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Inflammatory Cytokines, Behaviour and Age as Determinants of Self-rated Health in Women

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Abstract.

Self-rated health is a powerful and independent predictor of long-term health, but its biological basis is unknown. We have previously shown that self-rated health is associated with increased levels of circulating cytokines in women. The main aim of the present study was to increase the understanding of the association between markers of well-being such as self-rated health and cytokines and to investigate the impact of age on these associations.

In 174 female consecutive primary health care patients divided into three age groups, we examined subjective ratings of health and aspects of well-being, and circulating levels of interleukin (IL)-1 α , IL-1 receptor antagonist (IL-1ra), IL-6 and tumour necrosis factor (TNF)- α .

Poor self-rated health was significantly associated to higher levels of TNF- α in all age groups. For IL-1 α and IL-1ra, the correlations with self-rated health were significant only in the oldest age group. Lower ratings of other measures of health and well-being were related to higher levels of cytokines, most pronounced for TNF- α and IL-1 α and in the older age groups. More symptoms resembling a sickness response induced by inflammation were implicated to be associated with lower self-rated health.

The strength in the association between inflammatory cytokines and poor health perception increases with higher age, indicating an increased vulnerability for inflammatory activity in ageing. It is suggested that higher levels of TNF- α is connected to a sickness response that in turn is connected to self-rated health. The results provide a possible psychobiological basis to better understand diffuse subjective symptoms and poor subjective health in women.

Introduction

Symptoms that have no definite medical diagnosis are common in all areas of primary care as well as in specialty medicine [1]. Commonly presented symptoms can be connected to an identified organic disease in surprisingly few cases. For example, an organic etiology was demonstrated in only 16% of the cases with fatigue, headache, breast- or stomach pain, dizziness, constipation and insomnia in a study of primary health care patients, even though diagnostic testing was performed in more than two thirds of the cases [2]. Thus, symptoms that affect subjective health are common but often not connected to a specific disease. It has previously been shown that higher than average use of medical services is more likely in persons with medically unexplained symptoms and poor perceived health [3]. Frequent users of medical services have also been shown to exhibit high levels of psychosocial problems [4]. The development and use of validated assessments that include biomedical, experiential and psychosocial aspects of health is therefore a cogent issue.

The definition of self-rated subjective health is a patient's rating of her overall health on a scale from excellent to very poor [5] and this is shown to reflect problems that are both psychosocial and medical in nature [6]. Self-rated health has been suggested as a sensitive barometer of physiological states [7] and poor self-rated health is independently associated with increased mortality in men and women, in different age groups, in groups with different socio-economic status, over time, among persons with or without chronic illness, and in subjects with mild to moderate cognitive impairment [8-13]. Self-rated health predicts hospitalisation and frequent medical examinations in out-patient clinics [14, 15], making it a useful economical tool in health care. Because of the strong relation to future objectively verified health, self-rated health is a commonly used research tool. Although short, well validated and easy to administer and register, recordings of self-rated health is still very little used in clinical settings.

In spite of its predictive powers, neither the mechanisms of poor health perception nor the causes behind the associations to future health are known. However, we have previously shown that poor self-rated health is strongly associated with low fitness and energy, daily discomforts and presence of pain [6], factors that resemble sickness symptoms driven by immune activation. This response of diffuse symptoms, denoted sickness behaviour, consists of malaise, lassitude, fatigue, numbness, coldness, muscle and joint aches and reduced appetite, and is triggered mainly by inflammatory cytokines, such as IL-1 α , IL-6 and TNF- α ,

produced by activated cells of the immune system [16]. Indeed, we showed earlier that high circulating levels of TNF- α and IL-1 β were independently associated with poor self-rated health in female primary health care patients [17]. Moreover, this association was stronger than the relation between cytokines and the doctor's physical judgment of health, and independent of the presence of a diagnosis of acute or chronic inflammatory disease. Similarly, we showed that poor self-rated health was related to higher levels of IL-6 in a sample of 235 women with coronary heart disease after controlling for several possible confounders [18]. This is in agreement with an earlier study of a large sample of elderly patients (n=1727), where higher levels of IL-6 were associated with poor subjective health [19]. Self-rated health has also been shown to be independently associated with white cell count [7], another indicator of immune status. We argue that a system that informs the brain about changes in the micromilieu and that affects emotion, cognition and behaviour, like the sickness machinery, may be a good candidate to subserve subjective health perception. However, the connection between cytokines, sickness behaviour and self-rated health remains to be elucidated.

Nutritional status, above its effects on the immune system, may influence subjective health perception as it previously has been associated with depression and self-rated health [7, 20]. Adipose tissue is known to produce cytokines such as IL-6 and TNF- α [21], therefore, nutrition and body composition might influence the association between cytokines and self-rated health. The cytokine-like insulin-like growth factor (IGF)-I and one of its binding proteins IGF binding protein 1 (IGFBP-1) are nutritional markers [22]. IGF-I mirrors protein and energy intake as well as muscle mass, while IGFBP-1 correlates to energy intake and is inversely related to amount of adipose tissue and leptin [23-25]. The ratio, i.e. the relative amount of free IGF-I, is therefore an estimate for both nutrition and energy intake and insulin production. In addition, IGF-I and IGFBP-1 have cytokine-like properties and interact with the immune system [26, 27], and represent therefore factors of relevance when investigating the connection between cytokines and health.

