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Differential associations between relationship stressors and natural killer cell gene expression by race/ethnicity and sex among older U.S. adults

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ABSTRACT

Close interpersonal relationships can shape health, in part, through immune-related biological pathways. While chronic relational stress has been linked to inflammation and immune dysregulation, little is known about how such stressors relate to transcriptional markers of innate immune activity. As such, we investigated whether multiple forms of relationship stress were associated with altered expression of two genes related to natural killer cell function, *FCGR3A* and *NCAM1,* and whether these associations varied by sex or race/ethnicity. Data were drawn from the Midlife in the United States study, a population-based sample of midlife adults (n = 1,215) who provided whole-transcriptome RNA sequencing data and completed validated relationship stress measures. Covariate-adjusted linear mixed effects models, which included random intercepts for study site, quantified the associations of each stress domain z-score with log2(*FCGR3A*) and log2(*NCAM1*), and tested for moderation by sex and race/ethnicity. While males maintained relatively stable expression across stress domains, females showed significant positive associations between *FCGR3A* expression and both marital risk and spouse/partner strain. For participants in the non-Hispanic Other group, higher friend and cumulative strain was significantly associated with elevated *FCGR3A* expression. This group also exhibited significant *NCAM1* upregulation in response to family, friend, and cumulative strain. In contrast, Hispanic participants showed a non-significant trend toward *NCAM1* downregulation under relationship strain, but not significant changes in *FCGR3A*. These findings suggest that relationship stress may be differentially biologically embedded through changes in innate immune gene expression across demographic groups, highlighting the importance of social context in shaping transcriptional markers of immune function. Further research is needed to clarify whether these patterns confer adaptive immune readiness or contribute to long-term immune dysregulation.

1. Introduction

Emerging evidence from social genomics and psychoneuroimmunology suggests that social adversity can be biologically embedded through alterations in immune cell gene expression (Slavich & Cole, 2013; Slavich et al., 2023). This biological embedding can manifest in various ways, and one significant source of stress arises from close relationships (Kiecolt-Glaser et al., 2005). Stressors within these intimate connections, such as those with spouses, romantic partners, or family members, have been shown to adversely affect physical health, including elevated inflammation, disrupted sleep, and dysregulated cortisol responses (Chen et al., 2015; Jaremka et al., 2013; Kiecolt-Glaser et al., 2010; Miller et al., 2009), in part because of the emotional closeness, attachment styles, perceived importance, and potential for repeated exposure (Farrell & Simpson, 2017; Lapate et al., 2014; Randall & Bodenmann, 2009). Such stressors, including sustained social isolation or strain, can modulate key immunological pathways, including those involved in inflammation, cellular immunity, and antiviral defense (Cole et al., 2015; Cole et al., 2007; Leschak & Eisenberger, 2019) by altering transcriptional programs in circulating leukocytes (e.g., monocytes, natural killer cells; Cole et al., 2015). These effects may be especially consequential in midlife, a period marked by increased shifts in social roles and growing susceptibility to immune dysregulation (Boehme et al., 2020; Lachman et al., 2015; Lucas et al., 2007).

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However, despite growing evidence that interpersonal relationships can shape immune function at the molecular level, the specific gene-level indicators of immune vulnerability associated with relationship stress remain underexplored.

Among the immune cells affected by stress, natural killer cells are of particular interest due to their central role in innate immunity and their sensitivity to psychosocial stressors (Katz et al., 2025; Owen & Steptoe, 2003; Vivier et al., 2008). Natural killer cells are key components of the innate immune system, responsible for the early defense against virally infected cells through cytotoxic activity and cytokine production (Björkström et al., 2022; Vivier et al., 2008). Unlike T cells, natural killer cells respond rapidly and do not require prior antigen sensitization, making them critical for immediate immune responses (Alizadeh Zeinabad et al., 2023; Björkström et al., 2022). Their effectiveness is regulated by the expression of surface receptors and signaling pathways that control activation, adhesion, and cytotoxic function (Chen et al., 2024). Two genes of particular relevance are *FCGR3A* and *NCAM1*. *FCGR3A* encodes the low-affinity Fc gamma receptor Illa (*CD16*), a key mediator of antibody-dependent cellular cytotoxicity (Chen et al., 2024; Rebuffet et al., 2024), and *NCAM1* encodes neural cell adhesion molecule 1 (*CD56*), a glycoprotein critical for natural killer cell adhesion and activation (Chen et al., 2024; Rebuffet et al., 2024). Altered expression of these genes, whether up- or down-regulated, has been linked to shifts in natural killer cell cytotoxic function and innate immune regulation (Chen et al., 2024; Liu et al., 2021; Yandamuri et al., 2024).

