BMJ Open

POOR SELF-RATED HEALTH IS ASSOCIATED WITH LOW-GRADE INFLAMMATION IN 43,481 LATE ADOLESCENT MEN OF THE GENERAL POPULATION

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-009440
Article Type:	Research
Date Submitted by the Author:	17-Aug-2015
Complete List of Authors:	Warnoff, Carin; Karolinska Institutet, Clinical Neuroscience, Division of Psychology Lekander, Mats; Stress Research Institute, Stockholm University Hemmingsson, Tomas; Karolinska Institutet, Institute of Environmental Medicine Sorjonen, Kimmo; Karolinska institutet, Department of Clinical Neurosciences, Division of Psychology Melin, Bo; Karolinska institutet, Department of Clinical Neurosciences, Division of Psychology Andreasson, Anna; Stress Research Institute, Stockholm University; Karolinska Institutet, Neurobiology, Care Sciences and Society
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	Epidemiology , MENTAL HEALTH, IMMUNOLOGY, Public health < INFECTIOUS DISEASES

POOR SELF-RATED HEALTH IS ASSOCIATED WITH LOW-GRADE INFLAMMATION IN 43,481 LATE ADOLESCENT MEN OF THE GENERAL POPULATION

Anna Andreasson

Stress Research Institute

Stockholm University

SE-106 91 Stockholm

Sweden

Phone: +46 (0)8 5537 8903

Fax: +46 (0)8 5537 8900

E-mail: anna.andreasson@su.se

Carin Warnoff[1], Mats Lekander[1,2,3], Tomas Hemmingsson[4,5], Kimmo Sorjonen[1], Bo Melin[1], Anna Andreasson[2,3,6]

[1] Department for Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

[2] Stress Research Institute, Stockholm University, Stockholm, Sweden

[3] Osher Center for Integrative Medicine, Karolinska Institutet, Stockholm, Sweden

[4] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[5] Centre for Social Research on Alcohol and Drugs, Stockholm University, Stockholm, Sweden.

[6] Division of Family Medicine, Karolinska Institutet, Huddinge, Sweden

Self-rated health and inflammation in adolescent men

Key words: self-rated health, erythrocyte sedimentation rate, low-grade inflammation, military conscripts

Word Count: 83

Abstract

Objective

Self-rated health is a powerful predictor of long-term health and mortality, hence the importance of a better understanding of its biological determinants. Previous studies have shown that low-grade inflammation is associated with poor self-rated health in clinical and healthy populations, but the evidence is sparse in men and lacks completely for men in late adolescence.

The aim of this study was to investigate the association between low-grade inflammation and self-rated health in a very large population of late adolescent men.

Design

Data from 49,321 men (18-21 years) conscribed to military service in 1969 and 1970 was used. Inflammation had been measured through erythrocyte sedimentation rate (ESR). Self-rated health had been self-assessed on a five-point scale. Data from 43,481 conscripts with subclinical levels of ESR remained after exclusion of those with ESR <1 and >11. Associations were calculated using logistic regression analyses and Ordinary Least Square (OLS) regression. Adjustments were made for body mass index (BMI), socioeconomic position (SEP), inflammatory disease, emotional control, smoking, risky use of alcohol and physical activity.

Results

The odds of having Poor/Very poor self-rated health was 66 % higher for conscripts with elevated ESR levels (≥7 <11) (OR:1.66; 95%CI:1.29-2.14).

Conclusion

This study adds to the evidence of an association between low-grade inflammation and poor self-rated health across the life span in both men and women, providing further support for

inflammation as part of a general psychobiological process that underpins subjective health perception.

Strengths and limitations of this study

- This is the first study to investigate the association between low-grade inflammation and self-rated health in a large sample (n=49,321) of late adolescent men.
- Using data from the national military conscription register, encompassing nearly all Swedish men born in 1949-1951, eliminates selection bias.
- Adjustments were made for life-style patterns, demographic factors and psychological disposition.
- The cross-sectional design precludes conclusions about causality.

What is already known on this subject? Further knowledge of biological correlates to self-rated may provide a better understanding of the mechanisms behind the predictive properties of poor self-rated health. The association between inflammatory markers and self-rated health has so far mainly been investigated in women. The current study investigates such an association in late adolescent men.

What this study adds? The results from the present study suggests that inflammatory factors may be relevant for the biological underpinnings of self-rated health also in men of late adolescence and hence further support inflammation as a general factor in the psychobiological processes that underpin subjective health perception across the adult life span.

INTRODUCTION

Self-rated health is a single-item measure of an individual's perceived health status. A number of studies show that poor self-rated health predicts future adverse health outcomes, such as cardio-vascular events [1] and healthcare utilization [2], and is coupled to a near two-fold risk of premature mortality [3-5]. The predictive qualities of self-rated health remain after controlling for objective health and social and demographic risk factors [4].

Although the mechanisms that link self-rated health to future objectively verified ill-health are largely unknown, recent studies point at inflammation as an important determinant of how an individual perceives her global health status [6-8]. As part of the inflammatory response to acute infection or injury, pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α drive the acute phase response by increasing levels of acute phase proteins [9]. One of these proteins, fibrinogen, is a coagulation factor and is reflected by erythrocyte sedimentation rate (ESR). When inflammation is present, the fibrinogen causes erythrocytes to clot in rolls, thus sinking faster through a test tube, resulting in an increased ESR [10, 11]. Compared to other tests of inflammation, ESR is a simple and cost efficient way of establishing the presence of the acute phase reactants, and, indirectly, the activity of pro-inflammatory cytokines [9] making it a suitable marker of inflammation when collecting large amount of data.

One hypothesis to explain the observed association between low-grade inflammation and poor self-rated health is that inflammation related signals reach areas in the brain, including the insular cortex and the anterior cingulate cortex [12, 13], i.e. areas that are important in interpretation of bodily state and homeostatic changes [14]. As part of co-ordination of a sickness response, shifts in motivation and alterations of behaviors that promote healing and

recovery are thereby induced [15]. Symptoms of such inflammation-induced sickness behaviors include anhedonia, fatigue and increased sensitivity to pain, which are also determinants of subjective health perception [16]. Since low-grade inflammation is part of the pathology in major causes of premature mortality, such as cardio-vascular disease (see e.g. [17, 18]), type-2 diabetes [19], obesity [20] and certain types of cancer [21, 22] low-grade inflammation could be one factor linking poor self-rated health with future adverse health outcomes.

In order to investigate whether low-grade inflammation may be implicated in subjective health perception, a row of recent studies have examined the link between increased levels of pro-inflammatory cytokines and poor self-rated health [6-8, 16, 23, 24]. Other studies have examined the association between self-rated health and fibrinogen [25], ESR [26] and of another acute phase reactant, C-reactive protein (CRP)[7, 23, 27, 28]. So far, the evidence of a link between low-grade inflammation and self-rated health is more robust for women as compared to men [6-8, 16, 27], and the strength of the association has been indicated to increase with age [6, 16]. For instance, among 347 women 45 to 90 years old of the general population there was a significant association between IL-6 and poor self-rated health, particularly among those 65 years old and above [6]. In another study, 174 female primary health care patients of 18 years and older who were divided into three age groups, higher TNF-α was significantly associated with poor self-rated health in all groups, and higher IL-1ß and IL-1 receptor antagonist was associated with poor self-rated health in those over 65 years old [16]. Moreover, in 235 middle-aged and elderly women with coronary heart disease, high levels of CRP and IL-6 were associated with poor self-rated health [7].

Among the studies including both men and women, only two have performed sex-based stratified analyses [8, 27] and one study examined the interaction effect of sex and inflammation

on self-rated health [28]. A study of 170 female and 89 male primary health care patients showed a significant independent association between higher IL-1β and TNF-α and poor self-rated health only in women [8], but the lack of association in men could be due to small sample size and low power. Among 11,000 women and 5,000 men, a significant association between CRP and self-rated health remained only in women after adjustment for control factors [27]. However, in a population of 13,236 young adults aged 24-34 years, high sensitivity CRP above 3 mg/L was significantly associated with lower ratings of self-rated health after adjustment for health behaviors, self-reported illness and medication in both men and women. Inclusion of BMI fully attenuated the association between CRP and self-rated health in the women whereas a small but significant association remained in men [28].

The remaining studies encompassing both men and women reported significant associations between IL-6 and self-rated health [23, 24], and between fibrinogen and self-rated health [25] but as these studies are only adjusted for sex it is not clear if this association would be found in the male or female strata only.

The present study aims at investigating low-grade inflammation and subjective health perception in a very large, young and healthy population mainly free from medical conditions. We hypothesized that conscripts with elevated ESR levels had rated their health as poorer in this population of late adolescent men, a group that has not yet been investigated in this context.

METHODS

Participants

This study was based on data collected in 1969 to 1970 when 49,321 Swedish men born between 1949 and 1951 (aged 18-21 years) underwent a compulsory 2-day screening procedure prior to military service. During this time period, only 2-3 % of men eligible for military services were exempted from conscription, mainly due to severe disabilities or severe congenital disorders. All conscripts had answered questionnaires about social background, habits, psychological factors, social adjustment and health status and had been structured-interviewed by a psychologist. Finally, a physician examined all conscripts, and any somatic or psychiatric disorders were diagnosed according to the Swedish version of the International Classification of Disorders, version 8 (ICD-8). The present study was approved by the regional ethics board.

Measures

Self-Rated Health

The conscripts had been asked to assess their health, answering the question: "*In general, would you say your health right now is: Very good, Good, Fair, Poor or Very poor"?* The answers had been rated on a 5-point scale where 1="Very good", 2="Good", 3="Fair", 4="Poor" and 5="Very poor". Due to low numbers in the categories "Poor" and "Very poor", these were combined into one category in the logistic regression analyses.

Erythrocyte Sedimentation Rate

At physical examination, blood samples had been taken and ESR had been measured according to standard laboratory procedures (Westergren method)[9]. The ESR is affected by the hematocrit (Htc, i.e. the proportion of whole blood made up by erythrocytes), we therefore

corrected the ESR values for the hematocrit according to the formula ESR*Htc/45 [29]. Htc-corrected ESR values are used in all analyses and presentations of ESR values. Despite plausible inter-individual genetic variations [30], the upper limit of the normal range of ESR has, on group level, been found to correspond to the age in years divided by two [31]. The age span of the men included in this study ranged from 18 to 21 years. Based on the highest age included, the normal range was rounded off to <11 mm/hr. Thus, the 3.7 % of the participants with ESR ≥11 mm/hr (n=3,937) were excluded from the analyses. Those with ESR <1 mm/hr (N=1,903) were also excluded in order to reduce error of misclassifications [32]. The remaining 88.2 percent % of the (N=43,481) conscripts had ESR levels >1 < 11 mm/hr and were included in the analyses.

Body Mass Index

The conscripts' height and weight had been measured at the physical examination. Body mass index (BMI) is determined by calculating the ratio of weight to height squared (kg/m^2). Obesity and underweight as measured by very high or very low BMI have independently been associated with poorer self-rated health [33].

Socioeconomic Position

Parental socioeconomic position (SEP) was used as an indicator of childhood socioeconomic circumstances. Information about socioeconomic circumstances of the conscripts at 9 to 11 years of age was obtained from the National Population and Housing Census from 1960. The conscripts and the head of the household, usually the father, were linked through their personal identification number by Statistics Sweden. Based on the occupation of the head of the household seven socioeconomic groups were identified: (a) unskilled workers, (b) skilled

workers, (c) assistant non-manual employees, (d) non-manual employees at intermediate level, (e) non-manual employees at higher level, (f) farmers, and (g) those not classified into a socioeconomic group. Self-employed persons could not be identified in the census from 1960 where such persons were classified as employed according to occupation. Previous research have shown that childhood SEP is associated with markers of inflammation in adults [34, 35], and a previous study from this sample found a significant association between ESR and SEP [36], why SEP is included in the analyses.

Inflammatory Disease

Presence of one or more of the following medical conditions as registered for each conscript by a physician according to ICD-8 was adjusted for in the analyses: infectious disease, malignancies, lymphatic and haemotopoetic tumors, diabetes mellitus, asthma, gastrointestinal inflammation, hay fever, infection and inflammation in skin, arthritis and rheumatoid arthritis.

Emotional Control

The combined questionnaire and interview data had been used by a psychologist to evaluate emotional control rated on 5-point scale, based on self-reported anxiety, stress-tolerance, nervous problems, capacity for emotional commitment and control over aggression (a score of 1 to 2 represent *Low* emotional control). A previous study has shown that low emotional control was a confounding factor in the association between poor self-rated health and mortality [5] and was for that reason included in the analyses.

Smoking

Tobacco smoking has been associated with increased systemic inflammation in men [37, 38]. Smoking has also been associated with poor self-rated health [6, 39, 40] and was therefore included in the analyses. The self-reported number of cigarettes smoked per day had been rated on a 4-point scale where 1>20, 2=11-20, 3=1-10 cigarettes per day and 4=non-smoker.

Risky use of alcohol

Risky use of alcohol was estimated based upon questions on high consumption of alcohol: none vs. at least one of the following indicators– consumption of at least 250 g 100 % alcohol per week; use of alcohol to alleviate a hangover; having been apprehended for drunkenness; being drunk often.

Physical activity

We used active membership in sport clubs as a proxy for physical activity.

Statistics

To calculate the association between ESR and self-rated health, logistic regression analysis was used with ESR as the independent variable and self-rated health as the outcome variable (Table 2). In the logistic regression analyses, the group was dichotomized into those with ESR <7 mm/hr (n=41,064), and those with ESR ≥7 mm/hr (n=2,417), a cut-off used in previous analyses on this study sample [36].

Self-rated health was classified into four groups: 1=Very good, 2=Good, 3=Fair, or 4=Poor/Very poor. The effects of having elevated ESR serum levels (≥ 7 mm/hr) on the odds of having Good, Fair, or Poor rather than Very good (= reference) self-rated health was calculated.

As a second step, the association between ESR serum levels and self-rated health was adjusted separately for background variables BMI, SEP, presence of inflammatory disease, emotional control, smoking, risky use of alcohol and physical activity. Third, in the full model, the association between ESR levels and self-rated health was adjusted for all background variables together.

The association between ESR and self-rated health was also estimated using Ordinary Least Square (OLS) regression, in both univariate and multivariate models. In the adjusted models, the association between ESR and self-rated health was estimated adjusting for the effect of BMI, SEP, presence of inflammatory disease, emotional control, smoking, risky use of alcohol and physical activity. An α-value of .05 was used to test for statistical significance. All analyses were performed using SPSS statistics software version 21.

RESULTS

Participant characteristics in total and separated for those with lower (<7 mm/hr) and those with higher (≥7 mm/hr) ESR are shown in Table 1. The majority of participants had ESR below 7 mm/hr (91.2 %) and reported their health as Very good or Good (82.4 %). Conscripts with elevated ESR levels tended to have poor self-rated health and farmer background with higher frequency. Conscripts with lower ESR levels tended to have good self-rated health and non-manual SEP background with higher frequency.

