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RESEARCH ARTICLE

Social genomics, cognition, and well-being during the COVID-19 pandemic

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Abstract

INTRODUCTION: Adverse psychosocial exposure is associated with increased pro-inflammatory gene expression and reduced type-1 interferon gene expression known as the conserved transcriptional response to adversity (CTRA). CTRA is not well-studied in cognitive impairment but may contribute to late-life cognitive decline.

METHODS: We examined perceived stress, loneliness, well-being, and the impact of coronavirus disease 2019 (COVID-19) and the relationship to the expression of genes associated with the CTRA. Mixed-effect linear models were used to quantify associations between psychosocial variables and CTRA gene expression.

RESULTS: Eudaimonic well-being (EWB) was inversely associated with CTRA gene expression in participants with both normal cognition (NC) and mild cognitive impairment (MCI). Self-reported coping strategies differed by cognitive status and variably impacted CTRA gene expression.

DISCUSSION: EWB is an important correlate of stress, even in people with MCI. The prodromal cognitive decline appears to moderate the significance of coping strategies as a correlate of CTRA gene expression.

KEYWORDS
COVID, loneliness, mild cognitive impairment, social genomics, stress, well-being

Highlights

- Conserved transcriptional response to adversity (CTRA) gene expression is higher with lower eudaimonic well-being.
- Eudaimonic well-being was important in both participants with normal cognition and those with mild cognitive impairment.
- Coping strategies and impact on CTRA gene expression differed by cognitive status.
- Loneliness in a population with relatively low loneliness scores did not impact CTRA gene expression.

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative condition that is a common cause of both mild cognitive impairment (MCI) and dementia.[1,2] Psychosocial risk and resiliency factors can modulate the rate of subsequent cognitive decline in the context of developing neuropathologic changes in the brain, and many of these factors may be modifiable.[3] Key to developing interventions to harness such resilience effects is identifying the specific psychosocial processes that impact the biology of cognitive decline.

The conserved transcriptional response to adversity (CTRA)[4] is a pattern of leukocyte gene expression that has been observed across species (i.e., conserved) in response to a host of adverse social conditions and involves an increase in the expression of pro-inflammatory genes and a decrease in the expression of type I interferon response genes. Chronic low-level threat produces chronic activation of pro-inflammatory genes, which can contribute to the pathogenesis of a host of common chronic conditions such as AD and related dementias,[5] cardiovascular diseases, and neoplastic disorders[6,7]. This chronic, low-grade inflammation also increases with age ("inflammaging") and may be accelerated with chronic psychosocial adversity.[8] However, few studies have evaluated CTRA risk or resilience processes in the context of cognitive aging.

The CTRA was first identified in the context of loneliness,[9] subsequent works linked these effects to reduced levels of eudaimonic well-being (EWB), or a sense of purpose and meaning in life.[10] EWB has been linked to variations in cognitive aging with a lower risk of both AD and MCI over a 7-year follow-up period.[11] Given the potential role of inflammatory biology in cognitive aging, the CTRA-associated inflammatory biology may represent one mechanism through which psychosocial factors (i.e., a sense of purpose) could affect either risk or resiliency to cognitive decline.

We conducted genome-wide transcriptional profiling of dried blood spots collected during a period of significant psychosocial stress—the first 2 years of the COVID-19 pandemic—and examined links between CTRA gene expression and several psychosocial risk and resilience factors, including loneliness, perceived stress, and both hedonic well-being (HWB) and EWB. Analyses focused on understanding how the psychosocial correlates of CTRA gene expression may be similar to or different between those with normal cognition (NC) and those with MCI.

2 | METHODS

2.1 | Participants

All participants were previously enrolled in the Alzheimer's Disease Clinical Core cohort of the Wake Forest AD Research Center (WF ADRC) and underwent standardized evaluations in accordance with the National Alzheimer's Coordinating Center (NACC) protocol for data collection which meets uniformed data set (UDS) requirements. Specific inclusion and exclusion criteria for the Clinical Core are described elsewhere.[12] Yearly cognitive adjudication with a group of experienced clinicians provides a cognitive diagnosis of NC, MCI, or dementia. Only participants with NC or MCI were eligible for this study inclusion. The determination of MCI was made using clinical criteria according to NACC guidelines.[13] Both questionnaire responses and dried blood spot (DBS) collection were designed to be collected remotely. All study procedures were approved by the local Institutional Review Board. Written informed consent was obtained for all participants and/or their legally authorized representative. Questionnaires were administered via telephone between February 15, 2021, and July 21, 2021. DBS collection occurred a median of 8 days (range: -36–131 days) following questionnaire completion.