Despite these insights, few studies have examined how distinct domains of relationship stress, particularly during midlife, are associated with transcriptional markers of natural killer cell activity. Moreover, to our knowledge, no prior research has systematically assessed whether specific sources of relationship strain (e.g., partner, family, or friend) exert potential unique effects on natural killer cell-related gene expression in a population-based sample. To interpret these associations within a mechanistic framework, we draw on social-signal-transduction theory, which posits that interpersonal threat amplifies sympathetic (β-adrenergic) activity, precipitating the conserved transcriptional response to adversity (CTRA) in circulating leukocytes (Cole, 2014; Powell et al., 2013; Slavich et al., 2023). In parallel, β-adrenergic signaling rapidly mobilizes terminally differentiated $CD56^{dim}$ and $CD16^{bright}$ natural killer cells into circulation, a pattern reliably observed following psychosocial stressors known to activate β-adrenergic signaling, including social conflict and anticipatory stress (Bosch et al., 2005; Katz et al., 2025). These cells express high levels of CD16, encoded by *FCGR3A*, whose transcript abundance rises as natural killer cells complete maturation (Victor et al., 2018). In contrast, CD56, encoded by *NCAM1*, is most abundant on immature $CD56^{bright}$ natural killer cells and becomes progressively downregulated during differentiation (Bi & Wang, 2020; Melsen et al., 2016). Thus, the expression profile of *FCGR3A* and *NCAM1* is consistent with stress-related redistribution and activation of natural killer cells (Bigler et al., 2015; Powell et al., 2013).

Building on this evidence, we hypothesized that relationship stress would engage these stress-related immune-remodeling mechanisms, producing transcriptional changes in *FCGR3A* and *NCAM1*. Expression of *FCGR3A* and *NCAM1* is consistent with stress-related changes in the distribution and functional readiness of natural killer cells (Bigler et al., 2015; Powell et al., 2013) and may reflect a form of biologically embedding seen in other stress-related immune shifts such as the CTRA (Cole, 2019). The current study used data from the Midlife in the United States Study (MIDUS) to investigate whether multiple forms of relationship stress are associated with changes in *FCGR3A* and *NCAM1* among midlife U.S. adults. We also explored whether these associations varied by sex and race/ethnicity, given known social patterning in stress exposure and immune regulation (Bekhbat & Neigh, 2018; Ford et al., 2021). We aimed to identify transcriptional pathways through which chronic relationship stress may become biologically embedded, ultimately compromising innate immune health.

2. Materials and methods

2.1. Study design, setting, and sample

Data came from MIDUS, a population-based health cohort study of English-speaking American adults aged 25–74 (Brim et al., 2004). MIDUS 1 recruited the first cohort (n = 7,108; Wave 1) via random phone number selection during 1995–1996. In the second wave, MIDUS 2 improved its racial/ethnic representation by adding 592 African American participants from Milwaukee, Wisconsin (n = 5,555). The third wave (MIDUS 3) was initiated in 2013, enrolling 3,683 participants. To expand the original cohort (MIDUS 1), the MIDUS Refresher Study (MIDUS Refresher 1, 2011–2014) recruited 4,085 additional participants, including 508 African American adults from Milwaukee, Wisconsin.

Participants from MIDUS Refresher 1 and MIDUS 3 later joined follow-up biomarker projects (Dienberg Love et al., 2010). A total of 862 adults from MIDUS Refresher 1 enrolled in the MIDUS Refresher Biomarker Study (2012–2016) and 747 individuals from MIDUS 3 Study participated in the MIDUS 3 Biomarker Project (recruitment started in 2017). Of the 1,609 biomarker participants, 1,215 had available gene expression data.

After providing informed consent, biomarker study participants attended two-day clinic visits to provide biological measures. These participants received $200, along with reimbursement for transportation expenses. The MIDUS research team coordinated travel arrangements and provided additional accommodations, including childcare expense coverage and permission for older participants to bring a companion. Additional information about the study protocols can be found elsewhere (Brim et al., 2004; Dienberg Love et al., 2010; Radler, 2014). The University of Wisconsin Institutional Review Board approved all MIDUS studies. The New York University Institutional Review Board considered the present study exempt from review because the data were deidentified and publicly available (https://www.icpsr.umich.edu/web/ICPSR/series/203). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (von Elm et al., 2008).

2.2. Natural killer cell gene expression

Participants provided blood samples during two-day visits to clinical sites at Georgetown University, the University of Wisconsin-Madison, or the University of California, Los Angeles (Dienberg Love et al., 2010). Each participant fasted overnight, and on the second morning of their visit, a certified phlebotomist collected blood using BD Vacutainer CPT Tubes. After collection, white blood cells were separated from the samples and stored in deep-freeze conditions at temperatures between −60 °C and −80 °C. These frozen samples were then transported with dry ice to the MIDUS Biocore Laboratory, where they remained frozen at −65 °C until analyzed.