Table 1. *Participant characteristics separately for those with ESR < 7 (n = 41,064) and ESR ≥ 7 (n = 2,417). Group differences in frequencies have been tested with Chi Square test and differences in means with t-tests.*

Variable/category	ESR<7	ESR≥7	χ^2	Variable/category	ESR<7	ESR≥7	χ^2
Self-rated health (%)				SEP Father 1960 (%)			
Very good	41.1	34.8	22.17*	Worker, unskilled	33.3	35.6	3.42
Good	41.4	45.2	7.43*	Worker, skilled	21.5	21.7	0.07
Fair	13.8	14.6	1.01	Non-manual, assistant	10.1	9.5	0.88
Poor/Very poor	3.7	5.3	17.05*	Non-manual, intermed.	16.9	13.9	12.09*
Smoking per day (%)				Non-manual, higher	5.2	3.8	9.44†
> 20 cigarettes	3.7	3.4	0.31	Farmer	10.7	13.2	13.05*
11-20 cigarettes	23.4	22.4	0.85	Non-classified	2.3	2.4	0.07
1-10 cigarettes	31.9	32.2	0.04	Year of Birth (%)			
Non smoker	41.1	41.9	0.36	1949	5.4	4.6	2.36
Inflammatory disease (%)	9.0	9.6	1.29	1950	17.3	16.2	1.75
Low emotional control (%)	30.3	30.0	0.12	1951	77.3	79.2	1.06
Risky use of alcohol (%)	15.7	16.6	1.23	Self-rated health, M (SD)	1.80 (0.82)	1.91 (0.85)	-5.90*

Physical activity (%)	36.4	36.7	0.07	BMI, M (SD)	21.00 (2.57)	20.96 (2.80)	0.62

* $p < .001$; † $p < .05$

BMI=body mass index, ESR= erythrocyte sedimentation rate, SEP=socioeconomic position.

Table 2. *Crude and adjusted odds ratio of reporting Good, Fair and Poor SRH as compared to Very good SRH (reference) in those with ESR ≥ 7.*

Adjusted for	Good	Fair	Poor
Crude	1.29 (1.17-1.41)	1.25 (1.10-1.42)	1.72 (1.42-2.09)
BMI	1.29 (1.17-1.41)	1.25 (1.10-1.42)	1.71 (1.41-2.08)
SEP	1.27 (1.16-1.40)	1.24 (1.09-1.41)	1.74 (1.43-2.11)
Inflammatory disease	1.29 (1.17-1.41)	1.25 (1.10-1.42)	1.75 (1.44-2.13)
Emotional control	1.29 (1.18-1.42)	1.24 (1.08-1.43)	1.69 (1.36-2.10)
Smoking	1.30 (1.19-1.43)	1.27 (1.11-1.44)	1.79 (1.46-2.19)
Risky use alcohol	1.25 (1.12-1.38)	1.22 (1.06-1.40)	1.58 (1.27-1.97)
Physical activity	1.29 (1.18-1.42)	1.24 (1.09-1.41)	1.72 (1.41-2.09)
All above	1.26 (1.13-1.40)	1.25 (1.07-1.46)	1.66 (1.29-2.14)

BMI=body mass index, SEP=socioeconomic position.

There was a dose-response pattern between self-rated health and ESR (Table 2). The poorer rating of health, the higher the odds of having ESR above 7, and, consequently, conscripts with ESR ≥7 mm/hr had significantly higher odds of rating their health as less than Very good than did conscripts with ESR <7 mm/hr. The size of the association and the level of significance were largely unaffected by adjustments for BMI, SEP, inflammatory diseases, emotional control, smoking, risky use of alcohol and physical activity.

Ordinary Least Square (OLS) regression with 95% CI of the association between ESR and self-rated health is presented in Table 3. High levels of ESR were associated with poor self-rated health independent of BMI, SEP, presence of inflammatory disease, emotional control, smoking, risky use of alcohol and physical activity.

Table 3. *Crude and adjusted associations between ESR and self-rated health calculated with Ordinary Least Square (OLS) regression presented as OLS coefficient with 95% confidence intervals and beta coefficients.*

Adjusted for	Intercept	B	95% CI	beta	R^2
Crude	1.763	.016	.012-.020	.040	.002
BMI	1.966	.016	.012-.020	.039	.003
SEP	1.857	.016	.012-.020	.039	.002
Inflammatory disease	1.728	.016	.012-.020	.039	.021
Emotional control	1.595	.016	.013-.020	.040	.098
Smoking	1.657	.018	.014-.021	.043	.034
Risky use alcohol	1.738	.016	.012-.020	.039	.011
Physical activity	1.849	.016	.013-.020	.040	.022
All above	1.707	.017	.013-.021	.042	.133

BMI=body mass index, SEP=socioeconomic position.

DISCUSSION

The aim of this study was to investigate if there is an association between higher level of the inflammatory marker ESR and poor self-rated health in late adolescent men. The odds of having poor rather than very good self-rated health was elevated by approximately 70 % among individuals with higher ((≥7 mm/hr) as compared with lower (< 7 mm/hr) ESR levels.

This pattern was stable when relevant confounders (BMI, SEP, presence of inflammatory disease, emotional control, smoking, risky use of alcohol and physical activity) were controlled for. Hence, the present result is consistent with our hypothesis and adds to previous findings by indicating that low-grade inflammation is associated with lower self-ratings of health, also in late adolescent men.

The results of the present study are in contrast with the lack of association between inflammatory markers and self-rated health in men in the studies by Lekander and coworkers [8] and Tanno and coworkers [27]. In comparison to the present study, those studies are based on dissimilar methods and populations, with older participants (mean age 59 and 58 years, respectively, compared to 18-21 years in the present study). The study the study by Lekander and coworkers had a considerably smaller sample size and Tanno and coworkers (27) had an Asian population. However, the present results are in concordance with a previous study that demonstrated a small but significant association between CRP and self-rated health in young adult men 24 to 34 years old [28].

Demographic factors and life-style patterns have been associated with both low-grade inflammation and to poor self-rated health; factors that may constitute possible confounders in the association between ESR and self-rated health, such as aging [41], obesity [42], low SEP

[36], and smoking [6, 38]. Adjustments for BMI, SEP, inflammatory disease, emotional control, smoking, risky alcohol use, and physical activity did not, however, change the association between ESR and self-rated health in the present study. Also, individuals with a higher degree of inflammation did not introduce bias, as all conscripts with an ESR equal to or above 11 mm/hr were excluded. Unfortunately, data on diet was not available in the present study, which is a factor to take into account in future studies.

Our study sample consisted of 43,431 conscripts encompassing the majority of all Swedish men born in 1949 to 1951. Having a study sample that represents such a large percentage of the population is obviously advantageous in terms of power, but also eliminates the risk for selection bias. In the present material of late adolescent men, the majority of participants were, as expected, healthy. Altogether 82.6 % rated their health as Good or Very good, and 82.7 % had ESR values ≥1 and < 7 mm/hr. It cannot be excluded that in a current-day sample of young men the included factors would be differently distributed, and that e.g. low-grade inflammation would be more prevalent as obesity, which has been linked with low-grade inflammation [43, 44], almost doubled in prevalence between 1971 and 1993 among Swedish military conscripts [45]. However, the association between ESR and self-rated health in the present study was independent of background factors such as BMI and there is little reason to expect that the putative underlying biological mechanism by which inflammation is associated with subjective health perception would have changed.

Concerning validity, some discordance between ESR and other inflammatory markers has been documented. For instance ESR has been shown to rise and decrease slower than CRP (see e.g. [46]. However, the dose-responsive and independent relation between self-rated health and

ESR in the present study suggests that ESR is a marker for self-rated health, not merely reflecting manifest disease or chronic conditions.

In conclusion, the present study showed for the first time, a significant association between a measure of inflammation and self-rated health in late adolescent men. Although its observational and cross-sectional design precludes any conclusions about causality, evidence is here provided to further support inflammation as a general factor in the psychobiological processes that underpin subjective health perception across the adult life span.

Contributors ML, TH, BM, AA conceived of the study**.** CW drafted the manuscript. KS and TH performed the statistical analyses. All authors were involved in the discussion of the data and revised the manuscript for intellectual content.

Funding This study has not received funding.

Competing interests None declared.

Data sharing statement The study uses data from the Swedish conscription cohort which includes assessments of the physical and mental health status of all conscripts. Please contact the corresponding author for further information on data availability.

References

1. Grool, A.M., et al., *Self-rated health status as a risk factor for future vascular events and mortality in patients with symptomatic and asymptomatic atherosclerotic disease: the SMART study.* J Intern Med, 2012.
2. DeSalvo, K.B., et al., *Predicting mortality and healthcare utilization with a single question.* Health Serv Res, 2005. **40**(4): p. 1234-46.

3. DeSalvo, K.B., et al., *Mortality prediction with a single general self-rated health question. A meta-analysis.* J Gen Intern Med, 2006. **21**(3): p. 267-75.
4. Idler, E.L. and Y. Benyamini, *Self-rated health and mortality: a review of twenty-seven community studies.* J Health Soc Behav, 1997. **38**(1): p. 21-37.
5. Larsson, D., et al., *Self-rated health and mortality among young men: what is the relation and how may it be explained?* Scandinavian Journal of Public Health, 2002. **30**(4): p. 259-266.
6. Andreasson, A.N., et al., *Inflammation and positive affect are associated with subjective health in women of the general population.* Journal of health psychology, 2012.
7. Janszky, I., et al., *Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease.* Brain, Behavior, and Immunity, 2005. **19**(6): p. 555-563.
8. Lekander, M., et al., *Self-rated health is related to levels of circulating cytokines.* Psychosom Med, 2004. **66**(4): p. 559-63.
9. Saadeh, C., *The erythrocyte sedimentation rate: old and new clinical applications.* Southern medical journal, 1998. **91**(3): p. 220-5.
10. Heinrich, P.C., J.V. Castell, and T. Andus, *Interleukin-6 and the acute phase response.* The Biochemical journal, 1990. **265**(3): p. 621-36.
11. Janeway, C.A., et al., *Induced innate responses to infection*, in *Immunobiology* 2001, Garland Publishing: New York.
12. Hannestad, J., et al., *Glucose metabolism in the insula and cingulate is affected by systemic inflammation in humans.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2012. **53**(4): p. 601-7.

13. Harrison, N.A., et al., *Neural origins of human sickness in interoceptive responses to inflammation.* Biological psychiatry, 2009. **66**(5): p. 415-22.

14. Craig, A.D., *How do you feel? Interoception: the sense of the physiological condition of the body.* Nat Rev Neurosci, 2002. **3**(8): p. 655-66.

15. Dantzer, R., *Cytokine-induced sickness behavior: mechanisms and implications.* Ann N Y Acad Sci, 2001. **933**: p. 222-34.

16. Unden, A.L., et al., *Inflammatory cytokines, behaviour and age as determinants of self-rated health in women.* Clin Sci (Lond), 2007. **112**(6): p. 363-73.

17. Melamed, S., et al., *Association of fear of terror with low-grade inflammation among apparently healthy employed adults.* Psychosom Med, 2004. **66**(4): p. 484-91.

18. Yudkin, J.S., et al., *C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue?* Arterioscler Thromb Vasc Biol, 1999. **19**(4): p. 972-8.

19. Duncan, B.B., et al., *Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study.* Diabetes, 2003. **52**(7): p. 1799-805.

20. Bondia-Pons, I., L. Ryan, and J.A. Martinez, *Oxidative stress and inflammation interactions in human obesity.* Journal of physiology and biochemistry, 2012. **68**(4): p. 701-11.

21. Macarthur, M., G.L. Hold, and E.M. El-Omar, *Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy.* Am J Physiol Gastrointest Liver Physiol, 2004. **286**(4): p. G515-20.

22. Balkwill, F. and A. Mantovani, *Inflammation and cancer: back to Virchow?* Lancet, 2001. **357**(9255): p. 539-45.

23. Christian, L.M., et al., *Poorer self-rated health is associated with elevated inflammatory markers among older adults.* Psychoneuroendocrinology, 2011. **36**(10): p. 1495-504.

24. Cohen, H.J., et al., *The association of plasma IL-6 levels with functional disability in community-dwelling elderly.* Journals of Gerontology. Series A, Biological Sciences & Medical Sciences, 1997. **52**(4): p. M201-8.

25. Fielding, R., et al., *Subjective health and fibrinogen in a healthy Chinese cohort.* Br J Health Psychol, 2004. **9**(Pt 4): p. 523-32.

26. Nilsson, L.-G., et al., *The Betula Prospective Cohort Study: Memory, Health and Aging.* Aging, neuropsych, cogn 1997. **4**(1): p. 1-32.

27. Tanno, K., et al., *Poor self-rated health is significantly associated with elevated C-reactive protein levels in women, but not in men, in the Japanese general population.* Journal of psychosomatic research, 2012. **73**(3): p. 225-31.

28. Shanahan, L., et al., *Self-rated health and C-reactive protein in young adults.* Brain Behav Immun, 2014. **36**: p. 139-46.

29. Borawski, J. and M. Mysliwiec, *The hematocrit-corrected erythrocyte sedimentation rate can be useful in diagnosing inflammation in hemodialysis patients.* Nephron, 2001. **89**(4): p. 381-3.

30. Kullo, I.J., et al., *Complement receptor 1 gene variants are associated with erythrocyte sedimentation rate.* Am J Hum Genet, 2011. **89**(1): p. 131-8.

31. Miller, A., M. Green, and D. Robinson, *Simple rule for calculating normal erythrocyte sedimentation rate.* British medical journal, 1983. **286**(6361): p. 266.

32. Toss, F., A. Nordstrom, and P. Nordstrom, *Inflammation in young adulthood is associated with myocardial infarction later in life.* Am Heart J, 2013. **165**(2): p. 164-9.

33. Molarius, A., et al., *Socioeconomic conditions, lifestyle factors, and self-rated health among men and women in Sweden.* Eur J Public Health, 2007. **17**(2): p. 125-33.

34. Miller, G. and E. Chen, *Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence.* Psychosomatic medicine, 2007. **69**(5): p. 402-9.

35. Pollitt, R.A., et al., *Early-life and adult socioeconomic status and inflammatory risk markers in adulthood.* European journal of epidemiology, 2007. **22**(1): p. 55-66.

36. Karlsson, H., et al., *Association between erythrocyte sedimentation rate and IQ in Swedish males aged 18–20.* Brain, Behavior, and Immunity, 2010. **24**(6): p. 868-873.

37. Frohlich, M., et al., *Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95).* Eur Heart J, 2003. **24**(14): p. 1365-72.

38. Lao, X.Q., et al., *Smoking, smoking cessation and inflammatory markers in older Chinese men: The Guangzhou Biobank Cohort Study.* Atherosclerosis, 2009. **203**(1): p. 304-10.

39. Kirkland, S., L. Greaves, and P. Devichand, *Gender Differences in Smoking and Self Reported Indicators of Health.* BMC Womens Health, 2004. **4 Suppl 1**: p. S7.

40. Wang, M.P., et al., *Smoking is associated with poor self-rated health among adolescents in Hong Kong.* Nicotine Tob Res, 2012. **14**(6): p. 682-7.

41. Giunta, S., *Is inflammaging an auto[innate]immunity subclinical syndrome?* Immunity & ageing : I & A, 2006. **3**: p. 12.

42. Yudkin, J.S., et al., *Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link?* Atherosclerosis, 2000. **148**(2): p. 209-14.

