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Latent classes of adverse childhood experiences and changes in inflammation across middle age among urban-dwelling adults

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1. Introduction

Adverse childhood experiences (ACEs) are potentially traumatic events that occur from birth through adolescence. ACEs can include direct experiences of maltreatment, such as abuse and neglect, or exposure to stressful environments, such as households with intimate partner violence or a caregiver misusing substances (Felitti et al., 1998). ACEs are a pervasive problem in the United States, with about half of all children experiencing at least one ACE, and one in ten children experiencing three or more ACEs (Sacks & Murphey, 2018). ACEs are also a major public health concern: ACEs are linked with a myriad of chronic diseases in adulthood including cardiovascular disease, diabetes, obesity, and cancer (Hughes et al., 2017; Hughes et al., 2021; Petruccelli et al., 2019), and large cohort studies suggest that ACEs are associated with premature death (Brown et al., 2009; Kelly-Irving et al., 2013; Yu et al., 2022). ACEs disproportionately affect marginalized individuals, including those living with economic adversity and from racially/ethnically minoritized backgrounds (Giano et al., 2020; Sacks & Murphey, 2018). Thus, understanding, preventing, and mitigating the harmful effects of ACEs is critical for promoting health and reducing health inequities among marginalized individuals across the lifespan.

Although a robust body of evidence supports the connection between ACEs and health (Hughes et al., 2017; Hughes et al., 2021; Petruccelli et al., 2019), the biobehavioral mechanisms underlying this association remain poorly understood (Pino et al., 2022; Su et al., 2015; Wiss & Brewerton, 2020). One major pathway through which ACEs are hypothesized to get "under the skin" is through effects on inflammatory processes (Cooke et al., 2023; Danese & McEwen, 2012; Finlay et al., 2022). This hypothesis is rooted in *allostatic load theory*, which posits that chronic exposure to stressors, such as ACEs, contributes to prolonged activation of the stress response system (Finlay et al., 2022; Juster et al., 2010). Over time, this chronic stimulation of the sympathetic nervous system and down-regulation of anti-inflammatory pathways (i.e. *allostatic overload*) leads to 'wear and tear' on the immune system and persistent elevation of inflammatory levels (Danese & McEwen, 2012). The theories of *toxic stress* (Shonkoff et al., 2012), *embodiment* (Krieger, 2001), and the *Developmental Origins of Health and Disease* (Gluckman et al., 2010) also support the role of inflammation in the biological embedding of adversity (Almeida et al., 2019; Johnson et al., 2013). However, despite the strength and broad acceptance of these theories, empirical evidence of the association between childhood adversity and adulthood inflammation remains relatively weak (Baumeister et al., 2016; Brown et al., 2021; Kerr et al., 2021).

Biomarkers of inflammation have been widely studied in the context of childhood adversity, and often include measures such as c-reactive protein (CRP) and inflammatory cytokines (Condon, 2018; Juster et al., 2010). However, these studies are largely limited by cross-sectional designs or inclusion of a very small number of biomarkers (Kerr et al., 2021), and thus the association between ACEs and inflammation remains unclear. For example, results of a 2016 meta-analysis (n = 25 articles) suggest that exposure to childhood trauma is associated with increased CRP, interleukin (IL)-6, and Tumor Necrosis Factor-α (TNF-α) in adulthood (Baumeister et al., 2016). However, in a 2021 update of this review (N = 37 new articles), associations between childhood trauma and inflammatory markers were predominantly non-significant (Brown et al., 2021). In a systematic review of the association between childhood maltreatment and inflammation (n = 44 studies), childhood maltreatment was associated with elevated CRP in prospective studies (n = 3), but results of retrospective studies were mixed, and childhood maltreatment was not associated with IL-6 or TNF-a levels (Kerr et al., 2021).

Findings of these systematic reviews indicate several directions for future research. First, there is a need for a more comprehensive examination of inflammatory biomarkers. Although use of a single measure is

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often most feasible, one biomarker alone may not capture the complexity of effects on inflammatory processes, and is unlikely to be indicative of overall health (McEwen, 2015). There is also a pressing need to study the effects of ACEs on inflammation over time. Inflammation is an innate immune response to a wide range of exposures, including pathogens, injury, and metabolic stress (Antonelli & Kushner, 2017). Measurement of inflammation at a single time point may therefore be an unreliable reflection of an individual's typical inflammatory state (Zimmerman et al., 2010). Further, evidence suggests that inflammation *over time* may be an important predictor of illness and illness severity, and thus longitudinal studies of inflammation may provide more insight into the pathways linking ACEs with overall health (Boulogne et al., 2017; Eder et al., 2015; Meduri et al., 1995).

Recent studies suggest that past research may also be limited by the omission of potentially important moderating variables, such as sex, race, and socioeconomic status. For example, in a study of data from the Avon Longitudinal Study of Parents and Children (N = 4,887), maternal mental health problems were associated with CRP, but only for girls, while emotional abuse was associated with IL-6, but only for boys (Lacey et al., 2020a,b). Socioeconomic status may indicate the presence of other risk and protective factors that exacerbate or protect against the effects of ACEs. These may include housing instability, educational attainment, health behaviors, and the availability of resources, and many studies linking socioeconomic status with inflammation have implicated these social and behavioral risk factors as underlying this association (Chen & Lacey, 2018; Mainous et al., 2024; Misiak et al., 2022; Muscatell et al., 2020).

Race/ethnicity is also a potential moderator that has received very little attention in research on ACEs and inflammation. Race is a social construct, and thus does not have a direct impact on inflammatory trajectories (Smedley & Smedley, 2005). However, a growing body of literature demonstrates that experiences of racial discrimination contribute to increased inflammation among minoritized racial groups (Cuevas et al., 2020; Surachman et al., 2021). Individuals from minoritized racial backgrounds are also at increased risk for experiencing ACEs due to structural racism (Maguire-Jack et al., 2020), and both structural and interpersonal racism contribute to childhood toxic stress (Shonkoff et al., 2021). Understanding whether and how the association between ACEs and inflammation varies by race may provide important insight into the role of racism in exacerbating health inequities.

Finally, the effects of ACEs on inflammation may vary by the type of adversity experienced. For example, in their respective systematic reviews, Baumeister et al (2016) and Brown et al (2021) concluded that childhood abuse is more strongly associated with elevated inflammatory markers than childhood neglect. Further, evidence suggests that ACEs are often co-occurring. While past studies have typically relied on cumulative ACE scores or separate examination of each ACE exposure, examination of ACE patterns that occur within individuals is critical for comprehensively identifying childhood risk (Lacey et al., 2020a,b). Improved understanding of ACE patterns also has important implications for improved approaches to ACE screening and targeted intervention.

Overall, the extant literature suggests the need for longitudinal studies that include comprehensive measures of inflammation, evaluate differential associations of ACE patterns, and examine differences by sex, race, and socioeconomic status. In the current study, we address these gaps by conducting latent class analysis (LCA) to identify patterns of co-occurring ACEs in a prospective study of socioeconomically and racially diverse adults. We then examine associations between these ACE classes and changes in inflammation across middle age, including examination of moderation by sex, race, and socioeconomic status. We examine two indicators of inflammation – CRP, which has frequently been used in ACEs studies, and the systemic immune-inflammation index (SII), a comprehensive indicator of inflammation that is associated with increased risk of cardiovascular disease (Ye et al., 2022). Improved understanding of inflammation as a mechanism linking ACEs with health will help identify targets for intervention to mitigate the harmful effects of ACEs and reduce associated inequities across the lifespan (Danielson & Saxena, 2019; Srivastav et al., 2020).

