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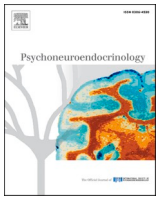

Neighborhood disadvantage and elevated *CD14* gene expression among middle-aged adults: Findings from the Midlife in the United States study

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ABSTRACT

Social and environmental factors are crucial in health, partly through immune system programming that begins decades before chronic disease onset. This study quantified the associations between neighborhood opportunity and *CD14* gene expression, a key marker of monocyte abundance and inflammatory potential in the circulating leukocyte pool. Neighborhood opportunity was measured using the Childhood Opportunity Index 3.0 reflecting Overall Neighborhood Opportunity and three subdomains (Education, Health and Environment, and Social and Economic Resources). Multivariable linear regression analyses among 1215 middle-aged adults (57 ± 12 years) from the Midlife in the United States Study revealed that individuals residing in disadvantaged neighborhoods had 36.6 % (95 % CI: 11.7–65.9 % elevation, $p = 0.002$) higher *CD14* gene expression levels than those in neighborhoods with high opportunity, even after adjusting for key sociodemographic characteristics and health behaviors. The Education domain (27.5 % elevation, 95 % CI: 5.0–54.8 % elevation, $p = 0.015$) and Social & Economic Resources domain (32.9 % elevation, 95 % CI: 8.7–62.5 % elevation, $p = 0.006$) strongly tracked with elevated *CD14* gene expression levels. These findings extend previous research showing how social factors "get under the skin" through sympathetic nervous system activation and altered myelopoiesis, producing a proinflammatory, glucocorticoid-resistant immune phenotype.

1. Introduction

Social and environmental determinants of health play a significant role in shaping disparities in chronic disease risk (Bailey et al., 2017; Williams et al., 2019). Among these determinants, neighborhood characteristics represent a well-established domain that has been linked to a wide range of chronic diseases, including hypertension (Kershaw et al., 2011), diabetes (Krieger et al., 2016), and obesity (Goodman et al., 2018). Emerging research suggests that one key pathway through which neighborhood conditions get under the skin to influence the onset of chronic diseases is through immune dysregulation and systemic inflammation (Berger et al., 2019; Ravi et al., 2021). For example, neighborhood disadvantage—marked by socioeconomic deprivation, limited access to nutritious food and healthcare, exposure to environmental toxicants, and ongoing psychosocial stress—has been associated with elevated levels of inflammatory biomarkers such as C-reactive protein and interleukin-6 (Broyles et al., 2012; Purser et al., 2008). Despite these associations, the cellular and molecular mechanisms that link neighborhood context to health outcomes remain poorly understood.

One cellular pathway that may play a role involves up-regulated monocyte production in response to chronic stress (Barrett et al., 2021; McKim et al., 2018; Powell et al., 2013; van der Heijden et al., 2020). As innate immune sentinels, monocytes are highly sensitive to environmental cues (Cole et al., 2011), and their relative abundance and inflammatory potential can be assessed through gene expression

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profiling. The *CD14* gene, which encodes a co-receptor for toll-like receptor 4 signaling, is pivotal in pro-inflammatory responses to endogenous damage-associated molecular patterns (Na et al., 2023). Upregulation of *CD14* expression has been observed in individuals with history of early-life adversity, a well-established source of chronic stress (Aschbacher et al., 2021; Bower et al., 2020; Kuhlman et al., 2024; Schwaiger et al., 2016). For example, in a study of 42 women with a mean age of 32 years, Aschbacher et al. (2021) found that early life adversity—as measured by the Life Stressor Checklist-Revised—was associated with higher *M1/M2* gene expression ratios in *CD14* + monocytes, indicating a pro-inflammatory imbalance. Similarly, Schwaiger et al. (2016) examined 60 healthy adults aged 45–60 years (30 with childhood adversity assessed via the German Childhood Trauma Questionnaire, 30 matched controls) and found that those with early adversity histories showed significantly enhanced pro-inflammatory signaling in isolated *CD14* + monocytes. Such heightened *CD14* expression, in turn, has been linked to metabolic dysfunction (Kang et al., 2022) and atherosclerosis (Hermansson et al., 2014), suggesting that *CD14* may serve as a key marker of monocyte mediation between adverse environmental exposures and immune-mediated disease risks.

