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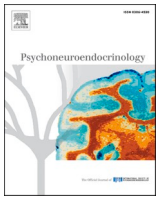

Differential expression of lymphocyte markers by neighborhood opportunity among US adults: Insights from the Midlife in the United States study

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ABSTRACT

Social and environmental neighborhood characteristics play important roles in promoting opportunities for healthy living. However, access to quality opportunities vary depending on where people live, largely due to structural injustices perpetuating inequities. Though the impacts of such injustices on physiological health outcomes are well-studied, little is known about how the underlying biological mechanisms facilitating these health outcomes may be influenced by constructs of neighborhood opportunity. To further investigate the relationship between neighborhood opportunity and immunoregulation, we used data from the Midlife in the United States study (n = 1215; mean age 56.9 years, SD = 12.2; 53.2% female, 73.0% non-Hispanic White) and the Child Opportunity Index 3.0 to examine how neighborhood opportunity may be associated with differing expression levels of *CD19* and *CD3*, canonical lineage markers for B and T cells. Primary analyses found that living in low Overall Neighborhood Opportunity areas was associated with significantly higher expression of *CD3* (38.5% elevation; 95% CI: 14.9%, 68.2%; $p < 0.001$) compared to high opportunity areas, adjusting for socio-demographic characteristics, health-related measures, and lifestyle factors. Secondary analyses of neighborhood opportunity subdomains found that higher *CD3* expression was significantly associated with low levels of Education Opportunity (32.9% elevation; 95% CI: 10.2%, 59.1%; $p = 0.003$) and Social and Economic Resources Opportunity (38.5% elevation; 95% CI: 14.9%, 68.2%; $p < 0.001$) compared to in high opportunity areas. These results suggest that social and educational neighborhood environments may play a role as social determinants of biological health, pointing to potential immunologic pathways through which neighborhood opportunity impacts health.

1. Introduction

Neighborhoods are central to where people live, learn, work, and grow, and thus are highly influential determinants of health (Arcaya et al., 2016; Diez Roux and Mair, 2010; Williams et al., 2019). The social and environmental characteristics of neighborhoods, such as access to quality education, employment opportunities, exposure to pollution, involvement in social networks, and much more, play important roles in promoting healthy living (Bailey et al., 2017; Diez Roux et al., 2016; Suiter and Meadows, 2023). However, the quality and ease of access to these factors vary significantly across neighborhoods.

These variations are not randomly distributed, but the result of historical and structural policies and practices that have systematically shaped access to opportunities and resources (Acevedo-Garcia et al., 2024; Bailey et al., 2017). For example, the legacy of redlining—a practice of the 1930s through which residents of minoritized communities were denied financial services, under the assumption they were too "high-risk" for investment—continues to shape contemporary neighborhood conditions (Aaronson et al., 2021). The qualities of a neighborhood can be measured using "neighborhood opportunity" scores, which reflect access to goods, services, and resources (Acevedo-Garcia et al., 2024). Although redlining has been illegal since

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1968, areas that were previously redlined by banks tend to have lower neighborhood opportunity scores compared to "greenlined," historically privileged neighborhoods (Acevedo-Garcia et al., 2024). These persistent inequities in neighborhood resourcing create environments that can fundamentally shape residents' health and wellbeing. As such, it is no surprise that residing in disinvested neighborhoods is associated with elevated risk for a wide range of health conditions, including cardiovascular disease (Andrews et al., 2026; Tamura et al., 2019), poor mental health (Sui et al., 2022; Visser et al., 2021), and overall mortality (Lawrence et al., 2024). However, the pathways through which neighborhood characteristics may elicit biological consequences and contribute to increased disease risk remain unclear.

Neighborhood opportunity may influence health outcomes through social signal transduction, a process by which psychosocial stressors triggered by adversity are translated into systemic biological changes (Cole, 2013, 2019; Slavich and Irwin, 2014). While the body is evolutionarily equipped to manage acute stressors via the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, chronic exposure to adverse conditions can precipitate long-term immune dysregulation by altering cell signaling cascades and gene regulation (Dhabhar, 2014). The neighborhood serves as a primary site of such exposure: living in under-resourced, disinvested, or heavily surveilled environments can induce a state of chronic perceived threat, repeatedly activating environmental danger appraisal systems in the brain (Baumer et al., 2023; Koss et al., 2014). These persistent threat signals initiate molecular cascades that can result in downstream biological consequences, such as dysregulated inflammatory gene expression that contributes to impaired immune cell production and function (Cole, 2019; Dhabhar, 2014).

Patterns of dysregulated gene expression can provide important insight on how psychosocial stress may elicit biological consequences, demarcating a launch point for hypothesis generation in the landscape of social signal transduction research. Genomic data collected through RNA sequencing is widely available in major longitudinal health studies (Bick et al., 2024; Cole et al., 2020; Hansen et al., 2025; Wu et al., 2025), making it an approachable and accessible source of data. Studies have found associations between neighborhood disadvantage (Boyle et al., 2024) and broad psychosocial stress exposure (Barnard et al., 2024) with irregular expression of proinflammatory pathway genes, indicating potential for extended exploration of immune actors that promote inflammation, such as lymphocytes. *CD19* and *CD3* are defining signaling markers of B and T lymphocytes, respectively (Martin, 2011; Wang et al., 2012), which act as primary coordinators of the adaptive immune response by relying on specific signaling cascades to regulate their populations and respond to immunological challenges (Dhabhar, 2014; LaRosa and Orange, 2008). RNA sequencing data cannot directly quantify circulating B or T cell abundance (Li et al., 2020; Su et al., 2024) or trafficking to specific tissues (Chia et al., 2016), two measures which may offer more direct insight into immune cell functionality but are not collected in MIDUS. However, quantifying *CD19* and *CD3* expression can offer a preliminary view of how up- or downregulation of these key signaling biomarkers may relate to different neighborhood opportunity contexts. Consequently, we apply the framework of social signal transduction to hypothesize that living in low opportunity environments is significantly associated with dysregulated levels of *CD19* and *CD3* gene expression.