2. Methods

2.1. Study overview

The current study uses data from three waves of the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study: baseline (2004–2009; wave 1) and two follow-up visits (2009–2013; 2013–2017). HANDLS is an on-going prospective cohort study of socioeconomically diverse White and African American adults aged 30–64 residing in Baltimore, MD (Evans et al., 2010). The sample was designed to recruit equally across 4 factors: 1) age via 7 five-year age groups between 30 and 64, 2) sex, 3) self-identified race (white or African American), and 4) poverty status defined as household income above or below 125% of the 2004 Federal poverty cutoff. The Institutional Review Board of the National Institutes of Health approved the HANDLS study protocol; all participants provided written informed consent. Additional details regarding the HANDLS study are reported elsewhere (e.g. (Evans et al., 2010; Wright et al., 2017) and study protocols for each wave of data collection are publicly available, e.g. (HANDLS, 2004).

2.2. Study cohort

In the current analysis, we included individuals who participated in the Wave 2 study visit and completed the ACE questionnaire. Two-thousand eight-hundred participants were available for Wave 2, with some loss from prior waves due to participant death, withdrawal from the study, or loss to follow-up. Of those available for Wave 2, $n = 2{,}147$ participated, reflecting relatively stable participation from prior visits (baseline: $n = 2{,}707$, Wave 1: $n = 2{,}275$). Due to time constraints, a significant proportion of participants in Wave 2 (28 %) did not receive the ACEs questionnaire. African American participants and those living below the poverty cutoff were less likely to have received the ACEs questionnaire compared to their counterparts ($p's < 0.001$), but there were no differences by gender. This resulted in a final sample of $n = 1{,}537$ participants with ACE data. In this final sample, the majority of participants were African American adults (n = 901, 59 %), female ($n = 903$, 59 %) and lived above the federal poverty cutoff (n = 972, 63 %), similar to the demographics of the baseline HANDLS cohort (Evans et al., 2010). Most participants in this final sample (>99 %) had complete data at all 3 visits for SII and CRP ($n = 1{,}528$ and $n = 1{,}530$, respectively).

2.3. Variables & measures

2.3.1. Adverse childhood experiences

ACEs were measured via retrospective self-report at Wave 2. Neglect-related items were drawn from the physical neglect and emotional neglect subscales of the Childhood Trauma Questionnaire (CTQ) Short Form, a well validated measure with high internal consistency and test–retest reliability in diverse samples of adults (Bernstein et al., 2003; Georgieva et al., 2021). All other ACE subtypes were assessed using items from Wave 2 of the original Adverse Childhood Experiences Study conducted at Kaiser Permanente in 1997, a reliable and widely used instrument that was used for the seminal research done in the ACEs field (Corso et al., 2008; Felitti et al., 1998). An overview of ACE subtype measurement is outlined below, and a complete list of ACE items is included in Appendix A.

Emotional Neglect. The emotional neglect composite consisted of the original 5 Likert-scale items from the CTQ Emotional Neglect subscale (Bernstein et al., 2003). Responses ranged from "never true" to "very often true." Based on the CTQ guidelines, sum subscale scores

greater than 10 indicated exposure to emotional neglect. Otherwise, participants with scores less than or equal to 10 were coded as "no" exposure.

Physical Neglect. The physical neglect composite consisted of the original 5 Likert-scale items from the CTQ Physical Neglect subscale (Bernstein et al., 2003). Scores greater than 5 were classified as exposed to physical neglect, while participants with scores less than or equal to 5 were coded as "no" exposure, following CTQ guidelines.

Psychological Abuse. Psychological abuse was measured using 2 Likert items ranging from "never" to "very often.". Participants were coded as not experiencing psychological abuse if they responded with "never" to both items. Otherwise, participants were classified as having exposure to psychological abuse.

Physical Abuse. Physical abuse was assessed using 1 Likert-scale item, with responses ranging from "never" to "very often." Participants who responded "never" to this item were coded as "no" exposure to physical abuse. Otherwise, participants were classified as having exposure to physical abuse.

Sexual Abuse. Childhood sexual abuse (CSA) was measured using 4 binary "yes"/"no" items, wherein participants endorsed whether they had experienced certain types of CSA. If participants endorsed at least one type of CSA, participants were classified as having exposure. Otherwise, participants were coded as "no" exposure.

Household Incarceration. Participants were asked if anyone in their household had been incarcerated before they turned 18 using a binary "yes"/"no" item. Participants were coded as "yes"/"no" exposure based on their response.

Parental Separation/Divorce. Participants were asked if their parents had separated or divorced before they turned 18. Exposure was categorized according to their response on the binary "yes"/"no" item.

Household Substance Use. Participants were asked if anyone in their household used "street drugs." Responses were coded based on a binary "yes"/"no" response.

Household Mental Illness. Exposure to mental illness was assessed using two items with a binary "yes"/"no" response option. Participants were asked: 1) did anyone in their household attempt suicide and 2) was anyone in their household "depressed or mentally ill". Participants were coded as no exposure if they responded "no" to both questions. Otherwise, they were coded as having exposure to mental illness in the household.

Witnessing Intimate Partner Violence. The witnessing Intimate Partner Violence (IPV) composite consisted of 4 Likert-scale items. Participants reported the frequency with which they witnessed their mother experience IPV, with responses ranging from "never" to "very often." Participants were coded as no exposure if they responded "never" to all items. Otherwise, participants were classified as having exposure to IPV.

2.3.2. Systemic inflammation

High-sensitivity c-reactive protein

High-sensitivity C-Reactive Protein (hsCRP) was used to measure low-grade chronic systemic inflammation at baseline, Wave 1, and Wave 2. Serum hsCRP is a reliable and commonly used biomarker of inflammation that is predictive of cardiovascular risk (Aguiar et al., 2013; Pearson et al., 2003). hsCRP was analyzed with an immunoturbidimeter (Siemens/Behring Nephelometer II) using 0.5–1 ml of blood plasma.

Systemic Immune-Inflammation index (SII)

Serum collected at baseline, Wave 1, and Wave 2 was also used to calculate the systemic inflammation index (SII), a commonly used index of inflammation (Amare, 2017). The SII is calculated as P * N/L, where P, N, and L represent platelet, neutrophil, and lymphocyte counts, respectively. Analyses were performed by Quest Diagnostics, and electronic cell sizing and counting/ cytometry/microscopy was used to determine WBC levels. The SII is intended to provide a comprehensive indicator of the balance between an individual's inflammation and immunity status (Ye et al., 2022), and elevated SII has been associated with increased risk for cardiovascular and all-cause mortality in adults (Xia et al., 2023).

2.3.3. Sociodemographic and Anthropometric measures

Participants reported on sociodemographic characteristics, including sex assigned at birth (female or male) and self-identified race (Black/African American or White). Poverty status was collected at baseline and defined as household income above or below 125 % of the 2004 Federal poverty cutoff (Services, 2003). BMI (kg/m^2) was assessed using height and weight measured during physical exams at baseline, Wave 1 and Wave 2.

2.4. Data analysis

All analyses were conducted in R 4.2.2 (R Core Team, 2021). We used descriptive statistics to describe ACEs experienced by individuals in the sample. To identify subgroups of participants with distinct ACEs exposures, latent class analyses (LCA) were modeled on the 10 dichotomous ACEs categories described above. Then, mixed effects regressions with centered age at 5 decades (i.e., centered at 50 and divided by 10) as the time-referent were performed for hsCRP and SII using the lme4 package[16]. First, the appropriate form of growth was determined (i.e., linear vs. quadratic); assumptions of normality were tested, and log-transformations were conducted to ensure assumptions of normality were not violated following transformation. Then, an interaction between ACE class, the appropriate form of growth and either race, sex or poverty status was tested. Next, backward elimination was employed to identify the most parsimonious set of significant interactions.

