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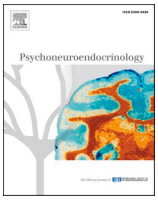

Social network position and the Conserved Transcriptional Response to Adversity in older Koreans

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ABSTRACT

Background: Social connections are crucial to human health and well-being. Previous research on molecular mechanisms in health has focused primarily on the individual-level perception of social connections (e.g., loneliness). This study adopted socio-centric social network analysis that includes all social ties from the entire population of interest to examine the group-level social connections and their association with a molecular genomic measure of health.

Methods: Using socio-centric (global) social network data from an entire village in Korea, we investigated how social network characteristics are related to immune cell gene expression among older adults. Blood samples were collected (N = 53, 65–79 years) and mixed effect linear model analyses were performed to examine the association between social network characteristics and Conserved Transcriptional Response to Adversity (CTRA) RNA expression patterns.

Results: Social network positions measured by *k*-core score, the degree of cohesive core positions in an entire village, were significantly associated with CTRA downregulation. Such associations emerged above and beyond the effects of perceived social isolation (loneliness) and biobehavioral risk factors (smoking, alcohol, BMI, etc.). Social network size, defined as degree centrality, was also associated with reduced CTRA gene expression, but its association mimicked that of perceived social isolation (loneliness).

Conclusions: The current findings implicate community-level social network characteristics in the regulation of individual human genome function above and beyond individual-level perceptions of connectedness.

1. Introduction

Humans are sociable; thus, maintaining healthy social interactions is essential for survival and well-being (Cacioppo et al., 2000, 2002; Holt-Lunstad, 2021). An increasing number of studies indicate that insufficient social connections are linked to adverse health outcomes, such as depressive symptoms (Cacioppo et al., 2010), cardiovascular diseases, stroke, and premature mortality (Hakulinen et al., 2018; Valtorta et al., 2016). Among the various candidate pathways linking social connections to physical health outcomes, the regulation of human genome function by "social signal transduction" provides one integrative view spanning multiple levels of analysis from the cognitive appraisal of the social environment to neural and endocrine physiology that ultimately impacts immune system function (Cole, 2014, 2019). One example of this general pathway involves a gene expression pattern known as the Conserved Transcriptional Response to Adversity (CTRA), which is characterized by up-regulation of pro-inflammatory gene expression and down-regulation of anti-viral gene expression via fight-or-flight signaling by the autonomic nervous system.

The up-regulated CTRA profile has been linked to various adverse social conditions including lower socioeconomic status (Miller et al., 2009a; Snyder-Mackler et al., 2019), chronic stress (Miller et al., 2009b, 2014), and grief resulting from a significant loss (O'Connor et al., 2014). Basic research indicates that the CTRA is mediated by stress-induced activation of the sympathetic nervous system, and resulting beta-adrenergic signaling processes that up-regulate transcription of

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pro-inflammatory genes while inhibiting expression of genes involved in Type I interferon innate antiviral responses (Cole, 2019; Heidt et al., 2014; McKim et al., 2018; Powell et al., 2013). These altered gene expression patterns have in turn been shown to promote chronic diseases such as cancer (Sloan et al., 2010), cardiovascular and metabolic diseases (Heidt et al., 2014; Simons et al., 2017). Furthermore, as the brain treats social isolation as a state of threat (Cacioppo and Cacioppo, 2018), up-regulation of CTRA expression has been also linked to chronic loneliness in both Western (Cole et al., 2007, 2015b) and Asian populations (Lee et al., 2021).