This study examines associations between neighborhood opportunity and *CD19* and *CD3* marker expression to further understand how one's neighborhood conditions may influence expression of specific immune function genes. To assess levels of neighborhood opportunity, we employed the Child Opportunity Index (COI) 3.0 as a multidimensional tool for investigating how one's current neighborhood resources impact growth across all age groups (Acevedo-Garcia et al., 2024; Crump et al., 2025; Noelke et al., 2024). Drawing on data from the Midlife in the United States (MIDUS) study, these analyses aim to shed light on potential pathways through which structural conditions may impact health down to the molecular level.

2. Materials and methods

2.1. Study design, setting, and sample

The MIDUS study is a national longitudinal cohort study that examines psychosocial traits of U.S. participants to understand health-related biopsychosocial pathways across the adult lifespan (Radler, 2014). MIDUS is an ongoing project coordinated by the University of Wisconsin–Madison. MIDUS 1 (1995–1996) constituted the first wave of data collection, recruiting 7108 U.S. adults aged 25–74 through random digital dialing. Participants completed telephone interviews and self-administered questionnaires focusing on psychological and social factors. MIDUS 2 (2004–2005) aimed to collect longitudinal follow-up data from MIDUS 1 participants. This wave included 4963 respondents from the original cohort and expanded to incorporate a new city-specific sample of 592 African American participants from Milwaukee, Wisconsin. MIDUS 3 (2013–2014) continued the longitudinal trajectory with 3683 participants from Wave 2. MIDUS Refresher Study (2011–2014) recruited an additional 4085 participants (including 508 African American participants from Milwaukee, Wisconsin) to replenish the MIDUS 1 cohort.

2.2. Biomarker studies

Optional follow-up biomarker studies were conducted for participants who completed surveys and were healthy enough to travel to one of three study sites: Georgetown University, the University of Wisconsin–Madison, and the University of California, Los Angeles (Dienberg Love et al., 2010). These biomarker studies provided comprehensive participant support, including detailed protocol information, $200 compensation for the two-day clinic visit, and full travel expense coverage. The MIDUS team arranged all travel logistics, allowed older participants to bring companions, and covered childcare expenses when needed. Biomarker participants underwent extensive data collection during a two-day clinic visit, including bodily fluid samples (e.g., fasting blood, 12-hour urine, and saliva), comprehensive physical examinations (e.g., blood pressure, morphology, and functional assessments), and self-report health questionnaires. These biological samples enabled examination of cardiovascular, neuroendocrine, inflammatory, musculoskeletal, and antioxidant systems.

The MIDUS Refresher Biomarker Study (2012–2016) enrolled 862 participants from the MIDUS Refresher 1 cohort. Separately, participants from the original MIDUS cohort completed a follow-up biomarker assessment at Wave 3 (MIDUS 3 Biomarker Project, 2017–2022), with 747 participants successfully completing this follow-up using the same protocol as the MIDUS Refresher Biomarker Study. Of the 1609 participants from the original MIDUS and Refresher cohorts, 1215 had valid gene expression data. All MIDUS study participants provided informed consent, and protocols were approved by the University of Wisconsin Institutional Review Board. Detailed protocols for all MIDUS studies have been previously described in the literature (Dienberg Love et al., 2010; Radler, 2014). This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (von Elm et al., 2007) and was considered exempt from review by the New York University Institutional Review Board.

2.3. Measurement of lymphocyte marker gene expression

Gene expression data were obtained from the MIDUS Biomarker Projects through a standardized protocol (Dienberg Love et al., 2010). Blood samples were collected via fasting blood draw on the morning of the second day of the clinic visit using BD Vacutainer CPT Tubes. Following collection, samples underwent immediate processing to isolate peripheral blood mononuclear cells, which were maintained at

−60℃ to −80℃ before shipment to the MIDUS biorepository for long-term storage at −65℃ until assay. Peripheral blood mononuclear cell gene expression profiling for the MIDUS Refresher Biomarker Study was performed during 2017–2018, while profiling for the MIDUS 3 Biomarker Project occurred from 2018 to 2022.

RNA extracted from stored peripheral blood mononuclear cells was assessed for yield and integrity prior to transcriptome profiling. Sequencing employed a 5' gene counting approach (Lexogen QuantSeq FWD) with Illumina HiSeq 4000 or NovaSeq platforms, generating over 10 million single-strand 65-nucleotide reads per sample. Read alignment to the human transcriptome was performed using STAR, with transcript abundance quantified at the gene level (Dobin et al., 2013). Expression values were normalized to transcripts per million, adjusted using 11 housekeeping genes as a reference panel (Eisenberg and Levanon, 2013), and log2-transformed. Samples with fewer than 5 million mapped reads or poor mapping efficiency were excluded from analysis.

This study focused on *CD19*, a canonical marker of B lymphocytes, and *CD3*, a defining marker of the T lymphocyte lineage (Martin, 2011; Wang et al., 2012). These markers were selected to assess relative regulation of B and T cells with the understanding that *CD19* and *CD3* mRNA expression levels do not match one-to-one cell counts (Li et al., 2020; Su et al., 2024), but broadly garner insight on either expansion of cell populations expressing these markers and potential up- or down-regulation of key signaling biomarkers. As such, it is important to note that any observed changes in *CD19* and *CD3* expression levels do not discern between fluctuations in overall cell composition and within-cell transcriptional differences. mRNA-based measures were used in lieu of protein-based flow cytometry, which could disentangle these observations but is not collected in MIDUS. Additionally, DNA methylation and white blood cell count data are not publicly available in the dataset, limiting further deconvolution analyses. Detailed methodological protocols are available on the MIDUS Colectica Portal (http://midus.colectica.org/) and in prior studies (Bather et al., 2025; Cuevas et al., 2020; Mann et al., 2020).