Past studies have identified associations between BMI and our inflammatory markers (Choi et al., 2013; Zhou et al., 2024), as well as between ACEs and BMI (Wiss & Brewerton, 2020). We therefore conducted additional analyses adjusting for time-varying BMI in order to examine whether the effects of ACEs on inflammation were present above and beyond the effects of BMI. We also planned to explore BMI as a mediator between ACEs and inflammatory profiles; however, ACEs were not directly associated with BMI in our sample, so indirect effects were not examined. Finally, we conducted a sensitivity analysis wherein participants with chronically elevated CRP (hsCRP $>$ 10 at all 3 visits) were removed from the analysis sample, as this may reflect the presence of chronic illness.

3. Results

3.1. Sample characteristics

At baseline, participants were a mean age of 47.50 years ($SD = 9.01$) and reported approximately 3 ACEs ($M = 2.70$, $SD = 2.29$) on average (Table 1). The average hsCRP at baseline was 4.58 mg/L ($SD = 8.84$) and was higher in women compared to men ($p = 0.004$). Baseline hsCRP levels did not differ by race nor poverty status. At baseline, average SII was 541.49 ($SD = 307.66$) and it was higher among women and White participants compared to men and African American participants ($p = 0.001$ and $p < 0.001$, respectively). There were no differences in baseline SII across poverty status. Average BMI at baseline was 30.13 kg/m^2 ($SD = 7.54$) and was significantly higher for women than men, $p < 0.001$ and for those above the poverty line than those below ($p = 0.020$). There were no racial differences in BMI at baseline.

The most commonly endorsed ACE was psychological abuse (46 %), followed by parental separation or divorce (43 %), witnessing IPV (33 %), sexual abuse (25 %), physical abuse (25 %), physical neglect (24 %), household mental illness (23 %), emotional neglect (20 %), household substance use (16 %), and parental incarceration (14 %). As reported in Table 1, the rate of ACE endorsement varied as a function of sex, race, or poverty status. Compared to men, women were more likely to report a higher total number of ACEs ($p = 0.037$), a history of sexual abuse ($p <$ 0.001), and exposure to a household member with mental illness ($p <$

Table 1
Baseline demographics.

Variable	Overall	Race			Sex			Federal Poverty Threshold		
	n's = 1284–1537	White (n = 636)	African American (n = 901)	*p*	Women (n = 903)	Men (n = 634)	*p*	Above (n = 972)	Below (n = 565)	*p*
Age	47.50 (9.01)	48.09 (8.86)	47.08 (9.10)	0.03	47.68 (9.22)	47.23 (8.71)	0.337	48.12 (9.01)	46.42 (8.92)	<0.001
ACE count	2.70 (2.29)	2.72 (2.37)	2.69 (2.24)	0.813	2.80 (2.47)	2.55 (2.02)	0.037	2.62 (2.26)	2.84 (2.35)	0.064
CRP[a]	1.26 (0.85)	1.28 (0.82)	1.25 (0.88)	0.55	1.38 (0.88)	1.08 (0.78)	<0.001	1.25 (0.83)	1.28 (0.89)	0.528
SII[a]	6.15 (0.55)	6.31 (0.48)	6.02 (0.58)	<0.001	6.21 (0.53)	6.07 (0.58)	<0.001	6.13 (0.56)	6.19 (0.54)	0.084
BMI	30.13 (7.54)	30.04 (7.52)	30.21 (7.56)	0.678	31.39 (8.13)	28.33 (6.17)	<0.001	30.48 (7.45)	29.50 (7.68)	0.02
Psychological Abuse	708 (46.2)	327 (51.7)	381 (42.4)	0.001	414 (46.1)	294 (46.4)	0.936	455 (47.0)	253 (45.0)	0.497
Physical Abuse	384 (25.1)	171 (27.1)	213 (23.7)	0.174	229 (25.5)	155 (24.5)	0.699	254 (26.2)	130 (23.2)	0.204
Sexual Abuse	387 (25.3)	177 (28.0)	210 (23.4)	0.056	285 (31.8)	102 (16.1)	<0.001	249 (25.7)	138 (24.6)	0.684
Household Substance Abuse	247 (16.1)	95 (14.9)	152 (16.9)	0.328	128 (14.2)	119 (18.8)	0.019	147 (15.1)	100 (17.7)	0.21
Parental Separation/ Divorce	663 (43.1)	233 (36.6)	430 (47.7)	<0.001	399 (44.2)	264 (41.6)	0.347	399 (41.0)	264 (46.7)	0.035
Household Mental Illness	358 (23.3)	191 (30.0)	167 (18.5)	<0.001	245 (27.1)	113 (17.8)	<0.001	222 (22.8)	136 (24.1)	0.626
Household Incarceration	221 (14.4)	60 (9.4)	161 (17.9)	<0.001	118 (13.1)	103 (16.3)	0.092	120 (12.3)	101 (17.9)	0.004
IPV exposure	505 (33.0)	194 (30.6)	311 (34.6)	0.113	312 (34.7)	193 (30.5)	0.091	315 (32.5)	190 (33.8)	0.642
Emotional Neglect	301 (19.9)	135 (21.4)	166 (18.7)	0.219	185 (20.8)	116 (18.5)	0.296	171 (17.7)	130 (23.6)	0.008
Physical Neglect	362 (23.8)	140 (22.2)	222 (24.9)	0.244	206 (23.1)	156 (24.8)	0.46	208 (21.6)	154 (27.7)	0.008

Note. [a] Variables are log-transformed. CRP, high sensitivity C-Reactive Protein; SII, Systemic Inflammation index; BMI, Body Mass Index; IPV, Intimate Partner Violence.

0.001), and were less likely to report household substance use ($p = 0.016$). Childhood experiences of psychological abuse ($p < 0.001$), sexual abuse ($p = 0.043$), parental separation/divorce ($p < 0.001$), and incarceration of a household member ($p < 0.001$) were reported more commonly among Black participants, while exposure to a household member with mental illness was reported more commonly among White participants ($p < 0.001$). Compared to those above the federal poverty cutoff, participants living below the poverty cutoff were more likely to endorse parental separation or divorce ($p = 0.030$), parental incarceration ($p = 0.003$), emotional neglect ($p = 0.006$), and physical neglect ($p = 0.007$).

3.2. Latent classes of adverse childhood experiences

We selected an LCA model with 5 classes as it had the best balance of power (i.e., classes were not too small to prevent moderation) and performance across indicators (see Table 2A and 2B). As displayed in Fig. 1, the referent class was labeled "Minimal Exposure" ($n = 748$, 43 %), as individuals in this class had minimal endorsement of any of the 10 ACEs. The other classes are labeled as follows: "Abuse" ($n = 261$, 20 %), as individuals in this class predominantly endorsed experiencing physical, psychological and/or sexual abuse; "Comprehensive" ($n = 241$, 16 %), as individuals this class endorsed experiencing an overwhelming majority of all ACE types; "Abuse & Household Dysfunction" ($n = 160$, 11 %) as individuals in this class endorsed experiencing different forms of abuse along with household dysfunction (e.g., household substance use); and "Neglect" ($n = 127$, 10 %), as individuals in this class predominantly endorsed experiencing physical and emotional neglect. Notably, African American participants were more likely to be in the Abuse & Household Dysfunction class than White participants, $p\ adj = 0.035$. Women were more likely than men to be in the Comprehensive class, $p\ adj < 0.001$, but less likely to be in the Neglect class, $p\ adj = 0.033$. Finally, those living above poverty cutoff were more likely to be in the Abuse class than those living below the poverty cutoff, $p = 0.007$.

