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Is Self-Rated Health Associated with Blood Immune Markers in Healthy Individuals?

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Abstract
Background Although self-rated health (SRH) has been established as a robust predictor of morbidity and mortality, the immunological mechanisms underpinning this relationship are poorly understood.
Purpose This study examined the association of SRH with humoral and cellular immune markers in healthy individuals who reported no physical illnesses.
Method A total of 116 healthy Japanese white-collar employees (79 women and 37 men) at a pharmaceutical company, aged 23–62 (mean 32) years, underwent a blood draw for the measurement of circulating immune (T, B, and natural killer) cells, inflammatory cytokines (interleukin-6 and tumor necrosis factor-α), and plasma immunoglobulin G (IgG) and completed a health survey including SRH. The question regarding SRH ranged from "very good" (coded 1) to "very poor" (coded 5). Hierarchical multiple regression analysis was carried out to calculate the relationship between SRH and immune markers.
Results In this sample, poor SRH was positively correlated with B ($CD19^+$) cell numbers (β=0.260, p<0.05) and IgG levels (β=0.335, p<0.01) even after adjusting for depressive symptoms, age, education, marital status, smoking, alcohol consumption, physical activity, body mass index, sex, and sex × SRH interaction. The interaction between SRH and sex on the immune markers was not significant.
Conclusion Although the connection between SRH and immune markers was not strong in this context, the results suggest that poor SRH may be associated with reduced humoral immune system capacity to respond to new/latent challenges. The results provide some support for the immunological basis of SRH in healthier individuals.

Keywords Self-rated health · Immune system · B cell · IgG · Cytokine · Psychoimmunology

Introduction

Self-rated health (SRH) has become an increasingly common measure used in population surveys. It is often based on a simple question where people are asked to rate their current overall health, typically on a four- or five-point scale ranging from "very good" to "very poor." Despite its simplicity, responses to this question have proven to be a robust predictor of important endpoints such as functional disability [1, 2], morbidity [3], and mortality [4–6]. SRH has also been shown to be a stronger predictor of these endpoints than physician-observed medical records [4]. A review of 27 community studies reported that SRH has strong predictive validity for mortality, independent of other physiological, behavioral, and psychosocial risk factors [7].

The fact that SRH holds considerable predictive validity in relation to morbidity, mortality, and other clinical outcomes brings up the possibility that SRH has a biological basis. To date, a number of studies have attempted to examine this

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possibility using various types of biomarkers [8–14]. These studies reported that poor SRH is positively associated with higher white blood cell counts [8], urinary epinephrine [9], ratio of cortisol to dehydroepiandrosterone sulfate [9], ratio of total to high-density lipoprotein (HDL) cholesterol [9], salivary cortisol [10], and high sensitive C-reactive protein [11] while being inversely related to albumin levels [8], hemoglobin [8], and HDL cholesterol [8, 12], although the results differed by sex. Additional studies in men reported that poor SRH is associated with paternal subfertility as represented by poorer semen quality, smaller testes size, and reduced s-testosterone [13, 14].

In line with these reports, several studies have explored the connection between SRH and immunobiomarkers. For example, in primary health care patients, significant associations were found between poor SRH and increases of inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-1 receptor antagonist (IL-1ra) in women [15]. The study confirmed that SRH was an independent and more robust predictor of those cytokine levels than physician-rated health even after controlling for confounders. More recently, the same research group found that the association between SRH and inflammatory cytokines became stronger with advancing age [16]. A study reported from Sweden suggested that poor SRH was positively associated with interleukin-6 (IL-6) in a sample of women hospitalized for acute myocardial infarction [17]. These studies imply that poor SRH is associated with increases in pro-inflammatory immune markers, although the study participants consisted of a group of patients with diagnosed conditions, which places limits on generalizability. Considering that participants in these previous studies were suffering from various disorders such as asthma, allergies, and other immune-related disorders, as well as cardiovascular diseases, it may be difficult to clearly distinguish between ratings of perceived health and variability in disease condition associated with increases of inflammatory cytokines [3]. Previous studies reported that cytokines such as tumor necrosis factor-α (TNF-α) and IL-6 increased with severity of stroke, heart failure, myocardial infarction, angina pectoris, obstructive lung disease, and acute abdominal disorder [18, 19], suggesting that disease severity may potentially confound the link between SRH and immune outcomes. Thus, an investigation with a healthier population may provide more direct insight into the association between SRH and immune status.