2.4. Neighborhood opportunity

Neighborhood opportunity was measured using the COI 3.0 (Noelke et al., 2024). Although originally developed to evaluate neighborhood conditions affecting childhood development, the COI's components are equally relevant for studying adult populations, as demonstrated in research examining associations with cardiometabolic risk and mortality (Gianaros et al., 2023; Slopen et al., 2023), allostatic load (Crump et al., 2025), and cellular senescence (Rodrigues et al., 2026) in adults. COI indicators were assessed at the time of survey and included social determinants of health studied in all age groups, including midlife and older adults, such as educational attainment (Muller et al., 2025), air pollution (Zou et al., 2025), walkability and food environments (Hyun et al., 2025), and housing quality (Bhat et al., 2022) (Table 1). Participants' census tract data, reflecting their residence at the time of survey completion, were linked to the COI 3.0 through a secure process conducted exclusively by the MIDUS Geocode team with special permission to protect participant privacy. Accordingly, neighborhood opportunity in this study captures concurrent residential conditions at the time of data collection, reflecting an exposure window with potentially direct relevance to immunoregulatory processes in adults.

The COI represents a methodological advancement over existing neighborhood assessment tools. Traditional measures like the Area Deprivation Index (Kind and Buckingham, 2018) and the Social Vulnerability Index (Flanagan et al., 2011) depend exclusively on American Community Survey data, employ unstandardized aggregation methods, and are limited in the range of neighborhood characteristics and number of constructs they represent. In contrast, the COI integrates diverse data sources—spanning the American Community Survey, Opportunity Insights, and the National Center for Charitable Statistics Internal Revenue Service Business Master File—while applying consistent

Table 1
Components of the Child Opportunity Index 3.0 (Noelke et al., 2024).

Domain	Indicators	Source
Education		
Early Childhood Education	Private pre-K enrollment	5-year American Community Survey
	Public pre-K enrollment	
Elementary Education	Reading and math test scores	Stanford Education Data Archive, Version 5.0
	Reading and math test score growth	
	Poverty-adjusted reading and math test scores	
Secondary & Post-Secondary Education	Advanced Placement course enrollment	U.S. Department of Education Office for Civil Rights Data Collection
	College enrollment in nearby institutions	5-year American Community Survey
	High school graduation rate	U.S. Department of Education EDFacts Four-Year Adjusted-Cohort Graduation Rates Data Files
Educational Resources	Adult educational attainment	5-year American Community Survey
	Child enrichment-related non-profits	National Center for Charitable Statistics Unified Business Master File
	Teacher experience	U.S. Department of Education Office for Civil Rights Data Collection
	School poverty	National Center for Education Statistics Common Core of Data
Health and Environment		
Pollution	Airborne microparticles	U.S. Environmental Protection Agency Fused Air Quality Surface Using Downscaling output files
	Ozone concentration	
	Industrial pollutants in air, water or soil	U.S. Environmental Protection Agency 2023 Aggregated Grid Cell Microdata Core files
	Hazardous waste dump sites	U.S. Environmental Protection Agency Superfund National Priorities List
Healthy Environments	Fast food restaurant density	DataAxle company database
	Healthy food retailer density	
	Extreme heat exposure	North American Land Data Assimilation System Phase 2 Primary Forcing Data, National Aeronautics and Space Administration Goddard Earth Sciences Data and Information Services Center
	NatureScore	NatureQuant
	Walkability	U.S. Environmental Protection Agency and U.S. General Services Administration Smart Location Database, version 3
Safety-Related Resources	Community safety-related non-profits	National Center for Charitable Statistics Unified Business Master File
	Vacant housing	5-year American Community Survey
Health Resources	Health-related non-profits	National Center for Charitable Statistics Unified Business Master File
	Health insurance coverage	5-year American Community Survey
Social and Economic Resources		
Employment	Employment rate	5-year American Community Survey
	High-skill employment rate	

(*continued on next page*)

Table 1 (*continued*)

Domain	Indicators	Source
	Full-time year-round earnings	
Economic Resources	Median household income	
	Poverty rate	
	Public assistance rate	
Concentrated Socioeconomic Inequity	Adults with advanced degrees	
	Very high-income households	
	Adults without high school degrees	
	Very low-income households	
Housing Resources	Broadband access	
	Crowded housing	
Social Resources	Mobility-enhancing friendships	Opportunity Insights
	Single-parent families	5-year American Community Survey
	Non-profit organizations	National Center for Charitable Statistics Unified Business Master File
Wealth	Homeownership rate	5-year American Community Survey
	Aggregate home values	
	Aggregate capital income	
	Aggregate real estate taxes	

standardization procedures across all components. Additionally, the COI synthesizes 44 distinct indicators across three conceptual domains: Education, Health and Environment, and Social and Economic Resources. Each indicator was standardized via z-score transformation, weighted, and aggregated to produce nationally referenced scores for both the overall scale and domain-specific subscales. Standard COI classification employs five tiers based on national percentile distributions: very low (bottom quintile), low (second quintile), moderate (middle quintile), high (fourth quintile), and very high (top quintile). For this analysis, we collapsed these into three meaningful categories: low opportunity (bottom two quintiles), moderate opportunity (middle quintile), and high opportunity (top two quintiles). This decision was made due to small sample sizes and to align with prior literature (Bather et al., 2025; Crump et al., 2025; Rodrigues et al., 2026).