43. Greenberg, A.S. and M.S. Obin, *Obesity and the role of adipose tissue in inflammation and metabolism.* Am J Clin Nutr, 2006. **83**(2): p. 461S-465S.

44. Gregor, M.F. and G.S. Hotamisligil, *Inflammatory mechanisms in obesity.* Annu Rev Immunol, 2011. **29**: p. 415-45.

45. Rasmussen, F., M. Johansson, and H.O. Hansen, *Trends in overweight and obesity among 18-year-old males in Sweden between 1971 and 1995.* Acta paediatrica, 1999. **88**(4): p. 431-7.

46. Bilgen, O., et al., *C-reactive protein values and erythrocyte sedimentation rates after total hip and total knee arthroplasty.* J Int Med Res, 2001. **29**(1): p. 7-12.

BMJ Open

POOR SELF-RATED HEALTH IS ASSOCIATED WITH LOW-GRADE INFLAMMATION IN 43,481 LATE ADOLESCENT MEN OF THE GENERAL POPULATION

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009440.R1
Article Type:	Research
Date Submitted by the Author:	23-Dec-2015
Complete List of Authors:	Warnoff, Carin; Karolinska Institutet, Clinical Neuroscience, Division of Psychology Lekander, Mats; Stress Research Institute, Stockholm University Hemmingsson, Tomas; Karolinska Institutet, Institute of Environmental Medicine Sorjonen, Kimmo; Karolinska institutet, Department of Clinical Neurosciences, Division of Psychology Melin, Bo; Karolinska institutet, Department of Clinical Neurosciences, Division of Psychology Andreasson, Anna; Stress Research Institute, Stockholm University; Karolinska Institutet, Neurobiology, Care Sciences and Society
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	Epidemiology , MENTAL HEALTH, IMMUNOLOGY, Public health < INFECTIOUS DISEASES

POOR SELF-RATED HEALTH IS ASSOCIATED WITH LOW-GRADE INFLAMMATION IN 43,481 LATE ADOLESCENT MEN OF THE GENERAL POPULATION

Anna Andreasson(Corresponding author)

Stress Research Institute

Stockholm University

SE-106 91 Stockholm

Sweden

Phone: +46 (0)8 5537 8903

Fax: +46 (0)8 5537 8900

E-mail: anna.andreasson@su.se

Carin Warnoff[1], Mats Lekander[1,2,3], Tomas Hemmingsson[4,5], Kimmo Sorjonen[1], Bo Melin[1], Anna Andreasson[2,3,6]

[1] Department for Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

[2] Stress Research Institute, Stockholm University, Stockholm, Sweden

[3] Osher Center for Integrative Medicine, Karolinska Institutet, Stockholm, Sweden

[4] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[5] Centre for Social Research on Alcohol and Drugs, Stockholm University, Stockholm, Sweden.

[6] Division of Family Medicine, Karolinska Institutet, Huddinge, Sweden

Self-rated health and inflammation in adolescent men

Key words: self-rated health, erythrocyte sedimentation rate, low-grade inflammation, military conscripts

Abstract

Objective

Self-rated health is a powerful predictor of long-term health and mortality, hence the importance of a better understanding of its biological determinants. Previous studies have shown that low-grade inflammation is associated with poor self-rated health in clinical and healthy populations, but the evidence is sparse in men and lacks completely for men in late adolescence. The aim of this study was to investigate the association between low-grade inflammation and self-rated health among conscripts. It was hypothesized that high levels of inflammatory factors would be associated with poor self-rated health.

Design

Data from 49,321 men (18-21 years) conscribed to military service in 1969 and 1970 was used. Inflammation had been measured through erythrocyte sedimentation rate (ESR). Self-rated health had been assessed on a five-point scale and was dichotomized into *Good* (“Very good”/”Good”/”Fair”) versus *Poor* (”Poor”/Very poor”). Data from 43,481 conscripts with normal levels of ESR remained after exclusion of those with ESR <1 and >11 mm/hr. Associations were calculated using logistic regression analyses. Adjustments were made for body mass index, socioeconomic position, inflammatory disease, emotion regulation, smoking, risky use of alcohol and physical activity.

Results

High levels of ESR was associated with a higher odds for poor self-rated health (OR:1.077 for each unit mm/hr increase in ESR, 95% confidence interval: 1.049-1.105).

Conclusion

The present study shows for the first time, a significant association between a marker of inflammation and self-rated health in late adolescent men providing evidence of an association between low-grade inflammation and poor self-rated health also in men, providing further support for inflammation as part of a general psychobiological process that underpins subjective health perception.

Strengths and limitations of this study

- This is the first study to investigate the association between low-grade inflammation and self-rated health in a large sample (n=49,321) of late adolescent men.
- Using data from the national military conscription register, encompassing nearly all Swedish men born in 1949-1951, eliminates selection bias.
- Adjustments were made for life-style patterns, demographic factors and psychological disposition.
- The cross-sectional design precludes conclusions about causality.

What is already known on this subject? Further knowledge of biological correlates to self-rated may provide a better understanding of the mechanisms behind the predictive properties of poor self-rated health. The association between inflammatory markers and self-rated health has so far mainly been investigated in women. The current study investigates such an association in late adolescent men.

What this study adds? The results from the present study shows an association between a marker of inflammation and self-rated health also in men of late adolescence providing further support for inflammation as part of a general psychobiological processes that underpin subjective health perception across the adult life span in both men and women.

INTRODUCTION

Self-rated health is a single-item measure of an individual's perceived health status. A number of studies show that poor self-rated health predicts future adverse health outcomes, such as cardio-vascular events [1] and healthcare utilization [2], and is coupled to a near two-fold risk of premature mortality [3-5]. The predictive qualities of self-rated health remain after controlling for objective health and social and demographic risk factors [4].

Although the mechanisms that link self-rated health to future objectively verified ill-health are largely unknown, recent studies point at inflammation as an important determinant of how an individual perceives her global health status [6-8]. As part of the inflammatory response to acute infection or injury, pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α drive the acute phase response by increasing levels of acute phase proteins [9]. One of these proteins, fibrinogen, is a coagulation factor and is reflected by erythrocyte sedimentation rate (ESR). When inflammation is present, the fibrinogen causes erythrocytes to clot in rolls, thus sinking faster through a test tube, resulting in an increased ESR [10, 11]. Compared to other tests of inflammation, ESR is a simple and cost efficient way of establishing the presence of the acute phase reactants, and, indirectly, the activity of pro-inflammatory cytokines [9] making it a suitable marker of inflammation when collecting large amount of data.

One hypothesis to explain the observed association between low-grade inflammation and poor self-rated health is that inflammation related signals reach areas in the brain, including the insular cortex and the anterior cingulate cortex [12, 13], i.e. areas that are important in interpretation of bodily state and homeostatic changes [14]. As part of co-ordination of a sickness response, shifts in motivation and alterations of behaviors that

promote healing and recovery are thereby induced [15]. Symptoms of such inflammation-induced sickness behaviors include anhedonia, fatigue and increased sensitivity to pain, which are also determinants of subjective health perception [16]. Since low-grade inflammation is part of the pathology in major causes of premature mortality, such as cardio-vascular disease (see e.g. [17, 18]), type-2 diabetes [19], obesity [20] and certain types of cancer [21, 22] low-grade inflammation could be one factor linking poor self-rated health with future adverse health outcomes.

In order to investigate whether low-grade inflammation may be implicated in subjective health perception, a row of recent studies have examined the link between increased levels of pro-inflammatory cytokines and poor self-rated health [6-8, 16, 23, 24]. Other studies have examined the association between self-rated health and fibrinogen [25], ESR [26] and of another acute phase reactant, C-reactive protein (CRP)[7, 23, 27, 28]. So far, the evidence of a link between low-grade inflammation and self-rated health is more robust for women as compared to men [6-8, 16, 27], and the strength of the association has been indicated to increase with age [6, 16]. For instance, among 347 women 45 to 90 years old of the general population there was a significant association between IL-6 and poor self-rated health, particularly among those 65 years old and above [6]. In another study, 174 female primary health care patients of 18 years and older who were divided into three age groups, higher TNF-α was significantly associated with poor self-rated health in all groups, and higher IL-1ß and IL-1 receptor antagonist was associated with poor self-rated health in those over 65 years old [16]. Moreover, in 235 middle-aged and elderly women with coronary heart disease, high levels of CRP and IL-6 were associated with poor self-rated health [7].

Among the studies including both men and women, only two have performed sex-based stratified analyses [8, 27] and one study examined the interaction effect of sex and inflammation on self-rated health [28]. A study of 170 female and 89 male primary health

care patients showed a significant independent association between higher IL-1β and TNF-α and poor self-rated health only in women [8], but the lack of association in men could be due to small sample size and low power. Among 11,000 women and 5,000 men, a significant association between CRP and self-rated health remained only in women after adjustment for control factors [27]. However, in a population of 13,236 young adults aged 24-34 years, high sensitivity CRP above 3 mg/L was significantly associated with lower ratings of self-rated health after adjustment for health behaviors, self-reported illness and medication in both men and women. Inclusion of BMI fully attenuated the association between CRP and self-rated health in the women whereas a small but significant association remained in men [28].

The remaining studies encompassing both men and women reported significant associations between IL-6 and self-rated health [23, 24], and between fibrinogen and self-rated health [25] but as these studies are only adjusted for sex it is not clear if this association would be found in the male or female strata only.

The present study aims at investigating low-grade inflammation and subjective health perception in a very large, young and healthy population, mainly free from medical conditions. The hypothesis was that conscripts with elevated ESR levels had rated their health as poorer in this population of late adolescent men, a group that has not yet been investigated in this context.

METHODS

Participants

This study was based on data collected in 1969 to 1970 when 49,321 Swedish men born between 1949 and 1951 (aged 18-21 years) underwent a compulsory 2-day screening

procedure prior to military service. During this time period, only 2-3 % of men eligible for military services were exempted from conscription, mainly due to severe disabilities or severe congenital disorders. All conscripts had answered questionnaires about social background, habits, psychological factors, social adjustment and health status and had been structured-interviewed by a psychologist. Finally, a physician examined all conscripts, and any somatic or psychiatric disorders were diagnosed according to the Swedish version of the International Classification of Disorders, version 8 (ICD-8). The present study was approved by the regional ethics board.

Measures

Self-Rated Health

The conscripts had been asked to assess their health, answering the question: "*In general, would you say your health right now is: Very good, Good, Fair, Poor or Very poor"?* The answers had been rated on a 5-point scale where 1="Very good", 2="Good", 3="Fair", 4="Poor" and 5="Very poor" and was dichotomized into *Good* (1-3) and *Poor* (4 and 5) self-rated health.

Erythrocyte Sedimentation Rate

At physical examination, blood samples had been taken and ESR had been measured according to standard laboratory procedures (Westergren method)[9]. The ESR is affected by the hematocrit (Htc, i.e. the proportion of whole blood made up by erythrocytes), we therefore corrected the ESR values for the hematocrit according to the formula ESR*Htc/45 [29]. Htc-corrected ESR values are used in all analyses and presentations of ESR values. Despite plausible inter-individual genetic variations [30], the upper limit of the normal range of ESR

has, on group level, been found to correspond to the age in years divided by two [31]. The age span of the men included in this study ranged from 18 to 21 years. Based on the highest age included, the normal range was rounded off to <11 mm/hr. Thus, the 3.7 % of the participants with ESR ≥11 mm/hr (n=3,937) were excluded from the analyses. Those with ESR <1 mm/hr (n=1,903) were also excluded in order to reduce error of misclassifications [32]. The remaining 88.2 percent % (n=43,481) of the conscripts had ESR levels >1 < 11 mm/hr and were included in the analyses.

Body Mass Index

The conscripts' height and weight had been measured at the physical examination. Body mass index (BMI) is determined by calculating the ratio of weight to height squared (kg/m^2). Obesity and underweight as measured by very high or very low BMI have independently been associated with poor self-rated health [33] and obesity has been associated with inflammation [34]. BMI was categorized into 4 groups: underweight (BMI<18.5), normal weight (BMI: 18.5-25), overweight (BMI: 25-30) and obesity (BMI>30) and normal weight was used as reference in the logistic regression analyses.

Socioeconomic Position

Parental socioeconomic position (SEP) was used as an indicator of childhood socioeconomic circumstances. Information about socioeconomic circumstances of the conscripts at 9 to 11 years of age was obtained from the National Population and Housing Census from 1960. The conscripts and the head of the household, usually the father, were linked through their personal identification number by Statistics Sweden. Based on the occupation of the head of the household seven socioeconomic groups were identified: (a) unskilled workers, (b) skilled workers, (c) assistant non-manual employees, (d) non-manual

employees at intermediate level, (e) non-manual employees at higher level, (f) farmers, and (g) those not classified into a socioeconomic group. Self-employed persons could not be identified in the census from 1960 where such persons were classified as employed according to occupation. Previous research have shown that childhood SEP is associated with markers of inflammation in adults [35, 36], and a previous study from this sample found a significant association between ESR and SEP [37], why SEP is included in the analyses.

Inflammatory Disease

Presence of one or more of the following medical conditions as registered for each conscript by a physician according to ICD-8 was adjusted for in the analyses: infectious disease, malignancies, lymphatic and haemotopoetic tumors, diabetes mellitus, asthma, gastrointestinal inflammation, hay fever, infection and inflammation in skin, arthritis and rheumatoid arthritis.

Emotion Regulation

The combined questionnaire and interview data had been used by a psychologist to evaluate emotion regulation (then termed 'emotional control') was rated on 5-point scale, based on self-reported anxiety, stress-tolerance, nervous problems, capacity for emotional commitment and control over aggression (a score of 1 to 2 represent *Low* emotion regulation). In a previous study, based on data from the same population, low emotion regulation was a confounding factor in the association between poor self-rated health and mortality [5] and it was also the covariate with the most prominent difference between conscripts with poor SRH and conscripts with good SRH. Persistent negative affect such as anger, anxiety and depression has been associated with inflammation and disease [38, 39, 40], hence the inclusion of emotion regulation in the analyses.

Smoking

Tobacco smoking has been associated with increased systemic inflammation in men [41, 42]. Smoking has also been associated with poor self-rated health [6, 43, 44] and was therefore included in the analyses. The self-reported number of cigarettes smoked per day had been rated on a 4-point scale where 1>20, 2=11-20, 3=1-10 cigarettes per day and 4=non-smoker.

Risky use of alcohol

Risky use of alcohol has been associated with elevated markers of inflammation [45]. Risky use of alcohol was estimated based upon questions on high consumption of alcohol: none vs. at least one of the following indicators– consumption of at least 250 g 100 % alcohol per week; use of alcohol to alleviate a hangover; having been apprehended for drunkenness; being drunk often.

Physical activity

We used active membership in sport clubs as a proxy for physical activity. Exercise has been shown to have anti-inflammatory effects [46], and low physical activity has been associated with worse self-rated health [47].

Statistics

To calculate the association between ESR and self-rated health, logistic regression analysis was used with ESR as the independent variable and self-rated health as the outcome variable. As a second step, the association between ESR serum levels and self-rated health was adjusted separately for background variables BMI, SEP, presence of inflammatory

disease, emotion regulation, smoking, risky use of alcohol and physical activity. Third, in the full model, the association between ESR levels and self-rated health was adjusted for all background variables together. The background variables were treated as categorical variables in the analyses.