Gene expression profiling was conducted from 2017 to 2018 on the MIDUS Refresher Biomarker Study cohort and from 2018 to 2022 on the MIDUS 3 Biomarker Project samples. Whole-transcriptome RNA sequencing was used to assess transcript abundance across the total collection of genes present in the human genome. The current investigation focused on *FCGR3A* and *NCAM1* as they are the primary markers used to define the two major human NK cell subsets ($CD56^{bright}$ and $CD56^{dim}$), which display distinct phenotypic and functional properties (Cooper et al., 2001; Poli et al., 2009). Expression was calculated as counts per million of total human transcriptome-aligned RNA sequencing reads, followed by log2-transformation as part of the standard MIDUS RNA sequencing data processing pipeline. The MIDUS RNA sequencing pipeline includes multiple quality control steps, including normalization to a panel of 11 reference genes, flooring at 1 transcript per million, and filtering based on sequencing depth, alignment, and mapping rates to ensure data precision (Dienberg Love et al., 2010).

Additional technical details about the gene expression profiling protocols are available through the MIDUS Colectica Portal and in prior publications (Bather et al., 2025; Cuevas et al., 2023; Mann et al., 2020).

Quality control metrics confirmed high-quality RNA sequencing data across all samples. The mean number of successfully mapped reads was 13.6 million, exceeding the recommended threshold of five million reads. Mapping efficiency averaged 89.8 %, surpassing the 80 % quality threshold. Technical reproducibility was demonstrated by a mean inter-sample transcriptome correlation of 0.828, indicating consistent gene expression profiles across the dataset.

2.3. Relationship stressors

Family strain. We measured family strain with the following items: "Thinking about the members of your family, not including your spouse/partner, how often: (1) do they make too many demands on you? (2) do they criticize you? (3) do they let you down when you are counting on them? (4) do they get on your nerves?" (Walen & Lachman, 2000). Participants responded using a four-point scale from *(1) never* to *(4) often*. These responses were averaged, with higher values indicating higher family strain (Cronbach's $\alpha = 0.82$).

Friend strain. We assessed friend strain using four items: (1) "How often do your friends make too many demands on you?" (2) "How often do they criticize you?" (3) "How often do they let you down when you are counting on them?" and (4) "How often do they get on your nerves?" (Walen & Lachman, 2000). Respondents used a four-point scale from *(1) never* to *(4) often*. Their responses were averaged, with higher scores denoting higher friend strain (Cronbach's $\alpha = 0.81$).

Marital risk. We assessed marital risk using the following questions: (1) "During the past year, how often have you thought your relationship might be in trouble?" (2) "It is always difficult to predict what will happen in a relationship, but realistically, what do you think the chances are that you and your partner will eventually separate?" (3) "How much do you and your spouse or partner disagree on the following issues?" (3a) "Money matters such as how much to spend, save, or invest." (3b) "Household tasks, such as what needs doing and who does it." (3c) "Leisure time activities, such as what to do and with whom" (Grzywacz & Marks, 2000; Walen & Lachman, 2000). A five-point scale from *(1) never* to *(5) all the time* was used for the first question; a four-point scale from *(1) not likely at all* to *(4) very likely* was used for the second question; and a four-point scale from *(1) not at all* to *(4) a lot* was used for the third question. Responses were summed such that higher values indicated higher marital risk (Cronbach's $\alpha = 0.84$). The minimum score was given to unmarried participants, aligning with prior research (Slopen et al., 2013).

Spouse/Partner strain. Six items were used to operationalize spouse/partner strain: (1) "How often does your spouse or partner make too many demands on you?" (2) "How often does he or she argue with you?" (3) "How often does he or she make you feel tense?" (4) "How often does he or she criticize you?" (5) "How often does he or she let you down when you are counting on him or her?" and (6) "How often does he or she get on your nerves?" (Walen & Lachman, 2000). Responses were scored on a four-point scale ranging from *(1) never* to *(4) often* then averaged (higher scores denoted higher spouse/partner strain; Cronbach's $\alpha = 0.88$). The minimum score was assigned to unmarried participants. All reported Cronbach's α values represent the measure's reliability among the analytic sample.

