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Applying Cumulative Disadvantage Theory to Understand Adversity across the Lifespan and Later Life Inflammation

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ABSTRACT

The theoretical perspectives of allostatic load and cumulative disadvantage can be used in tandem to consider the impact accumulated early and adult adversity has on health. I tested associations between early life and adulthood adversity on inflammation in the Einstein Aging Study (*N* = 205, Age Range = 70 – 89) with race as a moderator. Using regression and correlational models, significant effects were seen for adult life adversity and IL-6 in addition to TNF- α. Significant interactions were also seen for race modified association models. Contrary to initial hypotheses, increased early life and adult adversity were found to be related to lower levels of IL-10 and TNF- α. Additionally, as adverse events increased for Black participants, levels of the circulating inflammatory cytokines IL-6 and TNF- α decreased; for White participants, levels of IL-6 and TNF- α remained stable. Levels of the circulating biomarker MIF were also seen to be reduced among Black participants. These nuances within the findings may be able to be explained through psychosocial protective factors, resilience, and differences between MIF and traditional cytokine activation.

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CHAPTER 1

Introduction

Redness, swelling, and pain are all examples of physiological reactions to wounds that were coined inflammation, as early as Ancient Rome (Cavaillon, 2021). Throughout history, this inflammatory response became well recognized as an indication of biological phenomena, rather than a disease (Turk, 1994). Inflammation is widely recognized as a necessary step in the healing process, however, experiencing chronic inflammation has been linked with negative health outcomes such as cardiovascular disease, diabetes, and arthritis (Pahwa et al., 2022). Although research has shown implications of inflammation on health, less is known about what increases the risk of chronic inflammation. Specifically, a major area which little modern research has addressed is the compounding effect of both early life and adulthood adversity. The theoretical perspectives of allostatic load and cumulative disadvantage can be used in tandem to consider the impact accumulated adversity has on health outcomes. As such, the overarching goal of this thesis is to fill in this research gap by looking into the associations between early life and adulthood adversity on inflammation. Given adversity may vary across race, I also aim to assess whether associations between early life and adulthood adversity on inflammation vary by Black and White individuals.

Theoretical Perspectives

Allostatic Load

Stress and adversity have strong connections with health and well-being. The effects of adverse life events linger and manifest themselves into detrimental physical consequences that can persist throughout the lifespan. This phenomenon of adversity “getting under the skin” uses the perspective that the interactions between an individual’s biological responses and physical

environment have a bidirectional relationship (McEwen et al., 2012). To cope with environmental adversities, the body must work tirelessly to maintain homeostasis; McEwen (1998) coined the term "allostasis" to refer to the internal fluctuation needed to meet external needs (McEwen & Stellar, 1998).

The accumulation of repeated adversities adds up overtime, contributing to allostatic load which can catalyze the adoption of destructive health behaviors as a coping mechanism - such as smoking, excessive drinking, and lack of nutritious diet (Gudi et al., 2020). Exposure to adversity can result in negative long-term biological changes due to allostatic overload, meaning that the environmental pressures have overwhelmed the body, and the individual is unable to cope (Gudi et al., 2020). Two criteria must be met for the biological response to be classified as allostatic overload: (1) the individual must be experiencing an identifiable adversity that taxes their coping skills beyond their capacities and (2) the individual must experience somatosensory consequences resulting from the adversity – such as fatigue, restless sleep, or irritability (Gudi et al., 2020). Allostatic load may suggest that the conglomeration of adversity throughout the lifespan will be related to elevated inflammation in older adulthood. The accumulation of this overload across the lifespan can be better understood by utilizing the theoretical framework posed in cumulative disadvantage theory (Ferraro et al., 2012; O'Rand, 1996).

Cumulative Disadvantage Theory

Cumulative disadvantage theory may help us to understand why both childhood and adulthood adversities may work together to inform levels of inflammation. Cumulative disadvantage theory emphasizes that inequalities faced early in life can accumulate and shape the trajectory of an individual's development over time (Ferraro et al., 2012; O'Rand, 1996). Moreover, disadvantages experienced early in life lead to further disadvantages experienced later

in life (Ferraro et al., 2012; O'Rand, 1996). For example, living in poverty may increase the likelihood of living in a food desert and eating unhealthily, and result in an increased risk of diabetes or obesity. In addition, facing adversity during adulthood – that is, adversity encountered after the age of eighteen – is also related to elevated levels of inflammatory cytokines (Baumeister et al., 2016; Hostinar et al., 2015).

Individuals who have experienced early life and adult adversity may have a cumulative disadvantage contributing to elevated levels of circulating inflammatory cytokines. The effects of cumulative disadvantage are not often recognized by biomedical and behavioral research. For instance, in lifespan research examining the associations between childhood adversity and health outcomes (e.g., Baumeister et al., 2016; Hostinar et al., 2015), researchers do not account for adulthood adversities (e.g., divorce, bereavement) that could potentially contribute to poorer health. Similarly, research on adulthood adversity often does not consider childhood adversity (e.g., Baumeister et al., 2016; Hostinar et al., 2015). The studies noted here emphasize that little research has investigated how the cumulative effect of both early life adversity and adult adversity is associated with dysregulation of the immune system. As is reviewed further below, dysregulation of the immune system can contribute to chronic low-grade elevation of inflammatory cytokine levels. As such, the current thesis will aim to test the associations between both childhood and adulthood adversity and inflammation marked by circulating cytokines.

The Effect of Chronic Inflammation on Health Outcomes

The innate immune system is equipped with specialized leukocytes that defend against non-specific pathogens (Sergerstrom & Miller, 2004). Sub-divisions of granulocytes, such as neutrophils and macrophages, circulate the bloodstream to terminate pathogens via phagocytosis.