2.5. Covariates

Covariates included sociodemographic characteristics, health-related measures, and lifestyle factors. Sociodemographic variables assessed from self-report questionnaires included age (measured continuously), sex (male or female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic Other), marital status (married, divorced/separated/widowed, and never married), educational attainment (high school or less, some college/associate's degree, and college degree or higher), and annual household income from wages (under $50,000, $50,000 to $100,000, and $100,000 +). The "non-Hispanic Other" category encompassed participants identifying as Native American, Alaskan Native, Native Hawaiian, Pacific Islander, or Asian.

Health-related measures included the number of chronic health conditions, blood C-reactive protein (ug/mL), and personal cancer history. Participants reported the presence of 30 chronic health conditions over the preceding 12 months. Conditions spanned multiple organ systems and domains: respiratory (asthma/bronchitis/emphysema, tuberculosis, other lung problems), musculoskeletal (arthritis/rheumatism/bone-joint disease, sciatica/lumbago/recurring backache), dermatological (persistent skin trouble), endocrine (thyroid disease, diabetes/high blood sugar), allergic (hay fever), gastrointestinal (recurring stomach trouble/indigestion/diarrhea, constipation, gallbladder trouble, ulcer, hernia, hemorrhoids, swallowing problems), genitourinary (urinary/bladder problems), cardiovascular (hypertension, varicose veins requiring treatment, stroke), neurological (multiple sclerosis/epilepsy/other neurological disorders, migraine), immunological (HIV/AIDS, lupus/autoimmune disease), oral health (gum/mouth trouble, dental problems), podiatric (persistent foot trouble), and mental health/behavioral (anxiety/depression/emotional disorder, alcohol/drug problems, chronic sleep problems). A summed count was used as a continuous covariate. Blood C-reactive protein (ug/mL) was obtained from the biomarker assessments. Personal history of cancer was self-reported.

Lifestyle factors encompassed smoking status, past month alcohol consumption, and body mass index (BMI). Smoking status was classified as never, past, or current. Alcohol consumption patterns in the past month were categorized as never, less than one day weekly, one to two days weekly, or three or more days weekly. BMI (kg/m^2) was assessed in the biomarker studies and included as a continuous variable.

2.6. Statistical analysis

In the primary analyses, we fit separate regression models for log2-transformed *CD19* and *CD3* transcript abundance values. Each gene expression outcome was regressed on Overall Neighborhood Opportunity in Model 1 (unadjusted). Model 2 incorporated sociodemographic covariates (age, sex, race/ethnicity, marital status, educational attainment, and annual household income). Model 3 added health-related measures (number of chronic health conditions, C-reactive protein, and personal cancer history). To evaluate whether lifestyle factors might influence the association between neighborhood opportunity and gene expression outcomes, Model 4 further adjusted for smoking status, alcohol consumption, and BMI. Using this same tiered covariate adjustment strategy, we conducted secondary analyses examining each COI domain (Education, Health and Environment, and Social and Economic Resources) in relation to *CD19* and *CD3*. Regression coefficients were back-transformed to facilitate meaningful interpretation of associations using the formula $(2^{\beta}-1)\times 100$ to convert coefficients into percentage differences in gene expression levels.

We conducted several sensitivity analyses. First, we refit the primary models using COI quintiles instead of the 3-level categorical variable to assess robustness of findings to the categorization scheme. Second, we refit the primary models excluding participants with a personal history of cancer to ensure that results were not driven by this subgroup, in whom the biological relationship between neighborhood context and immune cell gene expression may operate differently. Third, because the Health and Environment domain comprises distinct environmental resources and hazards that may relate to immune functioning through different pathways (Algur et al., 2023; Iyer et al., 2022; K.-H. Kim et al., 2018), we fit separate models for each Health and Environment subdomain.

We employed multivariate imputation by chained equations to address incomplete covariate information using the *mice* package in R (van Buuren and Groothuis-Oudshoorn, 2011). Different statistical approaches were applied based on variable type: polytomous logistic regression for race/ethnicity (0.6% missingness) and marital status (0.1% missingness), ordinal logistic regression for educational attainment (0.1% missingness) and annual household income (7.7% missingness), predictive mean matching for the number of chronic health conditions (2.2% missingness), and logistic regression for personal cancer history (0.2% missingness). Results from regression models were pooled across ten imputed datasets using Rubin's rules (Rubin, 1987). All statistical computations were performed using R version 4.4.3 (R Core Team, R Foundation for Statistical Computing).

3. Results

3.1. Primary analyses

The sample included 1215 adults (mean age 56.9 years, SD = 12.2), with 53.2% female, 73.0% non-Hispanic White, and 79.9% having completed at least some college education (Table 2). In primary analyses, individuals living in low Overall Neighborhood Opportunity areas exhibited significantly higher *CD3* expression compared to those in high opportunity areas (Table 3). In Model 1 (unadjusted), *CD3* expression was 32.0% higher among residents of low opportunity neighborhoods (95% CI: 11.0%, 56.9%, $p = 0.002$). After adjustment for sociodemographic characteristics in Model 2, this association strengthened to 40.4% (95% CI: 16.5%, 69.3%, $p < 0.001$) and remained stable in Model 3 (39.5%, 95% CI: 14.9%, 68.2%, $p < 0.001$) with the addition of health-related covariates. In the final model additionally accounting for lifestyle factors, *CD3* expression remained 38.5% higher in the low opportunity group (95% CI: 14.9%, 68.2%, $p < 0.001$). *CD19* expression showed a similar pattern of elevated expression in the low opportunity group, though associations attenuated to non-significance after adjustment for lifestyle factors (Table 3). Sensitivity analyses using COI quintiles (Supplemental Table 1) and excluding participants with a personal history of cancer (Supplemental Table 2) yielded similar results.