2.4. Covariates

Sociodemographic covariates included age, sex, race/ethnicity, educational attainment, annual household income, and marital status. Age was measured continuously. Sex was coded as male or female. Race/ethnicity was operationalized as non-Hispanic White, non-Hispanic Black, Hispanic, or non-Hispanic Other (including Asian, Native American, Alaska Native, Native Hawaiian, and Pacific Islander). Educational attainment was classified as high school or less, some college/associate's degree, or college degree or higher. Annual household income was categorized as <$50,000, $50,000 to $100,000, or $100,000+. Marital status was grouped as married, divorced/separated/widowed, or never married.

Health behaviors included smoking status, alcohol consumption, and body mass index (BMI). Smoking status was coded as never, past, or current smoker. Past month alcohol consumption was classified as never, <1 day a week, 1–2 days a week, or 3 + days a week. BMI was measured continuously.

2.5. Statistical analysis

Summary statistics included means and standard deviations (SDs) for continuous variables and counts and percentages for categorical measures. We fit a series of linear mixed effects models with study site random intercepts to quantify the association of each relationship stress z-score with log2(*FCGR3A*) and log2(*NCAM1*) (Fitzmaurice et al., 2012). Model 1 expressed the gene expression measure as a function of the relationship stress z-score, age, sex, race/ethnicity, educational attainment, annual household income, and marital status. To ascertain whether this association strengthened or attenuated, we added health behaviors in Model 2. Model 3 added the interaction between relationship stressor and sex to Model 2. Model 4 added the interaction between relationship stressor and race/ethnicity to Model 2. Note that all *FCGR3A* models also controlled for log2(*CD14*). Lastly, we constructed a cumulative strain z-score by standardizing the sum of each relationship stress z-score. We fit the same models for this cumulative strain z-score. We employed multivariate imputation by chained equations to address missing data (Van Buuren & Groothuis-Oudshoorn, 2011). Multinomial logistic regression was used for race/ethnicity and marital status; ordinal logistic regression for educational attainment and annual household income; and predictive mean matching for BMI and relationship stress. Results were aggregated according to Rubin's rules (Rubin, 1987). We conducted all statistical analysis using R version 4.4.3 (R Core Team, 2023). All tests of statistical significance reflect a two-sided α of 0.05.

3. Results

3.1. Descriptive statistics

Table 1 provides summary statistics on the study population. Of the 1,215 adults (mean 57 years, SD 12), 53 % were female, 73 % identified as non-Hispanic White, and 62 % were married. Descriptive statistics by marital status are presented in Supplemental Table 1. Compared to those who were divorced/separated/widowed or never married, married individuals were more likely to be male, identify as non-Hispanic White, have a college degree or higher, and have an annual household income of at least $100,000 USD. Regarding health behaviors, married participants were more likely to have never smoked, more likely to have never consumed alcohol, and had lower mean BMIs.

3.2. Relationship stress and FCGR3A gene expression

Regression models with interaction terms indicated that the relationships of friend strain and cumulative strain with *FCGR3A* expression varied by race/ethnicity (Fig. 1, Panels A and B). For both stressor measures, non-Hispanic Black individuals showed high *FCGR3A* expression regardless of stress levels, while non-Hispanic White participants exhibited minimal change with increasing friend or cumulative strain. In contrast, Hispanic and non-Hispanic Other individuals demonstrated positive associations, with *FCGR3A* expression increasing with higher friend strain and cumulative strain. Sex moderated the associations of relationship-specific stressors with *FCGR3A* expression (Fig. 1, Panels C and D). While males maintained relatively stable

Table 1
Descriptive statistics of the study population, Midlife in the United States Study.

Characteristic	N = 1,215
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 or less	243 (20.0)
Some college/Associate's degree	378 (31.1)
College degree or higher	593 (48.8)
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)
Marital status, No. (%)	
Married	756 (62.2)
Divorced/Separated/Widowed	281 (23.1)
Never married	177 (14.6)
Missing	1 (0.1)
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 + days a week	295 (24.3)
Body mass index, Mean (SD)	28.9 (6.6)
Missing, No. (%)	39
Study site, No. (%)	
University of California, Los Angeles	387 (31.9)
University of Wisconsin-Madison	490 (40.3)
Georgetown University	338 (27.8)
Family strain, Mean (SD)	2.0 (0.7)
Missing, No. (%)	31
Friend strain, Mean (SD)	1.8 (0.6)
Missing, No. (%)	34
Marital risk, Mean (SD)	7.3 (3.0)
Missing, No. (%)	26
Spouse/Partner strain, Mean (SD)	1.7 (0.7)
Missing, No. (%)	29
Cumulative strain, Mean (SD)	12.9 (3.8)
Missing, No. (%)	53
***FCGR3A* gene expression level (log2-transformed normalized transcript per million value), Mean (SD)**	7.2 (2.4)
***NCAM1* gene expression level (log2-transformed normalized transcript per million value), Mean (SD)**	4.4 (2.6)
***CD14* gene expression level (log2-transformed normalized transcript per million value), Mean (SD)**	8.8 (2.2)

expression across stress levels, females showed significant positive associations between *FCGR3A* expression and both marital risk and spouse/partner strain. The full regression results can be found in Supplemental Tables 2–6.