This cascade of leukocytes and granulocytes in response to injury or infection can be categorized as inflammation. Inflammation can be detected by measuring biological markers circulating in the bloodstream. Biological markers, otherwise known as biomarkers, can be described as characteristics of an individual that give insight to biological, pathological, or pharmaceutical processes and can be measured objectively (Strimbu et al., 2010). Common biomarkers associated with elevated inflammation are IL-6, TNF- α, and C-reactive protein (CRP; Baumeister et al., 2016). These immune cells possess a distinct method of communication called cytokines. Cytokine molecules are released by macrophages to signal to the immune system that the site of infection or injury has been located, and more leukocytes are required to destroy the threat. Blood cells rush to the site of infection or injury, causing the affected individual to experience warmness, swelling, fever symptoms, or a slew of biological markers circulating throughout the blood. Clearly, in the presence of pathogens, the immune system initiates a momentary inflammatory response crucial to fighting harmful invaders. However, a prolonged immune response can lead to chronic inflammation (Baumeister et al., 2016; Pahwa et al., 2022; Strimbu et al., 2010).

Past research acknowledges the dangers of chronic inflammation. Chronic inflammation is recognized as a mechanism for allostatic load and poor health outcomes (McEwen & Stellar, 1998). Inflammation experienced over an extended duration of time can lead to tissue damage or the development of diseases (Pahwa et al., 2022). The risk for elevated or chronic inflammation increases with age and as such, older adults are disproportionally impacted by chronic inflammation-mediated diseases such as diabetes, cardiovascular diseases, and rheumatoid arthritis (Pahwa et al., 2022). Chronic elevation of inflammatory biomarkers is correlated with adversity experienced over time (Pahwa et al., 2022). The presence of acute or chronic

inflammation can be observed by detecting trace amounts of proinflammatory cytokine samples within blood samples. Given the host of outcomes associated with chronically elevated inflammation, further understanding of its mechanisms is required. Specifically, the main objective of this research is to examine the mechanism of lifetime adversity and its influence on inflammation.

Early Life Adversity

Importantly, both early life and adulthood adversity may be related to levels of inflammation in older adulthood. Previous research tends to compare participants who have solely had exposure to early life adversity or not (Andersen et al., 2022; Cunningham et al., 2022; Lee et al., 2023). Early life adversities are defined as exposure to environmental circumstances requiring adaptation (Lee et al., 2023). Commonly cited early life adversity includes circumstances such as neglect or exposure to abuse (physical, mental, sexual; Lee et al., 2023). Importantly, these early life adversities are considered early life because they occur prior to the age of eighteen and therefore encompass infancy, childhood, and adolescence (Merz et al., 2021).

Empirical evidence suggests that early life adversity is related to indicators of mental health like depression; findings revealed that early life adversity increased the odds of developing clinical depression by 20% (Lee et al., 2023). Moreover, experiencing adversity during childhood is related to chronically elevated levels of inflammatory cytokines in adulthood (Brown et al., 2021; Kiecolt-Glaser et al., 2018; Nusslock et al., 2016). Elevated levels of inflammatory cytokines such as IL-6, CRP, and TNF-α were seen among adults who had experienced adversities such as low socioeconomic status (SES), family instability, environmental toxins, and abuse during childhood (Brown et al., 2021; Kiecolt-Glaser et al.,

2018; Nusslock et al., 2016). This adversity experienced in childhood was related to increased immune dysfunction, sickness behaviors, and increased body mass index (BMI) later in adulthood (Brown et al., 2021; Kiecolt-Glaser et al., 2018; Nusslock et al., 2016). Notably, these studies do not take adulthood adversity into account, which may explain some association of elevated levels of inflammatory biomarkers seen in those who have experienced early life adversity. Furthermore, the impact of adulthood adversity in conjunction with early life adversity must be considered to gain a comprehensive understanding of the inflammatory response to adversity.

Adulthood Adversity

Similar to research on childhood adversity, research on adulthood adversity examines whether a person has experienced adversity within adulthood (Osborne et al, 2020; Rajasekera et al., 2021). For example, Osborne and colleagues (2020) link the pathological effects of adult adversity to cardiovascular disease, showing that there are various stressors such as marital strain, low income, and living in a high-crime area that can be considered adverse experiences that can heighten the likelihood of developing negative health outcomes. Moreover, the increased exposure to adversity was related to higher inflammation (Osborne et al., 2020). Articles such as these highlight the importance of adulthood adversities and their relation to the development of cardiovascular disease and inflammation; however, they fail to consider if early life adversities could be an additional factor contributing to the onset of this disease. Although several of the factors listed within this paper (e.g., low income, living in a high crime area) can be seen in both adulthood and early life, there is no explicit mention of adversities specific to early life that could influence the development of disease later in life. As such, there is a research gap in the

literature such that the influence of adversities experienced before the age of 18 are not being considered.

Race as a Moderator

In the National Institute of Aging (NIA) Health Disparities Research framework (e.g., Hill et al., 2015), race is considered a fundamental factor for consideration in research. Race may modify the strength of the relationship between the cumulative effect of childhood and adult adversity and the level of inflammatory cytokines. Specifically, inequity between races resulting from access to healthcare, economic stability, housing, public safety, and discrimination may inform associations between adversity and inflammation.

The weathering hypothesis may be leveraged to understand why race may inform associations between childhood and adulthood life adversity and inflammation. This hypothesis states that Black Americans experience higher rates of illness and disability as a response to systematic barriers and discrimination (Simons et al., 2020). Biological weathering has been applied to inflammation in minority samples; specifically, racial discrimination was related to elevated inflammation over time, which in turn, predicted chronic disease development (Simons et al., 2020). Other studies have also observed higher levels of inflammation in Black individuals compared to other racial groups. For example, Paalani and colleagues (2011) found that Black individuals displayed higher elevated levels of CRP and IL-6 compared to White individuals, and the authors discussed racial discrimination as a factor contributing to inflammatory diseases in Black individuals. Farmer and colleagues (2022) found that compared to White, Asian, and Hispanic people, Black individuals had higher levels of IL-6 and IL-1β. As such, utilizing race as a moderator will provide insight into the associations between being Black and having elevated levels of inflammation that could otherwise not have been explained without race as a moderator.

Current Study

Using data from the 2017-2018 wave of the Einstein Aging Study (EAS) – an ongoing National Institute of Health (NIH) funded project – this thesis intends to examine compounding adversity and its association with circulating inflammatory cytokines. This research takes a cumulative disadvantage theoretical perspective that childhood adversity and adulthood adversity do not exist in a vacuum but instead may accumulate over the lifespan to inform health. Additionally, the results of this research will provide inference to the value of retrospective self-report data provided by the Stress and Adversity Inventory (STRAIN). Given aforementioned research on childhood or adulthood adversity, it is hypothesized that the compounding adversities from both early life and adulthood contribute to higher levels of circulating inflammatory cytokines. Given previous empirical associations with race and inflammation, it is also hypothesized that higher levels of inflammatory cytokines will be observed in Black individuals compared to White individuals.

