Original Research

Differentially conserved transcriptomic response to adversity related to self-rated health in the multi-ethnic study of atherosclerosis

Pia Riestra[1], Samson Y Gebreab[1], Yongmei Liu[2], Ana V Diez Roux[3], Rumana R Khan[1], Amadou Gaye[1], Ruihua Xu[1] and SK Davis[1]

[1]National Human Genome Research Institute, Genomics of Metabolic, Cardiovascular and Inflammatory Disease Branch, Social Epidemiology Research Unit, National Institutes of Health, Bethesda, MD 20892, USA; [2]Department of Epidemiology and Prevention, Division of Public Health Sciences, Center for Human Genomics, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA; [3]Dean's Office, School of Public Health, Drexel University, Philadelphia, PA 19104, USA
Corresponding author: Pia Riestra. Email: teresa.riestra@nih.gov

Impact statement

In this work, we evaluated for the first time how self-rated mental (SRMH) and physical health (SRPH) influence the immune response at the molecular level in a large multi-ethnic cohort. We observed that both SRMH and SRPH are related to immunocompetence status. These findings indicated that the link between how we perceive our health and poorer health outcomes could be explained by alterations in the immune response by shifting the expression of genes related to the type I IFN response and antibody synthesis.

Abstract

Self-rated health (SRH) is considered a strong indicator of well-being and clinical health status and has been linked to inflammatory markers. The objective of this work was to examine how self-rated physical health (SRPH) and mental health (SRMH) influence the immune system through the regulation of a stress-related gene expression profile known as the 'conserved transcriptional response to adversity' (CTRA), which involves the up-regulation of pro-inflammatory genes and down-regulation of genes involved in type I interferon (IFN) response and antibody synthesis. CTRA expression data were derived from genome-wide transcriptional data on purified monocytes in 1264 adult participants from the multi-ethnic study of atherosclerosis. SRPH and SRMH were assessed through the SF-12 questionnaire. Multiple linear regression models were used to determine the association between the composite score of the CTRA subsets and SRPH and SRMH. Higher scores of SRPH and SRMH were associated with an increased expression of the overall CTRA profile. The individual gene subsets analysis did not reveal an increased expression of pro-inflammatory genes in persons with lower scores of SRH. However, we observed that higher scores of SRPH positively modulate the immune response through the up-regulation of both type I interferon response and antibody synthesis-related genes, while better scores of SRMH were associated with a down-regulation of genes involved in antibody synthesis. The significant association between SRH and a gene expression profile related to type I IFN response and antibody synthesis suggests that SRH may be linked to the immunocompetence status.

Keywords: Self-rated mental health, self-rated physical health, gene expression, social genomics, immune response

***Experimental Biology and Medicine* 2017; 242: 1812–1819. DOI: 10.1177/1535370217732030**

Introduction

Self-rated health (SRH), also known as self-assessed or perceived health, is an integrative and reliable indicator of overall, subjective mental and physical well-being of a person through the answer to simple questions. It is well established that SRH is a strong indicator of objective health status and is commonly used for health service evaluations in general population and patient surveys.[1] SRH may reflect illness indicators that are not bio-medically detectable or that are not included in a medical examination. Moreover, SRH has been shown to be correlated with objective well-being and health status assessed by laboratory parameters.[2] National and international studies have consistently demonstrated that SRH is a good predictor of mortality among individuals with different diseases after controlling for objective markers of disease severity.[3–5] In addition, poor SRH has also been related to different

adverse social conditions in different populations such as low income,[6] marital status, poor education, life stress, work strain,[7] and neighborhood deprivation.[8,9] Although there are different questionnaires, the short form of the SF-36, also known as the SF-12, is a 12-item questionnaire that has been widely validated across different populations and provides measurements of two main aspects of health status: The physical (PCS) and mental component summary (MCS) with higher scores representing better health.[10]