Previous analyses of social signal transduction into human gene regulation have generally involved self-reporting of subjectively perceived social conditions (e.g., loneliness, social support, etc.). As such, little is known about how broader characteristics of social networks might influence genomic activity within the individuals they enmesh (Cole, 2014; Steptoe, 2022). Social connections include multiple aspects, including structure (e.g., social network size, connectivity, etc.), functions (e.g., social support, instrumental assistance, etc.), and quality (e.g., relationship satisfaction) (Holt-Lunstad, 2017, 2021; Miller et al., 2009c). Moreover, while subjective perception and objective measures of social connection are often correlated, they are both conceptually distinct domains and include distinct features and content (Fiordelli et al., 2020; Rico-Uribe et al., 2016). In contrast to the individual-level perception of social relationships immediately surrounding a person (e.g., loneliness, social support), observed socio-centric social network analysis characterizes the broader system of social ties surrounding the individual at the group or community level (Burt et al., 2013; Smith and Christakis, 2008). Social networks can influence members' health through person-to-person contact, access to resources, social support, and transmission of infectious diseases such as severe acute respiratory syndrome (SARS) and pneumonia (Berkman et al., 2000; Meyers et al., 2003, 2005; Read et al., 2008). Previous studies suggest that social networks may also spread behavioral mediators of chronic disease, such as obesity, smoking, dietary characteristics, and sedentary lifestyle (Christakis and Fowler, 2007; Smith and Christakis, 2008). Thus, global social network analysis can provide additional information that may not be captured by perceived individual connectedness such as loneliness or social support.

Among the various aspects of social network structures, the present study focuses on two main variables: social network size and social network position. Social network size is defined as the total number of either inward (individual is referred to as a connection by others) or outward (individual refers to others as connections) social ties in the community. By contrast, core positions in social network are defined by *k*-core score that refers to membership in a tightly interconnected group or cluster; a *k*-core group consists of people who have at least *k* social ties with others in the same group (Kong et al., 2019; Malvestio et al., 2020; Seidman, 1983). These two measures can be obtained only from the socio-centric or global social network mapping, which can be created from the social network map of nearly all members of the population. Larger social network size and higher *k*-core score have been linked to lowered loneliness (Kim et al., 2022) and higher brain functional connectivity among older adults, which is further associated with higher cognitive function (Bang et al., 2019; Joo et al., 2017; Kwak et al., 2018). Previous research has often examined the direct and ego-perceived social connections to others, but less attention has been paid to network structure above and beyond individuals because most studies involve only sporadically sampled egocentric social networks and do not involve the global network map.

The present study aims to fill the gap in our understanding of how social network characteristics at community level are related to individual human genome function using socio-centric network analysis. Previous studies have shown significant links between subjectively perceived social isolation (loneliness) and immune gene expression patterns (Cole, 2007, 2015; Lee, 2021). However, the relationship between objective measures of social relationships and gene regulation is unknown, as no gene regulation studies have examined social network characteristics, which are often only modestly correlated with subjective social connection. To address this gap, we conducted a socio-centric network analysis of an entire village's older adult population to examine the association between social networks and CTRA gene expression, above and beyond individual perceptions of social isolation.

2. Methods

2.1. Participants

Participants were recruited from a population of the Korean Social Life, Health and Aging Project (KSHAP); KSHAP is a prospective cohort designed to examine social networks and health-related factors, and aging in Korean older adults (for details, please see Lee et al., 2014; Youm et al., 2014). The baseline survey targeted all inhabitants of Township L on Ganghwa Island, Korea, who were 65 years old or older, along with their spouses.

A total of 947 participants out of 1043 (90.8% response rate) in Cohort L participated the KSHAP and their socio-centric network characteristics at community level were collected starting in 2017. Among those, 126 registered neuropsychological assessments that were designed to examine the extensive neuropsychological assessment further. Pre-screened participants who met the following criteria were excluded: 1) diagnosed of neurological disorders/major psychiatric illness via telephone interview; 2) scored below 1.5 standard deviations (SD) after adjustments for age, sex, and education on the Mini-Mental State Examination for Dementia Screening (MMSE-DS); and 3) diagnosed of diabetes or hypertension. In the present study, participants were restricted to those registered in the subsample of the neuropsychological assessment study.