The purpose of this study was to understand the relationship between immune status and SRH among employees without a definitive health condition. We measured circulating inflammatory cytokines (IL-6 and TNF-α), together with numbers of differential lymphocyte subpopulations (T, B, and natural killer (NK) cells) and immunoglobulin G (IgG) levels in 150 white-collar daytime employees. We chose these immune markers because they are: (a) frequently used markers that are relatively sensitive to emotional and behavioral factors [20–22], (b) considered to reflect long-term status of humoral and cellular immune function [21, 23], and (c) comparable with previous studies [23]. Our primary hypothesis was that a poor rating of SRH is associated with the selected immune markers in the direction of reduced immune functioning.

Materials and Methods

Subjects and Procedure

The study design was cross-sectional and data were collected by self-administered questionnaires in March 2004 at a pharmaceutical company located in the Tokyo metropolitan area. All employees in this company were full-time white-collar daytime workers. In February 2004, the human resource division of the company announced the health survey and blood test to all employees verbally and by e-mail and asked them to participate. In the announcement, employees were instructed that there is no obligation for participating in this study, but each employee will receive feedback regarding their questionnaire survey and immunological assessment. They were told that the data would be kept confidential by the principal investigator of the National Institute of Occupational Safety and Health (A. N.) and would neither be disclosed to anyone in the company nor be used for personnel management or performance appraisal. Employees were also told that a blood draw for measuring immune function would be held at the workplace for 2 weeks during March. A total of 527 employees were listed as potential participants. Among them, 22 were excluded because they were either on long-term sick leave (mostly because of psychiatric disorders) or maternity leave. A survey questionnaire including purpose, instruction, and informed consent, was given to a total of 505 employees. They were requested to reply by mailing the consent letter and questionnaire to the investigators during 3 weeks in March. Two hundred and ninety employees agreed to participate in the questionnaire survey and replied with a signed consent form to the principal investigator (participation rate, 57.4%). One hundred and fifty-two employees participated in the blood test. Of these 152 employees, 150 also completed the questionnaire survey (two employees participated only in blood testing). To minimize the potential influence of acute infection, we excluded a participant with total leukocyte counts more than $12\times10^3/mm^3$. Of the remaining 149 employees, 11 were excluded because of missing data for one of the study parameters. An additional 22 employees were excluded in

order to eliminate the potential effects of health status on SRH and immune parameters (see "Potential Predictors/Independent Variables" for detail), which resulted in a final sample size of 116 healthy employees (79 women and 37 men). Participants were neither exposed to hazardous chemicals that could affect immunological outcomes nor had signs and symptoms of infection at the time of this study. The study protocol was reviewed and approved by the Institutional Review Board of the National Institute of Occupational Safety and Health, Japan. Written informed consent was obtained from all participants.

Measures

Self-Rated Health

SRH was assessed with a question: How would you describe your current health status? Response options were: (1) very good, (2) quite good, (3) neither good nor bad, (4) poor, or (5) very poor. Similar use of SRH is common in studies of this kind [8, 24, 25].

Immune Marker Analyses

Fasting blood samples were collected between 9:00 and 11:00 A.M. from participants to control for diurnal variations. Ethylenediaminetetraacetic acid dipotassium was used as an anticoagulant to collect venous blood from participants for measurement of leukocyte counts, immunofluorescence staining, cytokines, and plasma IgG. All samples were transported and handled at room temperature (i.e., 15–20°C). Immunofluorescence staining analysis was conducted within 24 h of blood collection. We determined counts of total leukocytes and total lymphocytes with an automated cell counter (Coulter Counter SP-VI, Coulter Electronics, Hialeah, Florida, USA) and lymphocyte subpopulations with flow cytometry analysis (EPICS XL, Beckman Coulter Inc., California, U.S.A.), as described in detail elsewhere [20, 26, 27]. The following sets of monoclonal antibodies were used to perform four-color direct immunofluorescence surface marker analysis: anti-CD45-FITC/anti-CD56-RD1 (NK cells)/anti-CD19-ECD (B cells)/anti-CD3-PC5 (T cells). A combination of mouse IgG1-FITC/mouse IgG1-RD1/mouse IgG1-ECD/Mouse IgG1-PC5 was used as the negative control. All monoclonal antibodies were purchased from Beckman Coulter Inc. We calculated the number in each lymphocyte subpopulation by multiplying lymphocyte counts by the percentage of positive cells in each category, as determined by flow cytometer.