3.2. Secondary analyses

Secondary analyses examined associations between specific neighborhood opportunity domains and *CD19* and *CD3* gene expression (Table 4). Low Education Opportunity was associated with 30.1% higher *CD19* expression in Model 1 (95% CI: 5.7%, 60.2%, $p = 0.013$), but this association attenuated to non-significance after adjustment for sociodemographic factors in Model 2 (20.6% elevation, 95% CI: −4.7%, 52.6%, $p = 0.12$). Similarly, low Social and Economic Resources Opportunity was associated with 33.8% higher *CD19* expression in Model 1 (95% CI: 8.7%, 65.9%, $p = 0.007$) but attenuated to non-significance in Model 2 (26.6% elevation, 95% CI: −0.7%, 60.2%, $p = 0.055$). The Health and Environment domain showed no significant associations in any model. However, subdomain analyses (Supplemental Table 3) revealed that low Health Resources Opportunity (health-related nonprofits and health insurance coverage) was associated with 52.6% higher *CD19* expression in Model 1 (95% CI: 19.7%, 94.5%, $p < 0.001$), persisting in the final adjusted model (Model 4: 42.4% elevation, 95% CI: 11.0%, 84.0%, $p = 0.006$). *CD3* expression showed more robust associations with the neighborhood opportunity subdomains (Table 4). Individuals in low Education Opportunity neighborhoods exhibited consistently elevated *CD3* expression, with associations strengthening from 31.0% in Model 1 (95% CI: 10.2%, 55.8%, $p = 0.002$) to 32.9% in Model 4 (95% CI: 10.2%, 59.1%, $p = 0.003$). Low Social and Economic Resources Opportunity showed a similar pattern, with 32.0% higher expression in Model 1 (95% CI: 10.2%, 56.9%, $p = 0.002$) strengthening to 38.5% in Model 4 (95% CI: 14.9%, 68.2%, $p < 0.001$). Subdomain analyses (Supplemental Table 4) indicated that low Health Resources Opportunity was associated with elevated *CD3* expression in Models 1 and 2 (both 32.1% elevation, 95% CI: 0.7%, 50.5%) but attenuated to non-significance in Model 3 (20.6% elevation, 95% CI: −1.4%, 47.4%, $p = 0.065$).

4. Discussion

This study investigated associations of neighborhood opportunity with *CD3* and *CD19* gene expression levels in a large sample of US adults, leveraging social signal transduction theory as a framework to understand how neighborhood opportunity may elicit biological consequences. Primary analyses indicated that living in areas characterized by low levels of Overall Neighborhood Opportunity was associated with

Table 2
Characteristics of participants from the Midlife in the United States study, overall and by neighborhood opportunity.

Characteristic	Overall	High	Moderate	Low
	N = 1215	N = 485	N = 241	N = 489
Age, Mean (SD)	56.9 (12.2)	57.9 (11.9)	56.4 (12.7)	56.2 (12.3)
Sex, n (%)				
Male	569 (46.8)	247 (50.9)	116 (48.1)	206 (42.1)
Female	646 (53.2)	238 (49.1)	125 (51.9)	283 (57.9)
Race/ethnicity, n (%)				
non-Hispanic White	887 (73.0)	409 (84.3)	206 (85.5)	272 (55.6)
non-Hispanic Black	203 (16.7)	17 (3.5)	15 (6.2)	171 (35.0)
Hispanic	39 (3.2)	15 (3.1)	6 (2.5)	18 (3.7)
non-Hispanic Other	79 (6.5)	40 (8.2)	13 (5.4)	26 (5.3)
Missing	7 (0.6)	4 (0.8)	1 (0.4)	2 (0.4)
Marital status, n (%)				
Married	756 (62.2)	344 (70.9)	179 (74.3)	233 (47.6)
Divorced/Separated/ Widowed	281 (23.1)	97 (20.0)	37 (15.4)	147 (30.1)
Never married	177 (14.6)	43 (8.9)	25 (10.4)	109 (22.3)
Missing	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
Educational attainment, n (%)				
High school or less	243 (20.0)	53 (10.9)	56 (23.2)	134 (27.4)
Some college/associate's degree	378 (31.1)	119 (24.5)	72 (29.9)	187 (38.2)
College degree or higher	593 (48.8)	313 (64.5)	112 (46.5)	168 (34.4)
Missing	1 (0.1)	0 (0.0)	1 (0.4)	0 (0.0)
Annual household income, n (%)				
< $50,000	571 (47.0)	180 (37.1)	97 (40.2)	294 (60.1)
$50,000 to $100,000	284 (23.4)	98 (20.2)	70 (29.0)	116 (23.7)
$100,000 +	267 (22.0)	167 (34.4)	54 (22.4)	46 (9.4)
Missing	93 (7.7)	40 (8.2)	20 (8.3)	33 (6.7)
Number of chronic health conditions, Mean (SD)	3.0 (3.0)	2.4 (2.4)	2.8 (3.0)	3.7 (3.3)
Missing, n (%)	27 (2.2)	10 (2.1)	4 (1.7)	13 (2.7)
Blood C-reactive protein (ug/mL), Mean (SD)	3.5 (5.3)	3.0 (5.3)	3.2 (4.5)	4.1 (5.7)
Personal cancer history, n (%)				
No	1038 (85.4)	411 (84.7)	201 (83.4)	426 (87.1)
Yes	175 (14.4)	73 (15.1)	40 (16.6)	62 (12.7)
Missing	2 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Smoking status, n (%)				
Never	721 (59.3)	322 (66.4)	152 (63.1)	247 (50.5)
Past	376 (30.9)	139 (28.7)	73 (30.3)	164 (33.5)
Current	118 (9.7)	24 (4.9)	16 (6.6)	78 (16.0)
Alcohol consumption, n (%)				
Never	397 (32.7)	121 (24.9)	76 (31.5)	200 (40.9)
< 1 day a week	324 (26.7)	127 (26.2)	67 (27.8)	130 (26.6)
1–2 days a week	199 (16.4)	88 (18.1)	40 (16.6)	71 (14.5)
3 + days a week	295 (24.3)	149 (30.7)	58 (24.1)	88 (18.0)
Body mass index (kg/m^2), Mean (SD)	30.0 (6.8)	28.7 (6.0)	29.9 (6.0)	31.4 (7.7)
CD19 gene expression level (log2-transformed	4.2 (2.4)	4.0 (2.4)	4.0 (2.3)	4.4 (2.5)