Neighborhood disadvantage could shape immune cell function through transcriptional pathways (Cole, 2019; Cunliffe, 2016). Nevertheless, previous research has primarily focused on individual-level indicators of social position (Knight et al., 2016; Powell et al., 2013), despite the fact that individuals are embedded within broader social and structural environments. In the broader literature, neighborhood disadvantage has been independently associated with adverse health outcomes, including cardiovascular disease, metabolic disorders, and early mortality, over and above individual-level socioeconomic factors (Bailey et al., 2017; Williams et al., 2019). This growing body of research suggests the need for a comprehensive cell-to-society analysis, which recognizes that the effects of neighborhood context are not merely proxies for individual disadvantage, but reflect distinct pathways of biological risk. In the present study, we seek to determine whether structural and community-level stressors are associated with biological embedding at the cellular and molecular level to contribute to dysregulated immune functioning, and ultimately, elevated risk of chronic disease onset.

Building on evidence that social stressors may reprogram immune function at the transcriptional level (Barrett et al., 2021; Heidt et al., 2014; Kuhlman et al., 2023; McKim et al., 2018; Powell et al., 2013; van der Heijden et al., 2020), this study quantified the association between neighborhood disadvantage and *CD14* gene expression in peripheral blood mononuclear cells from middle-aged and older adults exposed to a wide range of neighborhood conditions in the United States. We hypothesized that residing in a disadvantaged neighborhood would be associated with upregulated *CD14* expression. By focusing on *CD14*, this study aimed to identify cell-type-specific pathway linking neighborhood stressors to the circulating immune system's inflammatory potential and clarify how structural and community inequities may potentially contribute to subsequent poor health.

2. Materials and methods

2.1. Study design, setting, and sample

We used data from the Midlife in the United States (MIDUS) Study, a probability-based cohort study evaluating social, psychological, and behavioral determinants of health among US adults (Brim et al., 2004). The study recruited English-speaking, non-institutionalized adults aged 25–74 years.

2.1.1. Original MIDUS cohort

The original MIDUS cohort (MIDUS 1) enrolled 7108 participants nationally between 1995 and 1996. Wave 2 (MIDUS 2, conducted 2004–2005) included 4963 participants from the original cohort plus an additional 592 African Americans from Milwaukee, Wisconsin, who were recruited to enhance African American representation, for a total of 5555 participants. Wave 3 (MIDUS 3) began in 2013 with 3683 participants continuing from Wave 2.

2.1.2. MIDUS refresher study

From 2011–2014, the MIDUS Refresher Study (MIDUS Refresher 1) recruited an additional 4085 adults to replenish the baseline cohort, including an oversampling of 508 African Americans from Milwaukee, Wisconsin. Like participants in MIDUS 1–3, MIDUS Refresher 1 participants completed a survey at enrollment.

2.1.3. Biomarker studies

Participants who completed surveys and remained healthy enough to travel became eligible for biomarker studies (Dienberg Love et al., 2010). The MIDUS 3 Biomarker Project began enrollment in 2017, with 747 participants from across the national sample traveling to one of three clinical sites: Georgetown University, the University of Wisconsin-Madison, and the University of California, Los Angeles (Dienberg Love et al., 2010). Separately, 862 participants from MIDUS Refresher 1 enrolled in the MIDUS Refresher Biomarker Study, conducted from 2012 to 2016 using the same protocol as the MIDUS 3 Biomarker Project.

Both biomarker studies provided comprehensive participant support, including detailed information about the biological protocol, $200 compensation for the two-day clinic visit, and full coverage of travel expenses (Dienberg Love et al., 2010). The MIDUS team arranged all travel logistics and allowed older participants to bring companions. Childcare expenses were also covered when needed. Of the 1609 biomarker participants, 1215 had valid gene expression data. Details on the study protocols for all MIDUS studies have been previously described (Brim et al., 2004; Dienberg Love et al., 2010; Radler, 2014). All MIDUS study participants provided informed consent. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (von Elm et al., 2007). MIDUS study protocols were approved by the University of Wisconsin Institutional Review Board. The New York University Institutional Review Board considered this secondary analysis exempt from review.