2.1.1 | Perceived stress

The 10-item Perceived Stress Scale (PSS) measures an individual's perception of stress over the past month.[14] The questions were answered on a Likert scale ranging from "never" (0) to "very often" (4) after reversing the four positively stated questions. Individual items are summed to produce a total score and showed good internal reliability ($\alpha = 0.85$). Higher scores reflect higher levels of perceived stress.

2.1.2 | Loneliness

Loneliness was assessed using the University of California at Los Angeles (UCLA) Loneliness Scale, Version 3.[15] Participants rate statements to describe how often they feel the way described, ranging from "never" (0) to "often" (4). There were 20 statements, and 9 were reverse-coded

according to standard instructions. A total score was computed with higher scores indicating greater feelings of loneliness and showed good internal reliability ($\alpha = 0.85$).

2.1.3 | Coping

The Brief Coping Orientation to Problems Experienced Inventory (Brief-COPE) was developed by Carver[16] as an abbreviated version of the longer COPE, which contains 28 items measuring 14 factors of coping along a Likert scale ranging from "I have not been doing this at all" (0) to "I have been doing this a lot" (3). We added six questions related to positive distraction.[17] Consistent with prior research,[18] we performed a parallel factor analysis which identified a three-factor solution of Support (comprised of emotional support, instrumental support, and active coping items), Distraction and Reframing (comprised of positive distraction, positive reframing, and self-distraction), and Blame and Disengagement (comprised of self-blame and behavioral disengagement). Nonparticipating factors were denial, substance use, venting, planning, humor, religion, and acceptance.

2.1.4 | Hedonic and eudaimonic well-being

The Mental Health Continuum-Short Form (MHC-SF)[19] is a 14-item questionnaire derived from a 40-item questionnaire.[20] The MHC-SF was designed to measure hedonic and psychological well-being (PWB)and social well-being (SWB).[21,22] Respondents were asked to answer questions about the degree to which they have felt a given way over the past month ranging from "never" (0) to "every day" (5). Three questions were summed for HWB, five for SWB, and six for PWB. SWB and PWB together make up EWB. The overall internal reliability of the MHC-SF was good ($\alpha = 0.89$).

2.1.5 | COVID-19 specific experiences

Two questionnaires were given to assess the impact of COVID-19 on participants: the participant version of the COVID-19 Impact Survey, version 1[23] with supplemental questions from the Questionnaire for Assessing the Impact of the COVID-19 Pandemic and Accompanying Mitigation Efforts on Older Adults (QAICPOA).[24] For the purposes of this study, three questions were included in the analysis, all from the COVID-19 Impact Survey (questions 7, 8, and 9). Each of these questions was answered on a five-point Likert scale ranging from "not at all" (1) to extremely (5).

2.2 | Dried blood spot collection

After questionnaires were collected, participants were mailed a remote collection kit for the self-collection of dried blood spots. Training materials were adapted for use in our cohort from Allen et al. (see Supplemental Methods for further detail).[25]

RESEARCH IN CONTEXT

1. **Systematic review**: A review of the literature on adverse psychosocial experiences shows a well-described pattern of transcriptional changes, the conserved transcriptional response to adversity (CTRA), that provides a molecular source of the pro-inflammatory changes associated with psychosocial adversity. Little is known about how cognition impacts this response.
2. **Interpretation**: We found that, among psychosocial risk and resiliency factors examined, eudaimonic well-being (which includes a sense of purpose and meaning in life) was associated with a favorable CTRA gene expression profile, as expected from previous literature. Importantly, we found that this was true regardless of the cognitive status, either normal cognition or mild cognitive impairment (MCI), of our participants. Strategies used by participants to cope with stress did impact CTRA gene expression, and the effect was different depending on cognitive status.
3. **Future directions**: Stress has been recognized as a risk factor for cognitive decline, yet the mechanism through which this occurs remains unclear. Larger, more diverse studies of psychosocial adversity and its impact on CTRA-related genes are needed to better understand the role of embodiment of stress and the risk of cognitive decline in later life.