Recently, there has been a growing interest in how adverse socio-environmental circumstances play a role in influencing gene expression. Previous studies of the new field of human social genomics have linked different types of adverse socio-environmental conditions to a conserved transcriptional response to adversity (CTRA) in peripheral leukocytes, characterized by a decreased expression of genes related to the innate antiviral response also known as type I interferon (IFN) response and antibody synthesis, and increased expression of pro-inflammatory genes.[11,12] Historically, these transcriptional shifts are hypothesized to have been adaptive responses to physical threat in order to accelerate wound healing and limit infection.[13] However, such activation is not restricted to physical threats; it is also observed in the contemporary world under social adversities such as social isolation,[14] low socioeconomic status (SES),[15] childhood trauma,[16] and bereavement.[17,18] Moreover, this defensive gene expression response has also been observed in relation to psychological well-being; people who have high levels of hedonic well-being or happiness that comes from materialistic self-gratification presented an up-regulated expression of the CTRA genes, while people with eudaimonic well-being who experience a deep sense of purpose and meaning in life presented a down-regulation of the CTRA response. Studies in rodents and cell cultures have also demonstrated that the activation of a fight or flight response in the sympathetic nervous system mediated by β-adrenergic receptors plays a critical role evoking CTRA response in leukocytes.[19] Through a bioinformatics approach, monocytes and dendritic cells have been shown to be the principal mediators of this response,[20] and this bioinformatics inference has been confirmed in studies of isolated monocytes.[19]

To our knowledge, self-reported health has not been examined in relation to CTRA response. Self-reported health could be linked to CTRA response due to common social antecedents. For example, social circumstances may affect physical or mental health and may simultaneously affect gene expression. Alternatively, aspects of SRH may themselves affect gene expression, and thus gene expression could be one of the mechanistic links between self-reported health and specific health outcomes affected by immune function and inflammatory processes.[2,21,22] Another possibility is that gene expression may influence the disease processes that affect the experiences or perceptions generating SRH responses.

In the present study, we used a functional genomics approach to examine the relationships between two dimensions of SRH (self-rated physical health (SRPH) and self-rated mental health (SRMH)) and patterns of CTRA gene-expression in human monocytes in a large and well-characterized multi-ethnic sample from the multi-ethnic study of atherosclerosis (MESA).

We hypothesized that lower scores of SRPH and SRMH would be associated with monocyte gene expression characterized by an altered immune response similar to CTRA with an increased expression of pro-inflammatory genes and a decreased expression of genes related to the innate antiviral response and antibody synthesis. In addition, we explored whether this response was differentially related to SRMH and SRPH.

Material and methods

Study population

The MESA study is a large longitudinal cohort of 6814 men and women aged 45 to 84. The study was designed to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease. Mesa participants were sampled from six US sites. Beginning in 2000, extensive clinical, sociodemographic, lifestyle and behavior, laboratory, nutrition, and medication data were collected in five clinic visits.[23] The MESA Epigenomics and Transcriptomics Study was designed to obtain genome-wide methylomic and transcriptomic profiles of purified monocytes from 1264 randomly selected MESA participants aged 55 to 94 from four field centers (Baltimore, MD; Forsyth County, NC; New York, NY; and St Paul, MN). Participants self-identified themselves as Caucasian (46.6%), African American (21.5%) or Hispanic (31.8%). The study protocol was approved by the Institutional Review Board of all MESA field centers, the MESA Coordinating Center, and the University of Michigan. All participants signed informed consent.

SRH measures

SRH was measured using a slightly modified version of the 12-Item Short Form Health Survey, Version 2.0 (SF12v2).[24] The SF12v2 comprised a 12-item subset of the SF36v2. The PCS and MCS were each calculated applying scoring algorithms with weighted item responses on the same 12 questionnaire items.[10] For example, the PCS weighted questions about physical functioning, physical tasks, and bodily pain more heavily whereas the MCS weighted questions about social functioning and limitations due to emotional problems and mental health more heavily. Each score (range 0–100 points) was standardized according to the US standards; with the mean set to 50 and the standard deviation (SD) to 10, a higher score corresponds to better perceived health. Both the PCS and MCS component scores have adequate reliability and validity[24,25] and are widely used.[26] The SF12v2 was administered at the second MESA examination.