2.2. Ascertainment of CD14 expression levels

Blood samples for gene expression profiling were collected during participants' two-day clinic visits at one of the three site locations (Dienberg Love et al., 2010). The two-day clinic visit occurred at enrollment in the biomarker project. On the morning of the second day, following an overnight fast, a trained phlebotomist drew blood using BD Vacutainer CPT Tubes. Peripheral blood mononuclear cells were isolated from these samples and stored in freezers maintained at −60°C to −80°C until shipment on dry ice to the MIDUS Biocore Lab, where they were stored at −65°C until assayed.

Gene expression profiling was conducted between 2017 and 2018 for samples from the MIDUS Refresher Biomarker Study and between 2018 and 2022 for samples from the MIDUS 3 Biomarker Project. Whole-transcriptome RNA sequencing measured transcript levels for all human genes. For this investigation, we specifically focused on *CD14* gene expression levels. Expression values were quantified as transcript counts per million total human transcriptome-mapped RNA sequencing reads, log2-transformed, and floored at one transcript per million to reduce spurious variability. Additional technical details regarding the gene expression profiling methodology are available on the MIDUS Colectica Portal (http://midus.colectica.org/) and previous publications (Cuevas et al., 2023; Mann et al., 2020).

2.3. Neighborhood opportunity

Participants' census tract data were linked to the Childhood Opportunity Index (COI) 3.0, a comprehensive neighborhood opportunity metric (Noelke et al., 2024). Census tract data reflected the participant's residence during the time of survey completion. To protect participant privacy, the merging of COI data with MIDUS participants' census-tract information required special permission and was conducted exclusively by the MIDUS Geocode team. Although the COI was developed to evaluate neighborhood conditions affecting childhood development, its components—which assess factors such as concentrated inequity and housing resources—are equally relevant for studying adult populations (Noelke et al., 2024). For example, researchers have investigated the association of the COI with cardiometabolic risk and mortality in adults (Gianaros et al., 2023; Slopen et al., 2023).

The COI offers several advantages over other commonly used measures, such as the Area Deprivation Index (ADI) and the Social Vulnerability Index (SVI). While the ADI and SVI rely solely on American Community Survey estimates, the COI draws from multiple data sources, including the American Community Survey, the National Center for Charitable Statistics Internal Revenue Service Business Master File, Opportunity Insights, and NatureQuant, among others (Noelke et al., 2024). The ADI does not apply z-score transformations to its components before combining them into the overall index, while the COI standardizes all indicators before combining them into subdomain scores and the final COI score. A detailed comparison of the COI with the ADI and SVI can be found in the COI 3.0 Technical Documentation (Noelke et al., 2024).

The COI comprises 44 indicators organized into an overall score (Overall Neighborhood Opportunity) and three distinct subdomains: Education, Health and Environment, and Social and Economic Resources (Table 1). All 44 indicators were z-score transformed, weighted, then summed to create nationally normed metrics. The national-normed overall COI score and three subdomain scores were classified into five categories: very low (≤20th percentile), low (>20th to ≤40th percentile), moderate (>40th to ≤60th percentile), high (>60th to ≤80th percentile), and very high (>80th percentile). We consolidated these into three categories: low (≤40th percentile), moderate (>40th to ≤60th percentile), and high (>60th percentile).

Table 1
Indicators of each subdomain in the Childhood Opportunity Index 3.0 (Noelke et al., 2024).

Domain	Indicators
Education	• private pre-K enrollment • public pre-K enrollment • reading and math test scores • reading and math test score growth • poverty-adjusted reading and math test scores • Advanced Placement course enrollment • college enrollment in nearby institutions • high school graduation rate • adult educational attainment • child enrichment-related non-profits • teacher experience • school poverty
Health and environment	• airborne microparticles • ozone concentration • industrial pollutants in air • water or soil • hazardous waste dump sites • healthy food retailer density • extreme heat exposure • NatureScore • walkability • community safety-related non-profits • vacant housing • health-related non-profits • health insurance coverage
Social and Economic Resources	• employment rate • high-skill employment rate • full-time year-round earnings • median household income • poverty rate • public assistance rate • adults with advanced degrees • very high-income households • adults without high school degrees • very low-income households • broadband access • crowded housing • mobility-enhancing friendship networks • single-parent families • non-profit organizations • homeownership rate • aggregate home values • aggregate capital income • aggregate real estate taxes

