

Identifying Pathways of Physiological Deterioration to Understand Racial Disparities in Cognitive Status: A 4-way Mediation-Interaction Decomposition Analysis

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Abstract

Background: Exposure to interpersonal and structural racism may increase the risk of adverse cognitive aging in racialized groups. Physiological deterioration may lie on the causal pathway leading racism to cognitive aging, but this potential mediating role has never been investigated. We quantified the extent to which the racial disparity (a proxy measure of exposure to racism) in cognitive status was mediated through physiological biomarkers of inflammation, glucose homeostasis, cholesterol ratios, and renal functioning.

Methods: Data were from the US Health and Retirement Study in 2006 and 2008. We performed cross-sectional ($n = 9,107$) and 2-year follow-up analyses ($n = 6,147$) to explore the mediating roles of four physiological biomarkers in racial/ethnic disparities in prevalent and incident dementia. We used self-reported race/ethnicity as a proxy for exposure to structural and interpersonal forms of racism. Mediators were serum biomarkers of systemic inflammation (hsCRP), glucose homeostasis (HbA1C), cholesterol processing and atherosclerosis risk (TC/HDL-C ratio), and renal functioning (cystatin C). We performed a 4-way decomposition analysis that accommodated exposure-mediator interactions to identify natural direct and indirect effects.

Results: In this sample, the prevalence of dementia was 2.2% among non-Hispanic White, 8.5% among non-Hispanic Black, and 6.0% among Hispanic participants. Among non-Hispanic Black relative to non-Hispanic White participants, the mediating effect of HbA1C on prevalent dementia was 6% (95% CI: -4%, 16%) and the interaction effect with race was 11% (95% CI: -11%, 34%) (**Table 1**). Similarly, we estimated a mediating effect of cystatin C on prevalent dementia of 0% (95% CI: -2%, 2%) and an interaction effect with race of 10% (95% CI: -5%, 25%). For incident dementia, among non-Hispanic Black relative to non-Hispanic White participants, the mediating effect of hsCRP on incident dementia was 18% (95% CI: -6%, 41%), and the interaction effect with race was 45% (95% CI: -20%, 110%) (**Table 2**). Results were similar for Hispanic relative to non-Hispanic White participants.

Conclusions: The relationships between race/ethnicity and prevalent and incident dementia were not mediated by or interacted with serum biomarkers of physio-

logical deterioration. Racial disparities in cognitive status in mid-to-later life may be attributable to structural factors to racism and the mediating effects of other biomarkers.

Table 1: Single mediation-interaction 4-way decomposition analysis of serum biomarkers on prevalent dementia stratified by race/ethnicity in the Health and Retirement Study, waves 2006 and 2008