Sociodemographic covariates

Age at MESA exam 2 (calculated using date of birth); gender (male or female); self-reported race/ethnicity categorized as White Caucasian, African American, and Hispanic; and the highest year of education completed

were assessed via questionnaire. SES was assessed as annual personal income calculated by dividing annual household income (the midpoint of questionnaire-based categories) by the number of people it supported to account for family size. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared, and cigarette smoking and alcohol use were categorized into current consumption or no consumption. Working status was self-reported and recoded as employed, unemployed, and homemaker.

Gene expression profiling

As described elsewhere,[27] briefly, for monocyte purification, blood samples were collected in sodium heparin-containing Vacutainer CPTTM cell separation tubes (Becton Dickinson, Rutherford, NJ, USA) to isolate peripheral blood mononuclear cells from other elements within 2 h post-draw. Subsequently, monocytes were positively selected using anti-CD14-coated magnetic beads and the AutoMACs automated magnetic separation unit (Miltenyi Biotec, Bergisch Gladbach, Germany). Flow cytometry analysis revealed that the monocyte purity was consistently >90%.

RNA isolation was performed with the AllPrep DNA/RNA Mini Kit (Qiagen Inc., Hilden, Germany). RNA quality and quantity were assessed with a NanoDrop spectrophotometer. In addition, RNA integrity was assessed with the Agilent 2100 Bioanalyzer using RNA 6000 Nano Kit chips (Agilent Techonology Inc., Santa Clara, CA, USA) following manufacturer's instructions. Only RNA samples with RIN (RNA integrity) scores ≥9.0 were included in the expression microarrays. The median RIN for the 1264 samples was 9.9.

Genome-wide expression analysis was performed with the Illumina HumanHT-12 v4 Expression BeadChip and the Illumina Bead Array Reader, following the Illumina expression protocol. Biotin-labeled cRNAs were prepared using the Illumina TotalPrep RNA Amplification Kit (Ambion/Applied Biosystems, Darmstadt, Germany) from 500 ng of total RNA. Biotin-labeled cRNA of 700 ng were hybridized on the Illumina HT-12 version 4 beadchip according to manufacturer's instruction. To avoid batch effects across chips, a stratified random sampling technique was used to assign each sample to specific BeadChips and chip positions.

The initial data pre-processing for local background correction was performed with the Illumina's proprietary software GenomeStudio. QC analyses and bead-type summarization (average bead signal for each type after outlier removal) were performed using the beadarray package.[26] Detection p values were calculated using the negative controls on the array. Data pre-processing was performed with the neqc function of the limma package[27] which performs a normal–exponential convolution model analysis to estimate non-negative signal, quantile normalization, and log transformation. The multi-dimensional scaling plots showed that the control samples clustered together and detected three outliers that were subsequently removed from the analyses.

Statistical analysis

Descriptive statistics of the study participants were computed using means (SD) for continuous variables and proportions for categorical variables. ANOVA or chi-square analyses and t tests were used to compare SRMH and SRPH scores by participant's characteristics.

Genome-wide transcriptional profiling was carried out on isolated monocytes from all 1264 participants. Primary analyses focused on an a priori-defined contrast score representing the CTRA profile of up-regulated expression of pro-inflammatory genes (IL1A, IL1B, IL6, IL8, TNF, PTGS1, PTGS2, FOS, FOSB, FOSL1, FOSL2, JUN, JUNB, JUND, NFKB1, NFKB2, REL, RELA, and RELB) and down-regulated expression of genes involved in type I IFN responses (GBP1, IFI16, IFI27, IFI27L1-2, IFI30, IFI35, IFI44, IFI44L, 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).[12,28]

The statistical analysis was carried out in four stages:

1. Multiple linear regression models were fitted to estimate the association between each of the 47 CTRA genes and the standardized (z-score) values of SRMH and/or SRPH, with the gene expression value as the dependent variable. The model was adjusted for possible confounding factors, including age, sex, race/ethnicity, BMI, alcohol consumption, smoking, and SES measured as household income and education.
2. The above regression generated coefficients for each of the 11 predictor variables, of which the 2 of interest were those for the SRMH and SRPH. The 47 coefficients for SRMH and SRPH (one for each gene) were independently summed, after having first been multiplied by −1 in the case of the 34 genes that were expected to be down-regulated in CTRA.
3. An "average coefficient" for SRMH and SRPH was obtained by dividing the respective sums, obtained in step 2, by the number of CTRA genes (i.e. 47). This average coefficient represented the mean difference in gene expression associated with a one SD higher SMRH or SRPH. Subdomain-specific average coefficients were obtained by independently summing the coefficients and dividing by respective numbers of genes in each subdomain of CTRA (19-gene pro-inflammatory subset, the 31-gene IFN-related subset, and the 3-gene antibody-related subset).
4. The resulting average coefficients from step 3 were tested for a statistically significant difference from zero using a one-sample t test, i.e. the null hypothesis was that there was no difference between the average gene expression differences attributable to SRMH or SRPH. All analyses were conducted using SPSS 19 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of the study participants and correlates with SRMH and SRPH

Table 1 summarizes the baseline characteristics according to SRMH and SRPH scores. The participants' mean age was 60.16 ± 9.5 years. The sample was ethnically diverse (31.8% Hispanic, 21.52% African American, and 46.6% White Caucasian). The mean and SD of SRPH (49.69 and 8.49, respectively) are slightly below the average for the US population. As expected, the average score was significantly lower for African American female participants, and in those with lower SES, and with lower education level. The mean and SD of SRMH score were respectively 52.0 and 8.81, slightly above the national level. Compared to SRPH, the differences in SRMH scores across the participant characteristics were less pronounced. Only females (51.0 vs. 53.1; $p < 0.0001$) and participants within the lower SES (50.3 vs. 52.7; $p = 0.005$) presented significantly lower scores of SRMH. Interestingly, age was positively correlated with SRMH ($p < .0001$) and negatively correlated with SRPH ($p < 0.0001$). SRMH and SRPH were not correlated with each other ($r = -0.01131$; $p = 0.6922$).

CTRA transcriptome profile

Figure 1(a) and (b) displays the relationships between CTRA gene expression and SRMH and SRPH. We observed a significant increased expression of the entire CTRA gene set associated to higher scores of SRMH (6.10%; $p = 0.0001$) and SRPH (3%; $p = 0.002$) (Figure 1(a)). As shown in Figure 1(b), the analysis of specific subsets of CTRA genes show that higher levels of SRMH were linked to an up-regulated expression of type I IFN response genes (9.64%; $p = 0.0001$; Figure 1(b)) and down-regulated expression of genes involved in antibody synthesis genes compared to lower levels of SRMH (−6.18%; $p = 0.02$; Figure 1b). In contrast, higher levels of SRPH were associated with up-regulated expression of the type I IFN response genes (2.7%; $p = 0.0001$) and the antibody genes (7.4%; $p = 0.02$)

Table 1. Participants' baseline characteristics according to SRMH and SRPH scores.

		Pearson correlation coefficients or t test/ANOVA (p value) for association	
Variables	**Mean ± SD or %**	**SRMH**	**SRPH**
Age (years)	60.16±9.50	0.14087 <.0001	−0.13180 <.0001
Gender		<.0001	<.0001
Male	48.58%	53.16±8.21	50.67±7.68
Female	51.42%	51.05±9.24	48.76±9.10
Race		0.6149	0.0039
White Caucasian	46.68%	52.12±8.62	50.50±8.14
African American	21.52%	52.45±8.58	48.54±8.66
Hispanic	31.80%	51.76±9.25	49.25±8.79
SES (income)		0.0050	<.0001
Low <$20,000	17.06%	50.39±10.51	46.39±10.42
Medium ≥$20,000–49,999	42.16%	52.12±8.64	49.33±8.36
High >50,000	40.79%	52.75±8.10	51.40±7.32
Smoking history (%)		0.0482	0.0645
Current smoker	2.14%	55.45±4.09	52.73±4.14
Alcohol consumption (%)		0.1023	0.0008
Current alcohol	13.68%	52.36±8.48	50.32±8.00
Education		0.0807	<.0001
Low	34.15%	51.27±9.47	48.14±8.90
Middle	32.96%	52.40±8.50	49.07±8.96
High	32.88%	52.53±8.40	51.82±7.09
Working status		0.8670	<.0001
Employed	62.44%	52.01±8.72	50.89±7.59
Unemployed	29.00%	52.04±9.12	47.98±9.35
Homemaker	8.56%	52.50±8.48	46.75±9.86
BMI		0.6270	<.0001
18.31–25 kg/m^2 (normal weight)	20.41%	52.34±7.93	52.64±6.32
25–29 kg/m^2 overweight	40.43%	52.22±8.36	50.52±7.67
30+ kg/m^2 obese	39.16%	51.78±9.68	47.29±9.58
SRMH	52.08±8.81		−0.01131 (p=0.6922)
SRPH	49.69±8.49	−0.01131 (p=0.6922)	