2.4. Covariates

All covariates were extracted from self-reported surveys. Sociodemographic covariates included age (measured continuously), sex (male vs. female), educational attainment (<high school, high school/GED, some college and above), annual household income (<$50,000, $50,000 to $100,000, and $100,000 +), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Other). The non-Hispanic Other category included those who identified as Native American, Alaskan Native, Native Hawaiian, Pacific Islander, and Asian. Participants in the Hispanic category identified as Hispanic/Latino and of any race. Health behaviors included smoking status (never, past, current), past month alcohol consumption (never, <1 day a week, 1–2 days a week, 3–4 days a week, 5–6 days a week, every day), and body mass index (BMI, measured continuously).

2.5. Statistical analysis

In the primary analysis, we employed multivariable linear regression to quantify the relationship between Overall Neighborhood Opportunity and log2-transformed *CD14* gene expression levels (Hidalgo and Goodman, 2013). We fit three sequential models with increasing covariate adjustment. Model 1 expressed log2-*CD14* gene expression levels as a function of Overall Neighborhood Opportunity (unadjusted model). Model 2 controlled for sociodemographic characteristics (age, sex, race/ethnicity, educational attainment, and annual household income). Model 3 further incorporated health behavior covariates (smoking status, alcohol consumption, and BMI).

To gain deeper insights into which neighborhood dimensions strongly tracked with *CD14* gene expression levels, we conducted secondary analyses investigating each neighborhood opportunity subdomain (Education, Health and Environment, and Social and Economic Resources) separately. We applied the same three-model adjustment strategy used in the primary analysis. We used the inverse of the log2 transformation to interpret regression coefficients: $(2^{\beta} - 1) \times 100$. Analyses used R version 4.4.3 (R Core Team, R Foundation for Statistical Computing).

We addressed missing covariate data using multivariate imputation by chained equations with the *mice* R package (Buuren and Groothuis-Oudshoorn, 2011). The imputation approach varied by variable type: polytomous logistic regression for race/ethnicity (0.6 % missing), ordinal logistic regression for educational attainment (0.1 % missing) and annual household income (7.7 % missing), and predictive mean matching for BMI (3.2 % missing). We pooled all regression coefficients from the multivariable models across ten imputed datasets using Rubin's rules (Little and Rubin, 2019).

3. Results

3.1. Primary analysis

Among the 1215 adults analyzed (Table 2; mean 57 years, SD 12), 53 % were female, 73 % were non-Hispanic White, and 59 % never smoked. Primary analyses revealed neighborhood disadvantage was associated with a substantial elevation in *CD14* gene expression levels (measured in transcript counts per million; Table 3) within the overall peripheral blood leukocyte pool. Model 1 (unadjusted) indicated that individuals residing in areas with low Overall Neighborhood Opportunity had 17.3 % higher *CD14* gene expression levels than those in areas with high Overall Neighborhood Opportunity (95 % CI: 3.4 % reduction to 41.4 % elevation, $p = 0.11$). This association's magnitude increased to a 38.5 % elevation (95 % CI: 14.1–69.3 % elevation, $p = 0.001$) when controlling for age, sex, race/ethnicity, educational attainment, and annual household income (Model 2); and slightly attenuated when health behavior covariates were introduced in Model 3 (36.6 % elevation, 95 % CI: 11.7–65.9 % elevation, $p = 0.002$).