2.3 | Measurement of gene expression

DBS were stored at -80°C at the WF ADRC and then shipped as a single batch on dry ice to the UCLA Social Genomics Core Laboratory for transcriptome-wide RNA profiling and CTRA gene expression analyses as previously described and more fully described in the supplemental methods.[26,27] DBS samples yield RNA concentrations below the limit of RNA integrity assessment; however this is not a significant concern due to the high-efficiency mRNA-targeted cDNA library construction system, which is highly robust to low-RNA integrity numbers (i.e., RIN < 3). Among 171 assayed samples, routine post-assay data quality screening identified seven samples with insufficient RNA sequencing reads (< 5 million), eight additional samples with poor read mapping rates (< 70%), and six additional samples with poor signal-to-noise ratios (average profile correlation with other samples: $r < 0.50$), leaving a total of 148 valid RNA profiles available for analyses of CTRA. This 87% valid data yield is consistent with previous research involving genome-wide transcriptional profiling of DBS samples.[26,27]

2.4 | Statistical analysis

We used linear mixed-effect models to analyze the average expression of a prespecified set of CTRA indicator gene transcripts as a function of

psychosocial risk and resilience factors while controlling for covariates. Analyses focused on a prespecified set of 53 CTRA indicator genes used in previous research,[4,28] of which 43 were reliably detectable in this study, including 16 pro-inflammatory gene transcripts and 27 Type I interferon-related gene transcripts, and 10 of which were removed due to minimal expression levels or variation (SD < 0.5 log2 expression units). Gene-specific *z*-score signs were reversed for the antiviral gene set to reflect its inverse contribution to the CTRA profile.[4] Mixed models were estimated by maximum likelihood (SAS PROC MIXED) and specified fixed effects of indicator gene (repeated measure), cognitive status (normal vs. MCI), psychosocial risk/resilience factors, a cognitive status × psychosocial factor interaction term (testing for differences in CTRA association as a function of cognitive status), and covariates (age, sex, race, body mass index [BMI], history of regular smoking, and history of regular alcohol consumption at entry into the WF ADRC); a random effect of study participant; and a fully saturated (unstructured) variance-covariance matrix to account for residual heteroscedasticity and correlation across participants. In the event of a significant cognitive status x psychosocial factor interaction, additional follow-up "simple slopes" analyses quantified the association of psychosocial factors with CTRA gene expression nested within the cognitive status group. No more than 2.5% of data was missing for any given variable and only complete cases were analyzed.

TABLE 1 Demographics.

Parameter	NC ($n = 91$)		MCI ($n = 52$)		
	n	%	*n*	%	*p*-Value
Black participants	16	18	7	13	0.935
Women	67	74	32	62	0.134
Alcohol use	60	66	28	54	0.131
Tobacco use	4	4	3	6	0.715
Beta-blocker use	14	15	13	24	0.160
	mean	*(SD)*	*mean*	*(SD)*	
Age, years	71.4	8.4	75.7	7.4	**0.002**
Education, years	16.2	2.3	15.4	2.5	0.088
BMI	27.7	6.3	28.2	5.5	0.658
MoCA score, total	27.3	2.5	23.0	3.4	**<0.001**
Loneliness	31.8	8.8	35.8	10.4	**0.017**
Perceived stress	5.1	3.2	4.9	2.8	0.694
HWB	12.5	2.6	12.2	2.4	0.455
EWB	42.6	7.8	39.5	9.5	**0.042**
Coping—support factor	2.9	1.3	2.6	1	**0.021**
Coping—distraction and reframing factor	3.0	0.7	2.7	0.8	**0.033**
Coping—behavioral disengagement factor	1.3	0.4	1.3	0.5	0.956

Abbreviations: BMI, body mass index; EWB, eudaimonic well-being; HWB, hedonic well-being; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; NC, normal cognition.