An α-value of .05 was used to test for statistical significance. All analyses were performed using SPSS statistics software version 21.

RESULTS

Participant characteristics for conscripts with poor and conscripts with good self-rated health are presented in Table 1. The majority of the conscripts reported their self-rated health as good (96.2 %). Overall, conscripts with poor self-rated health were more likely to report poor health behaviors such as smoking and risky alcohol use and had a higher frequency of low emotion regulation than conscripts with good self-rated health.

was associated with a higher odds for poor self-rated health (OR=1.066 for each unit mm/hr increase in ESR, Table 2). The size of the association and the level of significance were largely unaffected by adjustments for BMI, SEP, inflammatory diseases, emotion regulation, smoking, risky use of alcohol and physical activity (OR=1.077).

DISCUSSION

The aim of this study was to investigate if there is an association between higher level of the inflammatory marker ESR and poor self-rated health in late adolescent men. The results of

this study show that the odds of having poor rather than good self-rated health was elevated by approximately 7 % per for each unit mm/hr increase in ESR.

This pattern was stable when relevant confounders (BMI, SEP, presence of inflammatory disease, emotion regulation, smoking, risky use of alcohol and physical activity) were controlled for. Hence, the present result is consistent with the hypothesis that inflammation is part of a general factor in the psychobiological processes that underpin subjective health perception also in late adolescent men, although the cross-sectional design of the present study precludes conclusions about causality.

The results of the present study are in contrast with the lack of association between inflammatory markers and self-rated health in men in the studies by Lekander and coworkers [8] and Tanno and coworkers [27]. In comparison to the present study, those studies are based on dissimilar methods and populations, with older participants (mean age 59 and 58 years, respectively, compared to 18-21 years in the present study). The study the study by Lekander and coworkers had a considerably smaller sample size and Tanno and coworkers [27] had an Asian population. However, the present results are in concordance with a previous study that demonstrated a small but significant association between CRP and self-rated health in young adult men 24 to 34 years old [28].

Demographic factors and life-style patterns have been associated with both low-grade inflammation and with poor self-rated health; factors that may constitute possible confounders in the association between ESR and self-rated health, such as aging [48], obesity [49], low SEP [37], and smoking [6, 42]. Adjustments for BMI, SEP, inflammatory disease, emotion regulation, smoking, risky alcohol use, and physical activity did not, however, change the association between ESR and self-rated health in the present study suggesting that the association is not dependent on any of the confounding variables. No assessments of sickness behavior were available in the present study and further studies are needed to investigate

sickness behavior as a mediating factor linking inflammatory factors and poor self-rated health. Also, individuals with a higher degree of inflammation did not introduce bias, as all conscripts with an ESR equal to or above 11 mm/hr had been excluded. Unfortunately, data on diet was not available in the present study, which is a factor to take into account in future studies.

Our study sample consisted of 43,431 conscripts encompassing the majority of all Swedish men born in 1949 to 1951. Having a study sample that represents such a large percentage of the population is obviously advantageous in terms of power, but also eliminates the risk for selection bias. In the present material of late adolescent men, the majority of participants were, as expected, healthy; altogether 82.6 % rated their health as "Good" or "Very good". It cannot be excluded that in a current-day sample of young men the included factors would be differently distributed, and that e.g. low-grade inflammation would be more prevalent as obesity, which has been linked with low-grade inflammation [50, 51], almost doubled in prevalence between 1971 and 1993 among Swedish military conscripts [52]. However, the association between ESR and self-rated health in the present study was independent of background factors such as BMI and there is little reason to expect that the putative underlying biological mechanism by which inflammation is associated with subjective health perception would have changed.

Concerning validity, there is some discordance between ESR and other inflammatory markers. For instance ESR has been shown to rise and decrease slower than CRP (see e.g. [53]. However, the dose-responsive and independent relation between self-rated health and ESR in the present study suggests that ESR is a marker for self-rated health, not merely reflecting manifest disease or chronic conditions.

In conclusion, the present study shows for the first time, a significant association between a marker of inflammation and self-rated health in late adolescent men providing evidence of an association between low-grade inflammation and poor self-rated health also in men, as previously demonstrated in women. Data is here provided to further support inflammation as a general factor in the psychobiological processes that underpin subjective health perception across the adult life span.

Contributors ML, TH, BM, AA conceived of the study**.** CW drafted the manuscript. KS and TH performed the statistical analyses. All authors were involved in the discussion of the data and revised the manuscript for intellectual content.

Funding This study has not received funding.

Competing interests None declared.

Data sharing statement No additional data available.

References

1. Grool, A.M., et al., *Self-rated health status as a risk factor for future vascular events and mortality in patients with symptomatic and asymptomatic atherosclerotic disease: the SMART study.* J Intern Med, 2012.
2. DeSalvo, K.B., et al., *Predicting mortality and healthcare utilization with a single question.* Health Serv Res, 2005. **40**(4): p. 1234-46.
3. DeSalvo, K.B., et al., *Mortality prediction with a single general self-rated health question. A meta-analysis.* J Gen Intern Med, 2006. **21**(3): p. 267-75.
4. Idler, E.L. and Y. Benyamini, *Self-rated health and mortality: a review of twenty-seven community studies.* J Health Soc Behav, 1997. **38**(1): p. 21-37.

5. Larsson, D., et al., *Self-rated health and mortality among young men: what is the relation and how may it be explained?* Scandinavian Journal of Public Health, 2002. **30**(4): p. 259-266.
6. Andreasson, A.N., et al., *Inflammation and positive affect are associated with subjective health in women of the general population.* Journal of health psychology, 2012.
7. Janszky, I., et al., *Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease.* Brain, Behavior, and Immunity, 2005. **19**(6): p. 555-563.
8. Lekander, M., et al., *Self-rated health is related to levels of circulating cytokines.* Psychosom Med, 2004. **66**(4): p. 559-63.
9. Saadeh, C., *The erythrocyte sedimentation rate: old and new clinical applications.* Southern medical journal, 1998. **91**(3): p. 220-5.
10. Heinrich, P.C., J.V. Castell, and T. Andus, *Interleukin-6 and the acute phase response.* The Biochemical journal, 1990. **265**(3): p. 621-36.
11. Janeway, C.A., et al., *Induced innate responses to infection*, in *Immunobiology* 2001, Garland Publishing: New York.
12. Hannestad, J., et al., *Glucose metabolism in the insula and cingulate is affected by systemic inflammation in humans.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2012. **53**(4): p. 601-7.
13. Harrison, N.A., et al., *Neural origins of human sickness in interoceptive responses to inflammation.* Biological psychiatry, 2009. **66**(5): p. 415-22.
14. Craig, A.D., *How do you feel? Interoception: the sense of the physiological condition of the body.* Nat Rev Neurosci, 2002. **3**(8): p. 655-66.
15. Dantzer, R., *Cytokine-induced sickness behavior: mechanisms and implications.* Ann N Y Acad Sci, 2001. **933**: p. 222-34.

16. Unden, A.L., et al., *Inflammatory cytokines, behaviour and age as determinants of self-rated health in women.* Clin Sci (Lond), 2007. **112**(6): p. 363-73.

17. Melamed, S., et al., *Association of fear of terror with low-grade inflammation among apparently healthy employed adults.* Psychosom Med, 2004. **66**(4): p. 484-91.

18. Yudkin, J.S., et al., *C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue?* Arterioscler Thromb Vasc Biol, 1999. **19**(4): p. 972-8.

19. Duncan, B.B., et al., *Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study.* Diabetes, 2003. **52**(7): p. 1799-805.

20. Bondia-Pons, I., L. Ryan, and J.A. Martinez, *Oxidative stress and inflammation interactions in human obesity.* Journal of physiology and biochemistry, 2012. **68**(4): p. 701-11.

21. Macarthur, M., G.L. Hold, and E.M. El-Omar, *Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy.* Am J Physiol Gastrointest Liver Physiol, 2004. **286**(4): p. G515-20.

22. Balkwill, F. and A. Mantovani, *Inflammation and cancer: back to Virchow?* Lancet, 2001. **357**(9255): p. 539-45.

23. Christian, L.M., et al., *Poorer self-rated health is associated with elevated inflammatory markers among older adults.* Psychoneuroendocrinology, 2011. **36**(10): p. 1495-504.

24. Cohen, H.J., et al., *The association of plasma IL-6 levels with functional disability in community-dwelling elderly.* Journals of Gerontology. Series A, Biological Sciences & Medical Sciences, 1997. **52**(4): p. M201-8.

25. Fielding, R., et al., *Subjective health and fibrinogen in a healthy Chinese cohort.* Br J Health Psychol, 2004. **9**(Pt 4): p. 523-32.

26. Nilsson, L.-G., et al., *The Betula Prospective Cohort Study: Memory, Health and Aging.* Aging, neuropsych, cogn 1997. **4**(1): p. 1-32.

27. Tanno, K., et al., *Poor self-rated health is significantly associated with elevated C-reactive protein levels in women, but not in men, in the Japanese general population.* Journal of psychosomatic research, 2012. **73**(3): p. 225-31.

28. Shanahan, L., et al., *Self-rated health and C-reactive protein in young adults.* Brain Behav Immun, 2014. **36**: p. 139-46.

29. Borawski, J. and M. Mysliwiec, *The hematocrit-corrected erythrocyte sedimentation rate can be useful in diagnosing inflammation in hemodialysis patients.* Nephron, 2001. **89**(4): p. 381-3.

30. Kullo, I.J., et al., *Complement receptor 1 gene variants are associated with erythrocyte sedimentation rate.* Am J Hum Genet, 2011. **89**(1): p. 131-8.

31. Miller, A., M. Green, and D. Robinson, *Simple rule for calculating normal erythrocyte sedimentation rate.* British medical journal, 1983. **286**(6361): p. 266.

32. Toss, F., A. Nordstrom, and P. Nordstrom, *Inflammation in young adulthood is associated with myocardial infarction later in life.* Am Heart J, 2013. **165**(2): p. 164-9.

33. Molarius, A., et al., *Socioeconomic conditions, lifestyle factors, and self-rated health among men and women in Sweden.* Eur J Public Health, 2007. **17**(2): p. 125-33.

34. Kantor, E. D., et al., *Lifestyle factors and inflammation: associations by body mass index.* PLoS One, 2013. 8(7), e67833.

35. Miller, G. and E. Chen, *Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence.* Psychosomatic medicine, 2007. **69**(5): p. 402-9.

36. Pollitt, R.A., et al., *Early-life and adult socioeconomic status and inflammatory risk markers in adulthood.* European journal of epidemiology, 2007. **22**(1): p. 55-66.

37. Karlsson, H., et al., *Association between erythrocyte sedimentation rate and IQ in Swedish males aged 18–20.* Brain, Behavior, and Immunity, 2010. **24**(6): p. 868-873.

38. Miller, G. E., et al,. *Cynical hostility, depressive symptoms, and the expression of inflammatory risk markers for coronary heart disease.* J Behav Med, 2013. 26(6): p. 501-515.

39. Pitsavos, C., et al., *Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study.* Atherosclerosis, 2006. 185(2): p. 320-326

40. Coccaro, E. F., Lee, R., & Coussons-Read, M. (2014). *Elevated plasma inflammatory markers in individuals with intermittent explosive disorder and correlation with aggression in humans.* JAMA Psychiatry, 71(2): p. 158-165.

41. Frohlich, M., et al., *Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95).* Eur Heart J, 2003. **24**(14): p. 1365-72.

42. Lao, X.Q., et al., *Smoking, smoking cessation and inflammatory markers in older Chinese men: The Guangzhou Biobank Cohort Study.* Atherosclerosis, 2009. **203**(1): p. 304-10.

43. Kirkland, S., L. Greaves, and P. Devichand, *Gender Differences in Smoking and Self Reported Indicators of Health.* BMC Womens Health, 2004. **4 Suppl 1**: p. S7.

44. Wang, M.P., et al., *Smoking is associated with poor self-rated health among adolescents in Hong Kong.* Nicotine Tob Res, 2012. **14**(6): p. 682-7.

45. Imhof, A., et al., *Effect of alcohol consumption on systemic markers of inflammation.* Lancet, 2001. 357(9258): p. 763-767.

46. Ford, E. S. *Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults.* Epidemiology, 2002. 13(5): p. 561-568

47. Manderbacka, K., Lahelma, E., & Martikainen, P. *Examining the continuity of self-rated health.* Int J Epidemiol, 1998. 27(2): p. 208-213.

48. Giunta, S., *Is inflammaging an auto[innate]immunity subclinical syndrome?* Immunity & ageing : I & A, 2006. **3**: p. 12.

49. Yudkin, J.S., et al., *Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link?* Atherosclerosis, 2000. **148**(2): p. 209-14.

50. Greenberg, A.S. and M.S. Obin, *Obesity and the role of adipose tissue in inflammation and metabolism.* Am J Clin Nutr, 2006. **83**(2): p. 461S-465S.

51. Gregor, M.F. and G.S. Hotamisligil, *Inflammatory mechanisms in obesity.* Annu Rev Immunol, 2011. **29**: p. 415-45.

52. Rasmussen, F., M. Johansson, and H.O. Hansen, *Trends in overweight and obesity among 18-year-old males in Sweden between 1971 and 1995.* Acta paediatrica, 1999. **88**(4): p. 431-7.

53. Bilgen, O., et al., *C-reactive protein values and erythrocyte sedimentation rates after total hip and total knee arthroplasty.* J Int Med Res, 2001. **29**(1): p. 7-12.

BMJ Open

IS POOR SELF-RATED HEALTH ASSOCIATED WITH LOW-GRADE INFLAMMATION IN A CROSS-SECTIONAL STUDY OF 43,110 LATE ADOLESCENT MEN OF THE GENERAL POPULATION?

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009440.R2
Article Type:	Research
Date Submitted by the Author:	29-Jan-2016
Complete List of Authors:	Warnoff, Carin; Karolinska Institutet, Clinical Neuroscience, Division of Psychology Lekander, Mats; Stress Research Institute, Stockholm University Hemmingsson, Tomas; Karolinska Institutet, Institute of Environmental Medicine Sorjonen, Kimmo; Karolinska institutet, Department of Clinical Neurosciences, Division of Psychology Melin, Bo; Karolinska institutet, Department of Clinical Neurosciences, Division of Psychology Andreasson, Anna; Stress Research Institute, Stockholm University; Karolinska Institutet, Neurobiology, Care Sciences and Society
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	Epidemiology , MENTAL HEALTH, IMMUNOLOGY, Public health < INFECTIOUS DISEASES

IS POOR SELF-RATED HEALTH ASSOCIATED WITH LOW-GRADE INFLAMMATION IN A CROSS-SECTIONAL STUDY OF 43,110 LATE ADOLESCENT MEN OF THE GENERAL POPULATION?

Anna Andreasson (corresponding author)

Stress Research Institute

Stockholm University

SE-106 91 Stockholm

Sweden

Phone: +46 (0)8 5537 8903

Fax: +46 (0)8 5537 8900

E-mail: anna.andreasson@su.se

Carin Warnoff[1], Mats Lekander[1,2,3], Tomas Hemmingsson[4,5], Kimmo Sorjonen[1], Bo Melin[1], Anna Andreasson[2,3,6]

[1] Department for Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

[2] Stress Research Institute, Stockholm University, Stockholm, Sweden

[3] Osher Center for Integrative Medicine, Karolinska Institutet, Stockholm, Sweden

[4] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[5] Centre for Social Research on Alcohol and Drugs, Stockholm University, Stockholm, Sweden.