3.2. Secondary analyses

Education and Social & Economic Resources emerged as the COI subdomains that most strongly tracked with elevated *CD14* gene expression (Table 4). Regression models showed that low Education opportunity was associated with a 29.2 % elevation in *CD14* gene expression (95 % CI: 6.4–56.9 % elevation, $p = 0.009$), adjusting for sociodemographic factors (Model 2, Table 4). Introducing health behaviors in Model 3 attenuated the magnitude of this association (27.5 % elevation, 95 % CI: 5.0–54.8 % elevation, $p = 0.015$). Low Social and Economic Resources significantly correlated with elevated *CD14* gene expression even after controlling for sociodemographic characteristics (Model 2: 35.7 % elevation, 95 % CI: 11.7–65.9 % elevation, $p = 0.002$) and health behaviors (Model 3: 32.9 % elevation, 95 % CI: 8.7–62.5 % elevation, $p = 0.006$). *CD14* gene expression levels did not significantly vary across levels of the Health and Environment domain (all $p > 0.05$).

4. Discussion

In a nationwide study of middle-aged and older adults, we found that neighborhood disadvantage was associated with elevated *CD14* expression in circulating monocytes. This association persisted even after adjusting for key sociodemographic characteristics and health behaviors. Our findings align with two theoretical frameworks that undergird the importance of a cell-to-society approach. The embodiment theory posits that structural conditions become biologically embedded through sustained exposure to social, economic, and environmental stressors (Krieger, 2005). Long-term social disadvantage can lead to physiological dysregulation through activation of stress-responsive pathways. As one example, the Conserved Transcriptional Response to Adversity provides one neuro-immune pathway through which adverse social conditions can become biologically embedded through sympathetic nervous system-induced up-regulation of immature "classical" monocyte production and a resulting skew toward pro-inflammatory gene expression at the expense of innate antiviral responses (Cole, 2019). Building on this, future research should examine how psychological distress and engagement in health-compromising behaviors, such as substance misuse or poor dietary patterns, interact with these biological pathways. For instance, psychological distress may amplify the body's pro-inflammatory response and health-compromising behaviors could further perpetuate inflammation and immune dysregulation, potentially creating a feedback loop that exacerbates the long-term effects of disadvantage on health. Understanding these dynamics could help elucidate the complex interplay between biological and behavioral factors in the context of social disadvantage.

Table 2
Summary statistics of 1215 participants from the Midlife in the United States study.

Age, Mean (SD)	56.9 (12.2)
Sex, No. (%)	
Male	569 (46.8)
Female	646 (53.2)
Race/ethnicity, No. (%)	
non-Hispanic White	887 (73.0)
non-Hispanic Black	203 (16.7)
Hispanic	39 (3.2)
non-Hispanic Other	79 (6.5)
Missing	7 (0.6)
Educational attainment, No. (%)	
< High school	48 (4.0)
High school/GED	195 (16.0)
Some college and above	971 (79.9)
Missing	1 (0.1)
Annual household income, No. (%)	
< $50,000	571 (47.0)
$50,000 to $100,000	284 (23.4)
$100,000 +	267 (22.0)
Missing	93 (7.7)
Smoking status, No. (%)	
Never	721 (59.3)
Past	376 (30.9)
Current	118 (9.7)
Alcohol consumption, No. (%)	
Never	397 (32.7)
< 1 day a week	324 (26.7)
1–2 days a week	199 (16.4)
3–4 days a week	133 (10.9)
5–6 days a week	81 (6.7)
Everyday	81 (6.7)
Body mass index, Mean (SD)	28.9 (6.6)
Missing, No. (%)	39 (3.2)
CD14 gene expression level (log2-transformed normalized transcript per million value), Mean (SD)	8.8 (2.2)
Overall Neighborhood Opportunity, No. (%)	
High	485 (39.9)
Moderate	241 (19.8)
Low	489 (40.2)
Education domain, No. (%)	
High	550 (45.3)
Moderate	206 (17.0)
Low	459 (37.8)
Health and Environment domain, No. (%)	
High	294 (24.2)
Moderate	311 (25.6)
Low	610 (50.2)
Social and Economic Resources domain, No. (%)	
High	487 (40.1)

(continued on next page)

Table 2 (*continued*)

Moderate	254 (20.9)
Low	474 (39.0)