Ageing is accompanied by increased circulating levels of inflammatory mediators such as the cytokines IL-6, IL-1ra and TNF- α , and acute phase proteins such as C-reactive protein (CRP) [28]. Elderly subjects show larger initial and prolonged cytokine responses to lipopolysaccharide and a pre-activation of circulating cytokine producing cells have been indicated in elderly [28, 29]. Higher age is associated with disrupted neuroendocrine input to the immune system [30, 31] which may decrease the homeostatic control of biological

processes that are of importance for well-being. In addition, stress-mediated effects on the immune system are in general larger in the aged population, as compared to the younger [32]. Therefore, we hypothesize that a relation between cytokines and markers of health and well-being could display different patterns in different age groups. Moreover, we hypothesize that the connection between self-rated health and cytokines is partly mediated by symptoms resembling cytokine induced sickness behaviours as observed in experimental studies [16]. The aim of the present study was to increase the understanding of the association between cytokines and different markers of health and well-being in females and to investigate the impact of age on these associations.

Method

Subjects

Participating subjects were consecutively recruited during two weeks in spring and two weeks in autumn (May/June and November/December) 2000 from the patients, 18 years or older, visiting a primary health care unit in Stockholm. Patients were given written information of the study. General information was given on posters in the primary health care unit, stating that participation was voluntary. Informed consent was obtained from all subjects. Patients with language difficulties were excluded. Blood samples and questionnaires were obtained from 174 women and 91 men, 66 % of eligible visitors. Earlier, we have demonstrated substantial connections between cytokines and self-rated health in women, but not in men [17]. Therefore, we have examined the relations between circulating cytokines, behaviour and self-rated health, and the influence of age, in women. The procedures followed were approved by the Local Committee of Human Experimentation at the Karolinska University Hospital, Stockholm, Sweden.

Measures of health and well-being

Assessment of health, psychosocial factors and background variables were done through questionnaires filled in by the patients before the consultation, and by one questionnaire filled in by the physician after the consultation. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m²). Educational attainment was classified according to five levels, ranging from compulsory education only to university education.

Health. Self-rated health was measured by the question: "How do you rate your general health?" The response alternatives were: "Very good" "Rather good" "Neither good nor poor"

“Quite poor” or “Very poor” (coded 1-5) [33]. The physician rated the patients’ health (“physical health”) on a scale from one to five using the following definitions: 1. No illness, no problems, no treatment. 2. No symptoms but under treatment for one or more slight problems without serious underlying causes. 3. Chronically or temporarily ill with one (or several) disease(s), which do not unduly limit normal activity (according to the patient’s age). 4. Chronically ill with symptoms that give only a limited reduction in age-appropriate normal activity, or temporary illness with similar limitations. 5. Acute or chronic illness with pronounced limitation of normal activity [34].

Occurrence of diagnose according to International Classification of Diseases (ICD)-10 were obtained from patient records [17].

General well-being. To measure general well-being, the Gothenburg Quality of Life Instrument (GQLI) was used [35]. GQLI comprises ratings of social well-being (home and family, housing, work situation, economy, leisure), physical well-being (vision, hearing, memory, appetite, fitness), and mental well-being (endurance, mood, energy, self-confidence, sleeping). All the areas were rated on Likert scales ranging from ‘very poor’ (1) to ‘excellent, could not be better’ (7). Pain was assessed by the following questions: Have you during the last three months been troubled with pain in neck and shoulder; back pain; pain in legs; joint aches; and/or pain in the body? These five items were answered with yes, every day; yes, often; yes, occasionally; never, coded as 1 to 4. The mean score was used in the analyses. Depressive symptoms were assessed with 9 questions answered as yes or no. The number of positive answers was summed up [36] so that higher value indicates more depressive symptoms. Quality of life was measured by the so called Ladder of Life, a ten grade scale that defines expectations for the present [37]. The first grade represents the worst possible and the tenth the best possible life, respectively.

In the multivariate analyses we used a weighted mean of the ratings of energy, sleep, appetite, fitness and memory together with the question about pain to form a provisional variable to reflect sickness behaviour.