Regarding cytokine analysis, whole blood was centrifuged and plasma samples were stored at −80°C in Pyrogen-free plastic tubes until analysis. Plasma cytokines (IL-6 and TNF-α) were determined using an enzyme-linked immunosorbent assay kit (Toray Fuji Bionics Inc., Tokyo, Japan). All the measurements were conducted in duplicate and the mean value was taken as the measured concentration. Minimum detectable levels for IL-6 and TNF-α were 0.4 and 2.0 pg/ml, respectively. The intra-assay coefficient of variation was <10% in each determination. Plasma IgG concentration was quantified by a turbidimetric immunoassay using a Hitachi automatic analyzer 7150 (Tokyo, Japan)

Potential Predictors/Independent Variables

The following factors were considered as potential predictors/independent variables for the analyses: age, sex, marital status (married or unmarried), highest educational level attained, smoking status, alcohol consumption, leisure time physical activity, height, weight, physical condition, and depressive symptoms. Educational levels were dichotomized into "16 years or less" and "more than 16 years." Smoking was assessed as current smoker, former smoker, and lifetime nonsmoker. In order to consider the cumulative effects of smoking on immune parameters, we calculated a Brinkman index (BI) as defined by multiplying the number of cigarettes smoked per day by the smoking years in current and former smokers [26]. Alcohol consumption was estimated by asking the usual amount of alcoholic drinks consumed per day and the number of occasions in a week that alcoholic drinks were consumed. We converted gross liquor consumption into net ethanol intake. We assessed leisure time physical activity by calculating the energy expenditure of habitual physical exercise. We asked frequency, type, and length of physical exercise per month and converted these data to metabolic equivalents (METs). Estimated METs were assigned to the physical activities according to their mean intensity levels. One MET corresponds to an energy expenditure of approximately 1 kcal kg^{-1} h^{-1}. Weekly leisure time physical activity was calculated from this questionnaire. Validity and test–retest reliability were previously confirmed [28]. For physical condition, participants were asked if they were treated for any symptoms or diseases, and as a result, 22 participants with the following disorders were excluded from the analyses: hypertension (n=4), hyperlipidemia (n=4), diabetes mellitus (n=1), menopausal disorder (n=1), major depression (n=1), severe allergy (n=1), autoimmune disease (n=1), arrhythmia (n=1), asthma (n=3), hyperthyroidism (n=1), liver disease (n=1), and common cold (n=3). Information on height (m) and weight (kg) were obtained to estimate body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters. Depressive symptoms were measured by a Japanese version of the Center for Epidemiologic Studies Depression (CES-D) scale [29–31]. The 20-item depressive symptom

scale measures the level of depressive symptoms experienced in the past week [32]. The internal consistency of the CES-D scale for the study sample was 0.83.

Statistical Analyses

We treated cytokine levels as continuous variables because a high-risk cutoff for the general population has not been well established [22]. Immune markers and continuous independent variables with a skewed distribution (SRH, CES-D scale score, age, BI, alcohol consumption, leisure time physical activity, and BMI) were logarithmically transformed to achieve a more normal distribution in values. Multiple regression analysis was used to examine the relationship between SRH (dependent variable) and independent variables (sex, age, CES-D scale score, education, marital status, BI, alcohol consumption, leisure time physical activity, and BMI). Hierarchical multiple regression analyses were performed to demonstrate the relationship between immune markers and SRH in three steps. First, an unadjusted (crude) relationship between SRH (independent variable) and immune markers (dependent variable) was tested. Second, the relationship between SRH and immune markers controlling for sex, age, and interaction between SRH and sex was calculated. Third, the relationship between SRH and immune markers controlling for all confounders was examined.