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Table 2 (*continued*)

Characteristic	Overall	High	Moderate	Low
	N = 1215	N = 485	N = 241	N = 489
normalized transcript per million value), Mean (SD)				
CD3 gene expression level (log2-transformed normalized transcript per million value), Mean (SD)	7.3 (2.0)	7.1 (2.0)	7.1 (2.0)	7.5 (2.1)
Education domain, n (%)				
High	550 (45.3)	443 (91.3)	88 (36.5)	19 (3.9)
Moderate	206 (17.0)	36 (7.4)	100 (41.5)	70 (14.3)
Low	459 (37.8)	6 (1.2)	53 (22.0)	400 (81.8)
Health and Environment domain, n (%)				
High	294 (24.2)	242 (49.9)	33 (13.7)	19 (3.9)
Moderate	311 (25.6)	145 (29.9)	78 (32.4)	88 (18.0)
Low	610 (50.2)	98 (20.2)	130 (53.9)	382 (78.1)
Social and Economic Resources domain, n (%)				
High	487 (40.1)	446 (92.0)	41 (17.0)	0 (0.0)
Moderate	254 (20.9)	39 (8.0)	174 (72.2)	41 (8.4)
Low	474 (39.0)	0 (0.0)	26 (10.8)	448 (91.6)

significantly elevated levels of *CD19* and *CD3* mRNA in peripheral blood mononuclear cells. These elevations persisted after adjustment for sociodemographic characteristics, health-related measures, and lifestyle factors. Secondary analyses of neighborhood opportunity subdomains found *CD19* and *CD3* expression levels to be most closely related to educational, social, and economic aspects of neighborhood opportunity, whereas the Health and Environment domain showed no significant associations with the selected lymphocyte markers.

These analyses suggest potential pathways through which adverse neighborhood conditions are hypothesized to elicit biological consequences. Limited access to social and economic resources—including COI factors such as stable employment, social service providers, mobility-enhancing networks, and quality housing—may lend to chronic threat perception and complicate acquisition of financial and social capital (Crump et al., 2025; Gilbert et al., 2022). Framed through social signal transduction theory, these findings suggest living in lower opportunity neighborhoods with limited access to capital may induce adversity-related stress responses that activate pathways regulating *CD19* and *CD3* expression (Cole, 2019; Klopack, Crimmins, et al., 2022; Raymond et al., 2021).

Interestingly, both low and moderate Education Opportunity were significantly associated with elevated *CD3* expression when compared to high Education Opportunity in the final adjusted model. This suggests transduction of *CD3* expression may be especially sensitive to social signals of Education Opportunity, even if the participant did not attend school in the neighborhood recorded at the time of survey completion. Institutional resource theory posits that the quality of institutions—in this case, schools—often reflect the quality of the neighborhoods in which they are situated, proposing school resource availability can act as a proxy indicator of broader community resource access (Bennett, 2011). Further, Education Opportunity-related influences on the health of middle-aged to older adults can be understood in broader contexts, such as through their roles as parents or guardians. Educational environments are foundational for building health literacy (Coughlin et al., 2020) and social capital (Gilbert et al., 2022), benefits of which can pass intergenerationally within a family (Bennett, 2011; Peterson et al., 2025) as well as have lasting impacts into adulthood. Additionally, while schools may serve as settings for early exposure to psychosocial stressors (Matheny et al., 1993; Whiting et al., 2021), they can also provide important adversity-buffering resources such as access to supportive adults (J. Kim, 2021) and mental health services (Golberstein et al., 2024). When these opportunities are absent or under-resourced, families with school-going children may be more likely to experience stress (Votruba-Drzal et al., 2021), which in turn may induce immune activation (Bellavance and Rivest, 2014; Zefferino et al., 2021). The significant elevations in *CD3* expression seen both in the low and moderate Education Opportunity domain groups suggest that tenants of the Education Opportunity domain may have particularly strong relationships with *CD3* regulation.

While associations between the Social and Economic Resources domain and Education domain with *CD3* expression persisted through final model adjustments, the initial associations observed with *CD19* expression attenuated after adjusting for sociodemographic factors. This divergence suggests that *CD3* and *CD19* regulatory mechanisms may be differentially sensitive to adverse conditions—a distinction supported by animal models of social adversity. For instance, chronic stress in mice has been shown to increase the relative proportion of circulating T cells while simultaneously causing a slight decline in B cell counts

Table 3
Primary analysis: associations between neighborhood opportunity and *CD19* and *CD3* expression (log2-transformed normalized transcript per million values) in the Midlife in the United States study.