Blood sampling

After consultation, 25 ml of venous blood was sampled in EDTA and serum gel-containing tubes. After centrifugation, and initial storage at -20°C, aliquots of 0.7 ml plasma were transferred to storage at -70°C. The majority of blood samples in the current study were drawn before noon. Plasma samples were used for measurement of TNF- α , IL-1 β , IL-6 and

IL-1ra. Cytokine analyses were done with high-sensitivity enzyme-linked immunoassays (Labora, Chemicon kit, Biosource International, USA for IL-1 β , IL-1ra and TNF- α , and Quantikine HS kit, R&D system, Abingdon, UK for IL-6). High levels of proinflammatory cytokines might influence nutritional status and vice versa [40, 41]. Therefore, the growth factor and metabolic marker insulin-like growth factor-1 (IGF-I) and one of its binding proteins, IGFBP-1, were analysed [22]. The IGF-I:IGFBP-1 ratio was used to provide an indirect measure of nutritional status [24, 25]. IGF-I was determined by radioimmunoassay after separation from IGFBPs by acid-ethanol extraction and cryoprecipitation [40]. IGFBP-1 was also measured by radioimmunoassay [41]. High-sensitivity CRP was analysed (before freezing), as it is widely used as a marker of infection in clinical settings. Patients that showed symptoms of acute infections at the physical examination (n=14) were asked to return two weeks after recuperation to allow time for levels of cytokines to normalize.

Statistical methods

Serum TNF- α , IL-1 β , IL-6, IL-1ra, IGF-I, IGFBP-1 and CRP distributions were positively skewed. Log transformation resulted in normalization of the distributions. In all statistical analyses, log-transformed values of these variables were used, however, in Table 1 the mean values are presented without log transformation. Two subjects with aberrant values in three cytokines, falling outside a range of mean \pm 3 standard deviations of the log values, were excluded from analyses. To investigate any age differences in the correlation patterns between cytokines and health variables, subjects were divided into three age groups: 18-49 years, 50-64 years and 65 years and above. Differences in study group characteristics between age groups were analysed with one-way analysis of variance. Associations between cytokines and health variables were calculated as Pearson product-moment correlations. Results were considered statistically significant at the 0.05 alpha level.

The associations between self-rated health and cytokines were further analysed in regression analyses with self-rated health as a dependent variable and physical health, IGF-I:IGFBP-1 ratio, sickness behaviour and levels of the respective cytokines as independent variables. Sickness behaviour was formed using a weighted mean of the ratings of energy, sleep, appetite, fitness and memory together with the question about pain. Lower levels indicate more pronounced sickness behaviour. The occurrence of cardiovascular disease, hypertension, allergy and rheumatic disease were included in the model as control variables.

In a further multivariate analysis we attempted to describe possible pathways for the observed effects. For this purpose a hypothetical model for the associations between variables was formed [42] including four levels. The first level included physical health (the physician's rating), the second level included the IGF-I:IGFBP-1 ratio and the selected cytokine, the third level sickness behaviour, and the fourth level self-rated health. Standardized regression coefficients were calculated by structural equation modelling, indicating the strength of the associations between the variables in the model, while controlling for the effects of any of the variables on the same level and any level above.

Results

Study group characteristics

In table 1, study group characteristics are presented and compared between the three age groups. In spite of the differences in mean age, most background variables and measures of health and well-being did not differ in general between groups. One exception was educational level, which was lower in the higher age groups. Also, depressive feelings and quality of life differed significantly between the groups, with highest levels of depressive feelings in the youngest age group and the highest reported quality of life in the middle age group.

IL-6 increased with increasing age whereas IL-1 β and IL-1ra tended to be higher in the middle age group. The middle age group had somewhat higher CRP levels. IGF-I decreased with higher age whereas IGFBP-1 was lowest in the middle age group and higher in the oldest age group. Thus, a less favourable nutritional status was found in the oldest age group, as indicated by a more than 50% lower IGF-I:IGFBP-1 ratio as compared to the younger groups.

Univariate relationships

To study the associations between cytokines on the one hand, and background characteristics, metabolic markers and variables of health and well-being on the other hand, correlational analyses were performed (see table 2).

Health. Worse self-rated health was significantly correlated with higher levels of TNF- α in all age groups, with increasingly stronger correlation coefficients displayed with higher age. For IL-1ra and IL-1 β , the correlations with self-rated health were only significant in the oldest age

group. Worse physical health (rating done by the physician) was significantly correlated to higher levels of IL-1ra in the two oldest age groups, but not to other cytokines or in the youngest age group.

General well-being. Several measures of well-being were significantly related to levels of cytokines, with higher levels of cytokines consistently associated with less satisfactory ratings of well-being and quality of life, more pain and more depressive feelings. This pattern was most pronounced for TNF- α and for IL-1 β in the older age groups.

Ratings of fitness and energy showed a uniform pattern with ratings of less satisfaction associated with higher IL-1ra in the two older groups and with higher TNF- α in the oldest age group. For IL-1 β , the pattern was partly similar, but significant only for fitness in the oldest age group. Worse quality of sleep and worse appetite were correlated with higher levels of TNF- α in the oldest age group. Lower ratings of memory were correlated with higher levels of IL-1ra in the youngest age group. More pain was correlated to higher levels of IL-6 and IL-1ra in the oldest age group. More depressive feelings and a lower quality of life were related to higher levels of TNF- α and IL-1 β in the oldest age groups. In addition, worse quality of life was also correlated with higher levels of IL-1ra in the middle age group.

Inflammatory and metabolic markers. CRP was positively correlated to IL-6 and IL-1ra in all three age groups, whereas no significant correlations between IGF-I, IGFBP-1 or the IGF-I:IGFBP-1 ratio and cytokines were found.