These variables were selected based on their possible associations with SRH and immune markers, as shown in previous studies [9, 15–17, 26, 33, 34]. The significance level for all statistical analyses was $p<0.05$ (two-tailed test). We analyzed the data using the Predictive Analytics Software version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Descriptive Statistics

Characteristics of the participants are shown in Table 1. Overall, 4.3% and 24.1% of participants rated their health

Table 1 Characteristics of study participants (n=116)

Variable	n (%)
Self-rated health[a]	
Very good	12 (10.3)
Quite good	67 (57.8)
Neither good nor bad	4 (3.4)
Poor	28 (24.1)
Very poor	5 (4.3)
Married	42 (36.2)
Educational status	
≤16 years	92 (79.3)
>16 years	24 (20.7)
Smoking status	
Current smoker	18 (15.5)
Former smoker	23 (19.8)
Lifetime nonsmoker	75 (64.7)
	Mean (SD, range)
Age (years)[a]	32.0 (7.2, 23–62)
Depressive symptoms (CES-D scale score)[a]	17.0 (11.1, 1–47)
Smoking (Brinkman index)[a,b]	26.2 (92.5, 0–680)
Alcohol consumption (grams ethanol/week)[a]	46.9 (72.9, 0–403)
Leisure time physical activity (METs/week)	4.6 (9.0, 0–38.5)
BMI (kg/height (m)^2)[a]	20.9 (3.0, 15.8–34.6)
Immune markers:[a]	
B ($CD19^+$) cells (cells/mm^3)	367 (301, 11–1,438)
Total T ($CD3^+CD56^-$) cells (cells/mm3)	1,210 (344, 524–2,023)
NK ($CD3^-CD56^+$) cells (cells/mm3)	232 (136, 41–678)
IgG (mg/dl)	1,209 (209, 683–1,754)
IL-6 (pg/ml)	1.16 (1.04, 0.40–9.60)
TNF-α (pg/ml)	16.8 (5.3, 2.0–43.7)

SD standard deviation, *CES-D* Center for Epidemiologic Studies Depression, *METs* metabolic equivalents, *BMI* body mass index, *NK* natural killer, *IgG* immunoglobulin G, *IL* interleukin, *TNF* tumor necrosis factor

[a] Although log-transformed values were used to approximate normal distribution in statistical analyses, mean values, SDs, and ranges are presented without log transformation to allow comparison with other studies

[b] Calculated by multiplying the number of cigarettes smoked per day by the smoking years for current and former smokers

as "very poor" and "poor," respectively. About one third of participants were married. Twenty-one percent of participants accomplished more than 16 years (graduate level) of education. Sixteen percent of participants were current smokers and 20% were former smokers. The average age was 32 years in this sample. The CES-D scale scores (depressive symptoms) was as high as 17.0 (SD 11.1). The mean Brinkman index was 26.2. Participants consumed an average of 46.9 g ethanol per week and spent 4.6 METs on leisure time physical activity per week. The average BMI was 20.9, with a range from 15.8 to 34.6. No participants in this sample showed clinically overt abnormalities of the immune markers.

Association Between SRH and Other Potential Predictors/Independent Variables

The relationship between SRH and other potential predictors/independent variables is shown in Table 2. Depressive symptoms was the only factor that significantly associated with poor SRH (β=0.406, p<0.001).

Association Between Immune Markers and SRH, Controlling for Potential Predictors/Independent Variables

Table 3 shows the results of hierarchical multiple regression analyses for the relationship between cellular and humoral immune markers with SRH. In step 1, the number of B ($CD19^+$) cells was positively but marginally correlated with SRH, while plasma IgG was significantly correlated with poor SRH (unadjusted correlation). In step 2, the number of B ($CD19^+$) cells and plasma IgG were significantly correlated with poor SRH (adjusted for age, sex, and sex × SRH interaction); the interactions between SRH and sex on the immune parameters were not significant in this sample. After controlling for all potential confounders, the association of SRH with B ($CD19^+$) cells and plasma IgG remained significant (step 3). Neither NK ($CD3^-CD56^+$) cells, T ($CD3^+CD56^-$) cells, IL-6, nor TNF-α correlated with SRH.

Analyses also revealed that alcohol consumption was inversely correlated with the number of T ($CD3^+CD56^-$) cells. IL-6 level was lower among married participants, but positively correlated with BMI. Men showed higher TNF-α level than women.

Discussion

A single measure of SRH has been reported to hold substantial predictive validity with regard to mortality and morbidity, as described earlier. Alteration of immune functioning is suspected to be a key mediator in connecting SRH and disease morbidity and mortality. In the current study, we examined the relationship between several blood immune markers and SRH among healthy individuals and found that poor SRH was associated with increases of B cells and plasma IgG, which may reflect an impaired humoral immunity. An impaired humoral immunity may correspond to a reduced immune system capacity to respond to new/latent challenges. In contrast, SRH appeared to be unrelated to T and NK cells and pro-inflammatory cytokines. Although the results must be interpreted with caution because of the cross-sectional nature of the study and small sample size, the findings provide some support for the immunological basis of SRH in healthier individuals.