CD14 expression indexes both the relative prevalence of monocytes in general, and particularly the prevalence of the relatively immature and pro-inflammatory "classical" subset of monocytes. The observed upregulation of *CD14*, a pattern recognition receptor central to lipopolysaccharide and damage-associated molecular pattern sensing (Na et al., 2023), may reflect a transcriptional "alert" state among residents of disadvantaged neighborhoods. This is consistent with prior work linking area-level deprivation to systemic inflammation (Dembowski et al., 2022) and the Conserved Transcriptional Response to Adversity (Cole, 2019). In addition, the observed elevation in *CD14* may also reflect stress-induced myelopoiesis, wherein chronic activation of the sympathetic nervous system activation enhances the bone marrow output of innate immune cells (Barrett et al., 2021; Heidt et al., 2014; McKim et al., 2018; Powell et al., 2013; Ritzel et al., 2023; van der Heijden et al., 2020). At the same time, neighborhood-level exposures, such as air pollution and violence, may prime pro-inflammatory signaling (Miller et al., 2022; Schurman et al., 2018). This dual mechanism—heightened monocyte production and increased environmental reactivity—could explain why immune changes persist even after adjusting for individual-level characteristics. At the molecular level, these patterns parallel the Conserved Transcriptional Response to Adversity, where chronic stress alters both inflammatory and antiviral gene expression in immune cells (Cole, 2019). *CD14*, as a key mediator of pathogen sensing and tissue repair (Na et al., 2023), may serve as a functional bridge between Conserved Transcriptional Response to Adversity and the systemic inflammation linked to neighborhood disadvantage.

Notably, the elevated *CD14* expression may have implications beyond acute inflammation. While short-term *CD14* upregulation supports pathogen detection (Carey et al., 2016), chronic elevation has been linked to metabolic and age-related inflammatory conditions and various vascular diseases (Pase et al., 2020). Given that persistent toll-like receptor 4/*CD14* signaling is associated with immune dysregulation and tissue dysfunction (Kim et al., 2023), our findings raise the possibility that neighborhood disadvantage could influence this pathway. However, further mechanistic work is needed to clarify whether this reflects an adaptive trade-off or a maladaptive consequence of chronic stress.

Taking a "cells to society" perspective helps explain these patterns via multilevel pathways. At the societal level, systemic inequities in school funding, neighborhood resources, and environmental quality generate chronic stressors. At the cellular level, these stressors promote a pro-inflammatory immune phenotype characterized by elevated *CD14*, a receptor central to sensing external pathogens and internal tissue damage (Na et al., 2023). This aligns with growing evidence that neighborhood conditions can durably reprogram immune cell function (Noppert et al., 2024), exacerbating place-based inequities.

The cross-sectional nature of our study, however, limits causal interpretation. As such, longitudinal designs are critical to establish temporality. Using census-tract-level data adds spatial granularity, but

Table 3
Primary analysis: adjusted associations between Overall Neighborhood Opportunity and *CD14* gene expression level within circulating blood (log2-transformed normalized transcript per million value) in the Midlife in the United States study.

	Model 1			Model 2			Model 3		
Characteristic	Beta	95 % CI	p-value	Beta	95 % CI	p-value	Beta	95 % CI	p-value
Overall Neighborhood Opportunity									
High	—	—		—	—		—	—	
Moderate	0.08	(−0.26, 0.41)	0.66	0.21	(−0.10, 0.53)	0.19	0.19	(−0.13, 0.50)	0.24
Low	0.23	(−0.05, 0.50)	0.11	**0.47**	**(0.19, 0.76)**	**0.001**	**0.45**	**(0.16, 0.73)**	**0.002**

Results were pooled across 10 multiple imputed datasets.
Bold indicates $p < 0.05$.
Model 1 was unadjusted.
Model 2 controlled for age, sex, race/ethnicity, educational attainment, and annual household income.
Model 3 controlled for age, sex, race/ethnicity, educational attainment, annual household income, smoking status, alcohol use, and body mass index.

Table 4
Secondary analysis: adjusted associations between neighborhood opportunity subdomains and *CD14* gene expression level within circulating blood (log2-transformed normalized transcript per million value) in the Midlife in the United States study.