Intercorrelations for cytokines, IGF-I, IGFBP-1 and CRP revealed an age specific pattern (data not shown). TNF- α was found to be positively and significantly correlated to the other three cytokines (IL-1 β , IL-1ra and IL-6) in the oldest age group, whereas no significant correlation was found in the other age groups. IL-1ra and IL-6, on the other hand, was positively and significantly correlated in the two youngest age groups. There was a significant negative correlation between IGF-I and IGFBP-1 only in the middle age group. The same pattern was seen for IGF-I and CRP. As expected, significant correlations between IGF-I:IGFBP-1 ratio and both IGF-I and IGFBP-1, positive respectively negative, were seen in all age groups.

Background variables. No significant correlations between age and the different cytokines were found within the respective age groups. Higher BMI was significantly correlated with higher levels of IL-1ra in all age groups and with IL-6 in the youngest age group. Education showed no significant correlations with cytokine levels with the exception for IL-1ra in the youngest age group.

Controlling for potentially inflammation-related diagnoses (allergy, hypertension, cardiovascular and rheumatic disease) did not change the results. In addition, the results did not change when excluding the women with CRP levels above 10 pg/ml. As BMI could be seen as a confounder, since obesity is linked to higher inflammatory cytokine levels [21], we also performed an analysis where we controlled the correlations between health variables and cytokines for BMI (data not presented). This did not affect the significant associations.

Multivariate analyses

Multiple regression analysis

The associations between health variables, measures of well-being and cytokines were further analysed in multiple regression analyses with the aim to study the respective variables' independent contributions to variance in self-rated health. In these analyses we used a weighted mean of the ratings of energy, sleep, appetite, fitness and memory together with the question about pain to form a provisional variable to reflect sickness behaviour. Self-rated health was used as dependent variable and physical health, IGF-I:IGFBP-1 ratio, sickness behaviour and the four cytokines were used as independent variables. Presence of the potentially inflammation-related diagnoses allergy, hypertension, cardiovascular and rheumatic disease were included as control variables. Table 3 shows β coefficients, amount of explained variance and level of significance obtained by testing the hypothesis that each respective regression coefficient is equal to zero. In large, the regression analyses mostly confirmed the results from the correlational analyses with respect to associations between self-rated health and cytokines. However, neither the association between self-rated health and TNF- α in the youngest age group, nor the association between self-rated health and IL-1ra in the oldest age group, did turn up significant.

The included variables explained more of the variance in self-rated health in the oldest age group (about 56-58 %) than in the younger age groups (24-41 %) for TNF- α and IL-1 β , with sickness behaviour, physical health and the respective cytokine as significant explanatory variables. The strongest explanatory variable, sickness behaviour, was significantly associated with self-rated health in all models. No significant associations between self-rated health and either IL-1ra or IL-6 were found.

Analysis of a hypothetical model

To describe possible pathways for the observed effects, we constructed a simplified model with physical health on the first level, the respective cytokine and nutritional status (IGF-I:IGFBP-1 ratio) on the second, sickness behaviour on the third and self-rated health on the fourth level, and calculated the associations between the included variables as standardized regression coefficients using structural equation models. As the two youngest age groups showed similar correlation patterns between cytokines and health markers, data from these age groups were combined to one group in the model. In figure 1 and 2, models for TNF- α and IL-1 β , are presented. Besides the significant associations with self-rated health found in the regression analyses, we could also establish some indirect associations. In the models analysed for TNF- α , self-rated health was significantly associated with physical health, sickness behaviour and TNF- α . In the oldest age group there was a significant association between TNF- α and sickness behaviour, which in turn was related to self-rated health, indicating that TNF- α also could have an indirect independent association with self-rated health mediated via sickness behaviour. In the younger age group, higher TNF- α was associated to worse nutritional status. In the models analysed for IL-1 β , self-rated health was significantly associated with physical health, sickness behaviour and in the oldest age group IL-1 β . In the youngest age group, higher IL-1 β was significantly associated with worse nutritional status.

The model was also tested for IL-1ra and IL-6 (data not shown). In the model for IL-1ra, as in the other models, physical health and sickness behaviour was independently associated with self-rated health. The youngest age group showed significant correlation between IL-1ra and sickness behaviour, indicating that IL-1ra could have an indirect effect on self-rated health via sickness behaviour. Between IL-1ra and the nutritional marker IGF-I:IGFBP-1 ratio a strongly significant negative correlation was found in both age groups, and the IGF-I:IGFBP-1 ratio was correlated with sickness behaviour in the age group 18-64, suggesting another pathway for indirect effects of IL-1ra on self-rated health. The associations between IL-6 and the other variables in the model were weak and not significant.

Discussion

The results of the present study indicate that several subjective ratings of health and behavioural variables are related to circulating levels of cytokines in an age-dependent pattern in women. This pattern of results was most pronounced for TNF- α and IL-1 β . Comparison

between the age groups showed that there was no difference in health indices, neither from the patient's nor the doctor's point of view. This suggests that the patients' state of health could be considered comparable between the age groups and would thus probably not confound the results.