Table 2B
Latent class analyses percent breakdown for ACEs (n = 1537).

Classes	%						
1	100						
2	67.7	32.3					
3	56.4	13.8	29.8				
4	10.6	29.3	16.1	44.0			
5	20.2	9.7	43.3	11.1	15.6		
6	8.9	9.3	12.4	7.1	43.3	18.0	
7	39.2	10.0	18.8	10.1	9.2	4.3	8.5

3.3. Associations between ACE classes and inflammation

Growth models revealed a quadratic form of growth for both hsCRP

Table 2A
Latent class analyses metrics for adverse childhood experiences (n = 1537).

Classes	Parameters	*df*	loglik	AIC	BIC	G^2	χ^2
1	10	1013	−8539.7	17099.4	17152.78	2894.51	42526.15
2	21	1002	−7789.08	15620.16	15732.25	1401.01	2533.432
3	32	991	−7639.11	15342.21	15513.01	1104.13	1728.99
4	43	980	−7539.29	15164.58	15394.09	904.12	1538.47
5	**54**	**969**	**−7486.65**	**15081.30**	**15369.53**	**798.23**	**1097.44**
6	65	958	−7459.25	15048.50	15395.44	743.12	1041.52
7	76	947	−7442.75	15037.51	15443.16	710.24	1093.21

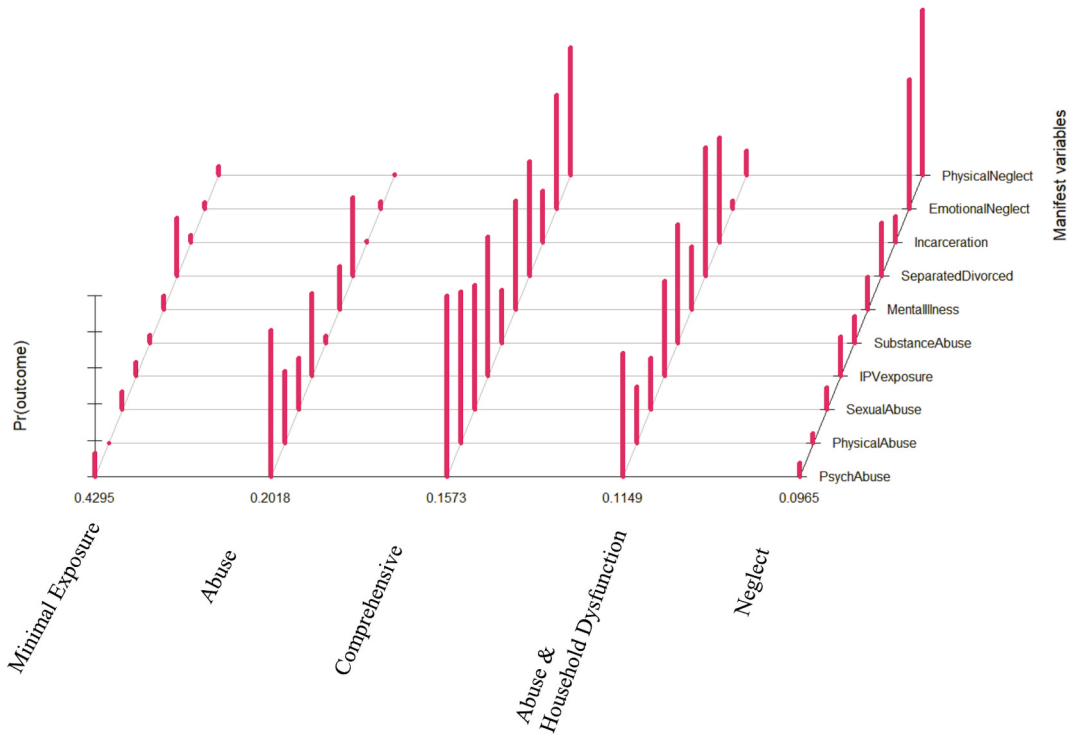

Fig. 1. Latent class analysis classes.

and SII. Notably, we log-transformed these outcomes after adding a constant of one, as QQ plots revealed violations of normality; the transformation resolved these issues. Thus, the values reported below are for log-transformed outcomes, not raw values.

3.3.1. *High-sensitivity c-reactive protein*

For hsCRP, the most parsimonious model revealed that the association between ACE class and linear change in CRP during adulthood differed by sex, as indicated by a significant 3-way interaction of ACE class by sex by time (decades), i.e., ACEclass × Sex × Age, $p = 0.026$ (Fig. 2; Table 3). To ease interpretation, the simple effects of this 3-way interaction are described below.

Overall, the combined fixed and random effects of the model explained 58 % of the variance in hsCRP; the fixed effects explained 4 % of the variance. On average, women in the Minimal Exposure class had higher hsCRP at age 30 than men, $b = 0.46$, $t(2960.57) = 3.69$, $p < 0.001$, 95 % CI (0.22, 0.71). The log-linear increase in hsCRP across each decade varied as a function of ACE class and sex ($p = 0.032$) (Table 4). Among women, the log-linear changes in CRP were greater for those in the Neglect class compared to the Minimal Exposure class. Specifically, women in the Neglect class had a faster increase than those in the Minimal Exposure class. In contrast, among men, the opposite was true, such that the log-linear increases were smaller for those in the Neglect class compared to the Minimal Exposure class. Notably, these findings disappeared after adjusting for time-varying BMI. Findings were unchanged in sensitivity analyses adjusting for chronically-elevated CRP.

3.3.2. *Systemic immune-inflammation index*

For SII, the most parsimonious model revealed that the association between ACE class and log-linear change in SII during adulthood differed by race, as indicated by a significant 3-way interaction of ACE class by race and time (decades), i.e., ACEclass × Race × Age, $p = 0.022$ (Fig. 3; Table 5). Again, the simple effects of this 3-way interaction are described below to aid interpretation.

Overall, the combined fixed and random effects of the model explained 62 % of the variance in SII; the fixed effects explained 9 % of the variance. For individuals in the Minimal Exposure class at age 30, women had higher SII scores on average than men, $b = 0.13$, $t(1487.41) = 4.92$, $p < 0.001$, 95 % CI (0.08, 0.1). Moreover, the average SII levels at age 30 also differed as function of ACE class and race. Among Black participants at age 30, SII scores did not differ by ACE class, $p > 0.05$. However, among White participants at age 30, those in the Abuse class, $b = 0.25$, $t(2839.97) = 2.16$, $p = 0.0231$, 95 %CI (0.02, 0.48), and Abuse & Household Dysfunction class, $b = 0.42$, $t(2906.73) = 2.70$, $p = 0.007$, 95 %CI (0.12, 0.72, had higher scores compared to the Minimal Exposure class.