3 | RESULTS

3.1 | Demographics and cognitive status

A total of 171 participants provided DBS samples (106 NC, 58 MCI, 1 Dementia, 6 Other/NA) with 148 of those samples (87%) yielding valid RNA data. Participants without diagnoses of NC or MCI were excluded from further analysis (4), and one participant completed a DBS without questionnaires and was excluded from further analysis, yielding a final analytic sample of 143 participants: 91 with NC and 52 with MCI. The mean age of our group was 72.9 ± 8.04 years, 16% were Black individuals, 69% were female, and 19% were treated with a beta-blocker. Participant demographic characteristics are summarized in Table 1.

3.2 | Cognitive impairment and the psychosocial correlates of CTRA

To determine how cognitive impairment might affect the relationship between psychosocial factors and CTRA gene expression, we compared the relation of CTRA gene expression to psychosocial risk factors (stress, loneliness), two distinct domains of well-being (HWB and EWB), and three distinct domains of coping (blame and disengagement, distraction and reframing, and social support) for NC and MCI groups while controlling for covariates. In each mixed model, sex, alcohol use at WF ADRC study entry, and tobacco use at WF ADRC study entry were significantly associated with CTRA gene expression (p's < 0.05). Additionally, we separately looked at the addition of education as a covariate, and while education was itself associated with CTRA gene expression, there was no substantial difference in our primary variables of interest (Table S1).

Consistent with previous reports,[10,29,30] CTRA gene expression was significantly associated with the two-dimensional representation of well-being (distinct hedonic and eudaimonic dimensions; $F(2, 129) = 4.93$, $p = 0.009$; Table 2, Model 1), with a significant inverse association with EWB (-0.045 $\log_2$ RNA per well-being SD ± 0.015 SE, $p = 0.003$). There was no significant association with HWB (+0.019 ± 0.015, $p = 0.225$). Neither stress nor loneliness showed any significant association with CTRA gene expression in this sample ($F(2, 130) = 0.37$, $p = 0.693$; individual p's > 0.50; Table 2, Model 2).

CTRA gene expression also varied significantly as a function of the three major dimensions of coping in this sample ($F(3, 126) = 7.22$, $p < 0.001$; Table 2 Model 3, Figure 1). However, we detected significant interactions between cognitive status and the brief-COPE as it relates to CTRA gene expression ($F(3, 123) = 9.07$, $p < 0.001$). Among those with normal cognitive function, coping through social support was associated with lower CTRA gene expression (-0.075 ± 0.017, $p < 0.001$) whereas coping by distraction/reframing was associated with higher CTRA gene expression (+0.086 ± 0.018, $p < 0.001$). Among those with MCI, coping by blame or disengagement was associated with a lower CTRA gene expression (-0.077 ± 0.018, $p < 0.001$).

TABLE 2 CTRA relationship to well-being, stress, loneliness, coping factors, and C19

Parameter	Model 1			Model 2			Model 3			Model 4		
Variables	***b***	**SE**	***p***	***b***	**SE**	***p***	***B***	**SE**	***p***	***b***	**SE**	***p***
EWB	−0.045	0.015	**0.003**									
HWB	0.019	0.015	0.225									
Perceived stress				0.001	0.013	0.939						
Loneliness				−0.011	0.013	0.417						
Self-blame/behavioral disengagement coping factor							−0.168	0.012	0.161[a]			
Distraction/reframing coping factor							0.063	0.015	**<0.001**[a]			
Support coping factor							−0.052	0.015	**<0.001**[a]			
C19-diagnosis										−0.144	0.058	**0.014**
C19-worry										0.024	0.015	0.105
C19-isolation										−0.027	0.011	**0.019**
C19-disruption										0.030	0.011	**0.011**

Abbreviations: CTRA, conserved translational response to adversity; C19, COVID-19; EWB, eudaimonic well-being; HWB, hedonic well-being; WF ADRC, Wake Forest Alzheimer's Disease Research Center.

[a]A significant interaction with cognitive status. Covariates in all mixed effects models included age, sex, race, body mass index, reported regular smoking at the WF ADRC study entry, and regular alcohol consumption at the WF ADRC Study entry.