3.3. Relationship stress and NCAM1 gene expression

Fig. 2 depicts results from mixed effects models examining *NCAM1* expression. Race/ethnicity moderated the associations between specific relationship stressors and *NCAM1* expression. Non-Hispanic Other individuals demonstrated positive associations, with *NCAM1* expression increasing with higher family strain, friend strain, and cumulative strain. In contrast, Hispanic participants exhibited negative trends across all three stressors. Non-Hispanic Black and White individuals maintained relatively stable *NCAM1* expression regardless of strain levels. Unlike the patterns observed for *FCGR3A*, sex did not moderate the relationships between relationship stressors and *NCAM1* expression. Supplemental Tables 7–11 present the complete regression results.

3.4. Sensitivity analyses

Among married participants only, we conducted sensitivity analyses for two models (marital risk and spouse/partner strain) across the two outcomes (log2-*FCG3RA* and log2-*NCAM1*). All results were similar to those obtained from the overall sample (Supplemental Tables 12–15).

4. Discussion

The current study provides novel evidence that relationship stress is associated with transcriptional changes in genes relevant to innate immune function among midlife U.S. adults. Specifically, we found that higher levels of marital risk, partner strain, friend strain, and cumulative strain were significantly associated with increased expression of *FCGR3A,* a gene central to natural-killer-cell-mediated cytotoxicity (Mahaweni et al., 2018), with these associations varying across specific sociodemographic groups. In contrast, *NCAM1*, a gene associated with immature, immunomodulatory natural killer cells (Mace et al., 2016; Poli et al., 2009), exhibited more context-dependent patterns across sociodemographic groups.

These findings partially support our hypothesis that chronic relationship stress would engage stress-related transcriptional adaptation in natural killer cells, producing changes in *FCGR3A* and *NCAM1* expression. Consistent with stress-related natural killer cell redistribution, relationship strain was associated with altered *FCGR3A* expression across multiple sociodemographic groups, suggesting redistribution of mature, cytotoxic natural killer cells in response to interpersonal stress (Bosch et al., 2005). However, rather than uniform directional changes in *NCAM1*, we observed subgroup-specific associations. Certain subgroups, such as non-Hispanic Other individuals, exhibited significant upregulation of *NCAM1* under strain, while Hispanic participants showed a nonsignificant trend toward downregulation.

This pattern aligns with prior evidence of β-adrenergic-mediated redistribution of cytotoxic natural killer cells into circulation (Bigler et al., 2015; Graff et al., 2018; Powell et al., 2013) and may represent a pathway parallel to the CTRA (Cole, 2019). However, the β-adrenergic mechanism remains hypothetical in the present study, as we did not