[6] Division of Family Medicine, Karolinska Institutet, Huddinge, Sweden

Self-rated health and inflammation in adolescent men

Key words: self-rated health, erythrocyte sedimentation rate, low-grade inflammation, military conscripts

ABSTRACT

Objective

Self-rated health is a powerful predictor of long-term health and mortality, hence the importance of a better understanding of its biological determinants. Previous studies have shown that low-grade inflammation is associated with poor self-rated health in clinical and healthy populations, but the evidence is sparse in men and lacks completely for men in late adolescence. The aim of this study was to investigate the association between low-grade inflammation and self-rated health among conscripts. It was hypothesized that high levels of inflammatory factors would be associated with poor self-rated health.

Design

Data from 49,321 men (18-21 years) conscribed to military service in 1969 and 1970 was used. Inflammation had been measured through erythrocyte sedimentation rate (ESR). Self-rated health had been assessed on a five-point scale and was dichotomized into *Good* (“Very good”/”Good”/”Fair”) versus *Poor* (”Poor”/Very poor”). Data from 43,110 conscripts with normal levels of ESR and who reported self-rated health remained after exclusion of those with ESR <1 and >11 mm/hr. Associations were calculated using logistic regression analyses. Adjustments were made for body mass index, socioeconomic position, inflammatory disease, emotion regulation, smoking, risky use of alcohol and physical activity.

Results

High levels of ESR was associated with a higher odds for poor self-rated health (OR:1.077 for each unit mm/hr increase in ESR, 95% confidence interval: 1.049-1.105).

Conclusion

The present study shows for the first time, a significant association between a marker of inflammation and self-rated health in late adolescent men providing evidence of an association between low-grade inflammation and poor self-rated health also in men, providing further support for inflammation as part of a general psychobiological process that underpins subjective health perception.

Strengths and limitations of this study

- This is the first study to investigate the association between low-grade inflammation and self-rated health in a large sample of late adolescent men.
- Using data (n=43,110) from the national military conscription register, encompassing nearly all the Swedish men born in 1949-1951, eliminates selection bias.
- Adjustments were made for life-style patterns, demographic factors and psychological disposition.
- The cross-sectional design precludes conclusions about causality.

INTRODUCTION

Self-rated health is a single-item measure of an individual's perceived health status. A number of studies show that poor self-rated health predicts future adverse health outcomes, such as cardio-vascular events [1] and healthcare utilization [2], and is coupled to a near two-fold risk of premature mortality [3-5]. The predictive qualities of self-rated health remain after controlling for objective health and social and demographic risk factors [4].

Although the mechanisms that link self-rated health to future objectively verified ill-health are largely unknown, recent studies point at inflammation as an important determinant of how an individual perceives her global health status [6-8]. As part of the inflammatory response to acute infection or injury, pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α drive the acute phase response by increasing levels of acute phase proteins [9]. One of these proteins, fibrinogen, is a coagulation factor and is reflected by erythrocyte sedimentation rate (ESR). When inflammation is present, the fibrinogen causes erythrocytes to clot in rolls, thus sinking faster through a test tube, resulting in an increased ESR [10, 11]. Compared to other tests of inflammation, ESR is a simple and cost efficient way of establishing the presence of the acute phase reactants, and, indirectly, the activity of pro-inflammatory cytokines [9] making it a suitable marker of inflammation when collecting large amount of data.

One hypothesis to explain the observed association between low-grade inflammation and poor self-rated health is that inflammation related signals reach areas in the brain, including the insular cortex and the anterior cingulate cortex [12, 13], i.e. areas that are important in interpretation of bodily state and homeostatic changes [14]. As part of co-ordination of a sickness response, shifts in motivation and alterations of behaviours that promote healing and recovery are thereby induced [15]. Symptoms of such inflammation-

induced sickness behaviours include anhedonia, fatigue and increased sensitivity to pain, which are also determinants of subjective health perception [16]. Since low-grade inflammation is part of the pathology in major causes of premature mortality, such as cardio-vascular disease (see e.g. [17, 18]), type-2 diabetes [19], obesity [20] and certain types of cancer [21, 22] low-grade inflammation could be one factor linking poor self-rated health with future adverse health outcomes.

In order to investigate whether low-grade inflammation may be implicated in subjective health perception, a row of recent studies have examined the link between increased levels of pro-inflammatory cytokines and poor self-rated health [6-8, 16, 23, 24]. Other studies have examined the association between self-rated health and fibrinogen [25], ESR [26] and of another acute phase reactant, C-reactive protein (CRP)[7, 23, 27, 28]. So far, the evidence of a link between low-grade inflammation and self-rated health is more robust for women as compared to men [6-8, 16, 27], and the strength of the association has been indicated to increase with age [6, 16]. For instance, among 347 women 45 to 90 years old of the general population there was a significant association between IL-6 and poor self-rated health, particularly among those 65 years old and above [6]. In another study, 174 female primary health care patients of 18 years and older who were divided into three age groups, higher TNF-α was significantly associated with poor self-rated health in all groups, and higher IL-1ß and IL-1 receptor antagonist was associated with poor self-rated health in those over 65 years old [16]. Moreover, in 235 middle-aged and elderly women with coronary heart disease, high levels of CRP and IL-6 were associated with poor self-rated health [7].

Among the studies including both men and women, only two have performed sex-based stratified analyses [8, 27] and one study examined the interaction effect of sex and inflammation on self-rated health [28]. A study of 170 female and 89 male primary health care patients showed a significant independent association between higher IL-1β and TNF-α

and poor self-rated health only in women [8], but the lack of association in men could be due to small sample size and low power. Among 11,000 women and 5,000 men, a significant association between CRP and self-rated health remained only in women after adjustment for control factors [27]. However, in a population of 13,236 young adults aged 24-34 years, high sensitivity CRP above 3 mg/L was significantly associated with lower ratings of self-rated health after adjustment for health behaviours, self-reported illness and medication in both men and women. Inclusion of BMI fully attenuated the association between CRP and self-rated health in women whereas a small but significant association remained in men [28].

The remaining studies encompassing both men and women reported significant associations between IL-6 and self-rated health [23, 24], and between fibrinogen and self-rated health [25] but as these studies are only adjusted for sex it is not clear if this association would be found in the male or female strata only.

The present study aims at investigating low-grade inflammation and subjective health perception in a very large, young and healthy population, mainly free from medical conditions. The hypothesis was that conscripts with elevated ESR levels had rated their health as poorer in this population of late adolescent men, a group that has not yet been investigated in this context.

METHODS

Study design

This cross-sectional study was based on data collected in 1969 to 1970 when 49,321 Swedish men born between 1949 and 1951 (aged 18-21 years) underwent a compulsory 2-day

screening procedure prior to military service. During this time period, only 2-3 % of men eligible for military services were exempted from conscription, mainly due to severe disabilities or severe congenital disorders. All conscripts had answered questionnaires about social background, habits, psychological factors, social adjustment and health status and had been structured-interviewed by a psychologist. Finally, a physician examined all conscripts, and any somatic or psychiatric disorders were diagnosed according to the Swedish version of the International Classification of Disorders, version 8 (ICD-8). The present study was approved by the regional ethics board.

Measures

Self-Rated Health

The conscripts had been asked to assess their health, answering the question: "*In general, would you say your health right now is: Very good, Good, Fair, Poor or Very poor"?* The answers had been rated on a 5-point scale where 1="Very good", 2="Good", 3="Fair", 4="Poor" and 5="Very poor" and was dichotomized into *Good* (1-3) and *Poor* (4 and 5) self-rated health.

Erythrocyte Sedimentation Rate

At physical examination, blood samples had been taken and ESR had been measured according to standard laboratory procedures (Westergren method)[9]. The ESR is affected by the hematocrit (Htc, i.e. the proportion of whole blood made up by erythrocytes), we therefore corrected the ESR values for the hematocrit according to the formula ESR*Htc/45 [29]. Htc-corrected ESR values are used in all analyses and presentations of ESR values. Despite plausible inter-individual genetic variations [30], the upper limit of the normal range of ESR

has, on group level, been found to correspond to the age in years divided by two [31]. The age span of the men included in this study ranged from 18 to 21 years. Based on the highest age included, the normal range was rounded off to <11 mm/hr. Thus, the 3.7 % of the participants with ESR ≥11 mm/hr (n=3,937) were excluded from the analyses out of whom 168 had rated their self-rated health as poor, 3,655 had rated their self-rated health as good, and 114 had missing self-rated health values. Those with ESR <1 mm/hr (n=1,903) were also excluded in order to reduce error of misclassifications [32] out of whom 148 had rated their self-rated health as poor, 1,739 as good, and 16 had missing values. A total of 43,110 out of the remaining 43,481 conscripts with ESR levels ≥1 and < 11 mm/hr had data on self-rated health and were included in the analyses.

Body Mass Index

The conscripts' height and weight had been measured at the physical examination. Body mass index (BMI) is determined by calculating the ratio of weight to height squared (kg/m^2). Obesity and underweight as measured by very high or very low BMI have independently been associated with poor self-rated health [33] and obesity has been associated with inflammation [34]. BMI was categorized into 4 groups: underweight (BMI<18.5), normal weight (BMI: 18.5-25), overweight (BMI: 25-30) and obesity (BMI>30) and normal weight was used as reference in the logistic regression analyses.

Socioeconomic Position

Parental socioeconomic position (SEP) was used as an indicator of childhood socioeconomic circumstances. Information about socioeconomic circumstances of the conscripts at 9 to 11 years of age was obtained from the National Population and Housing Census from 1960. The conscripts and the head of the household, usually the father, were

linked through their personal identification number by Statistics Sweden. Based on the occupation of the head of the household seven socioeconomic groups were identified: (a) unskilled workers, (b) skilled workers, (c) assistant non-manual employees, (d) non-manual employees at intermediate level, (e) non-manual employees at higher level, (f) farmers, and (g) those not classified into a socioeconomic group. Self-employed persons could not be identified in the census from 1960 where such persons were classified as employed according to occupation. Previous research have shown that childhood SEP is associated with markers of inflammation in adults [35, 36], and a previous study from this sample found a significant association between ESR and SEP [37], why SEP is included in the analyses.

Inflammatory Disease

Presence of one or more of the following medical conditions as registered for each conscript by a physician according to ICD-8 was adjusted for in the analyses: infectious disease, malignancies, lymphatic and haemotopoetic tumors, diabetes mellitus, asthma, gastrointestinal inflammation, hay fever, infection and inflammation in skin, arthritis and rheumatoid arthritis.

Emotion Regulation

The combined questionnaire and interview data had been used by a psychologist to rate emotion regulation (then termed ’emotional control’) on 5-point scale, based on self-reported anxiety, stress-tolerance, nervous problems, capacity for emotional commitment and control over aggression (a score of 1 to 2 represent *Low* emotion regulation). In a previous study, based on data from the same population, low emotion regulation was a confounding factor in the association between poor self-rated health and mortality [5] and it was also the covariate with the most prominent difference between conscripts with poor and conscripts with good

self-rated health. Persistent negative affect such as anger, anxiety and depression has been associated with inflammation and disease [38, 39, 40], hence the inclusion of emotion regulation in the analyses.

Smoking

Tobacco smoking has been associated with increased systemic inflammation in men [41, 42]. Smoking has also been associated with poor self-rated health [6, 43, 44] and was therefore included in the analyses. The self-reported number of cigarettes smoked per day had been rated on a 4-point scale where 1>20, 2=11-20, 3=1-10 cigarettes per day and 4=non-smoker.

Risky use of alcohol

Risky use of alcohol has been associated with elevated markers of inflammation [45]. Risky use of alcohol was estimated based upon questions on high consumption of alcohol: none vs. at least one of the following indicators– consumption of at least 250 g 100 % alcohol per week; use of alcohol to alleviate a hangover; having been apprehended for drunkenness; being drunk often.

Physical activity

We used active membership in sport clubs as a proxy for physical activity. Exercise has been shown to have anti-inflammatory effects [46], and low physical activity has been associated with worse self-rated health [47].

Statistics

To calculate the association between ESR and self-rated health, logistic regression analysis was used with ESR as the independent variable and self-rated health as the outcome

variable. As a second step, the association between ESR serum levels and self-rated health was adjusted separately for background variables BMI, SEP, presence of inflammatory disease, emotion regulation, smoking, risky use of alcohol and physical activity. Third, in the full model, the association between ESR levels and self-rated health was adjusted for all background variables together. The background variables were treated as categorical variables in the analyses. Data from 43,110 conscripts with self-rated health data and normal levels of ESR were included in the analyses. Missing values for background variables were excluded listwise.

An α-value of .05 was used to test for statistical significance. All analyses were performed using SPSS statistics software version 21.

RESULTS

Participant characteristics for conscripts with poor and conscripts with good self-rated health are presented in Table 1. The majority of the conscripts reported their self-rated health as good (96.2 %). Overall, conscripts with poor self-rated health were more likely to report poor health behaviors such as smoking and risky alcohol use and had a higher frequency of low emotion regulation than conscripts with good self-rated health.

Table 1. *Participant characteristics separately for men with poor self-rated health and men with good self-rated health. Group differences in frequencies have been tested with Chi Square test and differences in means with t-tests.*

	Self-rated health		
Variable/category	Poor	Good	
	n=1,618	n=41,492	
			χ^2
BMI			
<18.5	18.2	13.4	31.01*
18.5-25.0	74.4	80.0	29.32*
25.0-30.0	6.5	5.8	1.32
>30.0	0.8	0.8	0.00
Socioeconomic position (%)			
Worker, unskilled	32.6	33.5	0.61
Worker, skilled	21.9	21.5	0.21
Non-manual, assistant	10.0	10.1	0.03
Non-manual, intermediate	18.5	16.7	3.80
Non-manual, higher	5.7	5.1	1.26
Farmer	8.3	10.9	10.48*
Non-classified	2.9	2.2	3.04
Inflammatory disease (%)	22.6	8.5	377.98*
Low emotion regulation (%)	71.2	28.6	1313.11*
Smoking (%)			
> 20 cigarettes/day	14.5	3.2	555.13*
11-20 cigarettes/day	31.7	23.0	64.63*

1-10 cigarettes/day	25.1	32.2	35.34*
Non smoker	28.7	41.6	104.82*
Risky use of alcohol (%)	29.3	15.2	191.76*
Physical activity (%)	24.7	37.0	102.49*
			t
ESR, M (SD)	2.98 (2.19)	2.70 (1.98)	5.58*
BMI, M (SD)	20.79 (2.73)	21.00 (2.57)	-3.26*

*$p<.001$

BMI: body mass index, ESR: erythrocyte sedimentation rate.

High levels of ESR was associated with a higher odds for poor self-rated health (OR=1.066 for each unit mm/hr increase in ESR, Table 2). The size of the association and the level of significance were largely unaffected by adjustments for BMI, SEP, inflammatory diseases, emotion regulation, smoking, risky use of alcohol and physical activity (OR=1.077).

