

### **IRIS CANTOR-UCLA** WOMEN'S HEALTH CENTER

EDUCATION AND **RESEARCH CENTER** 

### Abstract

Inflammation is a necessary response to bodily insult and injury, but excessive and chronic inflammatory processes play a role in many diseases. For example, the inflammatory markers interleukin-6 (IL-6) and C reactive protein (CRP) are elevated in people with metabolic diseases, depression, low socioeconomic status, poor self-rated health (SRH), and in those who identify as Black. We evaluated the association between IL-6 and CRP with SRH among 2,118 participants in two cohorts (2004-2009 and 2012-2016) from the Biomarker Project in the Midlife in the US (MIDUS) study, a longitudinal study of participants ages 25-84. SRH was assessed in three ways in a phone interview 5 months to 5 years prior to inflammation measures: self-rated physical health, self-rated mental health, and health compared to others of the same age and gender. No significant difference in CRP levels was detected between cohorts. IL-6 was significantly higher in cohort 1. In bivariate analyses, a worse rating for all three SRH measures was associated with increased log-transformed IL-6 (Mean (SD) for SRHphysical excellent vs. fair/poor: 0.45 (0.78) vs. 1.10 (0.80)) and CRP (-0.12 (1.09) vs. 0.83 (1.24)). After controlling for cohort and several biological and social covariates in the model, self-rated mental health was not significantly associated with IL-6 or CRP. The relationship remained significant for the two other SRH measures, such that worse ratings were associated with increased inflammation. Significant covariates were educational attainment, race and ethnicity, number of chronic conditions, and BMI. This study identified several social and biological variables that may mediate the relationship between selfrated health and inflammatory markers. Future work can further investigate the mechanistic relationship and identify areas in which interventions may reduce inflammation.

### Background

- Inflammation is a necessary response to bodily insult and injury, but inappropriate and chronic inflammatory responses contribute to many diseases.
- The inflammatory markers IL-6 and CRP are elevated in people with metabolic diseases, depression, low socioeconomic status, poor self-rated health, and who identify as Black.
- Immune and nonimmune cells secrete IL-6 during inflammatory responses to mediate Bcell differentiation, acute phase responses, and chronic inflammatory states.
- CRP is an acute phase protein produced by the liver and is a commonly-used diagnostic tool to evaluate inflammatory-mediated diseases.

## Objective

- Compare levels of IL-6 and CRP between cohorts.
- Evaluate the association between IL-6 and CRP with 3 measures of self-rated health (SRH).

## Acknowledgements

This work was supported by the Leichtman-Levine TEM Summer Research Scholars Program of the Iris Cantor-UCLA Women's Health Center and the David Geffen School of Medicine at UCLA Short Term Training Program.

References: 1. Christian, Lisa M., Ronald Glaser, Kyle Porter, William B. Malarkey, David Beversdorf, and lanice K. Kiecolt-Glaser. "Poorer Self-Rated Health Is Associated with Elevated Inflammatory Markers among Older Adults." Psychoneuroendocrinology 36, no. 10 (November 2011): 1495–1504. https://doi.org/10.1016/j.psyneuen.2011.04.003. 2. Germolec DR, Shipkowski KA, Frawley RP, Evans E. Markers of Inflammation. In: DeWitt JC, Rockwell CE, Bowman CC, eds. Immunotoxicity Testing: *Methods and Protocols*. Methods in Molecular Biology. Springer; 2018:57-79. doi:10.1007/978-1-4939 8549-4\_5. 3. Gimeno D, Kivimäki M, Brunner EJ, et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol Med. 2009;39(3):413-423. doi:10.1017/S0033291708003723. 4. Stepanikova I, Bateman LB, Oates GR. Systemic Inflammation in Midlife: Race, Socioeconomic Status, and Perceived Discrimination. American *Journal of Preventive Medicine*. 2017;52(1):S63-S76. doi:10.1016/j.amepre.2016.09.026



### Participants and data collection

- measures of self-rated health.
- measured.

### Outcomes

### **Predictors**

- poor?

