle and chronic diseases: the Hoorn Study. Soc. Sci. Med. 118, 166–172.

Schrepf, A., Markon, K., Lutgendorf, S.K., 2014. From childhood trauma to elevated C-reactive protein in adulthood: the role of anxiety and emotional eating. Psychosom. Med. 76 (5), 327–336.

Scott, A.B., Reed, R.G., Garcia-Willingham, N.E., Lawrence, K.A., Segerstrom, S.C., 2019. Lifespan socioeconomic context: associations with cognitive functioning in later life. J. Gerontol.: Series B 74 (1), 113–125.

Skinner, H.G., Palma-Gudiel, H., Stewart, J.D., Love, S.-A., Bhatti, P., Shadyab, A.H., Wallace, R.B., Salmoirago-Blotcher, E., Manson, J.E., Kroenke, C.H., Belsky, D.W., Li, Y., Whitsel, E.A., Zannas, A.S., 2024. Stressful life events, social support, and epigenetic aging in the Women's Health Initiative. J. Am. Geriatr. Soc. 72 (2), 349–360. https://doi.org/10.1111/jgs.18726 cmedm.

Slavich, G.M., Roos, L.G., Mengelkoch, S., Webb, C.A., Shattuck, E.C., Moriarity, D.P., Alley, J.C., 2023. Social Safety Theory: Conceptual foundation, underlying mechanisms, and future directions. Health psychology review 17 (1), 5–59.

Slopen, N., Lewis, T.T., Gruenewald, T.L., Mujahid, M.S., Ryff, C.D., Albert, M.A., Williams, D.R., 2010. Early life adversity and inflammation in African Americans and whites in the midlife in the United States survey. Psychosom. Med. 72 (7), 694.

Stawski, R.S., Scott, S.B., Zawadzki, M.J., Sliwinski, M.J., Marcusson-Clavertz, D., Kim, J., Lanza, S.T., Green, P.A., Almeida, D.M., Smyth, J.M., 2019. Age differences in everyday stressor-related negative affect: a coordinated analysis. Psychol. Aging 34 (1), 91–105.

Stebbins, R.C., Maselko, J., Yang, Y.C., Plassman, B.L., Edwards, J.K., Aiello, A.E., 2022. Lifecourse traumatic events and cognitive aging in the health and retirement study. Am. J. Prev. Med. 63 (5), 818–826.

Suglia, S.F., Clausing, E.S., Shelton, R.C., Conneely, K., Prada-Ortega, D., DeVivo, I., Factor-Litvak, P., Cirillo, P., Baccarelli, A.A., Cohn, B., Link, B.G., 2024. Cumulative stress across the lifecourse and biological aging in adulthood. Psychosom. Med. https://doi.org/10.1097/PSY.0000000000001284.

Tschanz, J.T., Pfister, R., Wanzek, J., Corcoran, C., Smith, K., Tschanz, B.T., Steffens, D. C., Østbye, T., Welsh-Bohmer, K.A., Norton, M.C., 2013. Stressful life events and cognitive decline in late life: moderation by education and age. The Cache County Study. Int. J. Geriatr. Psychiatr. 28 (8), 821–830.

Tursich, M., Neufeld, R.W.J., Frewen, P.A., Harricharan, S., Kibler, J.L., Rhind, S.G., Lanius, R.A., 2014. Association of trauma exposure with proinflammatory activity: a transdiagnostic meta-analysis. Transl. Psychiatry 4 (7) e413–e413.

van Ockenburg, S.L., Tak, L.M., Bakker, S.J., Gans, R.O., de Jonge, P., Rosmalen, J.G., 2015. Effects of adverse life events on heart rate variability, cortisol, and C-reactive protein. Acta Psychiatr. Scand. 131 (1), 40–50.

Wang, D., Gruenewald, T., 2019. The psychological costs of social support imbalance: variation across relationship context and age. J. Health Psychol. 24 (12), 1615–1625.

Wheaton, B., Young, M., Montazer, S., Stuart-Lahman, K., 2013. Social stress in the twenty-first century. In: Handbook of the Sociology of Mental Health. Springer, pp. 299–323.

Wrzus, C., Hänel, M., Wagner, J., Neyer, F.J., 2013. Social network changes and life events across the life span: a meta-analysis. Psychol. Bull. 139 (1), 53–80.