CHAPTER 2

Methods

Procedure

The initial goal of the Einstein Aging Study (EAS) was to better understand cognitive and brain aging over time. The Albert Einstein College of Medicine recruited 298 participants aged 70 and older from the Bronx, NY. Approximately half (48%) of the participants were White; 39% were Black. Additionally, 65% of the participants identified as women. Eligibility criteria for the EAS included being able to speak English, permanent residency in Bronx County, New York City, being able to walk, and being 70 years old or above (Zhaoyang et al., 2022). After completing eligibility criteria through a phone screening and providing consent, participants were invited to a research clinic to complete surveys to assess demographics and standard psychosocial questionnaires, to complete the Stress and Adversity Inventory (STRAIN), and to undergo a neuropsychological battery to assess cognitive function and the first of two blood draws. They also received ecological momentary assessment (EMA) training on smartphones provided by the study team. Following this clinic visit, they engaged in the EMA testing period for 14 consecutive days. Upon completion, participants returned to the clinic to return smartphones and obtain a second blood draw. Compensation of $160 was distributed to participants who completed all data collection. Information about participants can be found in Table 2.1.

Measures

Inflammation

Participants obtained two blood draws before and after the 14-day EMA. Pre-EMA and post-EMA inflammatory biomarkers such as Interleukin (IL)-1β, IL-4, IL-6, IL-8, IL-10, C-

reactive protein (CRP), Tumor necrosis factor alpha (TNF-α), Macrophage migration inhibition factor (MIF), and Soluble urokinase plasminogen activator receptor (SuPAR) were assessed using the two blood samples. Certified phlebotomists collected the pre-EMA blood draw and post-EMA blood draw between the hours of 7:00 am and 11:00 am at the Albert Einstein College of Medicine where 5mL of blood were collected to assess basal and stimulated cytokines and CRP. Basal cytokines and CRP were centrifuged at 1500g for 15 minutes under standard conditions. Stimulated cytokines and CRP were exposed to bacterial lipopolysaccharide followed by centrifuge at 1500g for 15 minutes.

Stress and Adversity Inventory (STRAIN)

The STRAIN is a retrospective survey instrument that measures participant adversity over the lifetime, rather than one specific duration of time (Slavich et al., 2018; Slavich et al., 2019). The STRAIN measures acute and chronic stressors to assess cumulative adversity throughout the lifespan to observe the impact of stress on health. Frequency, duration, and intensity of stressors were evaluated by the STRAIN including stressors faced before the age of 18 and in adulthood. Participants took the STRAIN online through a self-administered survey containing approximately 220 questions, which was then broken down into 455 unique items.

Primary questions were used to determine the stressor's frequency; if the event occurred 1, 5-10, times, etc. Duration was assessed; if the event that occurred lasted a course of 0-3 months, 3-6 months, 6-12 months, 1-2 years, 2-5 years, or over 5 years. The approximate time frame was measured by assessing when the most severe period of the stressor happened in the individual's life; 1 month ago, 1 year ago, etc. Lastly, the perceived threat of the stressor was evaluated from slightly to extreme. Early adversity was assessed with questions that asked, "before the age of eighteen…"; items were summed so higher scores represented higher early life

adversity. Similarly, for adulthood adversity, items were summed so higher scores represented higher adulthood adversity.

Race

Participants were asked, "what is your race"? For the current study, race categories included 0 (*White*) and 1 (*Black*). Other race options included Hispanic White, Hispanic Black, and Asian. See Table 2.2 for more information of racial break-up.

Table 2.1

Descriptive Demographic Information

Sample Demographics	**N**	**Mean or %**	**SD**	**Range**
Age	205	75.9	4.34	70 - 89
BMI	205	29.4	6.06	18.6 - 65.0
Gender (female)	137	66.8%		
Gender (male)	68	33.2%		
MCI (no)	146	71.2%		
MCI (yes)	59	28.8%		
Early Life Adversity	205	2.68	3.24	0 - 24
Adult Life Adversity	205	19.2	10.5	1 - 64

Table 2.2

Race & Ethnicity Descriptive Information

Race & Ethnicity	**N**	**%**
White	89	43.4
Black	86	42.0
Hispanic White	23	11.2
Hispanic Black	4	2.00
Asian	2	1.00

Covariates

Age, body mass index (BMI), gender (0 = *male,* 1 = *female*), and mild cognitive impairment (MCI; 0 = *no MCI,* 1 = *MCI*) were included as covariates in secondary models.

Analytic Plan

Before data analysis, EAS cytokine biomarker sample data were cleaned and transformed, and composites of the pre-EMA and post-EMA biomarkers were calculated for each biomarker. All transformations and analyses were completed using SPSS Statistics version 29. Missing data labeled as "NA" was coded as "." so that SPSS could recognize missing as missing. Next, all biomarkers were log transformed to assist with positive skewed variables. Then pre-EMA and post-EMA data were averaged to compute the composite. Then, outliers were identified and not included in the final data set via winsorization. Winsorization is a common practice for inflammatory data because it reduces the effect of outliers and captures a more robust representation of the sample.

Primary Data Analysis

To determine the relationship between early life adversity, adulthood adversity, and inflammation levels, I ran correlations in SPSS. Specifically, early life adversity, adulthood adversity, IL-1b, IL-4, IL-6, IL-8, IL-10, CRP, TNF-a, MIF, and SuPAR were analyzed. To test the relationship race had on relation to these variables, additional correlations were run. To test whether early life and adulthood adversity both informed inflammatory biomarker levels, I ran multiple linear regressions with each inflammatory biomarker (IL-1b, IL-4, IL-6, IL-8, IL-10, CRP, TNF-a, MIF, and SuPAR) regressed on early life and adulthood adversity simultaneously. P-value at the 0.05 level was considered significant. Within the regression, the unstandardized coefficient beta (B) represented the slope. Then, to test whether race modified associations between early life and adulthood adversity on inflammation, I added an interaction term between

early life adversity and race, and adulthood adversity and race within the models. I then repeated these steps with the inclusion of covariates.