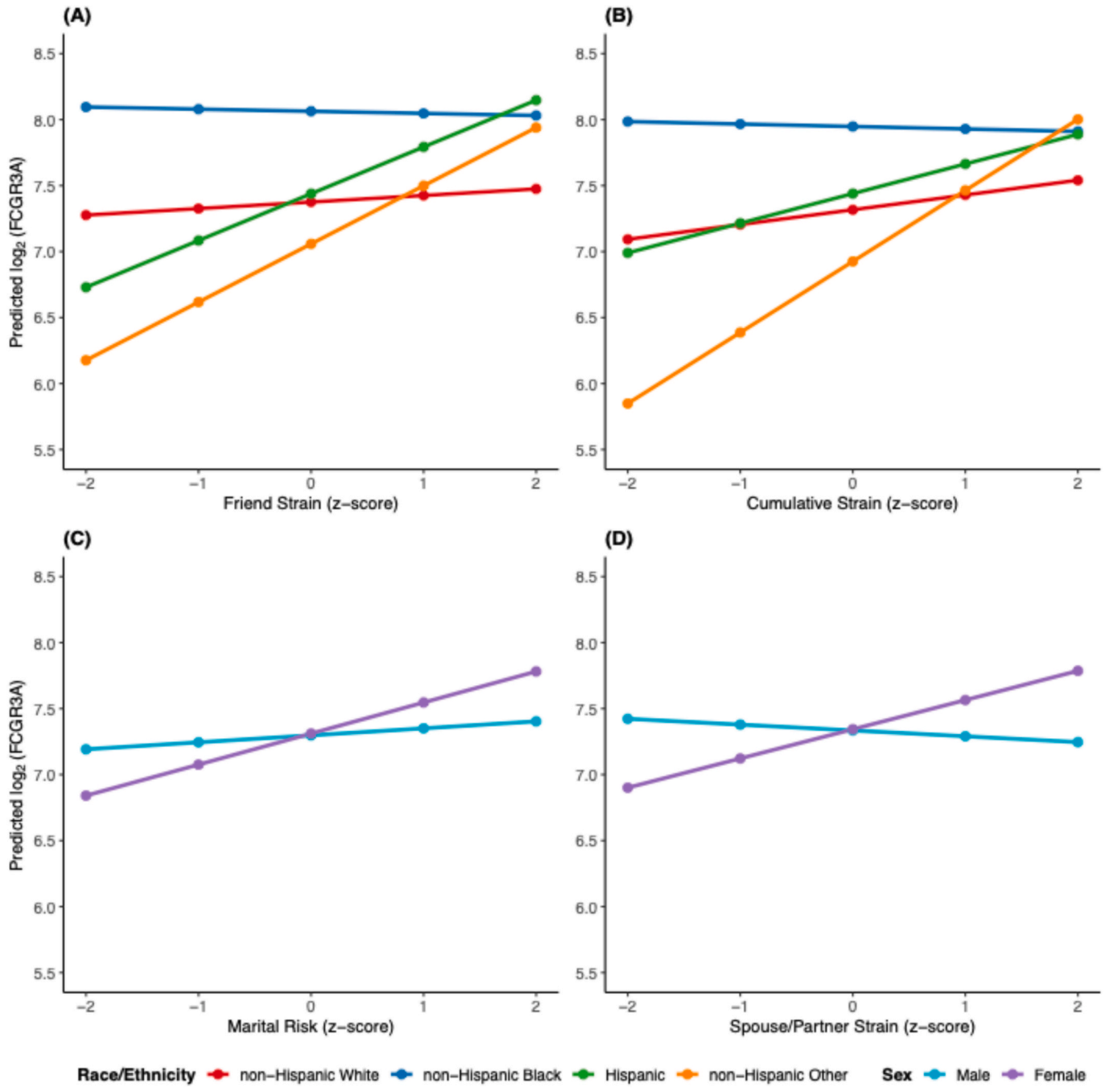

Fig. 1. Differential associations between relationship stressors and FCGR3A gene expression by race/ethnicity and sex among older U.S. adults, Midlife in the United States Study. Predictions were adjusted for covariates.

directly measure sympathetic nervous system activity or adrenergic signaling. Although the transcriptional shifts observed here are biologically plausible indicators of natural killer cell mobilization under perceived interpersonal threat (Dimitrov et al., 2010; MacCormack et al., 2021), future research should explicitly test whether stress-induced changes in *FCGR3A* and *NCAM1* expression are mediated through natural killer cell-specific adrenergic pathways.

While these mechanisms may operate broadly, our results also indicate that transcriptional responses to relationship stress are not uniform across the population. Variation by sex emerged prominently, with women showing stronger associations between *FCGR3A* expression and both marital risk and partner strain. This pattern is consistent with a broad literature indicating that women are more physiologically responsive to interpersonal conflict and may be more vulnerable to the psychological toll of relationship instability (Kiecolt-Glaser, 2018; Kiecolt-Glaser et al., 2005; Kiecolt-Glaser et al., 1996; Kiecolt-Glaser & Newton, 2001; Martinez-Muniz & Wood, 2020). In addition, women are more frequently exposed to abusive or coercive dynamics in close relationships, which can further amplify stress-related immune consequences (Yim & Kofman, 2019). That these associations emerged primarily in response to marital and partner stress, rather than more distal sources such as family or friend strain, reinforces the unique emotional significance of intimate partnerships and their possibly disproportionate influence of immune function in women (Kiecolt-Glaser, 2018).