Table 2 Multiple regression analyses with SRH as a dependent variable and sex, age, depressive symptoms, educational status, marital status, smoking, alcohol consumption, leisure time physical activity, and BMI as independent variables (n=116)

Self-rated health (dependent variable)[a]	β[b]	t	p
	Adjusted R^2=0.194 (p<0.001)		
Sex (women = 0, men = 1)	−0.116	−1.149	0.253
Lg Age (years)	0.005	0.049	0.961
Lg Depressive symptoms (CES-D scale score)	0.406	4.708	<0.001
Education ≤ 16 years (reference > 16 years)	−0.040	−0.437	0.663
Married (reference = unmarried)	−0.146	−1.505	0.135
Lg Smoking (Brinkman index)[c]	−0.080	−0.860	0.392
Lg Alcohol consumption (grams ethanol/week)	0.070	0.771	0.443
Lg Leisure time physical activity (METs/week)	−0.141	−1.606	0.111
Lg BMI (kg/height (m)^2)	0.036	0.379	0.705

Lg logarithmically transformed, *METs* metabolic equivalents, *BMI* body mass index

[a] Negatively oriented

[b] Standardized regression coefficient

[c] Calculated by multiplying the number of cigarettes smoked per day by the smoking years for current and former smokers

Table 3 Hierarchical multiple regression analysis for the association between immune markers and self-rated health (step 1), controlling for age, sex with interaction (sex × self-rated health; step 2), and controlling for all potential confounders (step 3) (n=116)

Immune markers (dependent variable)	Step 1			Step 2			Step 3		
	β^a	t	p	β^a	t	p	β^a	t	p
Lg B ($CD19^+$) cells	Adjusted R^2=0.018 (p=0.079)			Adjusted R^2=0.026 (p=0.138)			Adjusted R^2=0.001 (p=0.442)		
Lg Self-rated health[b]	0.164	1.772	0.079	0.267	2.421	0.017	0.260	2.098	0.038
Sex (women=0, men=1)				0.370	1.858	0.066	0.348	1.621	0.108
Lg Self-rated health × sex (interaction)				−0.301	−1.527	0.130	−0.347	−1.673	0.097
Lg Age (years)				0.050	0.540	0.590	−0.006	−0.054	0.957
Lg Depressive symptoms (CES-D scale score)							0.047	0.443	0.659
Education ≤ 16 years (reference > 16 years)							−0.018	−0.173	0.863
Married (reference = unmarried)							0.023	0.208	0.836
Lg Smoking (Brinkman index)[c]							0.114	1.087	0.279
Lg Alcohol consumption (grams ethanol/week)							−0.046	−0.458	0.648
Lg Leisure time physical activity (METs/week)							0.018	0.182	0.856
Lg BMI (kg/height (m)^2)							0.167	1.536	0.128
Lg NK ($CD3^-CD56^+$) cells	Adjusted R^2=0.001 (p=0.292)			Adjusted R^2=0.044 (p=0.060)			Adjusted R^2=−0.001 (p=0.460)		
Lg Self-rated health[b]	−0.099	−1.060	0.292	−0.025	−0.228	0.820	−0.026	−0.208	0.835
Sex (women=0, men=1)				0.333	1.686	0.095	0.399	1.861	0.066
Lg Self-rated health × sex (interaction)				−0.079	−0.406	0.685	−0.092	−0.442	0.659
Lg Age (years)				−0.049	−0.532	0.596	−0.049	−0.443	0.659
Lg Depressive symptoms (CES-D scale score)							−0.005	−0.050	0.961
Education ≤16 years (reference > 16 years)							−0.044	−0.426	0.671
Married (reference = unmarried)							−0.038	−0.352	0.726
Lg Smoking (Brinkman index)[c]							−0.077	−0.731	0.466
Lg Alcohol consumption (grams ethanol/week)							−0.068	−0.672	0.503
Lg Leisure time physical activity (METs/week)							−0.003	−0.035	0.972
Lg BMI (kg/height (m)^2)							−0.040	−0.363	0.717
Lg total T ($CD3^+CD56^-$) cells	Adjusted R^2=− 0.004 (p=0.442)			Adjusted R^2=−0.020 (p=0.776)			Adjusted R^2=0.036 (p=0.190)		
Lg Self-rated health[b]	0.072	0.772	0.442	0.008	0.074	0.941	0.075	0.619	0.537
Sex (women=0, men=1)				−0.216	−1.058	0.292	−0.179	−0.849	0.398
Lg Self-rated health × sex (interaction)				0.196	0.970	0.334	0.090	0.441	0.660
Lg Age (years)				−0.019	−0.202	0.840	−0.059	−0.546	0.586
Lg Depressive symptoms (CES-D scale score)							−0.072	−0.690	0.491
Education ≤16 years (reference > 16 years)							0.122	1.203	0.232
Married (reference = unmarried)							0.037	0.349	0.728
Lg Smoking (Brinkman index)[c]							−0.016	−0.159	0.874
Lg Alcohol consumption (grams ethanol/week)							−0.238	−2.387	0.019
Lg Leisure time physical activity (METs/week)							−0.002	−0.017	0.986
Lg BMI (kg/height (m)^2)							0.203	1.898	0.060