This study was conducted per the Declaration of Helsinki. Further, the institutional review boards of Yonsei University and Seoul National University approved the study protocol. Written informed consent was obtained from all participants. We have reported all measures, conditions, and data exclusions relevant to this analysis and how sample size was determined.

2.2. Blood collection and transcriptome profiling

Blood samples (2.5 ml) were collected into PAXgene RNA tubes and stored at −20 °C until analysis. The samples were shipped to the UCLA Social Genomics Core Laboratory, where the total RNA was extracted (Qiagen RNeasy), normalized, and sequenced by Lexogen Services GmbH using a high-efficiency mRNA-targeted assay (Lexogen QuantSeq 3' FWD) conducted on an Illumina NextSeq instrument following the manufacturer's standard protocols, as previously described (Lee et al., 2020, 2021). Sequencing targeted 5 million single-stranded reads per sample (achieved average = 7.3 million), each of which was mapped to the GRCh38 refence human transcriptome using the STAR aligner (average mapping rate = 99.5%). Gene transcript abundance per million mapped reads was floored at 1 to suppress spurious low-range variability and log2-transformed for linear statistical analyses as described below.

2.3. Measures

2.3.1. Social network measures

Social network measures collected at Wave 1 (2017) were assessed using the socio-centric (global) network of Township L. Using the information from a name generator in which participants named up to six discussion partners (including a spouse) who resided in the same town, the social connection map of the entire village was constructed (for details, please see Youm et al., 2014). Participants were asked, "from time to time, most people discuss things that are important to them with others. Looking back over the last 12 months, who are the people with

whom you most often discussed things that were crucial to you?" From the 947 survey participants, a network of the 1593 individuals and 2100 social ties in the village were constructed. Fig. 1 represents the global social network of the township L. The red nodes in the Fig. 1 indicate final sample included in the analysis. Based on this global social network of an entire village, social network variables were calculated using the Pajek software (Nooy et al., 2018).

The degree centrality was measured as the sum of in-degree and out-degree centrality. In-degree centrality refers to how many village residents nominated the respondent as a discussion partner, whereas out-degree centrality indicates number of discussion partners in the village the respondent nominated.

The core positions in social network were defined using the *k*-core score; the *k*-core of a network refers to the maximal set of nodes that have at least *k* connections within the group (Malvestio et al., 2020; Morone et al., 2019). In this study, *k*-core groups were identified in a directed network by disregarding the direction of ties. Fig. 2 illustrates *k*-core identification in a network of nine individuals.

As illustrated in Fig. 2, a high *k*-core group identifies a densely interconnected subgroup within a network, because an individual must have at least *k* social ties to be included in the group (Kong et al., 2019). Also, high *k*-core groups are supposed to occupy relatively core positions compared with low *k*-core groups, or those reside in peripheral positions in a network as seen in Fig. 2. In this respect, individuals with high *k*-core score tend to form a cohesive cluster where each has many friends inside the cluster that occupy the core position in village-wide social network.

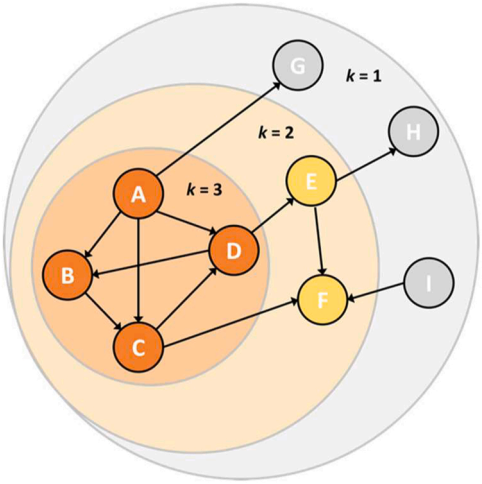

Fig. 2. An example of *k*-core score calculated for this study. A, B, C, D belongs to the 3-core group, since they are all connected to at least three other members inside the same group (orange circle). Meanwhile a group of A, B, C, D, E and F belong to 2-core group (yellow circle) since all five people are connected to at least two other people in the group. In this study, *k*-core score of a certain person is defined as the highest *k*-core group that person can belong to in the social network of the whole village.