We also observed race- and ethnicity-specific variation in

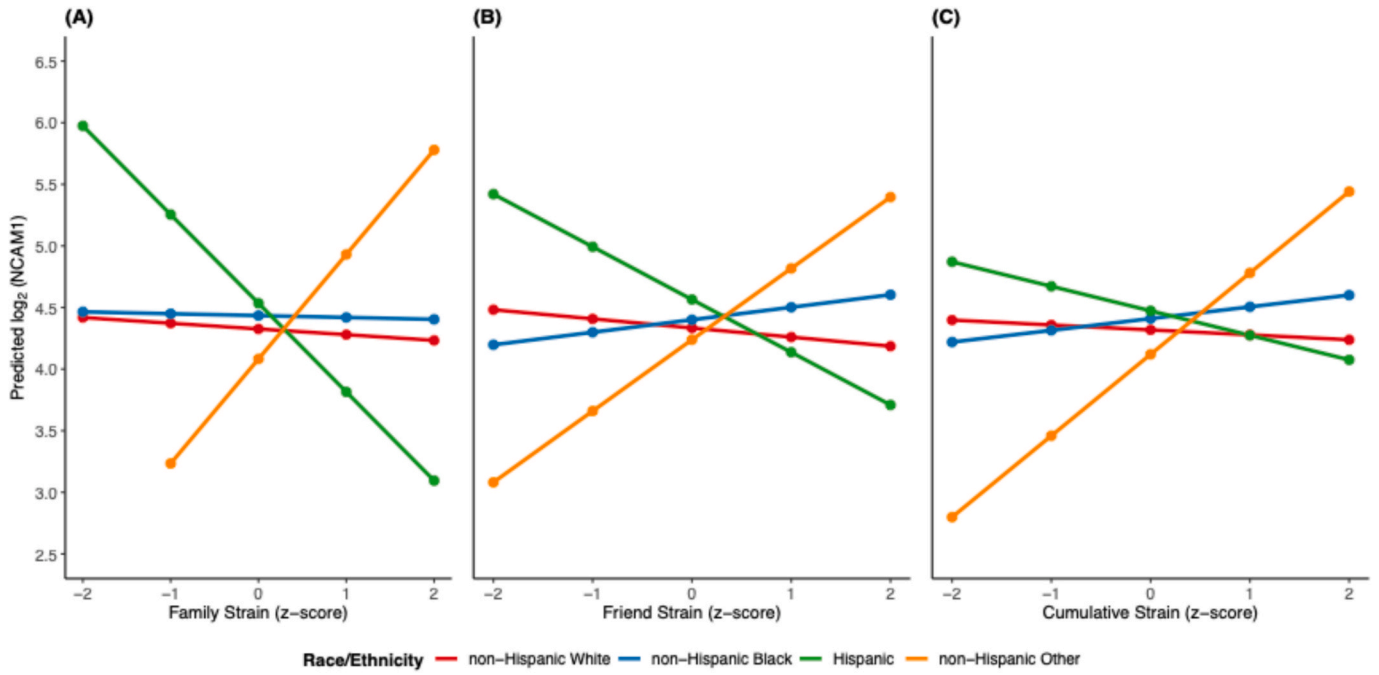

Fig. 2. Differential associations between relationship stressors and NCAM1 gene expression by race/ethnicity among older U.S. adults, Midlife in the United States Study. Predictions were adjusted for covariates.

transcriptional responses to relational stress. Non-Hispanic Other participants showed significant increases in *FCGR3A* expression in response to cumulative strain and significant upregulation of *NCAM1* in response to friend, family, and cumulative strain. These findings may reflect distinct natural killer cell adaptation pathways in these groups, potentially indicative of delayed differentiation, regulatory buffering, or heightened immune vigilance under chronic stress (Abel et al., 2018; Rebuffet et al., 2024). In contrast, Hispanic participants exhibited a nonsignificant trend toward *NCAM1* downregulation under strain, but no significant moderation of *FCGR3A*. Non-Hispanic Black participants demonstrated higher overall *FCGR3A* expression levels, though these were not significantly moderated by relationship stress.

These findings extend social-signal-transduction theory by demonstrating that chronic relationship stress engaged natural killer cell-specific transcriptional programs, consistent with β-adrenergic-mediated redistribution of $CD56^{dim}$ and $CD16^{bright}$ cytotoxic natural killer cells (Abel et al., 2018; Benschop et al., 1996; Bosch et al., 2005; Cole, 2019; Graff et al., 2018; Slavich & Irwin, 2014). However, the observed *FCGR3A* changes were not uniformly accompanied by corresponding *NCAM1* changes, as social-signal-transduction theory might suggest. Instead, *NCAM1* changes were directionally mixed, with some subgroups (e.g., Hispanic participants) showing a nonsignificant trend toward downregulation. This divergence from expectations of uniform downregulation of regulatory markers suggests that natural killer cell adaptation under stress may include compensatory regulatory responses that vary across identities and social contexts (Bird et al., 2024; Cuevas et al., 2023; Mace, 2023; Randolph et al., 2021; Schwane et al., 2020).