CHAPTER 3

Results

The number of adverse experiences faced during early life and adulthood was recorded numerically, indicated by the variables listed in Table 3.1. Means and standard deviations of inflammatory biomarkers are additionally noted in Table 3.1.

Table 3.1 Descriptive Statistics for Relevant Variables

	N	Mean	SD
IL-1B	186	1.09	0.05
IL-4	184	1.02	0.04
IL-6	187	2.63	2.69
IL-8	185	5.89	2.73
IL-10	187	1.29	0.21
TNF- α	187	3.15	0.88
CRP	183	4.92	4.15
SuPAR	163	4.71	1.24
MIF	163	199259.3	80735.3
Early Life Adversity	205	2.68	3.24
Adult Adversity	205	19.2	10.5

Note. IL = Inter-Leukin. TNF = Tumor Necrosis Factor. CRP = C-Reactive Protien. SuPAR = soluble urokinase Plasminogen Activator Receptor. MIF = Macrophage migration inhibitory factor. Cytokines were winsorized.

There was a significant correlation between early life adversity and adult adversity, $r(205) = .41$, $p < .001$, suggesting that more early life adversity was associated with more adult adversity, in this sample. Early life adversity was related to race, such that being Black was related to higher scores in early life adversity, $r(204) = 0.15$, $p = .03$. The inflammatory cytokine IL-8 was correlated with early life adversity, $r(185) = 0.05$, $p = .04$, suggesting that experiencing more adverse events before the age of 18 was related to elevated levels of circulating IL-8. Additionally, there was a significant correlation between the anti-inflammatory cytokine IL-10 and adult adversity, $r(187) = -0.06$, $p = .02$. According to these results, it can be inferred that there is an association between facing adversity after the age of 18 and decreased levels of IL-10,

and vice versa. In addition, both early life adversity and adult adversity were correlated with the inflammatory cytokine TNF-α, $r(187) = -0.16$, $p = .03$ and $r(187) = -0.17$, $p = .02$, respectively. As such, experiencing more adverse events before or after the age of 18 was associated with decreased levels of TNF- α and vice versa. Lastly, there was a significant correlation between race and IL-10, $r(187) = -0.15$, $p = .04$, suggesting that being Black was related to lower levels of the anti-inflammatory cytokine IL-10. Additional correlations are shown in Table 3.2.

Table 3.2 Early Life and Adulthood Adversity Biomarker Correlational Analysis (r)

	1.	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**	**11.**	**12.**
1. Early Adversity	-											
2. Adult Adversity	.41**	-										
3. Black race	.15*	.08	-									
4. IL1-B	.09	.02	.01	-								
5. IL-4	.003	-.04	.009	.35**	-							
6. IL-6	.001	.02	.03	.22**	.37*	-						
7. IL-8	.05	-.03	-.01	.12	.09	.16*	-					
8. IL-10	-0.03	-.06	-.15*	.15*	.14*	.07	.12	-				
9. TNF-A	-0.16*	-.17*	-.03	.23**	.31**	.25**	.17*	.23**	-			
10. CRP	.01	-.09	.14	.17*	.02	.11	-.004	-.04	.04	-		
11. SuPAR	-0.06	-.12	.02	.04	-.01	.27**	.15	.22**	.37**	.18*	-	
12. MIF	.07	-.13	.09	.29**	.03	-.04	.11	-.09	.09	.16	-.07	-

Note. IL = Inter-Leukin. TNF = Tumor Necrosis Factor. CRP = C-Reactive Protien. SuPAR = soluble urokinase Plasminogen Activator Receptor. MIF = Macrophage migration inhibitory factor. Cytokines were winsorized.

* < .05, ** p < .01

Primary Analyses

Each inflammatory biomarker was regressed on early life adversity and adult adversity within the same model to account for the variance of each type of adversity. These models were run with and without the addition of covariates (age, BMI, gender, and MCI) and can be found in Table 3.6.

As noted in the un-adjusted models in Table 3.6, there is only one significant association that emerged. This association was between adult adversity and MIF, b = 0.03, p = 0.03, 95% CI: [-2789.38, -131.03]. This model, with only early life and adulthood adversity included, accounted for 4% of the variance in MIF, which was a marginally significant amount of variance in MIF, $F(158, 161) = 2.19$, p = .03. With the addition of the covariates within the model, the association between adult adversity and MIF remained marginally significant, b = -0.17, p = 0.06, 95% CI: [-2746.78, -91.98] (see Table 3.6). Unlike the correlational analyses -which yielded significant results for IL-8, IL-10, and TNF- α- the only significant interaction was between the biomarker MIF and adult adversity within the regression for both unadjusted and adjusted models. The standardized coefficient beta indicates the magnitude of the increase or decrease in the select biomarker. As such, for every unit increase in adult adversity, there was a decrease in MIF by .17.

Table 3.3 Early Life and Adulthood Adversity Biomarker Correlational Significance Values (P-value no covariates)

	Early Adversity	Adult Adversity
IL-1B	0.206	0.803
IL-4	0.965	0.58
IL-6	0.992	0.814
IL-8	0.518	0.66
IL-10	0.721	0.385
TNF- α	0.032*	0.022*
CRP	0.884	0.191
SuPAR	0.433	0.121
MIF	0.4	0.09

Note. IL = Inter-Leukin. TNF = Tumor Necrosis Factor. CRP = C-Reactive Protien. SuPAR = soluble urokinase Plasminogen Activator Receptor. MIF = Macrophage migration inhibitory factor. Cytokines were winsorized $\alpha^* < 0.05$.

Table 3.4 Early Life and Adulthood Adversity Biomarker Correlational Significance Values (P-value covariates included)

	Early Adversity	Adult Adversity
IL-1B	0.327	0.991
IL-4	0.952	0.257
IL-6	0.942	0.101
IL-8	0.037*	0.632
IL-10	0.399	0.017*
TNF- α	0.234	0.389
CRP	0.67	0.283
SuPAR	0.106	0.112
MIF	0.513	0.142

Note. IL = Inter-Leukin. TNF = Tumor Necrosis Factor. CRP = C-Reactive Protien. SuPAR = soluble urokinase Plasminogen Activator Receptor. MIF = Macrophage migration inhibitory factor. Cytokines were winsorized $\alpha^* < 0.05$.