Mean ± SD is listed in the second column for continuous variable. Pearson correlation was used for each continuous variable with SRMH/SRPH. % is listed in the second column for categorical variables. Mean difference (for SRMH or SRPH) was tested for categorical variables by two sample t test or one-way ANOVA.

ANOVA: analysis of variance; BMI: body mass index; SRPH: self-rated physical health; SRMH: self-rated mental health

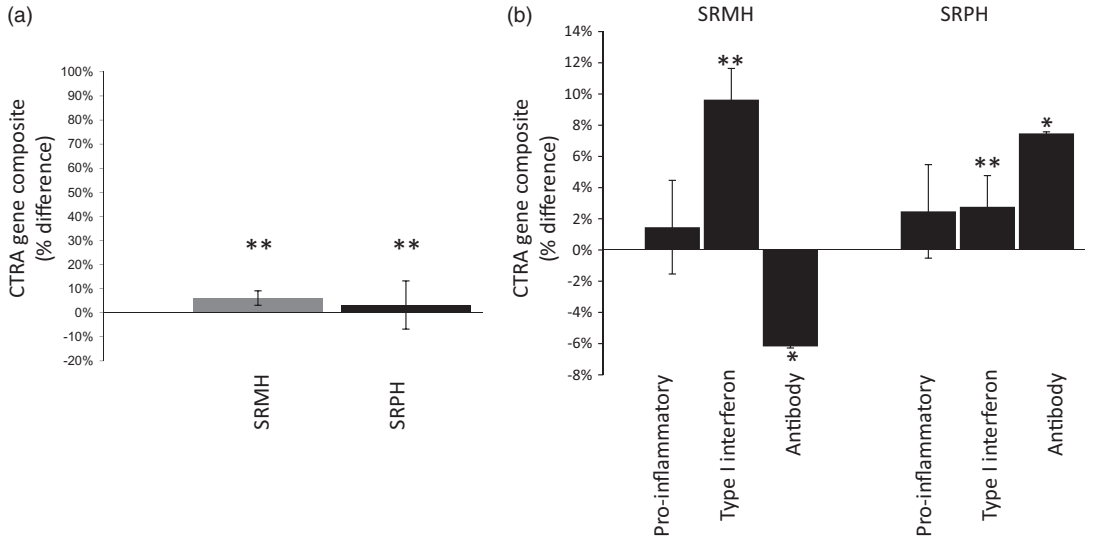

Figure 1. Expression of the CTRA gene set. (a) Linear model-based estimates of mean difference (±SEM) in expression in a 47-gene CTRA contrast score in monocytes from individuals with low levels versus high levels of self-rated mental and physical health (each adjusting for sociodemographic covariates). (b) Differential expression of CTRA subcomponents: 17 pro-inflammatory genes, 28 type I IFN response genes, and two antibody synthesis genes. **p value < 0.001.
CTRA: conserved transcriptional response to adversity; Type I IFN: type I interferon.

compared to lower levels of SRPH. However, we did not find any significant up-regulation of pro-inflammatory genes as a function of low scores of SRMH nor SRPH. The beta coefficients for each gene are reported separately as such in the supplemental data file.