While the upregulation of *NCAM1* among non-Hispanic Other adults was statistically significant, these associations should be interpreted as natural killer cell-specific transcriptional shifts rather than generalizable markers of systemic inflammation. Elevated *NCAM1* could indicate, for instance, stress-induced delays in natural killer cell maturation (Poli et al., 2009), expansion of immunomodulatory $CD56^{bright}$ subsets (Abel et al., 2018), or compensatory feedback to mitigate cytotoxic overactivation (Kumar, 2018). Although *NCAM1* is more prominently expressed on immature natural killer cells, it is not entirely absent on certain mature subsets (e.g., $CD56^{dim}CD16^{+}$; Abel et al., 2018; Poli et al., 2009; Scoville et al., 2017). Thus, transcriptional increases could also indicate proportional shifts among natural killer cell subpopulations rather than a wholesale return to an immature phenotype (Bosch et al., 2005; Melsen et al., 2016). In contrast, trends toward *NCAM1* suppression, such as those observed in Hispanic adults, may suggest a shift toward a more cytotoxic natural killer cell phenotype (Abel et al., 2018; Graff et al., 2018; Poli et al., 2009; Scoville et al., 2017). Future studies with larger, stratified samples are needed to test whether cultural, structural, or behavioral factors shape these immune responses to relationship strain.

These observations also nuance our understanding of immune embedding under chronic stress. While the CTRA describes a monocyte-driven inflammatory gene expression profile in response to social threat (Cole, 2019; Cole et al., 2015; Cole et al., 2011), our findings highlight natural killer cell-specific transcriptional shifts, particularly *FCGR3A* upregulation, as a potential parallel or complementary immune adaptation pathway. Whether this response reflects adaptive immune surveillance or early-stage immune dysregulation remains an open question for future research. Nonetheless, these findings highlight the importance of examining stress-induced immune changes at the cell-type level and through the lens of interpersonal relationships, identity, and context.

Despite its many strengths, several limitations must be acknowledged. First, the cross-sectional design of the study limits our interpretation of causality. As such, longitudinal studies are needed to clarify whether chronic relationship stress prospectively predicts natural killer cell-related gene expression and related health outcomes. Second, gene expression was measured in bulk leukocytes, limiting resolution of natural killer cell-specific effects. While we adjusted for log2(*CD14*) expression to account for variability in monocyte abundance, this approach does not capture differences in natural killer cell proportions or their specific subpopulations. As such, we cannot exclude the possibility that the observed associations reflect proportional shifts in natural killer cell subsets, rather than transcriptional modulation within individual cells. Future investigations should build on our work by including additional natural killer cell-related transcripts and integrating single-cell transcriptomics to capture a broader representation of natural killer cell functional diversity. Third, sample sizes for some racial and ethnic subgroups, especially Hispanic adults, were small, necessitating cautious interpretation and replication with larger, more diverse

cohorts. Fourth, relationship history data were limited; we did not ascertain whether unmarried participants were currently in long-term romantic relationships or had recently exited one. This absence of information constrains our ability to determine whether nonmarital long-term partnerships exert similar immunologic effects, thereby reducing the generalizability of conclusions regarding marital status. Finally, reliance on self-reported stress measures may introduce subjective bias, although these instruments are well validated and commonly used in psychosocial and genomic research.

Despite these limitations, the current study has several strengths and provides novel insights into how chronic relationship stress may shape immune biology in midlife. By integrating gene-level markers of natural killer cell activity with psychosocial stress exposure across multiple relationship domains and sociodemographic groups, we provide evidence for both the biological embedding of close relationship strain and the relevance of context in moderating these associations. Our use of direct gene expression measurement, targeting *FCGR3A* and *NCAM1*, combined with rigorous adjustment for *CD14* expression, sociodemographic covariates, and health behaviors, strengthens confidence in the specificity of these associations. These results advance our understanding of how immune pathways may be shaped by interpersonal stressors. Ultimately, these findings highlight the need for more integrative, biopsychosocial models of immune function, models that recognize not only the presence of stress, but also identity, relationships, and immune mechanisms through which it becomes biologically embedded.

5. Conclusion

The current study demonstrates that chronic relationship stress is associated with changes in the expression of genes central to natural killer cell function in a population-based sample of midlife adults. Specifically, expression of both *FCGR3A and NCAM1* varied across sociodemographic groups in response to multiple forms of relationship strain. *FCGR3A* expression increased particularly with marital risk, partner strain, and friend strain, while *NCAM1* expression showed divergent patterns. These findings suggest that chronic interpersonal stress may become biologically embedded through transcriptional remodeling of the innate immune system, reflecting stress-related changes in natural killer cell activity and distribution. Importantly, both the type of relationship stressor and the individual's social context shaped these transcriptional responses. By identifying immune pathways through which relational adversity may influence health, our work highlights the relevance of close interpersonal relationships for understanding long-term immune regulation and disease vulnerability.

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Clinical Trial Number

Not applicable.

CRediT authorship contribution statement

Mariana Rodrigues: Writing – review & editing, Writing – original draft, Project administration, Investigation. **Jemar R. Bather:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Adolfo G. Cuevas:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.106116.

Data availability

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

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