Table 3 (continued)

Immune markers (dependent variable)	Step 1			Step 2			Step 3		
	β^a	t	p	β^a	t	p	β^a	t	p
Lg IgG	Adjusted R^2=0.031 (p=0.032)			Adjusted R^2=0.053 (p=0.040)			Adjusted R^2=0.034 (p=0.200)		
Lg Self-rated health[b]	0.200	2.177	0.032	0.227	2.086	0.039	0.335	2.746	0.007
Sex (women=0, men=1)				0.059	0.299	0.766	0.072	0.342	0.733
Lg Self-rated health × sex (interaction)				−0.205	−1.055	0.294	−0.230	−1.126	0.263
Lg Age (years)				0.157	1.716	0.089	0.194	1.796	0.075
Lg Depressive symptoms (CES-D scale score)							−0.200	−1.919	0.058
Education ≤16 years (reference > 16 years)							0.051	0.506	0.614
Married (reference=unmarried)							0.102	0.954	0.342
Lg Smoking (Brinkman index)[c]							−0.025	−0.246	0.806
Lg Alcohol consumption (grams ethanol/week)							−0.040	−0.397	0.692
Lg Leisure time physical activity (METs/week)							0.013	0.135	0.892
Lg BMI (kg/height (m)^2)							0.024	0.229	0.820
Lg IL-6	Adjusted R^2=− 0.007 (p=0.614)			Adjusted R^2=0.020 (p=0.180)			Adjusted R^2=0.192 (p<0.001)		
Lg Self-rated health[b]	−0.047	−0.505	0.614	−0.041	−0.371	0.711	0.031	0.282	0.779
Sex (women=0, men=1)				0.129	0.645	0.520	0.314	1.629	0.106
Lg Self-rated health × sex (interaction)				0.090	0.457	0.649	−0.156	−0.836	0.405
Lg Age (years)				0.075	0.802	0.424	−0.101	−1.020	0.310
Lg Depressive symptoms (CES-D scale score)							−0.183	−1.913	0.058
Education ≤16 years (reference > 16 years)							−0.074	−0.803	0.424
Married (reference = unmarried)							−0.208	−2.124	0.036
Lg Smoking (Brinkman index)[c]							−0.150	−1.597	0.113
Lg Alcohol consumption (grams ethanol/week)							−0.108	−1.187	0.238
Lg Leisure time physical activity (METs/week)							−0.117	−1.309	0.193
Lg BMI (kg/height (m)^2)							0.294	3.001	0.003
Lg TNF-α	Adjusted R^2=0.001 (p=0.303)			Adjusted R^2=0.032 (p=0.107)			Adjusted R^2=0.095 (p=0.027)		
Lg Self-rated health[b]	−0.096	−1.034	0.303	−0.029	−0.262	0.794	−0.063	−0.534	0.594
Sex (women=0, men=1)				0.312	1.573	0.119	0.459	2.247	0.027
Lg Self-rated health × sex (interaction)				−0.083	−0.422	0.674	−0.228	−1.155	0.251
Lg Age (years)				−0.003	−0.029	0.977	−0.139	−1.326	0.188
Lg Depressive symptoms (CES-D scale score)							0.054	0.539	0.591
Education ≤16 years (reference > 16 years)							−0.115	−1.170	0.244
Married (reference = unmarried)							−0.185	−1.784	0.077
Lg Smoking (Brinkman index)[c]							−0.025	−0.248	0.805
Lg Alcohol consumption (grams ethanol/week)							−0.178	−1.845	0.068
Lg Leisure time physical activity (METs/week)							−0.086	−0.904	0.368
Lg BMI (kg/height (m)^2)							0.158	1.522	0.131