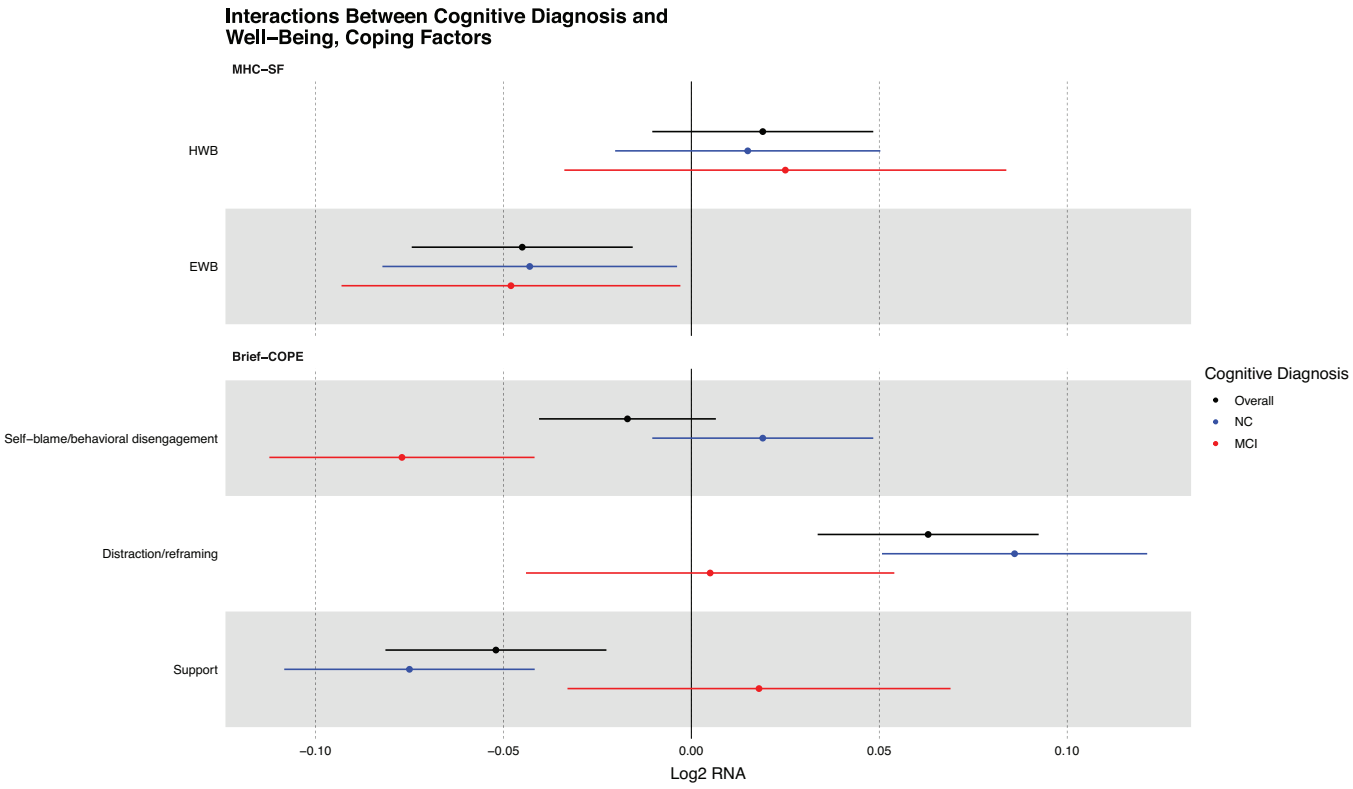

FIGURE 1 Interactions between cognitive diagnosis and well-being, coping factors. Forest plot demonstrating the strength of association (b ± SE) between the indicated predictor variable and the 53-gene CTRA contrast score for two dimensions of well-being and three coping factors. Brief-COPE, Brief Coping Orientation to Problems Experienced Inventory; CTRA, conserved transcriptional response to adversity; EWB, eudaimonic well-being; HWB, hedonic well-being; MHC-SF, Mental Health Continuum-Short Form