Log-linear changes in SII during adulthood also varied as a function of ACE class and race ($p = 0.027$) (Table 6). Among Black participants, the log-linear changes in SII were smaller for those in the Abuse class compared to the Minimal Exposure class. Specifically, Black participants in the Abuse class essentially had minimal change in their SII scores across adulthood, whereas those in the Minimal Exposure class first had a significant decrease in SII at age 30 and 40 followed by minimal change into later adulthood. In contrast, among White participants, a different pattern was observed. White participants in the Abuse class had a decrease in SII at age 30 and 40, followed by minimal change in later adulthood, whereas those in the Minimal Exposure class had minimal change in mid adulthood followed by significant increases in SII in later adulthood around age 60. Notably, these simple effects remained in sensitivity analyses adjusting for time-varying BMI and chronically-elevated CRP.

4. Discussion

In a longitudinal dataset of racially and economically diverse adults, we examined associations between clusters of ACE exposure and inflammation across adulthood. Using both a traditional measure of inflammation, c-reactive protein, and a novel, comprehensive measure, the systemic immune-inflammation index, we identified differences in trajectories of CRP and SII over time, as well as differences in magnitudes of effect size. For the CRP model, fixed effects explained 4 % of model variance, indicating a small effect of ACEs on changes in CRP.

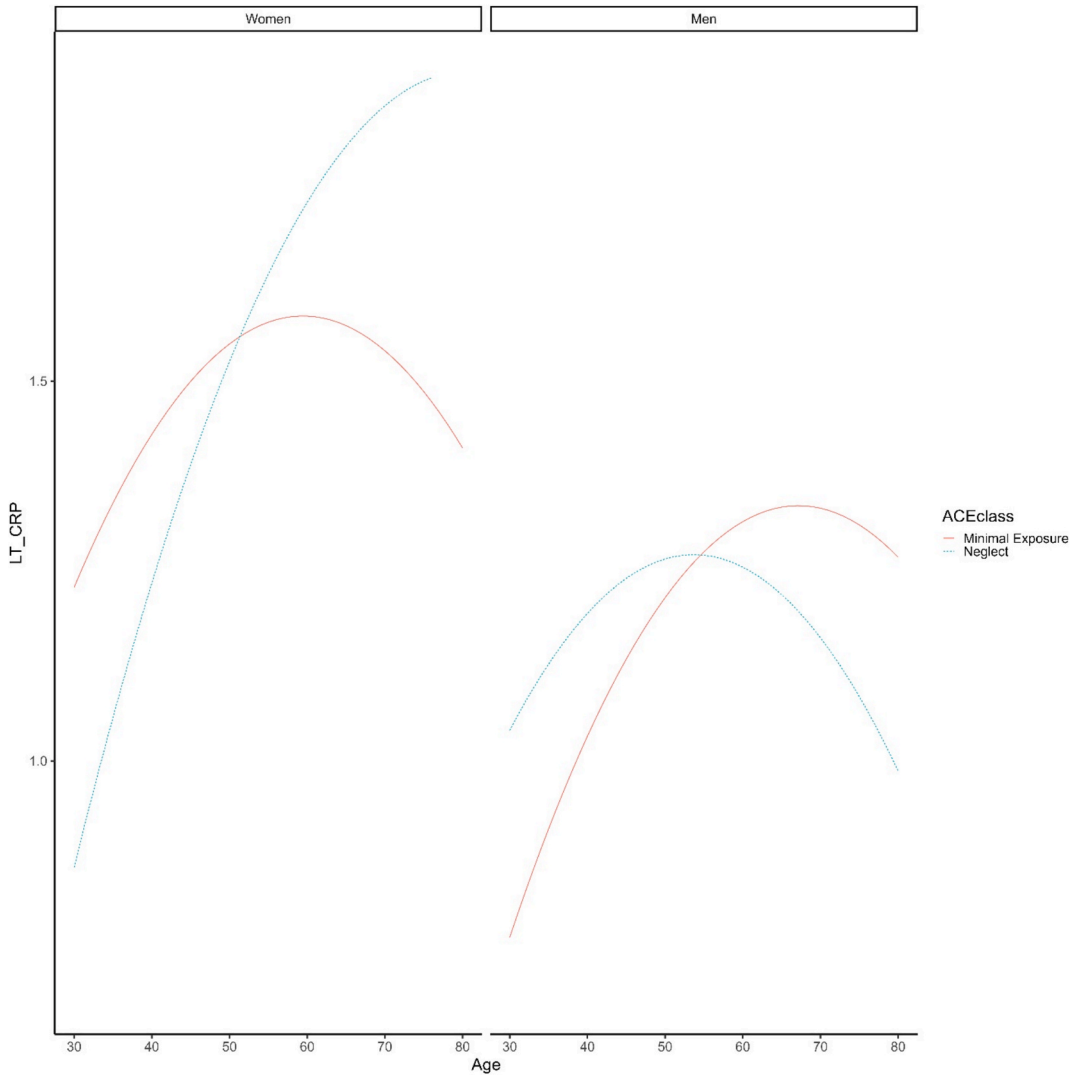

Fig. 2. Changes in hsCRP by sex and ACE class.

However, for the SII model, fixed effects explained 9 % of model variance, suggesting a small-to-medium effect of ACEs on changes in SII (Lorah, 2018). These findings suggest that a comprehensive measure of inflammation, such as SII, may provide a more robust assessment of the biological consequences of ACEs. Further, SII is significantly associated with risk for cardiovascular disease, including ischemic stroke, hemorrhagic stroke, myocardial infarction, and peripheral arterial disease (Ye et al., 2022). Thus, while our findings require replication, results of this study suggest inflammation may be an underlying mechanism linking ACEs with poor long-term health (Brown et al., 2021).

We identified five classes of self-reported ACE exposure: "Minimal Exposure," "Abuse," "Neglect," "Abuse & Household Dysfunction" and "Comprehensive." These classes are similar to patterns of ACEs reported in other studies. For example, in a study of adults in the 1958 British Birth cohort (N = 8,810), Lacey et al. (2020a,b) identified four ACE patterns based on retrospective report, which they labeled as "Low ACEs," "Parental mental health and substance misuse," "Maltreatment and conflict," and "Polyadversity," and ACE classes were associated with individual markers of inflammation (e.g. CRP, fibrinogen) (Lacey et al., 2020a,b). In a community sample of Canadian adults (N = 3,932), Dobson et al. (2021) identified four ACE classes using latent profile analysis: "No mistreatment," "Emotionally mistreated," "Sexually abused," and "Dysfunctional family environment"; and found ACE classes were associated with anxiety and depression (Dobson et al., 2021). Notably, our "Minimal Exposure" group included 43 % of the participants in our study. This percentage is much lower than the "minimal exposure" equivalent classes reported in other studies, which generally range from 60-80 % (Dobson et al., 2021; Lacey et al., 2020a, b; Lee et al., 2020; Parnes & Schwartz, 2022). This may be attributable to the HANDLS study design, which included purposive sampling by race and socioeconomic status (Karatekin & Hill, 2019; Lee et al., 2020; Misiak et al., 2022; SmithBattle et al., 2022), as racially minoritized and economically marginalized individuals are at increased risk for ACEs (Misiak et al., 2022). This also could be attributable to missing data in our cohort, as it is not possible to determine whether missing participants would have been in the "minimal exposure" group. However, participants who identified as African American or living below the federal poverty threshold were less likely to receive the ACE questionnaire compared with other groups, and thus it is more likely that ACEs are actually under-estimated in our sample.

The classes of ACE exposure identified in this study are consistent with dimensional models of early experience, including the Dimensional Model of Adversity and Psychopathology (McLaughlin & Sheridan, 2016) and life history models (Ellis et al., 2009). These models describe core underlying dimensions of early environments that occur across multiple adversity types, and often are categorized as threat/harshness, deprivation, and unpredictability (Ellis et al., 2022; McLaughlin et al., 2021). These models recognize the co-occurring nature of ACEs, which

Table 3
Log-transformed hsCRP mixed effects regression (n = 1530).

