

# Self-rated Health Is Related to Levels of Circulating Cytokines

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**Objective:** Self-rated health is a powerful and independent predictor of long-term health, but its biological basis is unknown. Because factors associated with poor self-rated health (eg, pain, daily discomforts, and low energy and fitness) resemble symptoms of a generalized cytokine-induced sickness response, we examined the relationship between circulating cytokines and self-rated health. **Methods:** In 265 consecutive primary health care patients (174 women and 91 men), we examined self-rated and physician-rated health, circulating levels of interleukin (IL)-1 $\beta$ , IL-1 receptor antagonist (IL-1ra), IL-6, and tumor necrosis factor (TNF)- $\alpha$  as determined from plasma samples using high-sensitivity enzyme-linked immunoassay. **Results:** Self-rated health correlated with levels of IL-1 $\beta$  ( $r = 0.27$ ;  $p < .001$ ), IL-1ra ( $r = 0.19$ ;  $p < .05$ ) and TNF- $\alpha$  ( $r = 0.46$ ;  $p < .001$ ) in women but not in men. Thus, poorer subjective health was associated with higher levels of inflammatory cytokines. Even when controlling for age, education, physical health, and diagnoses in multiple regression analyses, self-rated health was an independent and more robust predictor of cytokine levels than physician-rated health. **Conclusions:** The present findings suggest that an individual's health perception may be coupled to circulating cytokines. Because epidemiological research established that self-rated health predicts morbidity and mortality, the biological correlates and mechanisms of self-rated health need to be understood. **Key words:** self-rated health, sickness behavior, cytokines, immune system, psychoneuroimmunology.

IL = interleukin; TNF = tumor necrosis factor; SRH = self-rated health; ELISA = enzyme linked immunoassay; LPS = lipopolysaccharide.

## INTRODUCTION

The subjective health perceived by an individual at a certain time-point can contain important information beyond what may be obtained in everyday clinical practice. Self-rated health (SRH), a formalized measure of subjective health, shows surprising qualities, because it has been found to be an independent predictor of clinical outcome and mortality (1). Even when numerous health status indicators are available, poor SRH is independently associated with increased mortality in different socioeconomic groups, in different age groups, in men and women, over time, and among persons with or without chronic illness (2–6). However, the mechanisms for these associations are not known. In light of the importance of SRH, it is surprising to note that so little, if anything, is known about its biological underpinnings.

Drawing on data concerning immune-to-brain communication, it could be argued that the immune system can be involved in changing an individual's health perception. When the immune system of an organism is activated in response to, for example, infection, physiological adaptations are triggered in the acute-phase reaction. In the last decade, it has become increasingly clear that signals from the immune system also affect brain circuits to produce changes in behavior, cognition,

and emotion. This coordinated set of changes is collectively called sickness behavior, and is caused by pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)- $\alpha$  (7). In sickness, the individual experiences nonspecific symptoms of weakness, listlessness, changed sleep patterns, hyperalgesia and decreases in motivation and appetite (7,8). These data imply that the brain interprets these cytokines as "sickness signals" (7). It is reasonable to assume that the pattern of changes observed in sickness is selected to promote recuperation, and evidence suggests that the cytokine-induced effects on physiology and behavior represent highly conserved evolutionary adaptations (9–11). At higher body temperature, some pathogens may be obstructed, paralleled by increased efficiency in some immune processes (12). Furthermore, through changed behavior, the sick individual saves energy and also reduces the risk of predator exposure when being in a weakened state.

We have previously shown that low ratings of health are strongly associated with low fitness and energy, daily discomforts, and presence of pain (13). Thus, factors that are related to SRH resemble symptoms of immune-activated sickness. Therefore, we hypothesized that perception of subjective health is related to levels of inflammatory cytokines, in that poor subjective (self-rated) health is associated with higher levels of plasma cytokines.