- Epidemiological Studies Depression Scale (CES-D), cohort

### Analysis

- Descriptive statistics by cohort of
- transformed).
- each SRH measure

# **Associations between self-rated health and later chronic** inflammatory markers in two MIDUS cohorts

Grace Riley, Heather McCreath PhD, Teresa Seeman PhD, Janet Pregler MD David Geffen School of Medicine, University of California, Los Angeles

### Methods

The MIDUS study recruited two cohorts (C1 and C2) of participants ages 25-84 by random digit dialing and family referral (C1 2004-2006, n=4963; C2 2012-2014, n=3577). Additional participants (C1 2005-2006 n=592, C2 2012-2013 n=508) from Milwaukee, WI were recruited to include more Black participants. Participants completed a phone interview and self-administered questionnaire, including three

A subset of participants (C1 2004-2009, n=1255; C2 2012-2016 n=863) completed the Biomarker Project 5 months to 5 years after the phone interview and questionnaire. An additional survey was completed, blood samples collected, and height and weight

Serum IL-6 and serum CRP were measured at the University of Wisconsin, Madison and the University of Vermont, Burlington, respectively.

IL-6 (pg/mL) and CRP (μg/mL). Measures were log-transformed for all analyses.

Primary: Self-rated health (SRH) assessed by 3 questions in the phone interview Would you say your physical health is excellent, very good, good, fair, or poor? Would you say your mental or emotional health is excellent, very good, good, fair, or

Compared to most (men/women) your age, would you say your health is much better, somewhat better, about the same, somewhat worse, or much worse? Answers 'fair' or 'poor' and 'somewhat worse' or 'much worse' were combined into single categories 'fair/poor' and 'worse' due to low number of such responses. Covariates: age, gender, race and ethnicity, educational attainment, health insurance coverage, smoking status, body mass index (BMI), number of symptoms and chronic conditions, lifetime discrimination, Center for

demographics, outcomes, primary predictors, and covariates. Chi square and t-tests used to describe differences between cohorts. Bivariate analyses of primary predictors and covariates by each outcome (IL-6 and CRP, log-

Generalized linear models with all covariates by



C1: cohort 1 (2004-2009); C2: cohort 2 (2012-2016) SRH-Physical: self-rated physical health; SRH-Mental: self-rated mental health SRH-Comparison: self-rated health compared to others in same age-gender group

Table 1. Participant demog	Table 1. Participant demographics and characteristics					
	Cohort 1	Cohort 2				
	(N=1255)	(N=863)				
Characteristic	N (%) or mean (SD)	N (%) or mean (SD)				
Age*						
25-44	290 (23.1%)	306 (35.5%)				
45-64	700 (55.8%)	401 (46.5%)				
64-84	266 (21.1%)	156 (18.1%)				
Female*	713 (56.8%)	450 (52.1%)				
Race/ethnicity*						
Black	174 (13.9%)	125 (14.5%)				
White	928 (73.9%)	570 (65.1%)				
Multiracial/other	153 (12.2%)	168 (19.5%)				
Education*+						
HS grad/GED or less	350 (28.0%)	149 (17.3%)				
Some college or associates degree	375 (30.0%)	263 (30.5%)				
Bachelor's degree or more	527 (42.1%)	450 (52.2%)				
Covered by health insurance <sup>+</sup>	1147 (92.0%)	780 (90.8%)				
Months between sample collection and						
Phone interview*	27.8 (14.0)	22.3 (9.1)				
Self-administered questionnaire*	25.3 (14.2)	21.1 (9.0)				
IL-6 (pg/mL)*+	3.04 (3.0)	2.78 (2.4)				
Log IL-6*+	0.81 (0.8)	0.72 (0.8)				
CRP (µg/mL)⁺	3.02 (4.8)	2.96 (5.2)				
Log CRP <sup>+</sup>	0.41 (1.2)	0.34 (1.2)				
Current cigarette smoker*+	187 (14.9%)	94 (11.3%)				
BMI*+^						
Normal weight (18.5-24.9)	292 (23.4%)	209 (24.4%)				
Overweight (25-29.9)	440 (35.3%)	259 (30.2%)				
Obese (30.0+)	516 (41.4%)	390 (45.5%)				
Number of symptoms/chronic conditions	4.10 (3.0)	4.29 (3.4)				
Lifetime discrimination score <sup>+</sup>	1.22 (1.9)	1.20 (1.8)				
CES-D <sup>+</sup> °	8.73 (8.2)	9.26 (7.9)				
*Significant difference between cohorts <sup>+</sup> Total numbers lower due to missing data						

^Underweight (BMI<18.5) excluded due to low number °Center for Epidemiologic Studies Depression Scale, range 0-60, ≥16 suggests significant depressive symptoms

\* This study identified several social and biological variables that may mediate the relationship between self-rated health and inflammatory markers. \* Future work can further investigate the mechanistic relationship and identify areas in which interventions may reduce inflammation. \* SRH is strong enough to predict chronic inflammation despite the lag between SRH and blood collection (5 months-5 years), and elevation of inflammatory markers persists. \* The majority of Black participants were from Milwaukee. Differences in inflammation by race may be due to other unidentified factors.