	Unadjusted Model	Adjusted Model [b]
Intercept	1.17***	−0.23*
Age centered	0.24***	0.18**
ACEclassNeglect	−0.37	−0.23
ACEclassAbuse	0.03	0.04
ACEclassAbuse & Household Dysfunction	0.05	−0.08
ACEclassComprehensive	0.16	0.05
Sex	−0.46***	−0.29*
Race	0.03	0.02
Poverty Status	0.08	0.10**
Age centered^2	−0.04***	−0.03**
BMI	—-	0.05***
Age centered*ACEclassNeglect	0.17	0.12
Age centered*ACEclassAbuse	−0.02	−0.03
Age centered*ACEclassAbuse & Household Dysfunction	−0.04	0.01
Age centered*ACEclassComprehensive	−0.05	−0.02
Age centered*Sex	0.06	0.04
ACEclassNeglect*Sex	0.64*	0.55
ACEclassAbuse*Sex	0.09	0.05
ACEclassAbuse & Household Dysfunction*Sex	0.25	0.36
ACEclassComprehensive*Sex	0.04	0.23
Age centered*ACEclassNeglect*Sex	−0.28*	−0.21
Age centered*ACEclassAbuse*Sex	−0.01	−0.01
Age centered*ACEclassAbuse & Household Dysfunction*Sex	−0.13	−0.17
Age centered*ACEclassComprehensive*Sex	−0.04	−0.10

Note. [b] Model adjusted for time-varying body mass index (BMI).
Sex coded as Women = 0, Men = 1; Race coded as White = 0, AA = 1; Poverty Status: Above = 0, below = 1; Referent Class = Minimal Exposure. Age centered at 30.

Table 4
Simple effects of hsCRP mixed effects regression (n = 1530).

		Minimal Exposure		Neglect	
Sex	Age	Intercept	Slope	Intercept	Slope
Women	30	1.17***	0.24***	0.80***	0.42***
Women	40	1.37***	0.16***	1.18***	0.33***
Women	50	1.49***	0.08*	1.47***	0.25**
Women	60	1.53***	0.00	1.68***	0.17
Women	70	1.48***	−0.09	1.81***	0.09
Men	30	0.71***	0.31***	0.98***	0.20*
Men	40	0.98***	0.22***	1.14***	0.11
Men	50	1.16***	0.14***	1.21***	0.03
Men	60	1.26***	0.06	1.20***	−0.05
Men	70	1.28***	−0.02	1.11***	−0.13

Note. hsCRP was log-transformed prior to analyses.

may have differential effects based on timing, chronicity, severity, and ACE type, and cannot be captured by examining individual ACEs or a cumulative risk score (McLaughlin et al., 2021). The ACE classes we identified in the current study highlight the importance of this approach and offer new insights into early adverse experiences. For example, we expected experiences of household dysfunction (e.g., caregiver substance use) to be closely linked with deprivation among participants in our sample. While we did identify a "Comprehensive" class in which participants reported abuse, neglect, and household dysfunction, we also identified a distinct "Neglect" class in which participants did not report significant threat or unpredictability, and an "Abuse & Household Dysfunction" class in which participants did not report deprivation (i.e., neglect). The presence or absence of neglect in these classes suggests that early experiences fall into distinct patterns that should be considered in future studies. Additional research using an LCA approach with other cohorts will provide important insights into dimensions of early experiences and patterns of ACE clustering.

Results of this study suggest that the effects of ACEs on log-linear increases in CRP and SII across adulthood may vary by sex and race. Specifically, the effects of neglect exposure on CRP varied by sex, such that among women, log-linear increases over time were greater in the "Neglect" class compared to the "Minimal Exposure" class, but smaller among men (e.g., "Neglect" class compared to the "Minimal Exposure" class). These results are consistent with limited findings from past studies, which suggest that the effects of ACEs on inflammation may be stronger among women. For example, in a prospective study of young adults, history of maltreatment was associated with elevated CRP, but only among females (Osborn & Widom, 2020). In a study of undergraduate students, history of family dysfunction was associated with CRP levels, and this association was stronger among females (Kim et al., 2019).

While results of our study suggest ACEs explain 9 % of the variance in SII trajectories, the direction of effects was inconsistent with our hypothesis that ACEs would contribute to increased SII levels over time. For most of the subgroups of race by ACE class in this study, SII decreased over the middle adult lifespan. Past studies of SII have largely been cross-sectional in design, and even among longitudinal studies, SII has been examined at only a single time point (Del Brutto et al., 2023; Lai et al., 2023). To our knowledge, our study is the first to examine trajectories of SII across decades of adulthood. Thus, although our finding of decreased SII trajectories over time was unexpected, it may offer important insight into functioning of the immune system over time. Studies of other inflammatory biomarkers suggest that increased stress may suppress immune system functioning over time (Segerstrom & Miller, 2004), and thus the rate of decrease in SII may be an important indicator of immune functioning, above and beyond a single SII measure. Replication in other longitudinal studies is needed to improve understanding and aid interpretation of our SII findings.

Results of our study suggest that the effects of ACEs on SII also varied by race. Among White adults at age 30, those in the "Abuse" and "Abuse & Household Dysfunction" had higher SII levels compared to individuals in the "Minimal Exposure" class. However, among Black individuals at age 30, these abuse-related classes were associated with lower SII compared to those with Minimal Exposure. The effects of abuse-related classes on patterns of SII also differed by race over time. Black participants in the "Abuse" class had minimal changes in SII over time, compared to significant decreases at age 30 and 40 among Black participants in the "Minimal Exposure" class. Among White participants, those in the "Abuse" class had a decrease in SII at age 30 and 40, followed by minimal change in later adulthood, whereas those in the "Minimal Exposure" class had minimal change in SII across middle adulthood, followed by significant increases in SII in later adulthood. Again, these findings support evidence suggesting that exposure to excess or extreme stressors may also suppress the physiological stress response system and contribute to lower indicators of inflammation over time (Seiler et al., 2020). Thus, associations between abuse-related ACE classes and lower SII in Black individuals may indicate a suppressed immune system, rather than lower levels of stress. Alternatively, these associations could reflect the presence of unmeasured protective factors that may buffer the effects on ACEs on inflammation, such as education, self-esteem, secure attachment, family cohesion, social support, religiosity, and supportive communities (Meng et al., 2018). The critical role of these and other protective factors should be considered in future studies of ACEs, inflammation, and health.

Given known relationships between ACEs, obesity, and inflammation, we conducted additional analyses adjusting for time-varying BMI. Our results were largely unchanged, suggesting that ACE class may have a unique effect on inflammation that persists above and beyond the effects of BMI. However, our findings related to CRP and sex were no longer significant after adjusting for time-varying BMI, which suggests that BMI may explain the impact of ACE class on CRP changes, especially as it relates to sex differences. However, in our study, there was no direct relationship between ACE class and BMI. It is also unclear why adjusting for time-varying BMI altered the effect of ACE class on CRP, but not SII.