2.3.2. *Perceived social isolation (Loneliness)*

Loneliness was assessed using the 20-item Revised UCLALoneliness Scale (Russell, 1980). Participants rated how often they felt the way they did (e.g., "how often do you feel that you lack companionship?") using a four-point scale (1 =never, 4 =often; Cronbach's alpha = .88).

2.4. *Statistical analysis*

For the final dataset, we targeted 85 participants who were successfully followed up for medical examination out of the 126 registered participants. Of those, we excluded 3 samples with poor RNA quality, such as those with mapped reads < 5 million count (N = 2) or average inter-sample transcript abundance correlation < 0.80 (N = 1), as well as 12 samples form participants who reported recent illness such as a cold or headache, which might affect CTRA expression. We further excluded individuals who were considered "older elderly," defined as being above 2 SDs from the mean age of the sample, which was 80 years old (N = 17), leaving a total of 53 samples in the final analysis. Sensitivity analyses including the older elderly samples (N = 70) yielded broadly similar results.

The analyses focused on 53-CTRA the priori selected gene sets of 19 pro-inflammatory indicator genes and 34 genes involved in type I interferon responses and antibody production following the same procedures from previous studies (Cole et al., 2015a, 2020; Fredrickson et al., 2013, 2015; Kitayama et al., 2016; Lee, 2020, 2021); of the 53 genes analyzed, 19 were pro-inflammatory genes (*IL1A, IL1B, IL6, IL8, TNF, PTGS1, PTGS2, FOS, FOSB, FOSL1, FOSL2, JUN, JUNB, JUND,*

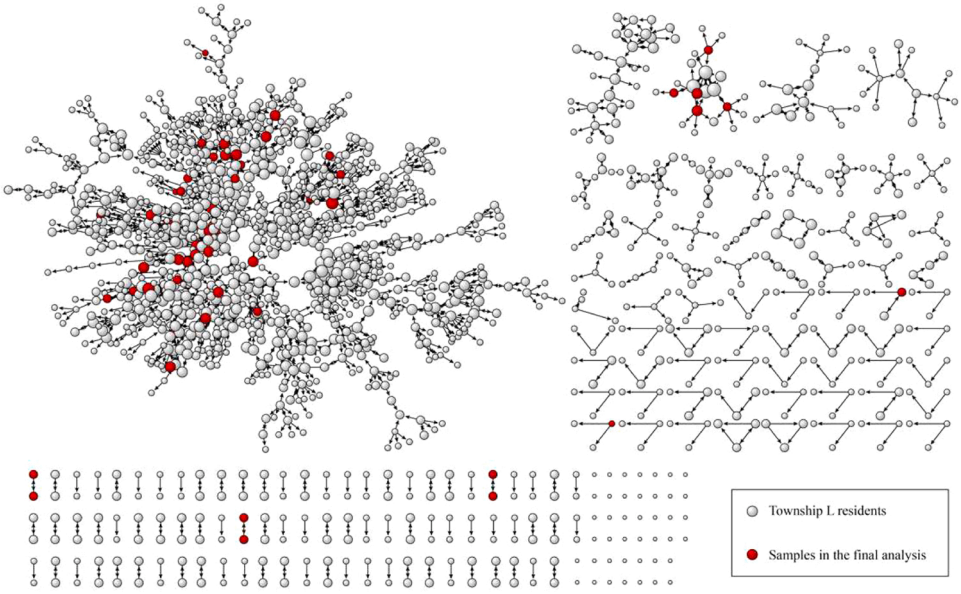

Fig. 1. The global social network map of the Township L. Circled nodes represent people and lines illustrate social ties between them. The red nodes indicate the participants of the final analysis (n = 53).