Table 3.5 Early Life and Adulthood Adversity Biomarker Regression Significance Values (P-value unadjusted)

	Early Adversity	Adult Adversity
IL-1B	0.202	0.756
IL-4	0.763	0.53
IL-6	0.92	0.799
IL-8	0.368	0.444
IL-10	0.991	0.43
TNF- α	0.189	0.125
CRP	0.437	0.131
SuPAR	0.824	0.177
MIF	0.116	0.031*

Note. IL = Inter-Leukin. TNF = Tumor Necrosis Factor. CRP = C-Reactive Protien. SuPAR = soluble urokinase Plasminogen Activator Receptor. MIF = Macrophage migration inhibitory factor. Cytokines were winsorized α* < 0.05.

Table 3.6

Early Life and Adulthood Adversity Biomarker Regression Analysis

	IL-1B	IL-4	IL-6	IL-8	IL-10	TNF- α	CRP	SuPAR	MIF
Unadjusted Models	β	β	β	β	β	β	β	β	β
Early Life Adversity	0.20	0.76	0.92	0.37	0.99	0.19	0.44	0.82	0.12
Adult Adversity	0.76	0.53	0.79	0.44	0.43	0.13	0.13	0.18	0.03
R^2	0.009	0.002	0.001	0.006	0.03	0.04	0.03	0.02	0.04
Adjusted Models									
Early Life Adversity	0.09	0.02	-0.02	0.09	0.05	-0.10	0.02	-0.03	0.01
Adult Adversity	-0.06	-0.08	0.03	-0.08	-0.10	-0.12	-0.01	-0.01	-0.02
R^2	0.02	0.009	0.03	0.01	0.06	0.06	0.03	0.03	0.05

Note. IL = Inter-Leukin. TNF = Tumor Necrosis Factor. CRP = C-Reactive Protien. SuPAR = soluble urokinase Plasminogen Activator Receptor. MIF = Macrophage migration inhibitory factor. Cytokines were winsorized. R^2 = unadjusted variance. Adjusted models covary for age, body mass index (BMI), gender, and mild cognitive impairment (MCI).

Interaction Model Effects

Regression models testing whether race was a moderator included interactions between race and early life adversity and race and adulthood adversity in the same model. Unadjusted and adjusted models standardized beta coefficients and R^2 can be found in Table 3.6. Three significant interactions emerged.

First, in unadjusted models, there was a significant interaction between adult adversity and race to predict IL-6, b =-0.16, *p* = *.05*, 95% CI: [-0.88, 0.005]. Significance values are indicated in Table 3.7, only IL-6, IL-10, and TNF- α are represented within the table due to these biomarkers producing the only significant interactions within this model. After including covariates, this interaction remained statistically significant, b = -0.17, *p* = .05, 95% CI: [-0.91, -0.009]. To probe this interaction, plot points and slopes were extrapolated, and this interaction was illustrated in Figure 3. 1. For Black participants, a steep trend line with a negative slope can be seen. This suggests that for Black participants, as adult adversity increases, IL-6 decreases. Conversely, for White participants, a relatively flat trend line with a slightly positive slope can be seen. This suggests as adult adversity increases, IL-6 also increases in White participants. Second, in unadjusted models, there was a significant interaction between adult adversity and race to predict IL-10, b = 0.16, *p* = .05, 95% CI: [0.001, 0.07]. After the inclusion of covariates, however, this interaction was no longer significant, b = 0.13, *p* = 0.10, 95% CI: [-0.006, 0.00]. Finally, in covariate adjusted models, there was a significant interaction with adult adversity and race to predict TNF- α, b = -0.16, *p* = .04, 95% CI: [-0.29, -0.004]. Figure 3.2 plots the interaction. For Black participants, a negative trend line that decreases can be seen. This suggests that for Black participants, as adult adversity increases, IL-6 decreases. Conversely, for White participants, a flat trend line with a slightly negative trend can be seen. This suggests as adult adversity increases, there is no significant change in IL-6 in White participants.

Table 3.6

Early Life and Adulthood Adversity Moderated by Race on Biomarker Regression

	IL-1B	IL-4	IL-6	IL-8	IL-10	TNF-α	CRP	SuPAR	MIF
Unadjusted Models	β	β	β	β	β	β	β	β	β
Early Life Adversity	.16	.04	.02	.08	-.01	-.08	.04	-.01	.13
Adult Adversity	-.01	-.04	.05	-.06	-.10	-.09	-.13	-.10	-.18
Race	-.01	-.007	-.009	-.02	-.11	-.04	.15	-.02	.08
Early Life*Race	.03	-.01	-.03	.05	.05	-.03	.03	-.06	-.08
Adult Adversity*Race	-.11	-.08	-.16	-.08	.16	-.13	-.01	-.08	.03
R^2	0.02	0.009	0.03	0.01	0.06	0.06	0.03	0.03	0.05
Adjusted Models									
Early Life Adversity	.11	.04	.01	.09	.01	-.08	.02	-.02	.12
Adult Adversity	-.04	-.06	.06	-.07	-.13	-.08	-.12	-.09	-.17
Race	-.06	-.05	-.01	-.03	-.12	-.02	.12	-.01	.07
Early Life*Race	.03	-.02	-.03	.04	.09	-.02	.01	-.02	.01
Adult Adversity*Race	-.12	-.10	-.17	-.08	.13	-.16	-.02	-.10	-.07
R^2	0.009	0.003	0.04	0.02	0.19	0.12	0.09	0.09	0.07

Note. IL = Inter-Leukin. TNF = Tumor Necrosis Factor. CRP = C-Reactive Protien. SuPAR = soluble urokinase Plasminogen Activator Receptor. MIF = Macrophage migration inhibitory factor. Cytokines were winsorized. R^2 = unadjusted variance. Adjusted models covary for age, body mass index (BMI), gender, and mild cognitive impairment (MCI).