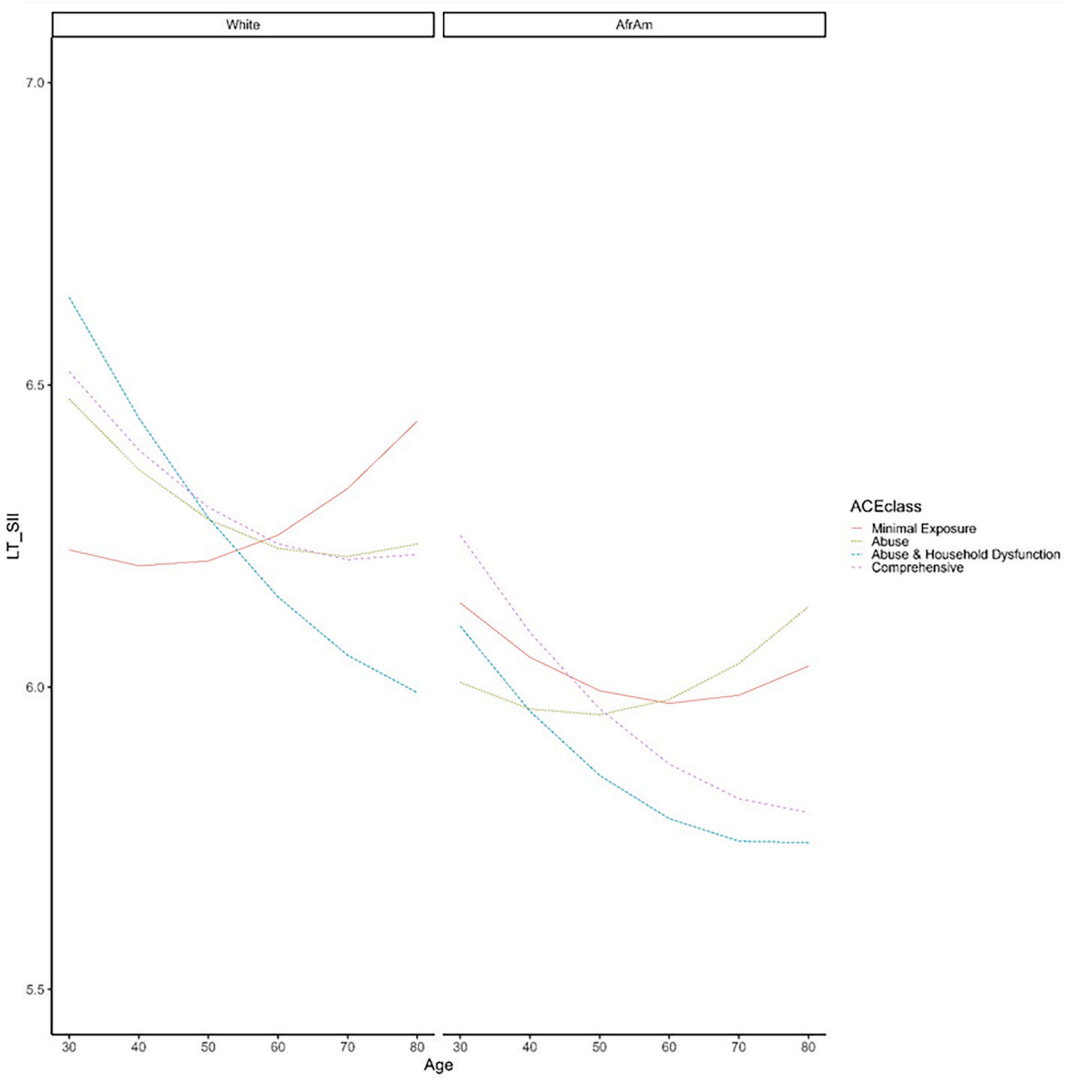

Fig. 3. Changes in SII by race and ACE class.

Future studies evaluating a potential mediating role of BMI may provide important insights into the association between ACEs and inflammatory trajectories.

In this study, the "Neglect" class was associated with effects on CRP, while the "Comprehensive," "Abuse," and "Abuse & Household Dysfunction" classes were associated with effects on SII. It is unclear whether this reflects differential effects of "threat" (i.e. abuse) and "deprivation" (i.e. neglect) related exposures, as seen in other studies (Baumeister et al., 2016; Brown et al., 2021), or the influence of other unmeasured factors, such as health behaviors. It is possible that the SII also provides a more robust evaluation of immune processes, and thus is an advantage over CRP, a single measure. The SII may also offer advantages over other comprehensive measures of inflammation, such as allostatic load indices. While allostatic load indices often include ten or more biomarkers (Beese et al., 2022), the SII integrates only three biomarkers, and therefore may be a more feasible and cost-effective approach for use in research, particularly in longitudinal studies. Future research comparing the SII to traditional allostatic load indices will provide information on the usefulness of incorporating the SII into future ACEs studies.

4.1. Strengths and limitations

Results of this study are limited by the use of retrospective measures of childhood adversity, which may be subject to recall or response bias. However, a very large body of evidence suggests that retrospective reporting of ACEs is still highly valuable for understanding effects of childhood adversity (Reuben et al., 2016). This study is also strengthened by our use of Latent Class Analysis to examine classes of ACE exposure, which provides new insights into co-occurring ACEs and their combined effect on inflammation. However, we were unable to assess the timing or severity of ACEs experienced, which is also likely to have an important effect on the way adverse experiences are biologically embedded (Hambrick et al., 2019; Merrick et al., 2020). Recent evidence also suggests that some traditionally measured ACEs, such parental separation/divorce, may not be predictive of poor child outcomes (Finkelhor, 2020). We were also unable to account for protective factors in childhood that may have buffered the effects of ACEs on inflammation.

Our analysis was also limited by the availability of biomarkers in the HANDLS dataset. Based on available markers, we calculated the SII, as recent research demonstrates significant associations between SII and cardiovascular disease (Xia et al., 2023; Ye et al., 2022). However, the SII has not been widely used as a proxy for systemic inflammation, and further research is needed to understand the relationship between SII and social measures, such as ACEs. Additionally, while CRP was available in the dataset, other commonly measured inflammatory biomarkers (e.g. IL-6, TNF-α) were not collected longitudinally in HANDLS study.

Table 5
Log-transformed SII Mixed Effects Regression (n = 1528).

	Unadjusted Model	Adjusted Model[b]
Intercept	6.27***	6.17**
Age centered	−0.04	−0.05
ACEclassNeglect	0.08	0.08
ACEclassAbuse	0.25*	0.27*
ACEclassAbuse & Household Dysfunction	0.42**	0.43**
ACEclassComprehensive	0.29*	0.27*
Race	−0.09	−0.09
Sex	−0.13***	−0.12***
Poverty Status	0.05	0.05*
Age centered^2	0.02*	0.02*
BMI	--	0.00*
Age centered*ACEclassNeglect	0.01	0.02
Age centered*ACEclassAbuse	−0.09*	−0.10*
Age centered*ACEclassAbuse & Household Dysfunction	−0.17*	−0.18*
Age centered*ACEclassComprehensive	−0.10*	−0.10*
Age centered*Race	−0.06*	−0.06*
ACEclassNeglect*Race	−0.19	−0.20
ACEclassAbuse*Race	−0.38*	−0.40*
ACEclassAbuse & Household Dysfunction*Race	−0.46*	−0.46*
ACEclassComprehensive*Race	−0.18	−0.17
Age centered*ACEclassNeglect*Race	−0.02	−0.02
Age centered*ACEclassAbuse*Race	0.14*	0.14*
Age centered*ACEclassAbuse & Household Dysfunction*Race	0.12	0.13
Age centered*ACEclassComprehensive*Race	0.03	0.03

Note. [b] Model adjusted for time-varying body mass index (BMI).
Sex coded as Women = 0, Men = 1; Race coded as White = 0, AA = 1; Poverty Status: Above = 0, below = 1; Referent Class = minimal exposure. Age centered at 30.