Table 2. *Crude and adjusted effects of ESR on the odds to have very poor/poor rather than fair/good/very good self-rated health.*

	Odds ratio (95% CI)	N
Crude	1.066 (1.043-1.091)	43,110
Adjusted for individual background variables		
BMI	1.064 (1.040-1.088)	43,067
Socioeconomic position	1.069 (1.045-1.093)	43,110
Inflammatory disease	1.066 (1.042-1.091)	43,110
Emotion regulation	1.070 (1.046-1.096)	42,930
Smoking	1.071 (1.047-1.096)	42,555
Risky use of alcohol	1.066 (1.039-1.093)	35,801
Physical activity	1.067 (1.043-1.091)	43,110
Adjusted for all background variables	1.077 (1.049-1.105)	35,553

ESR: erythrocyte sedimentation rate, BMI: body mass index.

DISCUSSION

The aim of this study was to investigate if there is an association between higher level of the inflammatory marker ESR and poor self-rated health in late adolescent men. The results of this study show that the odds of having poor rather than good self-rated health was elevated by approximately 7 % per for each unit mm/hr increase in ESR.

This pattern was stable when relevant confounders (BMI, SEP, presence of inflammatory disease, emotion regulation, smoking, risky use of alcohol and physical activity) were controlled for. Hence, the present result is consistent with the hypothesis that inflammation is part of a general factor in the psychobiological processes that underpin subjective health perception also in late adolescent men, although the cross-sectional design of the present study precludes conclusions about causality.

The results of the present study are in contrast with the lack of association between inflammatory markers and self-rated health in men in the studies by Lekander and co-workers [8] and Tanno and co-workers [27]. In comparison to the present study, those studies are based on dissimilar methods and populations, with older participants (mean age 59 and 58 years, respectively, compared to 18-21 years in the present study). The study by Lekander and co-workers had a considerably smaller sample size and Tanno and co-workers [27] had an Asian population. However, the present results are in concordance with a previous study that demonstrated a small but significant association between CRP and self-rated health in young adult men 24 to 34 years old [28].

Demographic factors and life-style patterns have been associated with both low-grade inflammation and with poor self-rated health; factors that may constitute possible confounders in the association between ESR and self-rated health, such as aging [48], obesity [49], low SEP [37], and smoking [6, 42]. Adjustments for BMI, SEP, inflammatory disease, emotion regulation, smoking, risky alcohol use, and physical activity did not, however, change the association between ESR and self-rated health in the present study suggesting that the association is not dependent on any of the confounding variables. No assessments of sickness behaviour were available in the present study and further studies are needed to investigate sickness behaviour as a mediating factor linking inflammatory factors and poor self-rated health. Also, individuals with a higher degree of inflammation did not introduce bias, as all

conscripts with an ESR equal to or above 11 mm/hr had been excluded. Unfortunately, data on diet was not available in the present study, which is a factor to take into account in future studies.

Our study sample consisted of 43,110 conscripts encompassing the majority of all Swedish men born in 1949 to 1951. Having a study sample that represents such a large percentage of the population is obviously advantageous in terms of power, but also eliminates the risk for selection bias. In the present material of late adolescent men, the majority of participants were, as expected, healthy; altogether 82.6 % rated their health as "Good" or "Very good". It cannot be excluded that in a current-day sample of young men the included factors would be differently distributed, and that e.g. low-grade inflammation would be more prevalent as obesity, which has been linked with low-grade inflammation [50, 51], almost doubled in prevalence between 1971 and 1993 among Swedish military conscripts [52]. However, the association between ESR and self-rated health in the present study was independent of background factors such as BMI and there is little reason to expect that the putative underlying biological mechanism by which inflammation is associated with subjective health perception would have changed.

Concerning validity, there is some discordance between ESR and other inflammatory markers. For instance ESR has been shown to rise and decrease slower than CRP (see e.g. [53]. However, the independent relation between self-rated health and ESR in the present study suggests that ESR is a marker for self-rated health, not merely reflecting manifest disease or chronic conditions.

In conclusion, the present study shows for the first time, a significant association between a marker of inflammation and self-rated health in late adolescent men providing evidence of an association between low-grade inflammation and poor self-rated health also in

men, as previously demonstrated in women. Data is here provided to further support inflammation as a general factor in the psychobiological processes that underpin subjective health perception across the adult life span.

Contributors: ML, TH, BM, AA conceived of the study. CW drafted the manuscript. KS and TH performed the statistical analyses. All authors were involved in the discussion of the data and revised the manuscript for intellectual content.

Funding: This study has not received funding.

Competing interests: None declared.

Data sharing statement: No additional data available.

REFERENCES

1. Grool, A.M., et al., *Self-rated health status as a risk factor for future vascular events and mortality in patients with symptomatic and asymptomatic atherosclerotic disease: the SMART study.* J Intern Med, 2012.
2. DeSalvo, K.B., et al., *Predicting mortality and healthcare utilization with a single question.* Health Serv Res, 2005. **40**(4): p. 1234-46.
3. DeSalvo, K.B., et al., *Mortality prediction with a single general self-rated health question. A meta-analysis.* J Gen Intern Med, 2006. **21**(3): p. 267-75.
4. Idler, E.L. and Y. Benyamini, *Self-rated health and mortality: a review of twenty-seven community studies.* J Health Soc Behav, 1997. **38**(1): p. 21-37.
5. Larsson, D., et al., *Self-rated health and mortality among young men: what is the relation and how may it be explained?* Scandinavian Journal of Public Health, 2002. **30**(4): p. 259-266.

6. Andreasson, A.N., et al., *Inflammation and positive affect are associated with subjective health in women of the general population.* Journal of health psychology, 2012.
7. Janszky, I., et al., *Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease.* Brain, Behavior, and Immunity, 2005. **19**(6): p. 555-563.
8. Lekander, M., et al., *Self-rated health is related to levels of circulating cytokines.* Psychosom Med, 2004. **66**(4): p. 559-63.
9. Saadeh, C., *The erythrocyte sedimentation rate: old and new clinical applications.* Southern medical journal, 1998. **91**(3): p. 220-5.
10. Heinrich, P.C., J.V. Castell, and T. Andus, *Interleukin-6 and the acute phase response.* The Biochemical journal, 1990. **265**(3): p. 621-36.
11. Janeway, C.A., et al., *Induced innate responses to infection*, in *Immunobiology* 2001, Garland Publishing: New York.
12. Hannestad, J., et al., *Glucose metabolism in the insula and cingulate is affected by systemic inflammation in humans.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2012. **53**(4): p. 601-7.
13. Harrison, N.A., et al., *Neural origins of human sickness in interoceptive responses to inflammation.* Biological psychiatry, 2009. **66**(5): p. 415-22.
14. Craig, A.D., *How do you feel? Interoception: the sense of the physiological condition of the body.* Nat Rev Neurosci, 2002. **3**(8): p. 655-66.
15. Dantzer, R., *Cytokine-induced sickness behavior: mechanisms and implications.* Ann N Y Acad Sci, 2001. **933**: p. 222-34.
16. Unden, A.L., et al., *Inflammatory cytokines, behaviour and age as determinants of self-rated health in women.* Clin Sci (Lond), 2007. **112**(6): p. 363-73.

17. Melamed, S., et al., *Association of fear of terror with low-grade inflammation among apparently healthy employed adults.* Psychosom Med, 2004. **66**(4): p. 484-91.

18. Yudkin, J.S., et al., *C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue?* Arterioscler Thromb Vasc Biol, 1999. **19**(4): p. 972-8.

19. Duncan, B.B., et al., *Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study.* Diabetes, 2003. **52**(7): p. 1799-805.

20. Bondia-Pons, I., L. Ryan, and J.A. Martinez, *Oxidative stress and inflammation interactions in human obesity.* Journal of physiology and biochemistry, 2012. **68**(4): p. 701-11.

21. Macarthur, M., G.L. Hold, and E.M. El-Omar, *Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy.* Am J Physiol Gastrointest Liver Physiol, 2004. **286**(4): p. G515-20.

22. Balkwill, F. and A. Mantovani, *Inflammation and cancer: back to Virchow?* Lancet, 2001. **357**(9255): p. 539-45.

23. Christian, L.M., et al., *Poorer self-rated health is associated with elevated inflammatory markers among older adults.* Psychoneuroendocrinology, 2011. **36**(10): p. 1495-504.

24. Cohen, H.J., et al., *The association of plasma IL-6 levels with functional disability in community-dwelling elderly.* Journals of Gerontology. Series A, Biological Sciences & Medical Sciences, 1997. **52**(4): p. M201-8.

25. Fielding, R., et al., *Subjective health and fibrinogen in a healthy Chinese cohort.* Br J Health Psychol, 2004. **9**(Pt 4): p. 523-32.

26. Nilsson, L.-G., et al., *The Betula Prospective Cohort Study: Memory, Health and Aging.* Aging, neuropsych, cogn 1997. **4**(1): p. 1-32.
27. Tanno, K., et al., *Poor self-rated health is significantly associated with elevated C-reactive protein levels in women, but not in men, in the Japanese general population.* Journal of psychosomatic research, 2012. **73**(3): p. 225-31.
28. Shanahan, L., et al., *Self-rated health and C-reactive protein in young adults.* Brain Behav Immun, 2014. **36**: p. 139-46.
29. Borawski, J. and M. Mysliwiec, *The hematocrit-corrected erythrocyte sedimentation rate can be useful in diagnosing inflammation in hemodialysis patients.* Nephron, 2001. **89**(4): p. 381-3.
30. Kullo, I.J., et al., *Complement receptor 1 gene variants are associated with erythrocyte sedimentation rate.* Am J Hum Genet, 2011. **89**(1): p. 131-8.
31. Miller, A., M. Green, and D. Robinson, *Simple rule for calculating normal erythrocyte sedimentation rate.* British medical journal, 1983. **286**(6361): p. 266.
32. Toss, F., A. Nordstrom, and P. Nordstrom, *Inflammation in young adulthood is associated with myocardial infarction later in life.* Am Heart J, 2013. **165**(2): p. 164-9.
33. Molarius, A., et al., *Socioeconomic conditions, lifestyle factors, and self-rated health among men and women in Sweden.* Eur J Public Health, 2007. **17**(2): p. 125-33.
34. Kantor, E. D., et al., *Lifestyle factors and inflammation: associations by body mass index.* PLoS One, 2013. 8(7), e67833.
35. Miller, G. and E. Chen, *Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence.* Psychosomatic medicine, 2007. **69**(5): p. 402-9.
36. Pollitt, R.A., et al., *Early-life and adult socioeconomic status and inflammatory risk markers in adulthood.* European journal of epidemiology, 2007. **22**(1): p. 55-66.

37. Karlsson, H., et al., *Association between erythrocyte sedimentation rate and IQ in Swedish males aged 18–20.* Brain, Behavior, and Immunity, 2010. **24**(6): p. 868-873.

38. Miller, G. E., et al,. *Cynical hostility, depressive symptoms, and the expression of inflammatory risk markers for coronary heart disease.* J Behav Med, 2013. 26(6): p. 501-515.

39. Pitsavos, C., et al., *Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study.* Atherosclerosis, 2006. 185(2): p. 320-326

40. Coccaro, E. F., Lee, R., & Coussons-Read, M. (2014). *Elevated plasma inflammatory markers in individuals with intermittent explosive disorder and correlation with aggression in humans.* JAMA Psychiatry, 71(2): p. 158-165.

41. Frohlich, M., et al., *Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95).* Eur Heart J, 2003. **24**(14): p. 1365-72.

42. Lao, X.Q., et al., *Smoking, smoking cessation and inflammatory markers in older Chinese men: The Guangzhou Biobank Cohort Study.* Atherosclerosis, 2009. **203**(1): p. 304-10.

43. Kirkland, S., L. Greaves, and P. Devichand, *Gender Differences in Smoking and Self Reported Indicators of Health.* BMC Womens Health, 2004. **4 Suppl 1**: p. S7.

44. Wang, M.P., et al., *Smoking is associated with poor self-rated health among adolescents in Hong Kong.* Nicotine Tob Res, 2012. **14**(6): p. 682-7.

45. Imhof, A., et al., *Effect of alcohol consumption on systemic markers of inflammation.* Lancet, 2001. 357(9258): p. 763-767.

46. Ford, E. S. *Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults.* Epidemiology, 2002. 13(5): p. 561-568

47. Manderbacka, K., Lahelma, E., & Martikainen, P. *Examining the continuity of self-rated health.* Int J Epidemiol, 1998. 27(2): p. 208-213.

48. Giunta, S., *Is inflammaging an auto[innate]immunity subclinical syndrome?* Immunity & ageing : I & A, 2006. **3**: p. 12.

49. Yudkin, J.S., et al., *Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link?* Atherosclerosis, 2000. **148**(2): p. 209-14.

50. Greenberg, A.S. and M.S. Obin, *Obesity and the role of adipose tissue in inflammation and metabolism.* Am J Clin Nutr, 2006. **83**(2): p. 461S-465S.

51. Gregor, M.F. and G.S. Hotamisligil, *Inflammatory mechanisms in obesity.* Annu Rev Immunol, 2011. **29**: p. 415-45.

52. Rasmussen, F., M. Johansson, and H.O. Hansen, *Trends in overweight and obesity among 18-year-old males in Sweden between 1971 and 1995.* Acta paediatrica, 1999. **88**(4): p. 431-7.

53. Bilgen, O., et al., *C-reactive protein values and erythrocyte sedimentation rates after total hip and total knee arthroplasty.* J Int Med Res, 2001. **29**(1): p. 7-12.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1 OK	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 OK	Explain the scientific background and rationale for the investigation being reported
Objectives	3 OK	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 OK	Present key elements of study design early in the paper
Setting	5 OK	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 OK	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7 OK	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* OK	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 OK	Describe any efforts to address potential sources of bias
Study size	10 OK	Explain how the study size was arrived at
Quantitative variables	11 OK	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 OK	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13* OK	**(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* OK	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15* OK	Report numbers of outcome events or summary measures
Main results	16 OK	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17 OK	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 OK	Summarise key results with reference to study objectives
Limitations	19 OK	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 OK	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 OK	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 OK	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

IS POOR SELF-RATED HEALTH ASSOCIATED WITH LOW-GRADE INFLAMMATION IN 43,110 LATE ADOLESCENT MEN OF THE GENERAL POPULATION?: A CROSS-SECTIONAL STUDY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009440.R3
Article Type:	Research
Date Submitted by the Author:	28-Feb-2016
Complete List of Authors:	Warnoff, Carin; Karolinska Institutet, Clinical Neuroscience, Division of Psychology Lekander, Mats; Stress Research Institute, Stockholm University Hemmingsson, Tomas; Karolinska Institutet, Institute of Environmental Medicine Sorjonen, Kimmo; Karolinska institutet, Department of Clinical Neurosciences, Division of Psychology Melin, Bo; Karolinska institutet, Department of Clinical Neurosciences, Division of Psychology Andreasson, Anna; Stress Research Institute, Stockholm University; Karolinska Institutet, Neurobiology, Care Sciences and Society
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	Epidemiology , MENTAL HEALTH, IMMUNOLOGY, Public health < INFECTIOUS DISEASES

IS POOR SELF-RATED HEALTH ASSOCIATED WITH LOW-GRADE INFLAMMATION IN 43,110 LATE ADOLESCENT MEN OF THE GENERAL POPULATION?: A CROSS-SECTIONAL STUDY

Anna Andreasson

Stress Research Institute

Stockholm University

SE-106 91 Stockholm

Sweden

Phone: +46 (0)8 5537 8903

Fax: +46 (0)8 5537 8900

E-mail: anna.andreasson@su.se

Carin Warnoff[1], Mats Lekander[1,2,3], Tomas Hemmingsson[4,5], Kimmo Sorjonen[1], Bo Melin[1], Anna Andreasson[2,3,6]

[1] Department for Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

[2] Stress Research Institute, Stockholm University, Stockholm, Sweden

[3] Osher Center for Integrative Medicine, Karolinska Institutet, Stockholm, Sweden

[4] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[5] Centre for Social Research on Alcohol and Drugs, Stockholm University, Stockholm, Sweden.