non-Hispanic Black participants vs non-Hispanic White participants								
Excess Risk	hsCRP N = 7055		HbA1C N = 7055		TC/HDL-C N = 7055		Cystatin C N = 7055	
RERI Total Effect	4.39***	[2.50,6.28]	4.16***	[2.35,5.96]	4.11***	[2.33,5.88]	3.89***	[2.06,5.73]
RERI Controlled Direct Effect	4.66***	[2.49,6.84]	3.65***	[1.67,5.63]	4.55***	[2.53,6.57]	3.51***	[1.57,5.44]
RERI Interaction Reference	-0.19	[-0.63,0.25]	0.27	[-0.26,0.79]	-0.58	[-1.69,0.53]	0.39	[-0.14,0.93]
RERI Interaction Mediation	-0.09	[-0.29,0.12]	0.21	[-0.20,0.62]	0.15	[-0.14,0.43]	-0.00	[-0.07,0.06]
RERI Pure Indirect Effect	0.01	[-0.02,0.04]	0.03	[-0.03,0.09]	-0.01	[-0.04,0.03]	-0.00	[-0.01,0.01]
Proportion Attributable								
Control Direct Effect	1.06***	[0.92,1.20]	0.88***	[0.65,1.11]	1.11***	[0.90,1.31]	0.90***	[0.75,1.05]
Interaction Reference	-0.04	[-0.14,0.05]	0.06	[-0.06,0.19]	-0.14	[-0.41,0.13]	0.10	[-0.05,0.25]
Interaction Mediation	-0.02	[-0.06,0.02]	0.05	[-0.05,0.15]	0.04	[-0.03,0.10]	-0.00	[-0.02,0.02]
Pure Indirect Effect	0.00	[-0.01,0.01]	0.01	[-0.01,0.02]	-0.00	[-0.01,0.01]	-0.00	[-0.00,0.00]
Mediated	-0.02	[-0.06,0.03]	0.06	[-0.04,0.16]	0.03	[-0.04,0.10]	-0.00	[-0.02,0.02]
Due to Interaction	-0.06	[-0.20,0.08]	0.11	[-0.11,0.34]	-0.11	[-0.31,0.10]	0.10	[-0.05,0.25]
Eliminated	-0.06	[-0.20,0.08]	0.12	[-0.11,0.35]	-0.11	[-0.31,0.10]	0.10	[-0.05,0.25]
Hispanic participants vs non-Hispanic White participants								
Excess Risk	hsCRP N = 6891		HbA1C N = 6891		TC/HDL-C N = 6891		Cystatin C N = 6891	
RERI Total Effect	0.26	[-0.38,0.89]	0.27	[-0.36,0.90]	0.38	[-0.33,1.09]	0.28	[-0.38,0.94]
RERI Controlled Direct Effect	0.19	[-0.45,0.84]	0.04	[-0.56,0.65]	0.10	[-0.51,0.70]	0.26	[-0.43,0.95]
RERI Interaction Reference	0.07	[-0.12,0.26]	0.12	[-0.09,0.33]	0.27	[-0.19,0.73]	0.04	[-0.15,0.22]
RERI Interaction Mediation	-0.01	[-0.04,0.02]	0.08	[-0.06,0.22]	0.01	[-0.03,0.05]	-0.01	[-0.05,0.03]
RERI Pure Indirect Effect	-0.00	[-0.01,0.01]	0.03	[-0.03,0.08]	0.00	[-0.01,0.01]	-0.01	[-0.03,0.01]
Proportion Attributable								
Control Direct Effect	0.76	[-0.10,1.62]	0.17	[-1.76,2.09]	0.25	[-1.01,1.52]	0.94**	[0.38,1.50]
Interaction Reference	0.29	[-0.71,1.28]	0.44	[-0.64,1.53]	0.72	[-0.51,1.95]	0.13	[-0.62,0.87]
Interaction Mediation	-0.04	[-0.18,0.10]	0.30	[-0.43,1.02]	0.03	[-0.08,0.13]	-0.03	[-0.20,0.14]
Pure Indirect Effect	-0.01	[-0.05,0.03]	0.09	[-0.19,0.37]	0.00	[-0.02,0.02]	-0.04	[-0.13,0.06]
Mediated	-0.05	[-0.20,0.11]	0.39	[-0.48,1.26]	0.03	[-0.09,0.14]	-0.06	[-0.29,0.16]
Due to Interaction	0.25	[-0.61,1.11]	0.74	[-1.06,2.54]	0.74	[-0.53,2.01]	0.10	[-0.48,0.67]
Eliminated	0.24	[-0.62,1.10]	0.83	[-1.09,2.76]	0.75	[-0.52,2.01]	0.06	[-0.50,0.62]

95% confidence intervals in brackets

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

RERI: excess risk due to interaction; hsCRP: high sensitivity C-reactive protein; HbA1C: glycosylated hemoglobin; TC/HDL-C: total cholesterol to high density lipoprotein ratio.

Table 2: Single mediation-interaction 4-way decomposition analysis of serum biomarkers on incident dementia stratified by race/ethnicity in the Health and Retirement Study, waves 2006 and 2008