As expected, levels of IL-6 increased with higher age [29], while other cytokines did not change. Expected as well, the levels of IGF-I and the IGF-I:IGFBP-1 ratio decreased with increasing age, indicating a less favourable nutritional status with higher age.

One explanation for the stronger correlation between self-rated health and cytokines with higher age in the present study could be an increased sensitivity to pro-inflammatory cytokines with increasing age. In support, lymphocytes display increased sensitivity to TNF- α induced apoptosis, suggested to depend on a deficiency in the nuclear factor (NF)- κ B-signalling pathway, with increasing age [43]. Moreover, recent evidence suggests age-related neurochemical differences that contribute to increased sensitivity to both stress and inflammation with age, based on an association between N-Sase (neutral sphingomyelin-specific phospholipase C9) activity and stress/inflammatory marker (e.g. heat shock protein 70 and IL-1 β) expression in e.g. the hippocampus and the frontal cortex in rodents [44]. In addition, peripheral injections of *Escherichia coli* has been shown to produce amnesia in 24 month old, but not 3 month old rats in hippocampus dependent memory, supporting the hypothesis that age is a vulnerability factor that increases the likelihood that an immune challenge will produce a cognitive impairment [45]. In addition, age moderates vulnerability to stress-related decreases in functional immune measures, possibly due to a decreased capacity of self-regulation with higher age [32]. Therefore, we postulate that a dysregulated cytokine response in elderly results in larger cytokine-mediated effects in the behavioural domain, thereby driving an individual's perception of decreased general health.

Besides the couplings between self-rated health and TNF- α and IL-1 β , other variables were significantly associated to these cytokines. We combined energy, sleep, appetite, fitness, memory and pain to form a provisional variable of sickness behaviour. In multivariate regression analyses, this variable explained most of the variance in self-rated health. To test our hypothesis that cytokines affect self-rated health via cytokine-induced sickness behaviour, we constructed a model that included physical health, nutritional status, sickness behaviour, self-rated health and the respective cytokine. A strong and significant association between sickness behaviour and self-rated health was found in both age groups, independent of cytokine studied. Besides the direct independent association between self-rated health and

TNF- α , an indirect association was also seen via sickness behaviour in the age group 65 years and above. Thus, in this age group our hypothesis was supported in the multivariate model, suggesting that higher levels of TNF- α leads to sickness behaviour that result, in turn, in poor self-rated health. The associations between IL-1 β and IL-1ra and sickness behaviour were significant in the younger and older age group respectively.

In the structural equation model, a lower IGF-I:IGFBP-1 ratio was associated with higher levels of TNF- α , IL-1 β and IL-1ra in the younger age group. Interestingly, both TNF- α and IL-1 β display anorexigenic properties [21], which could possibly be related to their association with poor nutritional status.

The use of a cross-sectional design in the present study, with only one measure of circulating cytokines and health related variables, entails cautiousness regarding interpretation and the possibility to infer causality behind the found associations. It is interesting to note, however, that single-sample measurements, detecting low-grade increases in levels of circulating cytokines such as TNF- α and IL-6, have been shown to be strong predictors of all-cause mortality in elderly [46, 47], and recurrent coronary events after myocardial infarction [48]. Nonetheless, the relations between age, cytokines, sickness behaviour and self-rated health should be further investigated in longitudinal studies and, preferable, with larger study samples that include both men and women. Also, future studies should include random selection from the general population to supplement the studies based on patient populations.

One explanation to the associations between self-rated health and cytokines could be that both factors are secondary to an inflammatory disease. In large, however, the pattern of results did not change when diagnoses, such as allergy, hypertension, cardiovascular and rheumatic disease or physical health was controlled for, supporting the stability of our findings. In addition, the results did not change when excluding the women with high CRP levels. Thus, the pattern between cytokines, behaviour and self-rated health is indicated to go beyond an explanation in terms of objectively verifiable disease.

Self-rated health is well validated and could well be introduced in clinical settings as a standardized measure that reflects both biomedical and psychosocial aspects of health that are needed in health care. Self-rated health could be a helpful device by giving a more complete view of the patient, summarizing information about various domains of health. Together with other health indicators, self-rated health would provide a straightforward, patient-centred and inexpensive method to identify persons at increased risk of mortality. Poor self-rated health, especially when objective disease markers are lacking, should be treated as other markers of

poor health as it is an independent predictor of mortality and morbidity. Poor self-rated health may be a sensitive marker of underlying illness or upcoming disease that may go otherwise undetected during routine examinations. Therefore, we suggest that self-rated health is registered in medical records and followed over time. This information could for example be used giving those with worse self-rated health opportunity to more intense treatment and care management programs. How such programs should be optimally designed needs to be further investigated.

Between one-third and two-thirds of patients attending general medical clinics do not receive a biomedical explanation for their distress [1] and a large number of patients present problems of a psychosocial nature. An increased understanding of the biological and psychological determinants of self-rated health may forward the understanding of the connection between subjective and often diffuse symptoms and objectively verified health measures such as morbidity and mortality, possible improving the care-taking of e.g. patients with unexplained medical symptoms.