Discussion

We explored the relationship between SRH and CTRA and observed a differential immune response in monocytes in relation to SRMH and SRPH. Contrary to our expectation, higher scores of both SRMH and SRPH were associated with an increased expression of the overall CTRA profile. Analyses for the gene subset involved in the CTRA profile did not reveal an increased expression of pro-inflammatory genes in persons with worse SRH. However, we did find that higher scores of SRPH positively modulate the immune response through the up-regulation of both, type I IFN response and antibody synthesis-related genes, while better scores of SRMH were associated with an up-regulated expression of genes involved in type I IFN response but with a down-regulation of genes involved in antibody synthesis.

Contrary to our hypothesis, we found that higher scores of both SRMH and SRPH (reflecting better health) were associated with increased (rather than decreased) expression of the overall CTRA profile. These findings are inconsistent with previous studies that suggested that physiological and physical distress may be linked with activation of nervous system-mediated signals that up-regulate the CTRA "defensive response" in anticipation of injury: e.g. a transcriptional induction of pro-inflammatory genes[12,29] accompanied by a decreased IRF1-related transcription of innate antiviral response or sympathetic nervous system (SNS)-development and mobilization of specific leukocyte subsets into circulation and tissue.[13,19,30] For example, increased CTRA gene expression has been observed among healthy individuals of low SES.[15,16] Perceived social isolation or loneliness[31] and social disconnection[32] have also been linked to increased CTRA gene expression. The unexpected association between better SRH and increased CTRA gene expression in our study requires confirmation in other populations. SRH is a subjective health evaluation and can be influenced by various psychosocial factors such as depression, functional impairment, or chronic illness,[28,33,34] which we did not take into account in our study. For example, psychosocial factors such as depression, stress, and isolation are known to be related to SRH,[28,33] and these variables have also been shown to be associated with CTRA.[19,31,35] However, given the directionality of the expected associations of these factors with SRH and CTRA expression, they are unlikely to explain the unexpected associations we observed.

However, analyses of the different immunologic components revealed different patterns for physical and mental health. Higher scores of SRPH were associated with up-regulation of type I IFN response and antibody synthesis-related genes, while better scores of SRMH were associated with an up-regulated expression of genes involved in type I IFN response but with a down-regulation of genes involved in antibody synthesis. The associations of SRPH and SRMH with the up-regulation of interferon response genes are in line with some previous studies.[18,36,37] For example, Knight et al. observed down-regulation of type I IFN response genes in low SES compared to high SES hematopoietic stem cell transplant recipients but found no associations of pro-inflammatory and antibody synthesis gene subsets with SES.[36] Similarly, in another work the authors found that spouses suffering complicated grief in response to bereavement presented a marked down-regulation of type I IFN-related transcripts compared to spouses with no complicated grief.[18] In addition, a recent study showed that a yogic meditation intervention could reverse

the pattern of increased NF-κB-related transcription of pro-inflammatory cytokines and decreased IRF1-related transcription of the innate antiviral response in healthy individuals under a significant life stressor.[37]

The decreased interferon response in subjects with low scores of SRH may have clinical implications for the resistance to infectious disease. SRH is often considered a confounder in analyses of vaccine effectiveness.[38] Furthermore, in a recent report, Cohen et al. demonstrated for the first time that SRH predicts susceptibility to the common cold in healthy adults suggesting a link between SRH and poorer immune system competence. Poor SRH is known to be a strong predictor of future health trajectories especially in older adults, including increased risk of mortality.[4,39,40] Our findings provide support for the conclusions reached by Cohen et al. regarding the possible role of type I IFN response as a mechanistic pathway linking SRH and future health.[41]

Regarding the expression of genes supporting antibody production, we found the opposite effect for SRMH and SRPH. As expected, participants with higher scores of SRPH presented an increased expression of genes involved in antibody synthesis which is consistent with previous data showing similar responses. For example, people experiencing high levels of eudemonic well-being compared to hedonic well-being or a better humoral response to vaccination related to positive affect as described by Marsland et al.[14,42] In contrast, we observed that participants with higher scores of SRMH experienced the opposite gene regulation resulting in a decreased expression of antibody synthesis-related genes. This finding is inconsistent with the fact that low scores of SRMH have been linked to social disconnectedness and perceived isolation,[43] and this subjective perception of social disconnection has a detrimental effect on the humoral immune response.[44] However, our results must be interpreted with caution because we focused only on a small number of genes related to antibody synthesis. In addition, our study is limited to monocytes and hence cannot rule out the possibility that B cells may be the main contributors to this type of antibody-related response as suggested by a study that mapped the cellular origin of transcripts found to be differentially expressed in response to social isolation.[20]