NFKB1, NFKB2, REL, RELA, and *RELB*) and were considered as positive indicators. The remaining 34 genes were involved in type I IFN responses (*GBP1, IFI16, IFI27, IFI27L1 −2, IFI30, IFI35, IFI44, IFI44 L, IFI6, IFIH1, IFIT1 −3, IFIT5, IFIT1L, IFITM1 −3, IFITM4P, IFITM5, IFNB1, IRF2, IRF7 −8, MX1 −2, OAS1 −3,* and *OASL*) and antibody synthesis (*IGJ, IGLL1,* and *IGLL3*) which were inverted to reflect their inverse contribution to the CTRA (Cole, 2019). Supplemental Table 1 contains descriptive statistics for expression levels of each transcript.

Using SAS PROC MIXED analysis, we examined the association between social network characteristics and CTRA gene expression patterns. To control for the correlation among multiple CTRA indicator transcripts within individuals, the 53 CTRA indicator genes were analyzed as repeated measures with a fully parameterized covariance matrix. This approach enables the specification of a heterogenous covariance structure across the genes and facilitates quantification of the association between the social network measures and CTRA gene expression using a single measure of average indicator gene expression (i.e., the analysis does not involve multiple testing across the multiple indicator genes). Covariates including sex, body mass index (BMI), and health-related behaviors such as smoking (currently smoking as 1 and no smoking as 0), alcohol consumption (more than once a week or more as 1 or less as 0), and BMI were controlled in the linear model (Cole et al., 2015b; Fredrickson et al., 2013; Lee et al., 2020, 2021). Table 1 presents the descriptive statistics of the key variables.

3. Results

We first examined the relationship between social network characteristics and perceived social isolation (loneliness). We found that the degree centrality (social network size) was not associated with loneliness, $r(51) = 0.12$, $p = .38$. However, core network position, defined by *k*-core score, was significantly associated with lower loneliness, $r(51) = -0.29$, $p = .04$.

Next, we tested the relationship between CTRA gene expression and social network variables after adjustment for potentially confounding factors including age, sex, BMI, and health-related behaviors. As depicted in Fig. 3A, core position (*k*-core score) and degree centrality were significantly inversely associated with CTRA gene expression, $b = -0.058$ standardized log2 mRNA abundance per score, SE= 0.008, $t(46) = -6.92$, $p < .0001$ and $b = -0.006$, SE= 0.003, $t(46) = -2.06$, $p = .046$, respectively. Given the significant positive association between loneliness and CTRA expression (b=.064, SE= 0.013 $t(46) = 4.84$, p <0.0001), we reassessed the relationship between CTRA expression and the social network variables after adjusting for the level of loneliness. After controlling for loneliness, degree centrality was no longer associated with CTRA expression, $b = -0.002$, SE= 0.003, $t(45) = -0.72$, $p = .477$. However, core position in social network (*k*-core score) continued to show an inverse association with CTRA level, $b = -0.052$, SE= 0.009, $t(45) = -6.05$, $p < .0001$ (Fig. 3B). The association between loneliness and CTRA gene expression remained significant when controlling for either degree centrality or core position, $b = 0.061$, SE= 0.013, $t(45) = 4.53$, $p < .0001$ and $b = 0.034$, SE= 0.013, $t(45) = 2.6$, $p = .013$, respectively.

Table 1
Characteristics of the participants.