Lg logarithmically transformed, *METs* metabolic equivalents, *BMI* body mass index

[a] Standardized regression coefficient

[b] Negatively-oriented

[c] Calculated by multiplying the number of cigarettes smoked per day by the smoking years for current and former smokers

The reason why poor SRH was associated with increases of B cells and IgG may be inferred as follows. It is possible that participants who rated their health as poor may be experiencing a higher level of emotional distress than participants who rated their health as good. Our analysis found that depressive symptoms (CES-D scale score) was the strongest factor that determined poor SRH (β=0.406, p<0.001; Table 2). Poor SRH, constituted by emotional distress, could negatively impact immune functioning [34], which is relevant to our results. To test this possibility, we have incorporated CES-D scale score into the analyses (Table 3, step 3), but the associations of SRH with B cells and IgG remained significant, suggesting that some other mechanisms may also be involved in explaining our findings. Although these speculation needs to be validated in future studies, they may partly account for our findings.

Several previous studies have reported a positive relationship between poor SRH and increased cytokines such as IL-6 [17, 35], IL-1β [15], IL-1ra [15], or TNF-α [15, 16]. However, these findings are not always consistent when the studies are compared to each other. For instance, Janszky et al. [17] found a positive relationship between poor SRH and IL-6, but not with IL-1ra, while Lekander et al. [15] observed a positive relationship between poor SRH and IL-1ra and TNF-α, but not with IL-6. A recent study by Unden et al. [16] observed that the relationship between poor SRH and cytokines (TNF-α and IL-1β) was significant in elderly women (aged over 65 years), but not in younger women (aged <50 years). They also reported that the relationship between SRH and IL-6 or IL-1ra was not significant in any age group. In this study, we failed to find a significant association between poor SRH and inflammatory cytokines (IL-6 and TNF-α), possibly due to the characteristics of the study participants, i.e., non-clinical young population. Humoral immune markers (B cell and IgG) may be more sensitive to poor SRH in a non-clinical population, whereas in an aged clinical population, inflammatory cytokines may be more responsive to poor SRH. However, more evidence is needed to confirm this possibility.

In this study, we excluded participants who reported physical illness, including immune-related disorders, to reduce its influence on the relationship between SRH and immune markers. Cott et al. [36] concluded in their study that a major contribution to poor health is the presence of chronic disorders, long-term disability, and pain, suggesting the importance of differentiating those with and without such conditions. If the present analyses included participants reporting physical illnesses, the relationship between SRH and immune markers may be obscured because we cannot exclude the possibility that the participants may rate their health poor because of their physical condition [3]. Thus, we believe that our analytical approach makes the relationship between SRH and immune functioning clearer as it is not mediated by health status.

Several limitations should be noted in relation to this study. First, the study was cross-sectional in nature; thus, no causal interpretations can be made. Second, although we excluded participants who reported physical illnesses by questionnaire and by interview on the day of the blood draw as well as by blood test results, we cannot exclude the possibility that the analyses included individuals who were unaware of their illnesses or in subclinical status. Third, response bias cannot be ignored because the final sample included in the analyses was 23% of all invited participants. Fourth, the relatively small sample size in addition to unequal number of females and males (79 vs. 37) might have produced statistically non-significant interactions between SRH and sex, which places limits on the generalizability of the study findings. Fifth, we did not obtain information on the use of contraceptive pills in women, which might have affected immunologic outcomes. Finally, we could not exclude the possibility that unmeasured or unknown confounders may explain the present finding.

Although our study has the limitations as discussed above, this study seems to be the first to report the relationship between SRH and the immune system in healthy individuals. Our investigation suggests that SRH is associated with immune system dynamics in healthy individuals, which provides some support for the psychoimmunological basis of SRH. Further research is needed to confirm the relationships between SRH, immunity, and long-term health outcomes in a prospective manner with a larger sample size.

Disclaimer The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health, USA.

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