non-Hispanic Black participants vs non-Hispanic White participants								
Excess Risk	hsCRP N = 5696		HbA1C N = 5696		TC/HDL-C N = 5696		Cystatin C N = 5696	
RERI Total Effect	1.58	[-0.19,3.35]	1.64	[-0.19,3.46]	1.60	[-0.20,3.40]	1.91	[-0.15,3.97]
RERI Controlled Direct Effect	0.82	[-0.76,2.41]	1.73	[-0.54,4.01]	1.62	[-0.22,3.45]	2.02	[-0.27,4.32]
RERI Interaction Reference	0.48	[-0.26,1.22]	-0.03	[-0.52,0.45]	0.01	[-1.49,1.51]	-0.12	[-0.69,0.45]
RERI Interaction Mediation	0.23	[-0.15,0.62]	-0.03	[-0.43,0.38]	-0.00	[-0.29,0.29]	0.01	[-0.06,0.09]
RERI Pure Indirect Effect	0.04	[-0.01,0.10]	-0.04	[-0.11,0.03]	-0.03	[-0.07,0.02]	-0.01	[-0.03,0.01]
Proportion Attributable								
Control Direct Effect	0.52	[-0.13,1.18]	1.06***	[0.54,1.58]	1.01**	[0.25,1.78]	1.06***	[0.81,1.31]
Interaction Reference	0.30	[-0.13,0.74]	-0.02	[-0.31,0.27]	0.01	[-0.93,0.94]	-0.06	[-0.34,0.22]
Interaction Mediation	0.15	[-0.07,0.37]	-0.02	[-0.26,0.22]	-0.00	[-0.18,0.18]	0.01	[-0.03,0.04]
Pure Indirect Effect	0.03	[-0.02,0.07]	-0.02	[-0.07,0.03]	-0.02	[-0.05,0.02]	-0.01	[-0.02,0.01]
Mediated	0.18	[-0.06,0.41]	-0.04	[-0.27,0.19]	-0.02	[-0.19,0.16]	0.00	[-0.03,0.04]
Due to Interaction	0.45	[-0.20,1.10]	-0.04	[-0.57,0.49]	0.00	[-0.75,0.76]	-0.06	[-0.30,0.19]
Eliminated	0.48	[-0.18,1.13]	-0.06	[-0.58,0.46]	-0.01	[-0.78,0.75]	-0.06	[-0.31,0.19]
Hispanic participants vs non-Hispanic White participants								
Excess Risk	hsCRP N = 5609		HbA1C N = 5609		TC/HDL-C N = 5609		Cystatin C N = 5609	
RERI Total Effect	0.80	[-0.61,2.20]	0.68	[-0.65,2.00]	0.59	[-0.65,1.84]	0.63	[-0.67,1.93]
RERI Controlled Direct Effect	0.55	[-0.77,1.87]	-0.19	[-1.13,0.75]	1.42	[-0.38,3.22]	0.27	[-0.89,1.43]
RERI Interaction Reference	0.30	[-0.31,0.90]	0.52	[-0.01,1.06]	-0.81*	[-1.51,-0.11]	0.48	[-0.23,1.19]
RERI Interaction Mediation	-0.04	[-0.14,0.06]	0.38	[-0.03,0.79]	-0.02	[-0.14,0.11]	-0.10	[-0.28,0.08]
RERI Pure Indirect Effect	-0.01	[-0.03,0.01]	-0.04	[-0.10,0.03]	0.00	[-0.02,0.02]	-0.02	[-0.05,0.01]
Proportion Attributable								
Control Direct Effect	0.69	[-0.00,1.39]	-0.28	[-2.11,1.54]	2.39*	[0.08,4.70]	0.43	[-0.69,1.54]
Interaction Reference	0.37	[-0.44,1.18]	0.77	[-0.35,1.90]	-1.36	[-3.61,0.89]	0.76	[-0.70,2.22]
Interaction Mediation	-0.05	[-0.19,0.09]	0.56	[-0.26,1.38]	-0.03	[-0.25,0.19]	-0.16	[-0.53,0.20]
Pure Indirect Effect	-0.01	[-0.05,0.02]	-0.05	[-0.19,0.09]	0.01	[-0.03,0.04]	-0.03	[-0.10,0.04]
Mediated	-0.07	[-0.23,0.10]	0.51	[-0.21,1.23]	-0.03	[-0.21,0.15]	-0.19	[-0.60,0.23]
Due to Interaction	0.32	[-0.38,1.02]	1.34	[-0.59,3.26]	-1.39	[-3.72,0.94]	0.60	[-0.55,1.74]
Eliminated	0.31	[-0.39,1.00]	1.28	[-0.54,3.11]	-1.39	[-3.70,0.92]	0.57	[-0.54,1.69]

95% confidence intervals in brackets

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

RERI: excess risk due to interaction; hsCRP: high sensitivity C-reactive protein; HbA1C: glycosylated hemoglobin; TC/HDL-C: total cholesterol to high density lipoprotein ratio.