	Men (N = 28)	Women (N = 25)	Total (N = 53)	p-value
Age	72.929 (3.185)	70.960 (4.458)	72.000 (3.927)	0.068
BMI	24.408 (2.548)	24.609 (4.783)	24.503 (3.734)	0.847
Current smoking				0.061
No	22 (78.6%)	24 (96.0%)	46 (86.8%)	
Yes	6 (21.4%)	1 (4.0%)	7 (13.2%)	
Alcohol consumption				< 0.001
Never/rarely	11 (39.3%)	21 (84.0%)	32 (60.4%)	
≥once a week	17 (60.7%)	4 (16.0%)	21 (39.6%)	
Loneliness	1.752 (0.474)	1.794 (0.458)	1.772 (0.462)	0.744
Degree centrality	4.893 (2.657)	3.600 (1.658)	4.283 (2.315)	0.041
Core position (*k*-core score)	2.536 (0.744)	2.440 (0.583)	2.491 (0.669)	0.608

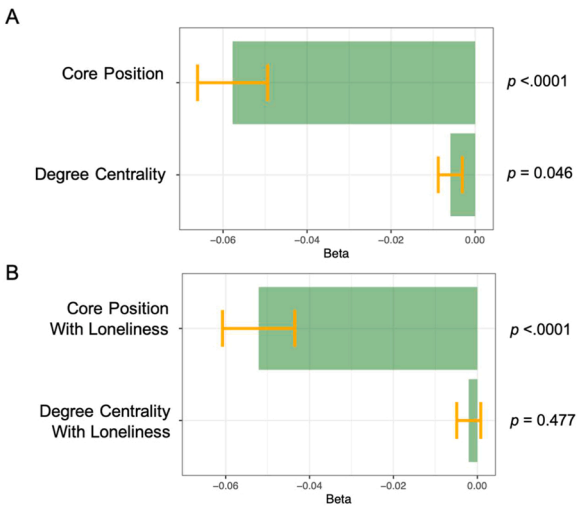

Fig. 3. Social network characteristics and CTRA gene expression without controlling for loneliness (A) and after controlling for loneliness (B). Bars represent beta coefficients ± standard errors.

4. Discussion

The present study examined the links between global social network characteristics and CTRA gene regulation in a geographically delimited community of Korean older adults. Taking advantage of comprehensive network mapping of community members, we found that those older adults with higher *k*-core scores (densely interconnected social clusters) showed significantly lower levels of CTRA gene expression than did those with lower *k*-core scores. Such associations emerged above and beyond the inversely correlated effects of subjective social isolation (loneliness), indicating a distinct role of positions in a social network above and beyond individual experiences of social isolation. Social network size, defined by degree centrality, was also associated with lower levels of CTRA gene expression, but these effects were rendered nonsignificant after controlling for perceived social isolation (loneliness). These findings reveal that multiple structural aspects of social networks may affect immune response gene expression, with some potentially acting through their effects on subjective perceptions whereas others appear to operate in distinction from perceived isolation (e.g., *k*-core score). Collectively, these results identify human genome regulation as one potential pathway through which social networks may be systematically related to the human health and disease risks that have long been recognized by social epidemiology.

The current findings expand the social signal transduction paradigm by examining group-level measures of social relationships. From an evolutionary perspective, social isolation is hypothesized to trigger a physiological threat response that increases inflammation and suppresses antiviral responses, which was likely adaptive under ancestral conditions due to an increased chance of bacterial infection by physical attacks but a reduced chance of person-to-person viral infection during periods of social isolation (Cacioppo and Cacioppo, 2018; Leschak and Eisenberger, 2019). This evolutionary framework explains previously observed relationships between perceived social isolation (e.g., loneliness) and upregulation of CTRA expression (Cole et al., 2007, 2015a, 2015b; Lee et al., 2021). Although social isolation is far less correlated

with physical injury and bacterial attack in contemporary society, the neuro-immune infrastructure remains encoded in our genome, and the mere perception of social isolation can still activate the social signal transduction pathway (Cole et al., 2015a; Leschak and Eisenberger, 2019). A few recent studies suggest increased plasma protein inflammatory markers (e.g., levels of C-reactive protein and Interleukin-6) with a smaller network size (Loucks et al., 2006; Yang et al., 2013), however, little is known about the relationship between observed social network structures and immune cell gene regulation (Cole et al., 2015a; Leschak and Eisenberger, 2019). Moreover, in that the relationships between observed and perceived social connection make it difficult to distinguish their respective effects on immune gene expression, studies need to measure both directly. By quantifying these two domains of social connections simultaneously, the current findings not only confirm the significant positive correlation of loneliness with CTRA expression but also identify significant additional associations between CTRA expression and global social network characteristics above and beyond the effects of loneliness.