Conclusion

In conclusion, it is suggested that the strength in the association between inflammatory cytokines and poor health perception increases with higher age. In addition, in higher age groups it is indicated that higher levels of TNF- α is connected to more symptoms resembling a cytokine-induced sickness-response (less satisfaction with energy, sleep, appetite, fitness, memory, and more pain) that in turn are strongly associated with lower self-rated health. The results from this and future studies may provide a fruitful psycho-biological basis to understand diffuse subjective symptoms and poor subjective health.

Conflict of Interest Statement

The authors have no conflicts of interests to state.

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Table 1. Descriptive data - Study group characteristics in the three age groups.

	Age group	-49 years n=53	50-64 years n=47	65- years n=73	F	Sign
Health *	Self rated health	2.55 (1.08)	2.52 (0.93)	2.60 (1.00)	0.1	n.s.
	Physical health	2.78 (1.17)	3.02 (1.26)	3.11 (1.09)	1.6	n.s.
General well-being †	Appetite	5.36 (1.58)	5.55 (1.39)	5.24 (1.59)	0.6	n.s.
	Energy	4.10 (1.57)	4.72 (1.51)	4.31 (1.69)	2.3	n.s.
	Fitness	4.27 (1.65)	4.39 (1.50)	3.92 (1.59)	1.5	n.s.
	Memory	4.94 (1.66)	5.14 (1.13)	4.85 (1.54)	0.6	n.s.
	Sleep	4.17 (1.92)	4.67 (1.94)	4.26 (1.95)	1.1	n.s.
	Pain	3.05 (0.82)	3.12 (0.71)	2.91 (0.87)	1.1	n.s.
	Depressive feelings	4.96 (2.66)	3.51 (2.67)	3.81 (2.58)	5.7	**
Quality of Life	6.04 (2.07)	6.90 (2.13)	5.22 (2.37)	8.6	***	
Inflammatory and Metabolic Markers	IL-1 β (pg/ml)	0.252 (0.273)	0.296 (0.340)	0.179 (0.223)	2.6	+
	IL-1ra (pg/ml)	95.48 (58.41)	138.7 (110.4)	123.6 (83.48)	2.7	+
	IL-6 (pg/ml)	2.35 (2.88)	2.73 (3.34)	3.65 (3.15)	7.5	**
	TNF- α (pg/ml)	1.25 (2.20)	0.94 (0.87)	1.58 (4.35)	0.4	n.s.
	CRP (pg/ml)	5.25 (11.53)	5.77 (14.56)	5.44 (10.30)	3.2	*
	IGF-1 (g/l)	240 (83.7)	194 (102.5)	140 (53.1)	36.2	***
	IGFBP1 (g/l)	21.0 (14.3)	16.11 (11.7)	29.4 (20.9)	8.2	***
	IGF-I:IGFBP1	17.70 (13.51)	16.56 (13.29)	7.90 (7.10)	21.7	***
Background characteristics	Age (years)	36.6 (8.9)	57.3 (3.9)	76.0 (7.1)	-	-
	Education	3.3 (1.4)	2.6 (1.6)	1.6 (0.9)	30.2	***
	Body Mass Index	25.0 (5.0)	26.9 (4.7)	25.6 (4.4)	2.3	n.s.

Continuous data are presented as mean (SD). Differences in means tested by F-test.

IL-1 β , interleukin-1 β ; IL-1ra, interleukin-1 receptor antagonist; IL-6, interleukin-6; IL-1ra, interleukin-1 receptor antagonist; CRP, C-reactive protein; IGF-I, insulin-like growth factor-I; IGFBP1, insulin-like growth factor binding protein 1.

* Higher ratings correspond to worse health.

† Higher ratings correspond to better appetite, energy, fitness, memory, sleep, Quality of Life, and more pain and depressive feelings.

+ p<0.10, * p<0.05, ** p<0.01, ***p<0.001

Table 2. Correlations between cytokines and health, general well-being, metabolic markers, CRP and background variables in the age groups –49 (n=53), 50-64 (n=47) and 65- (n=73) years