In a model that included both psychosocial risk factors (perceived stress, loneliness) and dimensions of well-being (eudaimonic, hedonic), CTRA gene expression remained significant; $F(2, 126) = 11.72$, $p < 0.001$; Table S2 Model 1), with a significant inverse relationship between CTRA gene expression and EWB (-0.076 ± 0.016, $p < 0.001$) and loneliness (-0.050 ± 0.015, $p < 0.001$) with no effect modification by cognitive diagnosis. There are significant correlations between EWB and HWB ($R = 0.60$), loneliness ($R = -0.59$), and perceived stress ($R = -0.42$). A model including both EWB and the three coping factors was also significantly associated with CTRA gene expression; $F(3, 123) = 7.01$, $p < 0.001$ (Table S2, Model 2). In this model, there was a significant inverse correlation between CTRA gene expression and EWB (-0.03 ± 0.012, $p = 0.013$) with no effect modification of cognitive diagnosis. However, we again detected significant interactions between cognitive status and the brief-COPE about CTRA gene expression ($F(3, 119) = 10.71$, $p < 0.001$). Among those with normal cognitive function, coping through social support was associated with a lower CTRA gene expression (-0.076 ± 0.017, $p < 0.001$) whereas coping by distraction/reframing was associated with a higher CTRA gene expression (+0.091 ± 0.017, $p < 0.001$). Among those with MCI, coping with blame or disengagement was associated with a lower CTRA gene expression (-0.080 ± 0.018, $p < 0.001$). There was no significant correlation between EWB and these coping factors.

Several COVID-19-related factors were associated with significant differences in CTRA gene expression, none of which differed by cognitive diagnosis ($F(3, 124) = 3.20$, $p = 0.026$; Table 2 model 4). A past diagnosis of COVID-19, either confirmed or suspected, was associated with a lower CTRA gene expression (-0.144 ± 0.058, $p = 0.014$). Of note, only 6 out of 143 (4%) of our participants reported a past COVID- diagnosis, and the timing of past infection was not documented. Participants who reported feeling isolated due to COVID-19 had a lower CTRA gene expression (-0.027 ± 0.011, $p = 0.019$), and those who reported higher distress had a higher CTRA gene expression (+0.030 ± 0.018, $p = 0.019$)The degree of worry about COVID-19 was not significantly associated with CTRA gene expression (+0.024 ± 0.015, $p = 0.105$).

The models presented in Table 2 were also evaluated in a stepwise fashion to understand whether the delay in DBS collection after questionnaire completion (Table S3), education (Table S1), or leukocyte subset composition (Table S4) impacted the results presented here and in each, there was no substantial change in the primary results presented here.

4 | DISCUSSION

Our analysis of genome regulation in the context of the COVID-19 pandemic during the period of general social distancing documented distinctive transcriptional correlates of well-being and dimensions of coping. In both MCI and NC, these data are consistent with previous research in identifying an inverse association of CTRA gene expression with EWB. For the NC group, CTRA gene expression was also inversely associated with coping through social support, but directly (unfavorably) associated with coping by distraction and reframing. By contrast, CTRA gene expression was not associated with either of those coping dimensions for individuals with MCI. The patterns of similar and distinct associations for MCI versus NC suggest that broad experiences of psychological and SWB remain centrally relevant to biobehavioral function in the context of MCI, whereas more specific dimensions of self-management and coping may become less relevant to individual biobehavioral function in the context of MCI as individuals come to depend more on others to help support activities of daily life and cope with the challenge, and thus less predominately dependent on their cognitive processes and coping responses.

High levels of loneliness have been shown to be associated with an upregulation of CTRA gene expression.[31] However, loneliness did not predict CTRA profile in our cohort, likely due to the relatively low loneliness scores among our participants. One previous study found that EWB had a stronger relationship with CTRA gene expression than did loneliness when considered simultaneously, suggesting that the two variables' effects may stem from their common involvement in SWB.[32] In a model containing both EWB and loneliness, we found that eudaimonia retained a significant inverse association with CTRA gene expression but a counterintuitive inverse relationship between loneliness and CTRA gene expression appeared after the shared variance between these two variables of interest was accounted for, a finding that will need to be explored in future work.