	Model 1			Model 2			Model 3		
Characteristic	Beta	95 % CI	p-value	Beta	95 % CI	p-value	Beta	95 % CI	p-value
Education domain									
High	—	—		—	—		—	—	
Moderate	0.14	(−0.21, 0.49)	0.43	0.10	(−0.22, 0.43)	0.53	0.09	(−0.23, 0.42)	0.58
Low	0.17	(−0.10, 0.44)	0.21	**0.37**	**(0.09, 0.65)**	**0.009**	**0.35**	**(0.07, 0.63)**	**0.015**
Health and Environment domain									
High	—	—		—	—		—	—	
Moderate	0.25	(−0.10, 0.59)	0.16	0.30	(−0.02, 0.63)	0.067	0.27	(−0.06, 0.59)	0.11
Low	0.16	(−0.15, 0.46)	0.31	0.27	(−0.02, 0.55)	0.068	0.23	(−0.06, 0.52)	0.12
Social and Economic Resources domain									
High	—	—		—	—		—	—	
Moderate	−0.04	(−0.36, 0.29)	0.83	0.21	(−0.10, 0.52)	0.19	0.18	(−0.13, 0.50)	0.25
Low	0.17	(−0.10, 0.45)	0.21	**0.44**	**(0.16, 0.73)**	**0.002**	**0.41**	**(0.12, 0.70)**	**0.006**

Results were pooled across 10 multiple imputed datasets.
Bold indicates $p < 0.05$.
Model 1 was unadjusted.
Model 2 controlled for age, sex, race/ethnicity, educational attainment, and annual household income.
Model 3 controlled for age, sex, race/ethnicity, educational attainment, annual household income, smoking status, alcohol use, and body mass index.

tracking individuals over time, particularly before and after neighborhood transitions, will provide more substantial causal evidence. Simultaneously, geospatial mapping of environmental exposures could disentangle psychosocial stress from direct immune-stimulatory effects. Moreover, future research is needed to determine whether elevated *CD14* represents a maladaptive response that contributes to chronic inflammation or an adaptive one that enhances protection in high-risk environments. Another limitation of the current investigation was the inability to account for within-census-tract correlation. Since the MIDUS Geocode team did the data merge to protect participant privacy, we could not perform multilevel modeling that nested participants within census tracts. Lastly, length of residence in the census tract was not available in the data, which may have introduced exposure misclassification bias.

Despite these limitations, our findings highlight *CD14* as a potential biomarker of biological embedding that could reflect the cumulative impact of place-based inequities on the immune system. Identifying such early biomarkers of immune dysregulation may offer intervention opportunities before the onset of inflammation-related diseases. Future studies should investigate whether improving neighborhood educational resources, for instance, attenuates monocyte activation and mitigates health risks. Ultimately, these findings position *CD14* as a potential marker of place-based immune programming, capturing how neighborhood environments shape disease susceptibility. By broadening our lens beyond traditional inflammatory models involving solely plasma biomarkers to consider cellular measures of immune plasticity, this work contributes to a more nuanced understanding of how structural- and community-level inequities may become biologically embedded.

5. Conclusions

In summary, this study showed that neighborhood disadvantage was associated with a substantial elevation in *CD14* gene expression among middle-aged adults in a national US cohort. In conjunction with prior research linking neighborhood conditions to transcriptional activity (Miller et al., 2022; Noppert et al., 2024; Smith et al., 2017), these results support the Conserved Transcriptional Response to Adversity (Cole, 2019) by identifying a cell-type-enriched marker associated with low neighborhood opportunity, even after adjusting for key sociodemographic factors and health behaviors. Although the cross-sectional design limits causal inference, these findings support a growing body of research demonstrating how inequitable social environments may reshape immune function at the molecular level (Miller et al., 2022; Noppert et al., 2024; Smith et al., 2017).

CRediT authorship contribution statement

Yanping Jiang: Investigation, Writing – review & editing. **Cole Steven W:** Writing – review & editing, Conceptualization, Investigation, Methodology. **Cuevas Adolfo G:** Writing – review & editing, Funding acquisition, Investigation, Conceptualization. **Bather Jemar R:** Methodology, Conceptualization, Writing – original draft, Formal analysis, Investigation. **Mariana Rodrigues:** Writing – original draft, Investigation.

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Declaration of Competing Interest

None.

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Data availability

The data that support this study's findings are publicly available on the MIDUS Colectica Portal.

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