Table 6
Simple effects of SII mixed effects regression (n = 1528).

		Minimal Exposure		Abuse	
Race	Age	Intercept	Slope	Intercept	Slope
White	30	6.27***	−0.04	6.51***	−0.13**
White	40	6.24***	−0.01	6.40***	−0.10*
White	50	6.25***	0.03	6.32***	−0.07
White	60	6.29***	0.06*	6.27***	−0.03
White	70	6.37***	0.09*	6.25***	0.00
African American	30	6.18***	−0.11**	6.05***	−0.06
African American	40	6.09***	−0.07*	6.00***	−0.03
African American	50	6.03***	−0.04	5.99***	0.01
African American	60	6.01***	0	6.02***	0.04
African American	70	6.02***	0.03	6.08***	0.08

Note. SII, systemic immune-inflammation index.

Future research using a broader scope of inflammatory markers will provide new and important insights regarding the effects of ACEs on inflammation across adulthood.

We did not find significant interactions by poverty status. However, poverty was measured only at the time of study entry and therefore may not be reflective of socioeconomic status during childhood or later in adulthood, which may have an effect on outcomes over time. Further, while poverty is an important risk factor for ACEs, ACEs occur across all income levels (Camacho & Henderson, 2022). We were also unable to examine four-way interactions between variables, due to small cell sizes, and thus we were unable to examine moderating factors in more depth.

Our results are also limited by study attrition and missing data. Among active participants in the parent HANDLS study, the attrition rate over the 15-year period from baseline (n = 2,707) to wave 2 (n = 2,147) was approximately 20 %. This is common in large epidemiological studies, especially with aging populations (Rhodes, 2005). A significant proportion of participants in Wave 2 (28 %) also did not receive the ACEs questionnaire due to time constraints, and this missing ACE data differed by race and poverty status. We also found differences by race and poverty status in missing inflammatory biomarker data, but these were driven by differences at baseline. Findings of the current study should be interpreted in light of these considerations.

Finally, the youngest HANDLS participants were age 30, and thus we do not have information on inflammatory biomarkers during adolescence or young adulthood. These missed periods may explain some of our unexpected findings. For instance, it is possible that biological embedding of ACEs occurred earlier than age 30, with SII increasing significantly during adolescence and young adulthood, therefore resulting in an elevated intercept in our sample (e.g., elevated SII at age 30 particularly in White participants). However, without this data, it is not possible to determine whether racial differences in SII at age 30 are the result of differences in inflammatory responses, such as hypo- versus hyper-active immune responses. Future studies starting at younger ages may provide important insights into trajectories of inflammation and the effects of ACEs over time.

4.2. *Implications and future directions*

Improved understanding of the association between ACEs and lifelong inflammation has important implications for health. For example, among participants in the English Longitudinal Study of Ageing (N = 4,382), elevated CRP levels mediated an association between ACEs and depressive symptoms, suggesting inflammation may be a psychobiological mechanism underlying the association between ACEs and mental health (Iob et al., 2020). In the current study, we chose to examine CRP and SII based on their established links with health outcomes, including cardiovascular disease (Xia et al., 2023; Ye et al., 2022). Although replication in other samples is needed, the clinical importance of SII in predicting cardiovascular health suggests that addressing ACEs should continue to be a critical public health initiative.

Greater insight into the dynamic and co-occurring nature of ACEs is also crucial for targeting intervention efforts and ultimately reducing health inequities related to childhood adversity. For example, understanding both the cumulative and differential effects of ACEs on health will allow for more specific ACE screening and intervention based on an individuals' unique risk and protective factors. Future ACEs research could also be expanded to include other childhood stressors, such as exposure to community violence, peer victimization, and direct or vicarious experiences of racial discrimination (Heard-Garris et al., 2018; Karatekin & Hill, 2019; Lee et al., 2020; SmithBattle et al., 2022). Sex or gender-specific effects also require investigation to effectively develop and target interventions.

5. Conclusion

This study contributes to a growing body of evidence demonstrating the associations between ACEs and inflammation. Our findings provide important novel insights into clustering of ACE exposure in a cohort that was purposively sampled for individuals with racially and economically marginalized backgrounds. Results suggest that classes of ACE exposure are associated with CRP and SII over time, but relationships may vary based on race and sex. These findings lay important groundwork for future longitudinal studies, including those with younger participants and multiple inflammatory biomarkers, which may provide important insights into the effects of ACEs and inflammation on health over time.

CRediT authorship contribution statement

Eileen M. Condon: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Ana I. Maldonado:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Michele K. Evans:** Writing – review & editing, Investigation. **Alan B. Zonderman:** Writing – review & editing, Supervision, Investigation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.06.018.

Data availability

Data will be made available on request.

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Appendix A. Adverse Childhood Experiences Questionnaire Items

ACE Subtype	Prompts & Items	Response Options
Emotional Neglect	*While you were growing up before you turned 18, is it true…* • That there was someone in your family who helped you feel important or special?* • That you felt loved?* • That people in your family looked out for each other?* • That people in your family felt close to each other?* • That your family was a source of strength and support?*	Never true / Rarely true / Sometimes true / Often true / Very often true
Physical Neglect	*While you were growing up before you turned 18, is it true…* • That you didn't have enough to eat? • That you knew there was someone to take care of you and protect you?* • That your parents were too drunk or high to take care of the family? • That you had to wear dirty clothes? • That there was someone to take you to the doctor if you needed it?*	Never true / Rarely true / Sometimes true / Often true / Very often true
Psychological Abuse	*How often did your parents, step-parents, or other adults living in your home…* • Swear at, insult, or put you down? • Threaten to hit you or throw things at you (but didn't actually do it)?	Never / Once or twice / Sometimes / Often / Very often
Physical Abuse	*How often did your parents, step-parents, or other adults living in your home…* • Hit you so hard that you had marks or were injured?	Never / Once or twice / Sometimes / Often / Very often
Sexual Abuse	*Before you were 18 years old, did an adult or older relative, a family friend, or a stranger ever…* • Touch or fondle you in a sexual way? • Have you touch their body in a sexual way? • Attempt oral, anal, or vaginal intercourse with you? • Actually have oral, anal, or vaginal intercourse with you?	Yes / No

Household Incarceration	*Before you were 18 years old….* • Did a household member go to prison?	Yes / No
Parental Separation/Divorce	*Before you were 18 years old….* • Were your parents ever separated or divorced?	Yes / No
Household Substance Use	*Before you were 18 years old….* • Did you live with anyone who used street drugs?	Yes / No
Household Mental Illness	*Before you were 18 years old….* • Was a household member depressed or mentally ill? • Did a household member attempt suicide?	Yes / No
Witnessing Intimate Partner Violence	*How often did your father or stepfather or your mother's boyfriend* • Push your mother, or grab her, slap her, or throw something at her? • Kick your mother, or bite her, hit her with fists, or hit her with something hard? • Repeatedly hit your mother for at least a few minutes? • Threaten your mother with a knife or gun, or use a knife or gun to hurt her?	Never / Once or twice / Sometimes / Often / Very often

Note. Emotional Neglect and Physical Neglect items are drawn from the Childhood Trauma Questionnaire Short Form (Bernstein et al., 1998). All others are drawn from Wave 2 of the Adverse Childhood Experiences study (Corso et al., 2008; Felitti et al., 1998).

*Indicates item was reverse scored