[6] Division of Family Medicine, Karolinska Institutet, Huddinge, Sweden

Self-rated health and inflammation in adolescent men

Key words: self-rated health, erythrocyte sedimentation rate, low-grade inflammation, military conscripts

ABSTRACT

Objective

Self-rated health is a powerful predictor of long-term health and mortality, hence the importance of a better understanding of its biological determinants. Previous studies have shown that low-grade inflammation is associated with poor self-rated health in clinical and healthy populations, but the evidence is sparse in men and lacking completely for men in late adolescence. The aim of this study was to investigate the association between low-grade inflammation and self-rated health among conscripts. It was hypothesized that high levels of inflammatory factors would be associated with poor self-rated health.

Design

Data from 49,321 men (18-21 years) conscripted for military service in 1969 and 1970 was used. Inflammation had been measured through erythrocyte sedimentation rate (ESR). Self-rated health had been assessed on a five-point scale and was dichotomized into *Good* (“Very good”/”Good”/”Fair”) versus *Poor* (”Poor”/”Very poor”). Data from 43,110 conscripts with normal levels of ESR and who reported self-rated health remained after exclusion of those with ESR <1 and >11 mm/hr. Associations were calculated using logistic regression analyses. Adjustments were made for body mass index, socioeconomic position, inflammatory disease, emotion regulation, smoking, risky use of alcohol and physical activity.

Results

High levels of ESR were associated with higher odds for poor self-rated health (OR: 1.077 for each unit mm/hr increase in ESR, 95% confidence interval: 1.049-1.105).

Conclusion

The present study shows for the first time, a significant association between a marker of inflammation and self-rated health in late adolescent men, adding to evidence of an association between low-grade inflammation and subjective health perception also in men, as previously demonstrated in women. Further support for inflammation as part of a general psychobiological process that underpins subjective health perception is hereby provided.

Strengths and limitations of this study

- This is the first study to investigate the association between low-grade inflammation and self-rated health in a large sample of late adolescent men.
- Using data (n=43,110) from the national military conscription register, encompassing nearly all the Swedish men born in 1949-1951, eliminates selection bias.
- Adjustments were made for life-style patterns, demographic factors and psychological disposition.
- The cross-sectional design precludes conclusions about causality.

INTRODUCTION

Self-rated health is a single-item measure of how an individual subjectively perceives her health status. A number of studies show that poor self-rated health predicts future adverse health outcomes, such as cardio-vascular events [1] and healthcare utilization [2], and is coupled with a near two-fold risk of premature mortality [3-5]. The predictive qualities of self-rated health remain after controlling for objective health, social and demographic risk factors [4].

Although the mechanisms that link self-rated health to future objectively verified ill-health are largely unknown, recent studies point at inflammation as an important determinant of subjective health perception [6-8]. As part of the inflammatory response to acute infection or injury, pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α drive the acute phase response by increasing levels of acute phase proteins [9]. One of these proteins, fibrinogen, is a coagulation factor and is reflected by erythrocyte sedimentation rate (ESR). When inflammation is present, the fibrinogen causes erythrocytes to clot in rolls, thus sinking faster through a test tube, resulting in an increased ESR [10, 11]. Compared to other tests of inflammation, ESR is a simple and cost efficient way of establishing the presence of the acute phase reactants and, indirectly, the activity of pro-inflammatory cytokines [9], making it a suitable marker of inflammation when collecting large amount of data.

One hypothesis to explain the observed association between low-grade inflammation and poor self-rated health is that inflammation related signals reach areas in the brain, including the insular cortex and the anterior cingulate cortex [12, 13], i.e. areas that are important in interpretation of bodily state and homeostatic changes [14]. As part of the co-ordination of a sickness response, shifts in motivation and alterations of behaviours that

promote healing and recovery are thereby induced [15]. Symptoms of such inflammation-induced sickness behaviours include anhedonia, fatigue and increased sensitivity to pain, which are also determinants of subjective health perception [16]. Since low-grade inflammation is part of the pathology in major causes of premature mortality, such as cardio-vascular disease (see e.g. [17, 18]), type-2 diabetes [19], obesity [20] and certain types of cancer [21, 22], low-grade inflammation could be one factor linking poor self-rated health with future adverse health outcomes.

In order to investigate whether low-grade inflammation may be implicated in subjective health perception, a row of recent studies have examined the link between increased levels of pro-inflammatory cytokines and poor self-rated health [6-8, 16, 23, 24]. Other studies have examined the association between self-rated health and fibrinogen [25], ESR [26] and of another acute phase reactant, C-reactive protein (CRP)[7, 23, 27, 28]. So far, the evidence of a link between low-grade inflammation and self-rated health is more robust for women compared to men [6-8, 16, 27], and the strength of the association has been indicated to increase with age [6, 16]. For instance, among 347 women 45 to 90 years old of the general population there was a significant association between IL-6 and poor self-rated health, particularly among those 65 years old and above [6]. In another study, in 174 female primary health care patients of 18 years and older who were divided into three age groups, higher TNF-α was significantly associated with poor self-rated health in all three age groups, whereas higher levels of IL-1ß and IL-1 receptor antagonist were associated with poor self-rated health in those over 65 years old [16]. Moreover, in 235 middle-aged and elderly women with coronary heart disease, high levels of CRP and IL-6 were associated with poor self-rated health [7].

Among the studies including both men and women, only two have performed sex-based stratified analyses [8, 27] and one study examined the interaction effect of sex and

inflammation on self-rated health [28]. A study of 170 female and 89 male primary health care patients showed a significant independent association between higher IL-1β and TNF-α and poor self-rated health only in women [8], but the lack of association in men could be due to small sample size and low statistical power. Among 11,000 women and 5,000 men, a significant association between CRP and self-rated health remained only in women after adjustment for control factors [27]. However, in a population of 13,236 young adults aged 24-34 years, high sensitivity CRP above 3 mg/L was significantly associated with lower ratings of self-rated health after adjustment for health behaviours, self-reported illness and medication in both men and women. Inclusion of BMI fully attenuated the association between CRP and self-rated health in women whereas a small but significant association remained in men [28].

The remaining studies encompassing both men and women reported significant associations between IL-6 and self-rated health [23, 24], and between fibrinogen and self-rated health [25]. As these studies were only adjusted for sex it is not clear if this association would be found in the male or female strata only.

The present study aims to investigate low-grade inflammation and subjective health perception in a very large, young and healthy population, mainly free from medical conditions. The hypothesis was that conscripts with elevated ESR levels had poorer self-rated health. This population of late adolescent men is a group that has not yet been investigated in this context.

METHODS

Study design

This cross-sectional study was based on data collected in 1969 to 1970 when 49,321 Swedish men born between 1949 and 1951 (aged 18-21 years) underwent a compulsory 2-day screening procedure prior to military service. During this time period only 2-3 % of men eligible for military services were exempted from conscription, mainly due to severe disabilities or severe congenital disorders. All conscripts had answered questionnaires about social background, habits, psychological factors, social adjustment and health status and had been structured-interviewed by a psychologist. Finally, a physician examined all conscripts, and any somatic or psychiatric disorders were diagnosed according to the Swedish version of the International Classification of Disorders, version 8 (ICD-8). The present study was approved by the regional ethics board.

Measures

Self-Rated Health

The conscripts had been asked to assess their health, answering the question: "*In general, would you say your health right now is: Very good, Good, Fair, Poor or Very poor"?* The answers had been rated on a 5-point scale where 1="Very good", 2="Good", 3="Fair", 4="Poor" and 5="Very poor" and were dichotomized into *Good* (1-3) and *Poor* (4 and 5) self-rated health.

Erythrocyte Sedimentation Rate

At physical examination, blood samples had been taken and ESR had been measured according to standard laboratory procedures (Westergren method) [9]. The ESR is affected by the hematocrit (Htc, i.e. the proportion of whole blood made up by erythrocytes), we therefore

corrected the ESR values for the hematocrit according to the formula ESR*Htc/45 [29]. Htc-corrected ESR values are used in all analyses and presentations of ESR values. Despite plausible inter-individual genetic variations [30], the upper limit of the normal range of ESR has, on group level, been found to correspond to the age in years divided by two [31]. The age span of the men included in this study ranged from 18 to 21 years. Based on the highest age included, the normal range was rounded off to <11 mm/hr. Thus, the 3.7 % of the participants with ESR ≥11 mm/hr (n=3,937) were excluded from the analyses out of whom 168 had rated their self-rated health as poor, 3,655 had rated their self-rated health as good, and 114 had missing self-rated health values. In order to reduce misclassifications errors those with ESR <1 mm/hr (n=1,903) were also excluded [32], out of whom 148 had rated their self-rated health as poor, 1,739 as good, and 16 had missing values. A total of 43,110 out of the remaining 43,481 conscripts with ESR levels ≥1 and < 11 mm/hr had data on self-rated health and were included in the analyses.

Body Mass Index

The conscripts' height and weight had been measured at the physical examination. Body mass index (BMI) is determined by calculating the ratio of weight to height squared (kg/m^2). Obesity and underweight as measured by very high or very low BMI have independently been associated with poor self-rated health [33] and obesity has been associated with inflammation [34]. BMI was categorized into four groups: underweight (BMI<18.5), normal weight (BMI: 18.5-25), overweight (BMI: 25-30) and obesity (BMI>30). Normal weight was used as reference in the logistic regression analyses.

Socioeconomic Position

Parental socioeconomic position (SEP) was used as an indicator of childhood socioeconomic circumstances. Information about socioeconomic circumstances of the conscripts at 9 to 11 years of age was obtained from the National Population and Housing Census from 1960. A conscript and the head of the household, usually the conscript's father, were linked through their personal identification number by Statistics Sweden. Based on the occupation of the head of the household seven socioeconomic groups were identified: (a) unskilled workers, (b) skilled workers, (c) assistant non-manual employees, (d) non-manual employees at intermediate level, (e) non-manual employees at higher level, (f) farmers, and (g) those not classified into a socioeconomic group. Self-employed persons could not be identified in the census from 1960 when such persons were classified as employed according to occupation. Previous research have shown that childhood SEP is associated with markers of inflammation in adults [35, 36], and a previous study from this sample found a significant association between ESR and SEP [37], why SEP is included in the analyses.

Inflammatory Disease

Presence of one or more of the following medical conditions as registered for each conscript by a physician according to ICD-8 was adjusted for in the analyses: infectious disease, malignancies, lymphatic and haemotopoetic tumors, diabetes mellitus, asthma, gastrointestinal inflammation, hay fever, infection and inflammation in skin, arthritis and rheumatoid arthritis.

Emotion Regulation

The combined questionnaire and interview data had been used by a psychologist to rate emotion regulation (then termed 'emotional control') on a 5-point scale, based on self-reported anxiety, stress-tolerance, nervous problems, capacity for emotional commitment and

control over aggression (a score of 1 to 2 represent *Low* emotion regulation). In a previous study, based on data from the same population, low emotion regulation was a confounding factor in the association between poor self-rated health and mortality [5] and it was also the covariate with the most prominent difference between conscripts with poor self-rated health and conscripts with good self-rated health. Persistent negative affect, such as anger, anxiety and depression, has been associated with inflammation and disease [38, 39, 40], hence the inclusion of emotion regulation in the analyses.

Smoking

Tobacco smoking has been associated with increased systemic inflammation in men [41, 42]. Smoking has also been associated with poor self-rated health [6, 43, 44] and was therefore included in the analyses. The self-reported number of cigarettes smoked per day had been rated on a 4-point scale where 1=>20, 2=11-20, 3=1-10 cigarettes per day and 4=non-smoker.

Risky use of alcohol

Risky use of alcohol has been associated with elevated markers of inflammation [45]. Self-reported use of alcohol was categorised as risky when consumption exceeded 250 g 100 % alcohol per week; alcohol was used to alleviate a hangover; having been apprehended for drunkenness; or being drunk often.

Physical activity

We used active membership in sport clubs as a proxy for physical activity. Exercise has been shown to have anti-inflammatory effects [46], and low physical activity has been associated with worse self-rated health [47].

Statistics

To calculate the association between ESR and self-rated health, logistic regression analysis was used with ESR as the independent variable and self-rated health as the outcome variable. As a second step, the association between ESR serum levels and self-rated health was adjusted separately for background variables BMI, SEP, presence of inflammatory disease, emotion regulation, smoking, risky use of alcohol and physical activity. Thirdly, in the full model, the association between ESR levels and self-rated health was adjusted for all background variables together. The background variables were treated as categorical variables in the analyses. Data from 43,110 conscripts with self-rated health data and normal levels of ESR were included in the analyses. Missing values for background variables were excluded listwise.

An α-value of .05 was used to test for statistical significance. All analyses were performed using SPSS statistics software version 21.

RESULTS

Participant characteristics for conscripts with poor self-rated health and conscripts with good self-rated health are presented in Table 1. The majority of the conscripts reported their self-rated health as good (96.2 %). Overall, conscripts with poor self-rated health were more likely to report poor health behaviours such as smoking and risky use of alcohol and had a higher frequency of low emotion regulation than conscripts with good self-rated health.

Table 1. *Participant characteristics separated for men with poor self-rated health and men with good self-rated health. Group differences in frequencies have been tested with Chi Square test and differences in means with t-tests.*

	Self-rated health		
Variable/category	Poor n=1,618	Good n=41,492	
			χ^2
BMI			
<18.5	18.2	13.4	31.01*
18.5-25.0	74.4	80.0	29.32*
25.0-30.0	6.5	5.8	1.32
>30.0	0.8	0.8	0.00
Socioeconomic position (%)			
Worker, unskilled	32.6	33.5	0.61
Worker, skilled	21.9	21.5	0.21
Non-manual, assistant	10.0	10.1	0.03
Non-manual, intermediate	18.5	16.7	3.80
Non-manual, higher	5.7	5.1	1.26
Farmer	8.3	10.9	10.48*
Non-classified	2.9	2.2	3.04
Inflammatory disease (%)	22.6	8.5	377.98*
Low emotion regulation (%)	71.2	28.6	1313.11*
Smoking (%)			
> 20 cigarettes/day	14.5	3.2	555.13*
11-20 cigarettes/day	31.7	23.0	64.63*

1-10 cigarettes/day	25.1	32.2	35.34*
Non smoker	28.7	41.6	104.82*
Risky use of alcohol (%)	29.3	15.2	191.76*
Physical activity (%)	24.7	37.0	102.49*
			t
ESR, M (SD)	2.98 (2.19)	2.70 (1.98)	5.58*
BMI, M (SD)	20.79 (2.73)	21.00 (2.57)	-3.26*

*$p<.001$

BMI: body mass index, ESR: erythrocyte sedimentation rate.