## METHODS

### Subjects

Participants were consecutively recruited from all patients, 18 years or older, attending a primary health care unit in Stockholm, Sweden during 2 weeks in spring and 2 weeks in autumn (May/June and November/December 2000). Patients with language difficulties were excluded. Of 490 eligible visitors, 325 (66%) wanted to participate. Some of the participants chose to answer only the questionnaire ( $N = 50$ ; 16 men and 34 women) and some to supply blood samples but not to answer the questionnaire ( $N = 10$ ; 2 men and 8 women). Questionnaires and blood samples were obtained from a total of 265 patients (174 women and 91 men). For sample characteristics, see Table 1. The dropouts did not differ from other participants in sex distribution, SRH, or physical health. However, patients who answered only the questionnaire were younger (mean 44 years vs. 59 years for the whole group). Because data were missing for a few participants,  $N$ s vary slightly for different analyses. Occurrence of diagnoses, obtained from patient records, is described in Table 2. The study protocol was in

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TABLE 1. Study Group Characteristics<sup>a</sup>

Variable	N	Group	Range	Mean	SD
Age	262	All	19–90	58.6	18.3
	90	Men		58.1	19.5
	172	Women		58.9	17.7
Education	248	All	1–6	2.38	1.45
	85	Men		2.33	1.38
	163	Women		2.41	1.49
Self-rated health	259	All	1–5	2.55	0.99
	89	Men		2.46	0.94
	170	Women		2.59	1.02
Physical health	257	All	1–5	2.83	1.13
	88	Men		2.55	1.04
	169	Women		2.98**	1.16

<sup>a</sup> Gender differences are tested with *t* test; \*\* *p* < .01.

TABLE 2. Occurrence of Diagnoses in Participating Subjects, Expressed as Percent of All Patients, Men and Women, Respectively

Diagnosis	All	Men	Women
Asthma	17	14	18
Cardiovascular disease	28	32	26
Hypertension	30	29	30
Diabetes	14	19	12
Lumbago/sciatica	19	20	19
Gastrointestinal disorders	33	30	34
Skin disease	36	27	41
Allergy	9	4	11
Depression	16	13	18
Fibromyalgia	6	6	6
Neoplastic disease	5	9	3
Hyperlipidemia	14	14	14
Thyroid disease	9	2	13
Rheumatic disease	4	1	6
Joint-related pain	31	23	35
No diagnosis	17	20	16

accordance with the ethical standards of the local committee on human experimentation at the Karolinska Hospital, Stockholm, Sweden.

### Measurements of Health and Demographic Variables

When registering for the visit, the patients were given written information about the study. General information was also given on posters. Participants filled out a questionnaire regarding health in a broad perspective, including reason for the visit, sociodemographic factors, and SRH.

Self-rated health was measured using the following question (SRH-5 (14)): "How would you rate your general state of health?". The response alternatives (coded as 1 to 5) were: Very Good, Quite good, Neither good nor poor, Quite poor, and Poor. Educational level was classified into 5 levels, from compulsory school (1) to university (5). After consultation, the physician filled out a questionnaire, rating the patient's health ("physical health") strictly based on medical criteria. The response alternatives (coded as 1 to 5) were: Healthy, Healthy with slight problems, Fair, Rather poor, and Poor (see 15). The interrater reliability of this questionnaire has been found to be good ( $r = .80$ ) (15). Response alternatives 3 to 5 include 70% of the cancer patients, 72% of hypertension, 86% of ischemic heart disease, 80% of asthma, and 100% of diabetes. The physicians were given training in how to use the scale in a pilot study.

### Blood Sampling Procedures

After consultation, 25 ml of venous blood was sampled in EDTA and serum gel-containing tubes. After centrifugation and initial storage at  $-20^{\circ}\text{C}$ , aliquots of

0.7 ml were transferred to storage at  $-70^{\circ}\text{C}$ . EDTA samples were used to analyze levels of IL-1 $\beta$ , IL-1 receptor antagonist (IL-1ra), IL-6, and tumor necrosis factor (TNF- $\alpha$  with high-sensitivity enzyme-linked immunoassay (Labora, Chemicon kit, Biosource International, USA). In addition to analysis of pro-inflammatory cytokines that are involved in the sickness response, IL-1ra was included to represent a factor that regulates IL-1 and its physiological consequences. Patients with acute infections ( $N = 14$ ) were asked to return 2 weeks after recuperation to allow time for levels of cytokines to normalize.

### Statistical Methods

In general, circulating levels of cytokines were low but in detectable ranges (Table 3). The distributions were positively skewed. Using log-transformed values gave a better fit to the normal distribution (Table 3). Three subjects with extreme values in three cytokines, falling outside a range of mean  $\pm 3$  SD on the log values, were excluded from analyses. Pearson correlations were calculated between health variables, background variables, and log values of cytokines. Multiple regression analyses were performed to analyze the relationships between SRH and cytokine values after controlling for age, education, and physical health (model I). Multiple regression analyses were also performed with diagnoses (model II) or number of diagnoses (model III) included in the model to control for conditions that could affect cytokine levels as well as subjective health. In the sample, 17.1% had no diagnosis, 21.3% had one diagnosis, 33.3% had 2 to 3 diagnoses, and 28.3% had 4 to 9 diagnoses.