Table 3.7 Early Life and Adulthood Adversity Biomarker Regression Significance Values (P-value adjusted)

	Early Adversity	Adult Adversity
IL-6	0.837	0.053*
IL-10	0.518	0.046*
TNF- α	0.189	0.040*

Note. IL = Inter-Leukin. TNF = Tumor Necrosis Factor. CRP = C-Reactive Protien. SuPAR = soluble urokinase Plasminogen Activator Receptor. MIF = Macrophage migration inhibitory factor. Cytokines were winsorized $\alpha^* < 0.05$.

Figure 3.1
IL-6 and Adult Adversity for Black and White Participants

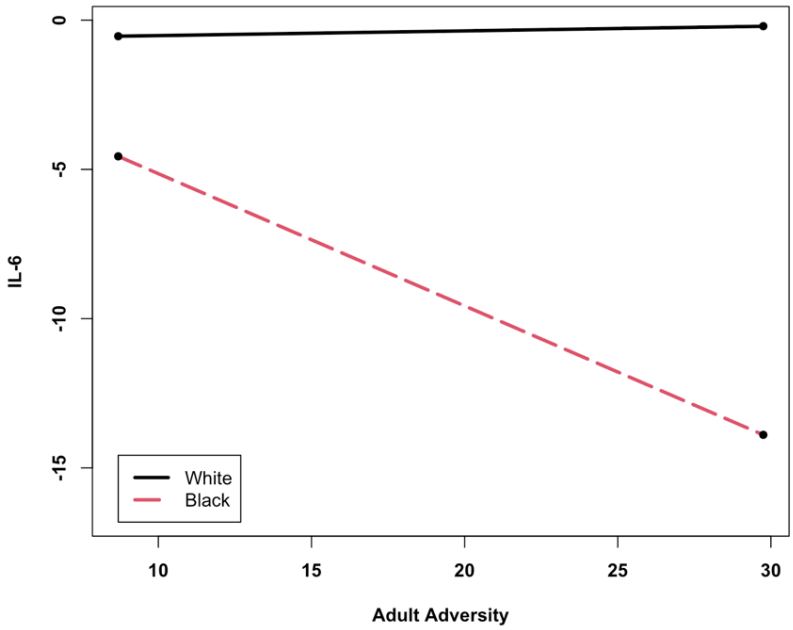
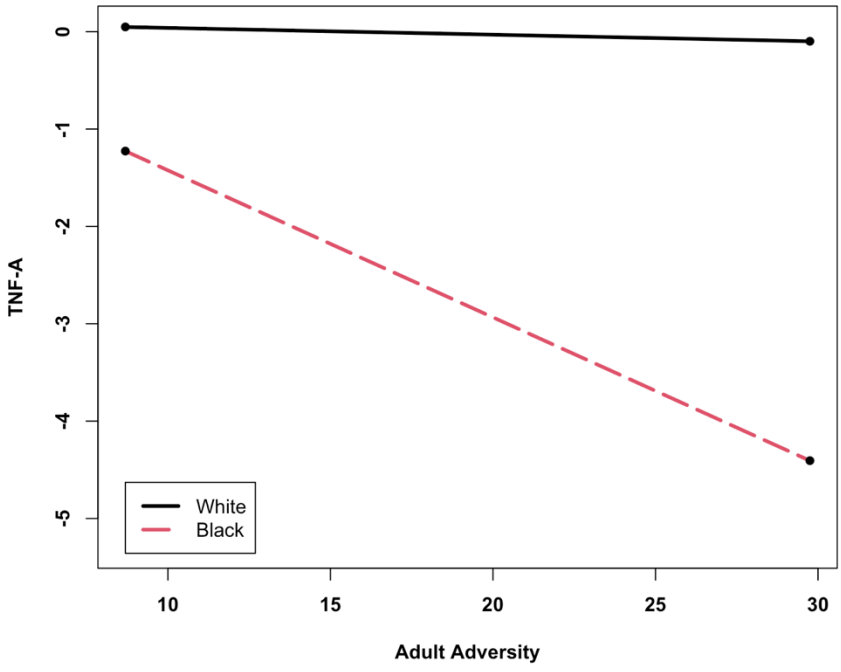


Figure 3.2
TNF- α and Adult Adversity for Black and White Participants



CHAPTER 4

Discussion

The current study aimed to assess the hypothesis that the compounding adversities from both early life and adulthood contribute to elevated levels of circulating inflammatory cytokines. I hypothesized that higher levels of cytokines would be observed in Black participants compared to White participants. I found that MIF decreased as adverse adulthood experiences increased, in addition to significant interactions with race and IL-6 and TNF- α. The current study adds to the literature by providing insight to the unique association between life time adversity and decreased inflammatory cytokines in Black individuals. Additionally, this research adds to the body of knowledge regarding the protein MIF and its relevancy as an indication of inflammation.

Correlational Analyses

The current study found that experiencing adversity before the age of 18 is associated with facing adversity later in life as well. Moreover, facing adverse events before the age of 18 is associated with increased circulating IL-8 production. This association was in line with hypotheses and previous literature (Brown et al., 2021; Kiecolt-Glaser et al., 2018; Nusslock et al., 2016) that more early life adversity would be related to increased levels of inflammation. Adult adversity was associated with lower levels of cytokine production.

Interestingly, a negative correlation was seen for both early life and adult adversity, suggesting that facing adverse events during early life in addition to adulthood was associated with lower levels of TNF- α. These findings do not support the proposed hypothesis that the cumulative disadvantage is related to elevated cytokine production. In essence, an inverse relationship between lifetime adversity and cytokine production was observed through correlational analysis which yielded unforeseen results.

Notably, increased early and adult adversity being related to lower levels of IL-10 and TNF- α could be a result of psychosocial protective factors utilized by older individuals to counteract adversity. Buchanan (2023) and colleagues explain how protective factors practiced in adulthood may be able to overcome cumulative adversity faced during early life (Buchanan et al., 2023). For example, psychosocial factors including emotional support from family members in addition to the quantity and quality of the support were seen to produce outcomes such as reduced depressive symptoms and cognitive wellness, which may extend to inflammatory biomarkers, as well. Further, the combination of these protective factors and their positive outcomes may result in the decrease of perceived stress, which in turn may reduce destructive coping mechanisms that can be detrimental to one's health. Coping mechanisms such as excessive drinking, smoking, and eating a diet consisting of high fat foods may be avoided as a result, which may lead to a subsequent decrease in circulating inflammatory cytokines.