Elevated levels of ESR were associated with higher odds for poor self-rated health (OR=1.066 for each unit mm/hr increase in ESR, Table 2). The size of the association and the level of significance were largely unaffected by adjustments for BMI, SEP, inflammatory diseases, emotion regulation, smoking, risky use of alcohol and physical activity (OR=1.077).

Table 2. *Crude and adjusted effects of ESR on the odds to have very poor/poor rather than fair/good/very good self-rated health.*

	Odds ratio (95% CI)[1]	N
Crude	1.066 (1.043-1.091)	43,110
Adjusted for individual background variables		
BMI	1.064 (1.040-1.088)	43,067
Socioeconomic position	1.069 (1.045-1.093)	43,110
Inflammatory disease	1.066 (1.042-1.091)	43,110
Emotion regulation	1.070 (1.046-1.096)	42,930
Smoking	1.071 (1.047-1.096)	42,555
Risky use of alcohol	1.066 (1.039-1.093)	35,801
Physical activity	1.067 (1.043-1.091)	43,110
Adjusted for all background variables	1.077 (1.049-1.105)	35,553

ESR: erythrocyte sedimentation rate, BMI: body mass index.
[1] Odds ratio for each unit mm/hr increase in ESR

DISCUSSION

The aim of this study was to investigate if there is an association between higher level of the inflammatory marker ESR and poor self-rated health in late adolescent men. The results of this study show that the odds of having poor rather than good self-rated health were elevated by approximately 7 % per for each unit mm/hr increase in ESR.

This pattern was stable when relevant confounders (BMI, SEP, presence of inflammatory disease, emotion regulation, smoking, risky use of alcohol and physical activity) were controlled for. Hence, the present result is consistent with the hypothesis that inflammation is part of a general factor in the psychobiological processes that underpin subjective health perception also in late adolescent men, although the cross-sectional design of the present study precludes conclusions about causality.

The results of the present study are in contrast with the lack of association between inflammatory markers and self-rated health in men in the studies by Lekander and co-workers [8] and Tanno and co-workers [27]. In comparison to the present study, those studies are based on dissimilar methods and populations, with older participants (mean age 59 and 58 years, respectively, compared to 18-21 years in the present study). The study by Lekander and co-workers had a considerably smaller sample size, and Tanno and co-workers [27] had an Asian population. However, the present results are in concordance with a previous study that demonstrated a small but significant association between CRP and self-rated health in young adult men 24 to 34 years old [28].

Demographic factors and life-style patterns have been associated with both low-grade inflammation and with poor self-rated health; factors that may constitute possible confounders in the association between ESR and self-rated health, such as aging [48], obesity [49], low SEP [37], and smoking [6, 42]. Adjustments for BMI, SEP, inflammatory disease, emotion regulation, smoking, risky alcohol use, and physical activity did not, however, change the association between ESR and self-rated health in the present study suggesting that the association is not dependent on any of the confounding variables. Also, individuals with a higher degree of inflammation did not introduce bias, as all conscripts with an ESR equal to or above 11 mm/hr had been excluded. No assessments of sickness behaviour were available in the present study and further studies are needed to investigate sickness behaviour as a

mediating factor linking inflammatory factors and poor self-rated health. Unfortunately, data on diet was not available in the present study, which is a factor to take into account in future studies.

Our study sample consisted of 43,110 conscripts encompassing the majority of all Swedish men born in 1949 to 1951. The large sample size allows for a more accurate estimate of the association between high levels of ESR and poor self-rated health. Having a study sample that represents such a large percentage of the population also eliminates the risk for selection bias. In the present material of late adolescent men, the majority of participants were, as expected, healthy; altogether 82.6 % rated their health as “Good” or “Very good”. It cannot be excluded that in a current-day sample of young men the included factors would be differently distributed, and that e.g. low-grade inflammation would be more prevalent since obesity, which has been linked with low-grade inflammation [50, 51], almost doubled in prevalence between 1971 and 1993 among Swedish military conscripts [52]. However, the association between ESR and self-rated health in the present study was independent of background factors such as BMI and there is little reason to expect that the putative underlying biological mechanism by which inflammation is associated with subjective health perception would have changed.

Concerning validity, there is some discordance between ESR and other inflammatory markers. For instance ESR has been shown to rise and decrease slower than CRP (see e.g. [53]). However, the independent relation between self-rated health and ESR in the present study suggests that ESR is a marker for self-rated health, not merely reflecting manifest disease or chronic conditions.

In conclusion, the present study shows for the first time a significant association between elevated levels of ESR and poor self-rated health in late adolescent men, providing evidence of an association between low-grade inflammation and subjective health perception

also in men, as previously demonstrated in women. Data is here provided to further support inflammation as a general factor in the psychobiological processes that underpin subjective health perception across the adult life span.

Contributors: ML, TH, BM, AA conceived of the study. CW drafted the manuscript. KS and TH performed the statistical analyses. All authors were involved in the discussion of the data and revised the manuscript for intellectual content.

Funding: This study has not received funding.

Competing interests: None declared.

Data sharing statement: No additional data available.

REFERENCES

1. Grool, A.M., et al., *Self-rated health status as a risk factor for future vascular events and mortality in patients with symptomatic and asymptomatic atherosclerotic disease: the SMART study.* J Intern Med, 2012.
2. DeSalvo, K.B., et al., *Predicting mortality and healthcare utilization with a single question.* Health Serv Res, 2005. **40**(4): p. 1234-46.
3. DeSalvo, K.B., et al., *Mortality prediction with a single general self-rated health question. A meta-analysis.* J Gen Intern Med, 2006. **21**(3): p. 267-75.
4. Idler, E.L. and Y. Benyamini, *Self-rated health and mortality: a review of twenty-seven community studies.* J Health Soc Behav, 1997. **38**(1): p. 21-37.
5. Larsson, D., et al., *Self-rated health and mortality among young men: what is the relation and how may it be explained?* Scandinavian Journal of Public Health, 2002. **30**(4): p. 259-266.

6. Andreasson, A.N., et al., *Inflammation and positive affect are associated with subjective health in women of the general population.* Journal of health psychology, 2012.
7. Janszky, I., et al., *Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease.* Brain, Behavior, and Immunity, 2005. **19**(6): p. 555-563.
8. Lekander, M., et al., *Self-rated health is related to levels of circulating cytokines.* Psychosom Med, 2004. **66**(4): p. 559-63.
9. Saadeh, C., *The erythrocyte sedimentation rate: old and new clinical applications.* Southern medical journal, 1998. **91**(3): p. 220-5.
10. Heinrich, P.C., J.V. Castell, and T. Andus, *Interleukin-6 and the acute phase response.* The Biochemical journal, 1990. **265**(3): p. 621-36.
11. Janeway, C.A., et al., *Induced innate responses to infection*, in *Immunobiology* 2001, Garland Publishing: New York.
12. Hannestad, J., et al., *Glucose metabolism in the insula and cingulate is affected by systemic inflammation in humans.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2012. **53**(4): p. 601-7.
13. Harrison, N.A., et al., *Neural origins of human sickness in interoceptive responses to inflammation.* Biological psychiatry, 2009. **66**(5): p. 415-22.
14. Craig, A.D., *How do you feel? Interoception: the sense of the physiological condition of the body.* Nat Rev Neurosci, 2002. **3**(8): p. 655-66.
15. Dantzer, R., *Cytokine-induced sickness behavior: mechanisms and implications.* Ann N Y Acad Sci, 2001. **933**: p. 222-34.
16. Unden, A.L., et al., *Inflammatory cytokines, behaviour and age as determinants of self-rated health in women.* Clin Sci (Lond), 2007. **112**(6): p. 363-73.

17. Melamed, S., et al., *Association of fear of terror with low-grade inflammation among apparently healthy employed adults.* Psychosom Med, 2004. **66**(4): p. 484-91.

18. Yudkin, J.S., et al., *C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue?* Arterioscler Thromb Vasc Biol, 1999. **19**(4): p. 972-8.

19. Duncan, B.B., et al., *Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study.* Diabetes, 2003. **52**(7): p. 1799-805.

20. Bondia-Pons, I., L. Ryan, and J.A. Martinez, *Oxidative stress and inflammation interactions in human obesity.* Journal of physiology and biochemistry, 2012. **68**(4): p. 701-11.

21. Macarthur, M., G.L. Hold, and E.M. El-Omar, *Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy.* Am J Physiol Gastrointest Liver Physiol, 2004. **286**(4): p. G515-20.

22. Balkwill, F. and A. Mantovani, *Inflammation and cancer: back to Virchow?* Lancet, 2001. **357**(9255): p. 539-45.

23. Christian, L.M., et al., *Poorer self-rated health is associated with elevated inflammatory markers among older adults.* Psychoneuroendocrinology, 2011. **36**(10): p. 1495-504.

24. Cohen, H.J., et al., *The association of plasma IL-6 levels with functional disability in community-dwelling elderly.* Journals of Gerontology. Series A, Biological Sciences & Medical Sciences, 1997. **52**(4): p. M201-8.

25. Fielding, R., et al., *Subjective health and fibrinogen in a healthy Chinese cohort.* Br J Health Psychol, 2004. **9**(Pt 4): p. 523-32.

26. Nilsson, L.-G., et al., *The Betula Prospective Cohort Study: Memory, Health and Aging.* Aging, neuropsych, cogn 1997. **4**(1): p. 1-32.
27. Tanno, K., et al., *Poor self-rated health is significantly associated with elevated C-reactive protein levels in women, but not in men, in the Japanese general population.* Journal of psychosomatic research, 2012. **73**(3): p. 225-31.
28. Shanahan, L., et al., *Self-rated health and C-reactive protein in young adults.* Brain Behav Immun, 2014. **36**: p. 139-46.
29. Borawski, J. and M. Mysliwiec, *The hematocrit-corrected erythrocyte sedimentation rate can be useful in diagnosing inflammation in hemodialysis patients.* Nephron, 2001. **89**(4): p. 381-3.
30. Kullo, I.J., et al., *Complement receptor 1 gene variants are associated with erythrocyte sedimentation rate.* Am J Hum Genet, 2011. **89**(1): p. 131-8.
31. Miller, A., M. Green, and D. Robinson, *Simple rule for calculating normal erythrocyte sedimentation rate.* British medical journal, 1983. **286**(6361): p. 266.
32. Toss, F., A. Nordstrom, and P. Nordstrom, *Inflammation in young adulthood is associated with myocardial infarction later in life.* Am Heart J, 2013. **165**(2): p. 164-9.
33. Molarius, A., et al., *Socioeconomic conditions, lifestyle factors, and self-rated health among men and women in Sweden.* Eur J Public Health, 2007. **17**(2): p. 125-33.
34. Kantor, E. D., et al., *Lifestyle factors and inflammation: associations by body mass index.* PLoS One, 2013. 8(7), e67833.
35. Miller, G. and E. Chen, *Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence.* Psychosomatic medicine, 2007. **69**(5): p. 402-9.
36. Pollitt, R.A., et al., *Early-life and adult socioeconomic status and inflammatory risk markers in adulthood.* European journal of epidemiology, 2007. **22**(1): p. 55-66.

37. Karlsson, H., et al., *Association between erythrocyte sedimentation rate and IQ in Swedish males aged 18–20.* Brain, Behavior, and Immunity, 2010. **24**(6): p. 868-873.

38. Miller, G. E., et al,. *Cynical hostility, depressive symptoms, and the expression of inflammatory risk markers for coronary heart disease.* J Behav Med, 2013. 26(6): p. 501-515.

39. Pitsavos, C., et al., *Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study.* Atherosclerosis, 2006. 185(2): p. 320-326

40. Coccaro, E. F., Lee, R., & Coussons-Read, M. (2014). *Elevated plasma inflammatory markers in individuals with intermittent explosive disorder and correlation with aggression in humans.* JAMA Psychiatry, 71(2): p. 158-165.

41. Frohlich, M., et al., *Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95).* Eur Heart J, 2003. **24**(14): p. 1365-72.

42. Lao, X.Q., et al., *Smoking, smoking cessation and inflammatory markers in older Chinese men: The Guangzhou Biobank Cohort Study.* Atherosclerosis, 2009. **203**(1): p. 304-10.

43. Kirkland, S., L. Greaves, and P. Devichand, *Gender Differences in Smoking and Self Reported Indicators of Health.* BMC Womens Health, 2004. **4 Suppl 1**: p. S7.

44. Wang, M.P., et al., *Smoking is associated with poor self-rated health among adolescents in Hong Kong.* Nicotine Tob Res, 2012. **14**(6): p. 682-7.

45. Imhof, A., et al., *Effect of alcohol consumption on systemic markers of inflammation.* Lancet, 2001. 357(9258): p. 763-767.

46. Ford, E. S. *Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults.* Epidemiology, 2002. 13(5): p. 561-568

47. Manderbacka, K., Lahelma, E., & Martikainen, P. *Examining the continuity of self-rated health.* Int J Epidemiol, 1998. 27(2): p. 208-213.

48. Giunta, S., *Is inflammaging an auto[innate]immunity subclinical syndrome?* Immunity & ageing : I & A, 2006. **3**: p. 12.

49. Yudkin, J.S., et al., *Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link?* Atherosclerosis, 2000. **148**(2): p. 209-14.

50. Greenberg, A.S. and M.S. Obin, *Obesity and the role of adipose tissue in inflammation and metabolism.* Am J Clin Nutr, 2006. **83**(2): p. 461S-465S.

51. Gregor, M.F. and G.S. Hotamisligil, *Inflammatory mechanisms in obesity.* Annu Rev Immunol, 2011. **29**: p. 415-45.

52. Rasmussen, F., M. Johansson, and H.O. Hansen, *Trends in overweight and obesity among 18-year-old males in Sweden between 1971 and 1995.* Acta paediatrica, 1999. **88**(4): p. 431-7.

53. Bilgen, O., et al., *C-reactive protein values and erythrocyte sedimentation rates after total hip and total knee arthroplasty.* J Int Med Res, 2001. **29**(1): p. 7-12.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1 OK (a) Title, page 3 (b) Page 3	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 OK Pages 5-7	Explain the scientific background and rationale for the investigation being reported
Objectives	3 OK Page 7	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 OK Title, pages 3, 7-8	Present key elements of study design early in the paper
Setting	5 OK Pages 7-8	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 OK Pages 7-8	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7 OK Pages 8-11	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* OK 8-11	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 OK Pages 7-8	Describe any efforts to address potential sources of bias
Study size	10 OK Pages 7-9	Explain how the study size was arrived at
Quantitative variables	11 OK Pages 8-12	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 OK (a) Pages 11-12 (b) Table 1 (c) Pages 9,12 (d) n/a (e) n/a	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13* OK (a) Pages 8-9 and Table 2 (b) Pages 8-9	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram

Descriptive data	14*OK (a) Table 1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	(b) Table 2	(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15* OK Table 1.	Report numbers of outcome events or summary measures
Main results	16 OK (a) Page 15, 8-11, Table 2 (b) Pages 9 (c) n/a	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 OK n/a	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 OK Page 15-16	Summarise key results with reference to study objectives
Limitations	19 OK Page 17	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 OK Pages 15-18	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 OK Page 17	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 OK Page 18	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.