### RESULTS

Table 1 shows study group characteristics. The mean of SRH was 2.55, falling between "Quite good" and "Neither good nor poor." Similarly, the mean of the physicians' ratings, physical health, was 2.83. There were no gender differences in age, education, or SRH. However, physical health was rated as slightly lower for women as compared with men. Also, women had lower levels of IL-6 (Table 3). The correlation between SRH and physical health was similar for men and women (0.24;  $p < .05$  and 0.29;  $p < .001$ , respectively).

Table 4 shows correlations between sample characteristics and levels of cytokines for the whole group and separately by sex. A strong positive association between age and IL-6 was observed in men and women, whereas higher age was associated with higher level of TNF- $\alpha$  only in men. Higher education was correlated with lower levels of IL-1ra, but when analyzed separately, the association was significant only for women (Table 4).

For the entire sample, SRH correlated highly with IL-1 $\beta$  and TNF- $\alpha$ , and tended to correlate with IL-1ra (Table 4). Thus, self-rated poor health was associated with higher levels of cytokines. Physical health correlated positively and significantly to levels of IL-1ra, and showed a tendency toward a positive correlation to IL-1 $\beta$ . Separate analysis for men and women revealed a sex-specific pattern, with significant correlations between SRH and soluble cytokines in female but not male patients. Highly significant associations were observed between SRH and IL-1 $\beta$  and TNF- $\alpha$ , and a significant but somewhat weaker association with IL-1ra. Physical health was positively correlated with IL-1ra and IL-1 $\beta$  in women, but not in men.

Multiple regression analyses with age, education, SRH, and physical health as independent variables confirmed the results from the univariate correlational analysis, indicating that SRH was independently related to levels of IL-1 $\beta$  and TNF- $\alpha$  in women, but not in men (Table 5, model I). Moreover, except

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**TABLE 3. Descriptive Statistics of Plasma Cytokines**

Variable	N	Group	Range	Median	Mean	SD	Skewness	
							Ordinary	Logarithm
IL-1 $\beta^a$	262	All	0.0–2.05	0.17	0.25	0.28	2.52	–0.88
	90	Men		0.21	0.25	0.22	2.26	–1.23
	172	Women		0.16	0.25 <sup>†</sup>	0.31	2.48	–0.44
IL-1ra <sup>a</sup>	262	All	25–586	86.6	117.9	86.8	1.87	0.20
	90	Men		82.8	116.0	87.4	2.05	0.42
	172	Women		90.0	118.8	86.7	1.80	0.24
IL-6 <sup>a</sup>	262	All	0.0–8.44	0.45	0.81	1.10	3.89	–0.79
	90	Men		0.54	0.96	1.23	3.66	–1.97
	172	Women		0.40	0.74**	1.02	4.06	–0.73
TNF- $\alpha^a$	262	All	0.9–53.4	0.80	1.46	4.18	9.35	–0.87
	90	Men		0.83	1.73	5.69	8.64	–0.78
	172	Women		0.78	1.31	3.12	7.07	–0.75

<sup>a</sup> Levels of cytokines expressed in pg/ml. Gender differences are tested with *t* test on the log value <sup>†</sup>  $p < .10$ ; \*\*  $p < .01$ . IL, interleukin; TNF, tumor necrosis factor.

for a positive correlation with IL-1ra in women, physical health was not significantly related to cytokine levels. In addition, to control for presence of diagnoses that could be associated with changed levels of cytokines and subjective health perception, the multiple regression analysis was repeated with all diagnoses introduced as dummy variables (yes/no) replacing physical health. The significant relations between SRH and IL-1 $\beta$  and TNF- $\alpha$  were not reduced (Table 5, model II). Likewise, repeating the multiple regression analysis with number of diagnoses replacing physical health did not weaken the relations between SRH and cytokines (Table 5, model III). In sum, controlling for an aggregate measure (physical health) as well as for individual diagnoses or number of diagnoses did not change the observed relations between subjective health and levels of cytokines.