		Age group	IL-1 α	IL-1ra	IL-6	TNF- α	
Health	Self-rated health	-49	0.12	0.03	0.03	0.32*	
		50-64	0.15	0.24	-0.03	0.45**	
		65-	0.48***	0.32**	0.13	0.55***	
	Physical health	-49	0.06	-0.01	-0.08	0.13	
		50-64	0.26	0.36*	-0.01	-0.04	
		65-	0.20	0.29*	0.11	0.18	
General well-being	Appetite	-49	-0.15	-0.14	-0.12	0.12	
		50-64	0.00	-0.09	-0.15	-0.06	
		65-	-0.17	-0.16	-0.17	-0.26*	
	Energy	-49	-0.19	-0.01	0.01	-0.10	
		50-64	0.08	-0.41***	-0.20	-0.01	
		65-	-0.22	-0.28*	-0.11	-0.29*	
	Fitness	-49	-0.15	-0.19	-0.07	-0.13	
		50-64	-0.03	-0.35*	-0.19	-0.03	
		65-	-0.30*	-0.27*	-0.17	-0.36**	
	Sleep	-49	-0.10	-0.05	-0.04	-0.10	
		50-64	-0.19	0.07	-0.04	-0.28+	
		65-	-0.13	-0.12	0.06	-0.26*	
	Memory	-49	-0.13	-0.34*	-0.18	-0.29	
		50-64	0.23	-0.01	-0.22	0.11	
		65-	0.07	0.12	0.06	0.11	
	Pain	-49	0.05	0.03	0.03	0.05	
		50-64	0.01	-0.18	-0.22	-0.22	
		65-	-0.18	-0.31**	-0.25*	-0.15	
	Depressive feelings	-49	0.09	-0.23	-0.23	0.07	
		50-64	0.21	0.11	0.00	-0.09	
		65-	0.26*	0.20	0.03	0.27*	
	Quality of life	-49	-0.02	0.04	0.11	-0.10	
		50-64	-0.06	-0.38*	-0.19	0.08	
		65-	-0.30*	-0.15	-0.12	-0.30*	
	CRP and metabolic markers	IGF-I	-49	0.00	-0.16	-0.01	0.03
			50-64	0.10	-0.04	-0.22	-0.07
			65-	0.02	0.09	0.11	0.11
		IGFBP1	-49	-0.12	-0.13	-0.07	0.23
			50-64	0.15	-0.16	0.20	-0.11
			65-	-0.01	-0.17	0.04	0.06
IGF-1:IGFBP1		-49	0.11	0.11	0.06	-0.19	
		50-64	-0.06	0.10	-0.24	0.05	
		65-	0.02	0.18	0.02	0.02	
CRP		-49	-0.05	0.47***	0.47***	0.06	
		50-64	-0.20	0.42**	0.64***	0.06	
		65-	0.08	0.40***	0.54***	0.16	
Background Variables		Age	-49	0.20	0.12	0.03	0.16
			50-64	0.11	0.21	0.10	0.05
			65-	-0.02	0.04	0.12	0.19
	BMI	-49	-0.07	0.40**	0.37**	0.18	
		50-64	-0.22	0.43**	0.29	0.04	
		65-	-0.05	0.46***	0.18	-0.03	
	Education	-49	0.21	-0.44**	-0.07	-0.16	
		50-64	-0.24	-0.24	-0.07	-0.16	
		65-	0.07	-0.12	0.15	0.05	

Associations between cytokines and health, general well-being, metabolic markers, CRP and background variables calculated as Pearson product-moment correlations.

See table 1 for abbreviations.

+ p<0.10, * p<0.05, ** p<0.01, ***p<0.001

Table 3. Multiple regression analyses with self-rated health as a dependent variable and physical health, IGF-I:IGFBP-1, sickness behaviour and cytokines as independent variables.*

	Age	Physical health		IGF-I:IGFBP-1		Sickness behaviour		Cytokine (TNF- α , IL-1 β , IL-6 or IL-1ra)		R ² ‡
		β †	P	β †	P	β †	p	β †	P	
TNF- α	-49	0.15	n.s.	0.16	n.s.	-0.57	***	0.17	n.s.	39.5
	50-64	0.25	+	0.27	+	-0.43	**	0.41	***	41.4
	65-	0.17	*	-0.07	n.s.	-0.47	***	0.42	***	58.6
IL-1 β	-49	0.16	n.s.	0.13	n.s.	-0.59	***	0.03	n.s.	36.6
	50-64	0.15	n.s.	0.31	+	-0.49	**	0.13	n.s.	23.5
	65-	0.19	*	-0.06	n.s.	-0.50	***	0.39	***	56.2
IL-6	-49	0.09	n.s.	0.16	n.s.	-0.68	***	0.08	n.s.	47.4
	50-64	0.26	n.s.	0.19	n.s.	-0.57	**	-0.03	n.s.	27.3
	65-	0.25	*	-0.07	n.s.	-0.53	***	-0.10	n.s.	43.6
IL-1ra	-49	0.16	n.s.	0.13	n.s.	-0.54	***	-0.07	n.s.	37.0
	50-64	0.17	n.s.	0.30	+	-0.50	**	0.08	n.s.	22.6
	65-	0.22	*	-0.06	n.s.	-0.52	***	0.05	n.s.	43.0

* Adjusted for cardiovascular disease, allergy, hypertension, rheumatic disease

† Standardized regression coefficients

‡ Explained variance adjusted for degree of freedom

Age groups -49 (n=53), 50-64 (n=47) and 65- (n=73) years

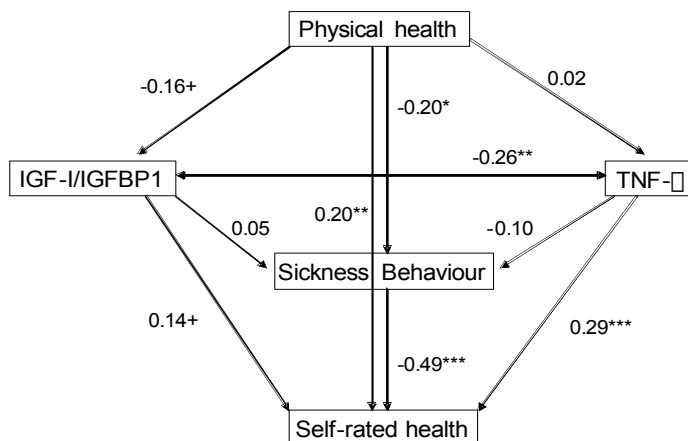
See table 1 for abbreviations.