Lastly, a significant relationship between race and IL-10 was found, which suggests that there may be an association between being Black and having lower levels of IL-10. Similarly, this result does not support the hypothesis that Black participants would possess elevated levels of cytokines compared to their White counterparts. Similarly, regarding psychosocial protective factors, the hardy traits that accompany resilience may explain lower levels of IL-10 in Black participants. Although lower levels of proinflammatory cytokines – such as TNF-α and IL-6 – may be an indication of sound health, low levels of anti-inflammatory cytokines – such as IL-10 – may indicate a decline in health and be a precursor to disease. This phenomenon of Black participants having lower anti-inflammatory cytokines may be a result of those from African descent having a historically low white blood cell and neutrophil count (Lim et al., 2010; Reich et al., 2009). Lower amounts of white blood cells and neutrophils may lead to a less robust

inflammatory cascade in the presence of an invader, thus producing reduced levels of the anti-inflammatory cytokines necessary for healing. Essentially, Black individuals may express a dampened inflammatory response, which may lead to the development of disease later on due to the inability to fight infections or viruses. In light of these findings, based on the question that determined race of the participants, it cannot be fully determined if the Black participants within the study came from African descent. With this consideration in mind, the justification of low white blood cell and neutrophil count must be interpreted with discretion. A last consideration worth noting is that Black participants in this study were more likely to experience early life adversity. Additionally, the participants within this study are a group of reasonably healthy older adults. Being age 70 and above, ambulatory, and able to participate fully in the study are hallmark indications of the participants' sound health. Considering this, older Black adults who have experienced early life adversity in this study may have built up resilience to current adult adversity. This claim is speculation and further investigation would need to be carried out in order to make more robust associations.

Early and Adult Adversity Informing Inflammation

After accounting for the role of early life adversity, there was a significant association between adult adversity and MIF, such that increased adult adversity was related to decreased MIF. MIF has been shown to be a highly valued protein with cytokine-like properties. Many have argued that MIF has earned the right to be classified as a cytokine, while others label the biomarker as simply a protein (Calandra & Roger, 2003; Grieb et al., 2010; Paiva et al., 2009). Nonetheless, it has been widely agreed that MIF plays a role in directing the release of macrophages and other leukocytes, ultimately contributing to the innate immune response. These

results show that the presence of adult adversity is associated with reduced levels of circulating MIF.

When accounting for the effect of adversity regarding inflammatory cytokines, MIF produced a significant interaction for adult adversity within the unadjusted and adjusted regression models, while none of the more common biomarkers did. This finding may be a result due to differences between MIF and traditional cytokine activation. MIF production is typically stimulated upon the presence of immune complexes (ICs), which describes a host of antibody and antigen interactions (Bernhagen et al., 2007; Paiva et al., 2009). Traditional cytokines are released in response to macrophage activity and are recruited through positive feedback loops to fight infections (Descoteaux & Duque, 2014). Perhaps adult adversity is associated with the reduced production of ICs, thus relating to the dampened MIF immune response. Despite these findings, MIF has not been thoroughly explored as a biomarker used to evaluate inflammation as a result of adversity. The novelty of this protein and relevance to evaluating lifetime adversity must be further explored before definitive conclusions are made. Furthermore, given the marginal significance after the inclusion of covariates, we should also note that these findings should be interpreted with caution.

Race as a Moderator

Significant interactions were revealed between adult adversity and race to predict IL-6 and TNF- α. Notably, as adverse events increased for Black participants, circulating inflammatory cytokine production decreased; for White participants, levels of IL-6 and TNF- α remained approximately stable. The findings of lower circulating cytokine production seen in Black participants are contrary to the initial hypothesis and may be the result of resilience. Resilience in simple terms can be described as the adaptation to adversity over an extended

period of time (Taylor et al., 2020). Taylor (2020) and colleagues explain how Black individuals have endured historically oppressive events which in turn have led to a decline in Black health in America. Despite this, resilient traits may serve as a protective factor, thus reducing circulating levels of proinflammatory cytokines such as TNF-α and IL-6 in Black individuals. Individual attributes such as hardiness, optimism, social connectedness, and perceived personal control may explain the reduction in circulating cytokines seen in the current study (Dantzer et al., 2018). As such, this sample may be showing resilience at the biological level.

Limitations and Future Directions

Although this study provides a unique ability to examine race as a moderator of associations between adversity and inflammation in older adulthood, it is not without limitations. A restriction present in the current study is the lack of prospective adversity data. Participants documented adverse early life and adulthood events via retrospective data collection methods. The use of retrospective data may present the disadvantage of recall bias; as such, participants may not have fully recalled all events of adversity throughout their life span. Moreover, as the primary goal of the EAS was to test cognitive functioning over time, a small number of participants report mild cognitive impairment (MCI), which may affect their ability to recall information.

Another limitation is that the EAS was limited to only participants within the Bronx, NY area, meaning that there may be environmental factors that the sample of participants face that are not generalizable to the entire U.S. population. Future studies are required to further assess the relationship between adversity across the life course and inflammatory cytokines. A prospective longitudinal study is needed to capture adversity and circulating cytokines as they occur in real time. A prospective cohort study recruiting adolescents and following them

throughout adulthood is required to fully understand cumulative disadvantage in regard to inflammation. Finally, I did not include daily levels of stress as a covariate which may confound associations between short-term, transient phenomena like inflammation and retrospective reports of adversity.

Conclusion

This study yields findings that can contribute to the overall understanding of how the accumulation of adversity can impact circulating inflammatory cytokine levels. There may be an association between facing more adverse events and having lower circulating inflammatory cytokines. This research also displays how people minoritized as Black may have reduced circulating inflammatory cytokines, possibly due to a reduced white blood cell and neutrophil count or the protective factor of resilience. Furthermore, this study delves into the utilization of MIF in adversity induced inflammation. In the end, this study highlights how the severity of adversity faced by older adults has the potential to be alleviated through the implementation of various psychosocial protective factors. Lastly, this study highlights the necessity of promoting resilience in Black older adults to improve healthy aging at the biological level.