## DISCUSSION

As hypothesized, SRH was significantly associated with levels of cytokines involved in sickness behavior and inflammation. However, when analyzed separately by sex, the effects were significant only for women. Thus, female patients

with subjective perceptions of poor health showed higher levels of IL-1 $\beta$ , IL-1ra, and TNF- $\alpha$ . The physician's assessment of the patients' health (physical health) was related to 1 cytokine, showing a significant association with IL-1ra in the same direction as for SRH. However, as confirmed in the multivariate models, SRH was a stronger and more robust predictor of cytokine levels as compared with physical health. The observations support the notions that immune activation is associated with vague symptoms of malaise and that interoceptive perception is influenced by immune-related activity (16,17). This fact might also explain why cytokines were more strongly related to SRH than to physical health.

In animals and humans, peripheral administration of cytokines, or endotoxin stimulation of cytokines, results in changes in neural and neuroendocrine circuits, behavior, cognition, and emotion (18,19). For example, humans who are injected with low-dose *Salmonella abortus equi* endotoxin show cognitive and emotional changes (eg, increased anxiety) that are significantly correlated with the amounts of TNF- $\alpha$  ( $r = 0.60$  to  $r = 0.75$ ), IL-1ra, and IL-6 in peripheral blood (20). Interestingly, these effects are observed at low doses of

**TABLE 4. Pearson Correlations Between Study Group Characteristics and Levels of Cytokines**

Variable	N	Group	Lg IL-1 $\beta$	Lg IL-1ra	Lg IL-6	Lg TNF- $\alpha$
Age	262	All	–0.08	0.08	0.32***	0.06
	90	Men	0.06	0.00	0.32**	0.23*
	172	Women	–0.15 <sup>†</sup>	0.13 <sup>†</sup>	0.33***	–0.03
Education	248	All	0.06	–0.18**	–0.07	–0.04
	85	Men	–0.03	–0.01	0.08	0.02
	163	Women	0.11	–0.26***	–0.13	–0.06
Self-rated health <sup>a</sup>	259	All	0.21***	0.10 <sup>†</sup>	–0.02	0.30***
	89	Men	0.11	–0.08	–0.08	–0.07
	170	Women	0.27***	0.19*	0.02	0.46***
Physical health <sup>a</sup>	257	All	0.12 <sup>†</sup>	0.20**	0.06	0.07
	88	Men	0.12	0.12	0.11	0.08
	169	Women	0.16*	0.23**	0.08	0.09

<sup>a</sup> Higher health ratings correspond to worse health; <sup>†</sup>  $p < .10$ ; \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$ . Lg = logarithmic; IL = interleukin; TNF = tumor necrosis factor.

**TABLE 5.** Association Between Self-rated Health and Circulating Cytokines in Men and Women Controlling for Age, Education, Physical Health (Model I), for Age, Education, Diagnoses (Model II), and Age, Education, Number of Diagnoses (Model III)

	Lg IL-1 $\beta$		Lg IL-1ra		Lg IL-6		Lg TNF- $\alpha$	
	Men	Women	Men	Women	Men	Women	Men	Women
Model I								
N	82	157	82	157	82	157	82	157
R <sup>2a</sup>	0.0	8.6	0.0	9.1	6.7	8.1	5.3	19.3
Age <sup>b</sup>	-0.07	-0.14	-0.06	-0.02	0.29*	0.35***	0.26*	-0.06
Education <sup>b</sup>	0.02	0.04	-0.02	-0.21*	0.15	0.07	0.08	-0.05
Self-rated health <sup>b</sup>	0.02	0.24**	-0.13	0.13	-0.11	0.01	-0.14	0.46***
Physical health <sup>b</sup>	0.14	0.12	0.15	0.17*	0.05	0.05	0.07	-0.04
Model II								
N	84	160	84	160	84	160	84	160
Self-rated health <sup>b</sup>	0.20	0.32***	-0.13	0.13	-0.06	-0.02	-0.05	0.45***
Model III								
N	84	160	84	160	84	160	84	160
Self-rated health <sup>b</sup>	-0.11	0.28***	-0.14	0.13 <sup>†</sup>	-0.08	0.01	-0.04	0.46***

<sup>a</sup> Explained variance adjusted for degrees of freedom.

<sup>b</sup> Standardized regression coefficients for each variable's unique contribution.