Wyman and colleagues[33] demonstrated that Black and American Indian/Alaskan Native participants reported lower life satisfaction than White participants, but similar scores on positive affect, meaning in life, and purpose in life. Measures of executive functions, but not episodic memory, were higher in those with higher life satisfaction scores. PWB is a multi-dimensional construct and includes evaluative well-being related to evaluations made about life, HWB or pleasures and satisfaction from life, and EWB or a sense of greater purpose in life.[34] Subjective clinical complaints associated with MCI, such as memory concerns, are predictive of reduced PWB in individuals.[35] It is possible that subjective clinical complaints associated with MCI lead to the observed reduction in EWB among MCI participants in this study. Interventions targeting subjective self-reported health and emotional factors related to well-being have the potential to improve EWB and reduce the associated upregulation in the CTRA profile.

Strategies used for coping with psychosocial stress in MCI have been assessed in prior work, though this is the first study to evaluate its molecular correlates in gene expression. Coin and colleagues[36] assessed coping strategies in people living with MCI and dementia and found that individuals with greater cognitive impairment had poorer coping strategies. This association remained present even after adjusting for pre-pandemic depression, suggesting that less efficient coping strategies may have exposed those with a greater degree of cognitive impairment to more psychosocial stress related to pandemic-related social distancing. In a study of coping strategies during restricted movement, travel and assembly in Malaysia, older adults with cognitive frailty (i.e., concurrent cognitive and physical impairment that is conceptualized as a multifaceted, age-related syndrome) tended to use religion, acceptance, and positive reframing (i.e., active coping), while

self-blame, denial, and substance use (i.e., avoidant coping) were the least commonly used.[37] Our study adds to this literature in defining the molecular correlates of coping in the context of immune cell gene expression. We found that only those with NC demonstrated a reduction in CTRA gene expression with the use of social support. Among those with NC, coping based on distraction and reframing was associated with elevated CTRA gene expression. One possibility is that, as individuals develop prodromal cognitive decline, self-appraised coping strategies may become less clearly associated with actual coping strategies. A similar pattern is seen in the self-appraisal of cognitive impairment, where those with MCI demonstrate a progressive underappreciation of their own cognitive deficits.[38] Given that possibility, it is notable that EWB remains an important correlate of molecular well-being regardless of cognitive status, and that consummatory sources of HBW remain a risk even in the context of MCI. This pattern could potentially reflect that persons with MCI may be "outsourcing" their coping to their caregivers/support network; thus, their own psychological reactions bear little relationship to their CTRA biology, whereas their engagement with others (SWB) is the primary psychosocial source of biological resilience.

Several issues limit the interpretation of the present results. In this sample, people with cognitive impairment were both older and lonelier than those without cognitive impairment, and this range restriction could have contributed to the lack of association observed for loneliness and CTRA gene expression among those with MCI. While the mean delay in collection of DBS after questionnaire data was 8 days with a standard deviation of 20.3 days, there were participants who had DBS collection more distant from the time of questionnaire collection (range: 36–131 days). This did not seem to impact the robustness of our findings (see Table S1). Our MCI sample was smaller than our NC sample, potentially leading to asymmetric power across subgroups. Because our data come from a single regional context, it is unclear whether our findings would hold across all individuals with MCI, and future work should focus on larger and more broadly representative samples, adjust for multimorbidity, and include repeated assessments of both psychosocial variables and CTRA longitudinally, as well as long-term evaluation of subsequent cognitive trajectory related to CTRA assessment. Additionally, our work did not separate CTRA into the subcomponents of pro-inflammatory and type 1 interferon-related gene expression which limits our ability to determine whether one distinct component contributes more than another. To examine this robustly, a larger sample size will be needed, and future work should examine this.

Despite these limitations, our work demonstrates several important findings. This is the first study to demonstrate similar transcriptional correlates of eudaimonic versus HWB in individuals with MCI compared to NC individuals. It is well-established that individuals with greater EWB (i.e., a sense of purpose in life) demonstrate a reduced CTRA gene expression profile,[29,30,32] and past work has found a significant reduction in the risk of AD and MCI associated with a greater sense of purpose in life.[11] The findings here suggest one potential mechanism through which this psychological resiliency factor may function, mediating a lower inflammatory burden and protecting against the "inflammaging" that has been proposed to contribute to the AD neuropathological cascade.

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CONFLICT OF INTEREST STATEMENT

All authors report no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All human subjects provided informed consent to participate in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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