+ p<0.10, * p<0.05, ** p<0.01, ***p<0.001

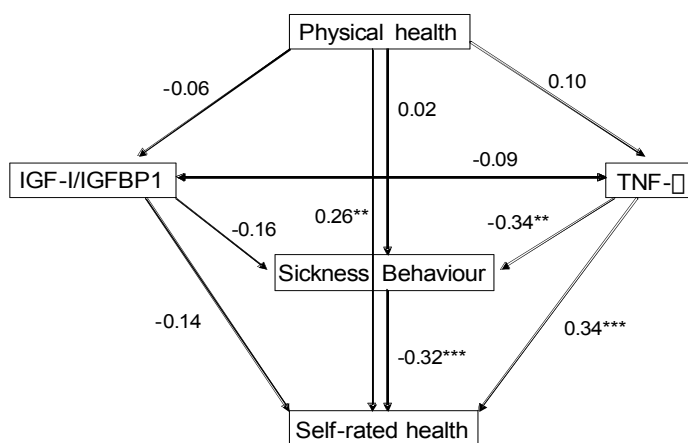
Sickness behaviour was formed using a weighted mean of the ratings of energy, sleep, appetite, fitness and memory together with the question about pain. Lower levels indicate more pronounced sickness behaviour.

Figure 1. Associations between physical health, IGF-I/IGFBP-1, TNF- α , sickness behaviour and self-rated health.

age group 18-64 years



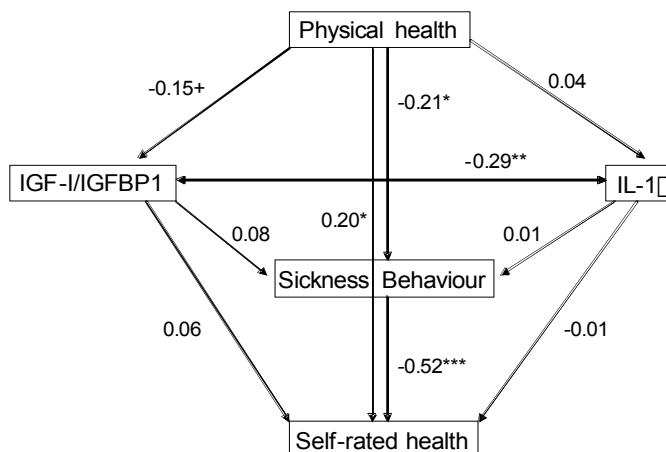
age group 65 years and above



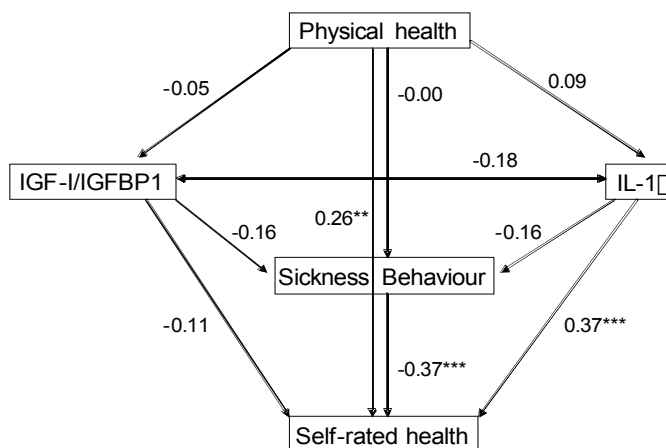
Age group 18-64 years n=100. Age group 65 years and above n=73. + p<0.10, * p<0.05, ** p<0.01, ***p<0.001
 Lower levels of sickness behaviour correspond to more pronounced sickness behaviour, and poor self-rated health corresponds to higher levels. Sickness behaviour was formed using a weighted mean of the ratings of energy, sleep, appetite, fitness and memory together with the question about pain.

Figure 2. Associations between physical health, IGF-I/IGFBP-1, IL-1 α , sickness behaviour and self-rated health.

age group 18-64 years



age group 65 years and above



Age group 18-64 years n=100. Age group 65 years and above n=73. + p<0.10, * p<0.05, ** p<0.01, *** p<0.001
 Lower levels of sickness behaviour correspond to more pronounced sickness behaviour, and poor self-rated health corresponds to higher levels. Sickness behaviour was formed using a weighted mean of the ratings of energy, sleep, appetite, fitness and memory together with the question about pain.