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Academic Vita

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EDUCATION

The Pennsylvania State University, University Park, PA
Bachelor of Science, Biobehavioral Health

Relevant Coursework: Introductory Biology, General Chemistry, Organic Chemistry, Anatomy and Physiology, Principles of Nutrition, Neuroanatomy Behavior and Health, Principles of Epidemiology, Molecular Cell Biology, & Health Promotion

HONORS AND AWARDS

Dean's List
President's Freshman Award Recipient
Schreyer Honors College
NASA Pennsylvania Space Grant Consortium Recipient
S & T Ross Trustee Honors College Scholarship Recipient
Hintz Biobehavioral Health Scholarship Recipient
Radomsky/Ellzey Honors Scholarship Recipient
Alpha Epsilon Delta Pre-Health Honors Society
Summer Success Scholarship Recipient
Graham Open Doors Honors Scholarship Recipient
Ready to Succeed Scholarship Recipient
Resident Assistant of the Month (March)

RESEARCH EXPERIENCE

Mechanisms of Emotion, Stress, and Health Laboratory,
Department of Biobehavioral Health
Research Assistant, April 2023 – Present
Advisors: Dr. Graham-Engeland & Dr. Witzel Conducted research on anticipatory stress cortisol by compiling and creating literature reviews, empirical articles, and systematic reviews. Collaborated with Dr. Graham-Engeland and Dr. Witzel to synthesize undergraduate honors thesis regarding the timing of early life adversity and its relationship to proinflammatory dysregulation and the development of chronic diseases during adulthood. Utilization of Einstein Aging Study to observe proinflammatory biomarkers in participants such as IL1 and IL6.

Motivation Laboratory,
Department of Kinesiology
Research Assistant, January 2022 – August 2023
Advisor: Dr. Conroy Compiled and analyzed post study interviews to gain participant feedback regarding Precision AIM trial. The Precision AIM study used technology to promote exercise in low activity adults. Text alerts, mobile phone applications, and wearable exercise monitoring

devices were used in order to accomplish this. The focus of this study was to discover the appropriate number of notifications exercise applications should send users to effectively encourage activity. Initialized activity monitor devices, downloaded and coded participant data, and completed daily participant compliance checks.

BBH 411W (Research and Applications) and BBH 397 (Honors Research Strategies)
Fall Semester 2022 & Spring Semester 2023
Advisors: Dr. Kamens & Dr. Gyekis Generated and interpreted original behavioral and biomedical data through statistical software. With a focus on public health data provided by the CDC's NHANES study in addition to data gathered independently from the Biobehavioral Health student population. Honed skills in communicating health related information to professional and non-professional audiences.

PRESENTATIONS

The NASA PA Space Grant Consortium, The Pennsylvania State University, University Park, PA, November 2022, Ashley-Douglas, S. "Precision AIM: The Impact of Motivation on Physical Activity".

LEADERSHIP AND SERVICE

The Pennsylvania State University, Department of Biobehavioral Health
Learning Assistant for BBH 310, 411W, & 440, August 2023 – Present
Provided learning support to over 30 students through one-on-one peer tutoring on research methods and applications through office hours. Educated students on experimental and observational research designs and their use. Assisted students with scientific writing such as hypothesis generation, literature review synthesis, empirical research, and citations. Provided technical support with SPSS and guided how to create simple regressions, multiple regressions, correlations, histograms, bar charts, etc. Attended weekly learning assistant meetings to discuss and overcome challenges such as low student attendance. Sent weekly announcements to students to remind them to attend learning assistant sessions as needed.

The Pennsylvania State University, Residence Life
Resident Assistant, June 2022 – Present
Foster community by hosting regular meetings, social events, and engagement with residents. Encouraged academic excellence through promoting Penn State learning centers and group tutoring sessions. Formed personal relationships with residents and aided them in times of homesickness, loneliness, and distress. Responsible for Residence Hall bulletin board creation and announcement postings. Stay in regular contact with residents via email and Microsoft Teams communications. Uphold protocol to promote safety within Residence Halls by educating residents on fire and emergency evacuation. Encourage security by conducting duty rounds in Residence Halls and being on call from 8:00pm to 7:00am in case of residential emergencies. Ability to communicate with law and emergency medical service personnel in the likelihood of an emergency. Writing skills to form detailed incident reports. Attend regular meetings with

Residence Life Coordinator and fellow Resident Assistants to discuss needs of residents and how to meet them.

The Pennsylvania State University, Alpha Epsilon Delta Pre-Health Honors Society
Diversity in Health Taskforce Discussion Leader, September 2022 – December 2022
Spark discussion regarding injustices faced by minorities in healthcare. With a focus on pregnancy related disparities, geographical barriers to healthcare, substance abuse, and accessibility for those with disabilities. Facilitate group presentations and lead group discussions.

The Pennsylvania State University, Career Services
Outreach Intern & Diversity in STEM Conference Leader, August 2021- August 2022
Take professional headshots of students and promote professionalism. Lead presentations for first year students regarding the resources Penn State Career Services offers. Offer resume building at university wide table events. Encourage students to visit Professional Attire Closet to receive a free professional outfit. Lead Diversity in STEM Conference to empower students of color to pursue a career in STEM. Student panel discussions were led by fellow students of color and keynote speakers shared their hardships and successes as underrepresented individuals in the STEM field.

Park Forest Preschool Board Volunteer
Public Outreach and Fundraising Committee Board Member, May 2021- May 2022
Serve low-income families and preschool age children through fundraising for student school supplies. Created digital posters to promote preschool fundraising events to local community. Monitored social media engagement, performance, and demographic analytics.

The Pennsylvania State University, Podcast Co-Host
Recreation Park and Tourism Management Department, November 2020
Co-hosted a three-part podcast alongside Professor Matthew Bakowicz. Interviewed panelists on their experience being an underrepresented person of color in their field. With a goal to encourage other underrepresented students to pursue careers that they are passionate about.

HEALTHCARE EXPERIENCE
Emergency Medical Technician (EMT-B), June 2023 – Present
Practicing EMT at Centre Life Link Emergency Medical Services, *State College, PA.* Certified emergency medical services vehicle operator. Pennsylvania and nationally registered provider. Specialized in pre-hospital care and proper patient care report documentation.

TECHNICAL SKILLS
Computational: SPSS, Red Cap, and Microsoft Office suite
Communications: scientific writing, creative writing, and public speaking