The current findings suggest a protective role of social network positions in maintaining favorable immune cell gene regulation patterns. Belonging in higher *k*-core groups indicates not only membership in more cohesive social groups but may also higher status in the hierarchy of social relations. In that both degree centrality and community structure were correlated with *k*-core structure of empirical networks (Malvestio et al., 2020), individuals in higher *k*-core groups may feel a greater sense of belongingness within a community, have timely access to valuable information or gossip, and/or be seen as more prestigious and influential. Moreover, considering that a lack of sense of belongness can lead to elevated stress levels (Rohleder, 2014; Wirtz and Känel, 2017), membership in higher *k*-core groups may contribute to reduced CTRA gene expression possibly via reduced stress levels. Furthermore, based on previous research linking both subjective and objective measures of social status to reduced CTRA gene expression (Castagné et al., 2016; Knight et al., 2016; Levine et al., 2017; Miller et al., 2018; Murray et al., 2019; Powell et al., 2013; Shanahan et al., 2022), it could be speculated that the protective effect of higher social status on immune cell gene regulation can possibly mediate the link between higher *k*-core groups, who may have higher status in the hierarchy of social network, and CTRA gene expression. Taken together, our findings highlight the importance of social network positions as potential determinants of an individual's health status. These results also underscore the need to consider social network status in addition to loneliness when developing future clinical interventions for older adults.

The present study has several limitations. First, our study benefits from a global network mapping from one entire town in Korea, which can be created only if individual connection data are available for most community members. As far as we are aware, this is the only sample that includes both global network mapping and individual gene expression profiling. As such, caution should be exercised when generalizing the findings to other ethnic or age groups or different cultures, and there is a great need to replicate and extend these findings in other larger samples. Second, given that the present study examined the association between prior social network measures and later-assessed immune cell gene expression patterns, we have assumed that social adversity may influence CTRA expression. However, based on previous findings of the bidirectional interactions between social behavior and inflammation (Eisenberger et al., 2017; Muscatell et al., 2016), it is conceivable that chronic inflammatory biology may result in reduced social activity and thereby affect social network position. Experimental manipulations will be required to definitively resolve the causal direction of the associations observed here. Third, considering that social connections can be both beneficial and detrimental (Uchino and Eisenberger, 2019; Uchino and Rook, 2020), future research should integrate emotional aspects of social relationships (e.g., interpersonal stress) with the social network structures to examine their collective effects on health. Moreover, as this study was not pre-registered, future replications with pre-registered hypotheses are necessary. Finally, it should be noted that the present study focused solely on the CTRA RNA profile using a pre-defined set of 53 genes related to inflammation and antiviral response. While treating these 53 genes as parallel indicators of the CTRA profile allowed us to capture the gene expression patterns in a simple and efficient way, it is important to acknowledge that there are other ways of measuring the CTRA (Cole, 2019) and that other aspects of gene regulation may also be sensitive to social network structures and remain to be discovered in future research.

5. Conclusions

The present findings indicate that a membership in a densely interconnected high-status social subgroup is associated with lower CTRA gene expression. The current findings implicate the structure of social networks in the regulation of individual human genome function, which may have a distinct role from the gene regulatory effects of perceived connectedness. Given the relations between CTRA gene expression and health outcomes documented in previous research, the present findings suggest that social network positions may have implications for the biological health and well-being of older adults. Future studies examining the additive or synergetic effect of multifactorial aspects of social connections should further establish the health implications of social relationships.

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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.

Data Availability

The data are available from the corresponding author upon request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106342.

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