<sup>†</sup>  $p < .10$ ; \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$ . Lg = logarithmic; TNF = tumor necrosis factor.

endotoxin, selected not to elicit manifest symptoms of physical sickness (20). However, it should be noted that plasma concentrations of cytokines were indicated to be higher than in the present study. Endotoxin administration causes increased sleepiness and changes in sleep patterns (21), and cytokine therapy for cancer, for example, results in adverse side effects, such as dysphoria, anhedonia, helplessness, and fatigue (16). Thus, peripheral activation of the cytokine network results in symptoms similar to those that have been shown to be associated with poor SRH (13). Indeed, in an earlier study of a large elderly sample ( $N = 1727$ ) found that higher levels of IL-6 were associated with functional disability, and reported a significant but relatively weak correlation (Spearman's  $Rho = 0.10$ ) between IL-6 and subjective health (22).

The reason for a gender difference in the relationships between SRH and cytokines in the present study is not apparent. Few differences between males and females in cytokine induced sickness behavior have been reported. One exception is that sexual activity is suppressed in female but not male rats after immune activation, paralleled by a higher prostaglandin E2 response, and a lower corticosterone response, to IL-1 in females (23). However, it is well known that women in general differ from men in terms of immune characteristics, with higher prevalence of autoimmune diseases, allergies, etc. In addition, females display more frequent but milder health problems (24). A higher immunoreactivity has been reported in female mice, with a greater tendency than males both to generate and to respond to activating signals (25). Interestingly, a recent study shows that glucocorticoid sensitivity, measured as dexamethasone inhibition of lipopolysaccharide (LPS)-stimulated cytokine production, shows large gender differences that are also differentially modulated by exposure to psychosocial stress (26).

It should also be noted that women and men are shown to differ in health judgments. Poor subjective health has been shown to be associated with more subjective symptoms, eg,

pain, in women, and more with symptoms that are related to function in men (27). Differences in the bases of self-reported health have led to the suggestion that women are more inclusive in their judgments, being more sensitive to the overall quantity of their negative feelings rather than to their specific sources (28). Hence, it is reasonable that symptoms of a sickness response are more considered by women than men when forming a judgment of personal health status. Thus, if subjective health perception is affected by cytokines, the perceived symptoms are expected to be diffuse and subjective in nature. Therefore, we suggest that the stronger relations between SRH and cytokines in women as compared with men are due to such sex-related differences in health apprehension.

Importantly, the cytokine network can be activated through multiple modes of action. Both peripheral and central immune stimulation (injection of LPS or IL-1 $\beta$ ) releases a cascade of cytokines in the brain (among them IL-1 $\beta$ , IL-1ra, IL-6, and TNF- $\alpha$ ), followed by typical behavioral changes (16). In addition, both central and peripheral cytokines can be released in response to psychological stress (9), and cytokines as IL-1 can activate the adrenocortical axis at the level of the brain (18,29). Moreover, aspects of an LPS-induced sickness response, eg, suppressed feeding, can be behaviorally conditioned to, and subsequently triggered by, a novel taste stimulus (30). Thus, a sickness response can be released through stimulation of a cytokine network that can but must not originate from immune stimulation in the periphery. It is also interesting to note that sensory aspects of immune activity can be conveyed to the brain from the periphery by ascending fibers in the vagus nerve and that this pathway can be activated by very low doses of IL-1 $\beta$  or endotoxin (9).

To confirm the stability of the current findings, future research on biological correlates of subjective health should include repeated measures of both biological and psychological data, as well as potentially confounding variables such as

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medication or treatment effects. Interestingly, single-sample measurements of inflammatory markers, among them circulating TNF- $\alpha$  and IL-6, have shown predictive validity in other areas, in that increased cytokine levels are connected with recurrent coronary events (31,32). Even though the majority of blood samples in the current study were drawn before noon, timing of blood sampling was not entirely standardized. SRH is considered a relatively stable construct, but circadian rhythms are shown for cytokines. At least for stimulated cytokines, the largest variations in production of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  are shown in the evening and at night (33,34), with relatively less variability between morning and afternoon hours. Earlier studies have shown synergistic effects between IL-1 $\beta$  and TNF- $\alpha$ , eg, in inducing behavioral changes (16), consonant with the similar patterns observed between these two cytokines and SRH in the present data. Further improvements of future studies could consist of using more specific diagnosis categories to better characterize the study samples.

Because SRH predicts morbidity and mortality and provides an important tool to screen for high-risk groups or as endpoint in clinical trials (1), the delineation of the biological determinants of poor subjective health is an important matter. To our knowledge, this is the first comprehensive report on the subject.

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