	Model 1		Model 2		Model 3		Model 4	
Characteristic	**Beta (95% CI)**	**p-value**	**Beta (95% CI)**	**p-value**	**Beta (95% CI)**	**p-value**	**Beta (95% CI)**	**p-value**
CD19								
Overall Neighborhood Opportunity								
High	—		—		—		—	
Moderate	−0.04 (−0.41–0.33)	0.82	−0.02 (−0.40–0.35)	0.90	−0.02 (−0.40–0.35)	0.90	−0.05 (−0.42–0.33)	0.81
Low	**0.43 (0.13–0.73)**	**0.005**	**0.36 (0.02–0.70)**	**0.037**	**0.35 (0.01–0.69)**	**0.044**	0.32 (−0.03–0.66)	0.073
CD3								
Overall Neighborhood Opportunity								
High	—		—		—		—	
Moderate	−0.02 (−0.33–0.29)	0.89	0.06 (−0.24–0.36)	0.70	0.05 (−0.24–0.35)	0.72	0.06 (−0.24–0.36)	0.72
Low	**0.40 (0.15–0.65)**	**0.002**	**0.49 (0.22–0.76)**	**< 0.001**	**0.48 (0.20–0.75)**	**< 0.001**	**0.47 (0.20–0.75)**	**< 0.001**

Abbreviation: CI = Confidence Interval
Results are pooled across ten multiple imputed datasets.
Bold indicates $p < 0.05$.
Model 1 is unadjusted.
Model 2 = Model 1 + age + sex + race/ethnicity + marital status + educational attainment + annual household income
Model 3 = Model 2 + number of chronic health conditions + C-reactive protein + personal cancer history
Model 4 = Model 3 + smoking status + past month alcohol consumption + body mass index

Table 4
Secondary analysis: associations between neighborhood opportunity subdomains and *CD19* and *CD3* expression (log2-transformed normalized transcript per million values) in the Midlife in the United States study.

	Model 1		Model 2		Model 3		Model 4	
Characteristic	**Beta (95% CI)**	**p-value**	**Beta (95% CI)**	**p-value**	**Beta (95% CI)**	**p-value**	**Beta (95% CI)**	**p-value**
CD19								
Education domain								
High	—		—		—		—	
Moderate	0.28 (−0.10–0.67)	0.15	0.29 (−0.10–0.67)	0.15	0.29 (−0.10–0.68)	0.14	0.30 (−0.09–0.69)	0.13
Low	**0.38 (0.08–0.68)**	**0.013**	0.27 (−0.07–0.61)	0.12	0.25 (−0.09–0.59)	0.14	0.23 (−0.11–0.57)	0.18
Health and Environment domain								
High	—		—		—		—	
Moderate	0.30 (−0.09–0.68)	0.13	0.19 (−0.20–0.58)	0.34	0.19 (−0.20–0.57)	0.35	0.17 (−0.22–0.56)	0.40
Low	0.32 (−0.01–0.66)	0.058	0.26 (−0.09–0.60)	0.14	0.25 (−0.10–0.60)	0.16	0.23 (−0.12–0.57)	0.20
Social and Economic Resources domain								
High	—		—		—		—	
Moderate	0.03 (−0.34–0.39)	0.88	0.04 (−0.33–0.42)	0.83	0.04 (−0.34–0.42)	0.84	0.02 (−0.36–0.39)	0.93
Low	**0.42 (0.12–0.73)**	**0.007**	0.34 (−0.01–0.68)	0.055	0.33 (−0.02–0.67)	0.064	0.28 (−0.07–0.63)	0.11
CD3								
Education domain								
High	—		—		—		—	
Moderate	**0.35 (0.03–0.67)**	**0.034**	**0.33 (0.02–0.63)**	**0.038**	**0.32 (0.01–0.63)**	**0.040**	**0.33 (0.02–0.64)**	**0.037**
Low	**0.39 (0.14–0.64)**	**0.002**	**0.44 (0.17–0.70)**	**0.001**	**0.41 (0.14–0.68)**	**0.003**	**0.41 (0.14–0.67)**	**0.003**
Health and Environment domain								
High	—		—		—		—	
Moderate	0.27 (−0.05–0.59)	0.10	0.22 (−0.09–0.53)	0.16	0.21 (−0.10–0.52)	0.18	0.20 (−0.11–0.51)	0.21
Low	0.09 (−0.19–0.37)	0.52	0.10 (−0.17–0.37)	0.47	0.06 (−0.22–0.33)	0.68	0.05 (−0.23–0.32)	0.73
Social and Economic Resources domain								
High	—		—		—		—	
Moderate	−0.03 (−0.34–0.27)	0.83	0.11 (−0.19–0.41)	0.47	0.11 (−0.19–0.40)	0.48	0.11 (−0.19–0.41)	0.46
Low	**0.40 (0.14–0.65)**	**0.002**	**0.50 (0.23–0.78)**	**< 0.001**	**0.48 (0.21–0.76)**	**< 0.001**	**0.47 (0.20–0.75)**	**< 0.001**

Abbreviation: CI = Confidence Interval
Results are pooled across ten multiple imputed datasets.
Bold indicates $p < 0.05$.
Model 1 is unadjusted.
Model 2 = Model 1 + age + sex + race/ethnicity + marital status + educational attainment + annual household income
Model 3 = Model 2 + number of chronic health conditions + C-reactive protein + personal cancer history
Model 4 = Model 3 + smoking status + past month alcohol consumption + body mass index

(Domínguez-Gerpe and Rey-Méndez, 2001) and significant decreases in meningeal B cells (Lynall et al., 2021). In humans, the physiological translation of psychosocial stress into B cell regulation remains an emerging field with mixed results. Recent studies found that interpersonal discrimination was positively associated with T cell counts (Aronoff et al., 2022; Kranz et al., 2026). However, findings regarding B cells are less uniform; while Aronoff et al. found no significant association, Kranz et al. found an association between discrimination and higher counts of both total and "exhausted" memory B cells. These discrepancies might be due to differing types of adversities, as well as varied sociodemographic, health, or behavioral factors (Ahmetspahic et al., 2018; Hathaway et al., 2024; Klopack, Thyagarajan, et al., 2022).