### Results

	Characteristic	Log IL-6	Log CRP
٩ge	e		
	25-44	0.55 (0.8)*	0.34 (1.3)
4	45-64	0.78 (0.7)	0.40 (1.2)
	64-84	1.06 (0.7)	0.38 (1.1)
Ge	nder		
	Female	0.80 (0.8)	0.56 (1.2)*
	Male	0.74 (0.8)	0.16 (1.1)
Rad	ce/ethnicity		
	Black	1.10 (0.8)*	0.84 (1.2)*
,	White	0.67 (0.8)	0.28 (1.2)
	Multiracial/other	0.81 (0.8)	0.47 (1.2)
Edu	ucation		
	HS grad/GED or less	0.97 (0.8)*	0.69 (1.2)*
	Some college or associates degree	0.82 (0.8)	0.49 (1.2)
	Bachelor's degree or more	0.64 (0.8)	0.15 (1.2)
Cov	vered by health insurance		
,	Yes	0.75 (0.8)*	0.35 (1.1)*
	No	0.97 (0.7)	0.71 (1.2)
Cui	rrent cigarette smoker		
	Yes	0.95 (0.8)*	0.57 (1.2)*
	No	0.75 (0.8)	0.35 (1.2)
ЗN	11		
	Normal weight (18.5-24.9)	0.38 (0.8)*	-0.32 (1.1)

Table 2. Mean (SD) log IL-6 and log CRP by

participant characteristics

Normal weight (18.5-24.9)	0.58 (0.8)	-0.52 (1.1)			
Overweight (25-29.9)	0.71 (0.7)	0.22 (1.1)			
Obese (30.0+)	1.04 (0.7)	0.91 (1.1)			
Number of symptoms/chronic conditions <sup>+</sup>	0.30*	0.16*			
Lifetime discrimination score <sup>+</sup>	0.12*	0.15*			
CES-D^	0.12*	0.11*			
*A significant difference exists between at least two of the categories					

Spearman correlation coefficient is reported

^Pearson correlation coefficent is reported

Table 3. Multivariate models of SRH measures with IL-6 and CRP							
	SRH-Physical		SRH-n	SRH-mental		SRH-Comparison	
	IL-6*	CRP	IL-6	CRP	IL-6	CRP	
Characteristic	В	В	В	В	В	В	
Self-rated health measure <sup>+</sup>	-0.12	-0.23	-0.02	-0.04			
Much better	-	-	-	-	-0.28	-0.44	
Somewhat better	-	-	-	-	-0.22	-0.33	
Worse	-	-	-	-	0.05	0.02	
Older age (45+)	-0.21	<.01	-0.20	0.02	-0.24	-0.04	
Men	-0.02	-0.34	-0.01	-0.32	0.00	-0.31	
Race/ethnicity							
Black	-0.25	-0.22	-0.29	-0.30	-0.28	-0.29	
Multiracial/other	-0.02	0.02	-0.05	-0.03	-0.05	-0.03	
ess than college education	0.06	0.17	0.07	0.20	0.06	0.18	
No health insurance coverage	-0.14	-0.12	-0.17	-0.19	-0.17	-0.18	
Current cigarette smoker	0.04	-0.09	0.07	-0.04	0.05	-0.05	
3MI (overweight or obese)	-0.09	-0.17	-0.09	-0.17	-0.09	-0.17	
Number of symptoms/chronic							
conditions	0.04	0.03	0.06	0.05	0.05	0.04	
_ifetime discrimination score	0.02	0.06	0.03	0.07	0.02	0.06	
CES-D	<.01	<.01	<.01	<.01	<.01	<.01	
Cohort 2	0.02	0.01	0.02	0.02	0.02	0.01	
Log values of IL-6 and CRP were used							

<sup>+</sup>Comparison groups for SRH-physical and SRH-mental is 'excellent', SRH-comparison is 'about the same' Significant relationships are bolded

### **Conclusion and Limitations**



A National Study of Health & Well-Being







- IL-6 was significantly higher in cohort 1. There was no difference in CRP between cohorts (Table 1).
- C2 participants reported SRH significantly lower than C1 (Figure 1). In multivariable models, SRH-physical and SRH-comparison were
- significantly associated with IL-6 and CRP but SRH-mental was not.
- Significant covariates in all models were educational attainment, race and ethnicity, BMI, and number of chronic conditions. Cohort was not a significant predictor in any of the models.