We found no associations of SRMH and SPRH with a proinflammatory response, which is inconsistent with previous findings. For example, Cole et al. have reported up-regulation of associations of proinflammatory response associated with different kinds of adverse social circumstances.[14,18,31] Furthermore, a proinflammatory shift was also recently reported among persons with poor psychological resilience[45] and in extrovert personalities compared to conscientious individuals.[46] Miller et al. also found that low social class at early ages was associated with increased proinflammatory gene expression in healthy adults.[31] The reasons for the lack of associations of both SRMH and SRPH with inflammatory response in our study are not clear. It is possible that the proinflammatory transcriptional response related to SRH is selectively upregulated in specific cell types. For example, a previous study showed that the specific monocyte subset CD1++/CD16, corresponding to the classical monocytes, is the key mediator of the pro-inflammatory transcriptional response related to adverse social conditions.[31] In addition, it is also possible that the lack of association in our study may be due other unaccounted confounding of psychosocial factors (e.g. social isolation, anxiety, stress, depression), which are known to correlate with both SRH and proinflammatory gene-expression. Future studies should replicate to test the inflammatory response and should asses this transcriptional response within isolated populations of other candidate cell types.

To the best of our knowledge, our study is among the first to examine the relationship between SRH and CTRA gene expression in a large multi-ethnic population-based sample, demonstrating an association of better scores of SRPH and SRMH with increased expression of genes involves in type I IFN response and a differential response in the antibody synthesis in relation to higher scores of SRPH and SRMH. SRMH and SRPH were not correlated supporting the conclusion that both SRPH and SRMH had unique associations with the gene expression profiles we investigated.

The present work is limited in drawing causal inferences because of the cross-sectional design and by its observational nature. We were unable to account for the possible effects of an ongoing infectious condition on the expression of genes associated with immune system response and did not have measures of immune system functional activity. Our work did not focus on individual gene-level associations. SRH can be considered a relatively stable construct over time, and hence cross sectional associations at a point in time could reflect more long term effects. In addition, the correlational design precludes drawing any causal conclusions and we cannot rule out the possibility that CTRA signaling might influence the own perception of perception of health. Finally, while we controlled for the most relevant social and biological variables there are other possibilities we have not covered, including underlying medical conditions or lifestyle and genetic factors. Among the strengths of this study are the large sample size, the geographic and ethnic diversity of the MESA cohort, and the use of a reliable and validated measure of SRH across different populations.

In conclusion, we found significant association between SRH and monocyte gene expression related to type I IFN response and antibody synthesis genes, suggesting that SRH may be linked to immunocompetence. We identified an association between perceived health and monocyte gene expression characterized by activation of the innate antiviral response and divergent response (i.e. SRMH vs. SRPH) in genes related to antibody synthesis. More studies are needed to better evaluate and potentially validate the present findings and to elucidate the pathways linking SRH and immune function.

Author contributions: All authors participated in the design, interpretation of the studies, analysis of the data and review of the manuscript; P.R. conceived and designed the study, drafted the manuscript and performed the

statistical analysis. S.Y.G. critically reviewed the manuscript and contributed with the statistical analysis. R.R.K., R.X., A.G., A.V.D.R., L.Y., and S.K.D. contributed in the data interpretation, drafting the manuscript, and its critical review.

ACKNOWLEDGEMENTS

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesanhlbi.org/. We would like to thank Cindy Clark, NIH Library Editing Service, for reviewing the manuscript. This work was supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-001079, and UL1-TR-000040. The MESA Epigenomics and Transcriptomics Study was funded by a National Heart, Lung, and Blood Institute grant (R01HL101250) to Wake Forest University Health Sciences.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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(Received April 5, 2017, Accepted August 25, 2017)