From an immunological perspective, future studies could investigate whether heightened sensitivity of T cell regulation to adverse environments may be rooted in the signaling hierarchy between these cell types. A hypothetical pathway further research could explore concerns the role T cells play in B cell activation (Cano and Lopera, 2013; Ossendorp et al., 2023), by which chronic exposure to low opportunity environments may maintain a low-level T cell response that fails to reach the threshold necessary to signal increased CD19 B lymphocyte production. This threshold effect could explain why T cell indicators are more consistently associated with psychosocial stressors, but B cell indicators are not (Aronoff et al., 2022; Klopack, Crimmins, et al., 2022). Longitudinal analyses would provide clarity on the temporal ordering of such pathways.

Initially, no significant associations were observed between the Health and Environment domain with either marker. However, supplementary analyses revealed a persistent association between *CD19* elevation and low Health Resources Opportunity, which is a specific component of the subdomain including nonprofit access and insurance coverage. Given the critical role of these resources in preventative care and chronic disease management (Cha et al., 2025; Nguyen et al., 2021), this finding highlights a specific biological consequence that may be closely tied to resource deprivation. In contrast, built environment subdomains—such as those related to pollution and food accessibility—did not show robust associations. Since these factors are often tightly coupled with household socioeconomic status (Carvajal et al., 2025; Lawrence et al., 2024), it is possible that covariate adjustments masked their individual associations. Future research should aim to further disentangle these specific environmental subdomain associations.

Taken together, these findings suggest that different dimensions of neighborhood opportunity may influence distinct arms of the adaptive immune system through unique social signal transduction pathways. Low access to components of the Social and Economic Resources domain and Education domain may affect *CD19* expression through sociodemographic characteristic, behavioral, and physiological health pathways yet to be understood, while limited Education Opportunity and Social and Economic Resources Opportunity may shape *CD3* expression more directly through restricting access to protective resources and adversity-buffering environments. Future work can focus on identifying the biobehavioral pathways through which neighborhood opportunity elicits biological consequences, including how adverse environments, lifestyle factors, and psychosocial resources could interact to shape immune profiles over time.

These results should be understood in the context of their limitations that point to opportunities for continuing research. First, the cross-sectional design of data collection limits analyses from drawing causal conclusions about the association between neighborhood opportunity and lymphocyte regulation, as well as temporal ordering. Neighborhood

opportunity was taken at a single timepoint, not accounting for length of residency, relocation, neighborhood transformations, and individual adaptation to low opportunity environments. Further research is needed to assess whether healthier individuals are sorting into higher opportunity neighborhoods to ascertain neighborhood opportunity as an appropriate exposure. Second, these results focus on objective measures of neighborhood opportunity and do not account for subjective measures that indicate individuals' perceptions of their neighborhood. Although the COI 3.0 aims to construct detailed profiles of neighborhoods based on a variety of structural and environmental resources, personal perceptions of meaningful neighborhood assets can provide unique insight on different dimensions of neighborhood opportunity (Bather et al., 2024; Gocer et al., 2023). While the COI accounts for many important subdomains of opportunity, many historical and structural factors critical to the inception and perpetuation of inequities are not included in the measure at present. Explicit incorporation of these structural underpinnings could provide greater depth of understanding when investigating the persistent and generational impact of neighborhood opportunity on immune dysregulation. Finally, due to the absence of direct measures of B and T cell abundance (e.g., white blood cell counts via flow cytometry), which could serve as more relevant indicators of immune dysregulation, this study used mRNA expression levels to investigate regulation of the defining signaling biomarkers for these two immune cell populations. Gene expression can vary by cell, with *CD19* and *CD3* expression not necessarily reflecting a one-to-one match with B and T cell abundance (Li et al., 2020; Sanchez and Golding, 2013). Variations in expression levels may be due to changes in immune cell population expansion or within-cell transcription fluctuations, which require either different measures of cell composition or deconvolution-based adjustment requiring DNA methylation data not available in the public MIDUS dataset. Future research would benefit from more direct measures of T and B cell prevalence that can both definitively identify individual cells and define multi-marker combinations needed for determining the development and differentiation status of those cells (e.g., enumerating distinct pools of naïve/immature, effector, memory, and terminally differentiated/senescent cell types). Further studies could also investigate T cell markers such as *CD4*, *CD8*, or memory subsets to better understand which specific T cell markers may be upregulated as associated with living in low opportunity environments. This could provide more functional insight into the biological mechanisms involved in lymphocyte population dynamics.

5. Conclusions

These findings document significant elevations in *CD3* expression among individuals living in neighborhoods of limited social, educational, and economic opportunity, as well as potential for further investigation of factors influencing the pathway for altered *CD19* expression. Further research leveraging functional markers of the adaptive immune system could help clarify why these shifts in *CD3* and *CD19* expression were seen in differing domains of neighborhood opportunity, as well as if these elevations took place in specific T or B cell subsets. Future studies could also explore whether these indicators of immune dysregulation in certain neighborhoods may be linked with specific physiological health outcomes, potentially generating insight on how the causal biological pathways may be mapped across structural, individual, and molecular variables. Given the present results, this study marks an important early step into the landscape of research on how the social and built environments of a neighborhood may influence immune health, which is critical for both individual and generational health outcomes.

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CRediT authorship contribution statement

Steven W. Cole: Writing – review & editing, Methodology, Investigation, Conceptualization. **Adolfo G. Cuevas:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Emiko O. Kranz:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Xiaoyan Zhang:** Writing – review & editing, Investigation. **Alisha A. Crump:** Writing – review & editing, Investigation. **Jemar R. Bather:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Shumeng Feng:** Writing – review & editing, Methodology, Investigation, Formal analysis.

Declaration of Competing Interest

The authors declare no known competing financial interests or personal relationships that may or may appear to influence the research reported in this paper.

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Clinical trial number

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2026.107945.

Data availability statement

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

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