Is inflammation related to self-rated health and mortality in men?

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IS INFLAMMATION RELATED TO SELF-RATED HEALTH AND MORTALITY IN MEN?

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Abstract

Self-rated health is a powerful predictor of long-term health, but relatively little is known about what determines an individual’s rating of her perceived health status. Psychoneuroimmunological research has found links between immune activity and behaviour, and a relation between low-grade inflammation and poor self-rated health, primarily in women. The principal aim of this paper was to examine the relation between self-rated health and inflammation, measured by erythrocyte sedimentation rate (ESR), in young men. A secondary objective was to investigate whether self-rated health and ESR may be associated to mortality. Pearson correlation and Cox regression analyses were used to examine data collected in 1969-70 when 49,321 men underwent military conscription, together with information from the national cause of death register in 2006. Background factors (BMI, emotional control, psychiatric diagnosis and smoking) were included in multivariate analyses. The results show that self-rated health was significantly related to ESR ($r=0.08$, $p<0.001$), also after control for background factors. Furthermore, subjects with poor self-rated health had a near two-fold increased risk of mortality during 37 years of follow-up. In addition, ESR was a significant predictor of mortality ($\beta=0.051$, $p<0.002$). To conclude, in this cohort of young, healthy men, the association between self-rated health and inflammation was significant but modest. Instead, low emotional control showed a stronger independent correlation to poor self-rated health ($r=-0.284$, $p<0.001$). Moreover, adding to a growing body of evidence, poor self-rated health was a strong predictor of mortality.

"From simple to complex, for millions of years, brains have been first about the organism that owns them."

Antonio Damasio, Descartes’ Error (1994)

Self-rated health is a single-item measure of an individual’s self-assessed health status, based upon the question “How would you rate your general health?”. The assessment is thought to reflect a wide range of health related factors and is a strong predictor of long-term health and mortality (Gerber, Benyamini, Goldboult, & Drory, 2009). In some studies, it has even been a better predictor of morbidity and mortality than an objective medical evaluation carried out at

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the same point in time (Lekander, Elofsson, Neve, Hansson, & Undén, 2004). Often measured on a five-point scale, ranging from excellent to very poor, a large number of studies have revealed that there is an independent, near two-fold increased risk of mortality at follow-up among those who rate their health as poor or very poor compared to those who rate their health as good or excellent (DeSalvo, Bloser, Reynolds, He, & Muntner, 2005). Despite its wide use in epidemiologic studies since the 1950s, the underlying mechanisms of the predictive qualities of self-rated health are still, to a large extent, unknown. The fundamental mechanisms of perceived health—that is, what determines an individual’s subjective health experience at a certain point in time—are also largely unidentified.

Research within the field of psychoneuroimmunology has introduced a theory that may illuminate mechanisms of how health is subjectively perceived. It is known that the immune system initiates inflammatory activity and that this happens along with the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system as a response to a stressor (Maier & Watkins, 1998). Pro-inflammatory cytokines, which act as intercellular messengers, are involved in inducing and coordinating the inflammatory response. It is also known that cytokines act on centres in the brain which induce widespread changes of behaviour referred to as sickness-behaviours. These clusters of behaviours, thus concurrent with immune activity, include diffuse symptoms of illness such as disturbed sleep, fatigue, pain, gastro-intestinal problems and a depressed mood. Because sickness-behaviours also limit exposure to further threats and promote energy saving conduct, it has been suggested that the changes of physiology, cognition and overt behaviour are in fact a motivational state, helping the organism to restore homeostasis through reorganization of behaviour (Lekander, 2002; Maier & Watkins, 1998). However, even though inflammation and the accompanying sickness-behaviours may be adaptive reactions to acute stressors, there is evidence that chronic inflammation is a central component of severe pathology such as diabetes, different types of cancer, depression, autoimmune (a state in which the immune system reacts against components of the own body) and cardio-vascular disease (Brotman, Golden, & Wittstein, 2007; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). In fact, factors such as pain, low fitness and fatigue have been associated with poor self-rated health—symptoms that resemble immune-activated sickness-behaviours (Lekander et al., 2004). Therefore, self-rated health has been hypothesized to correlate with inflammation. Studies that strengthen this theory have shown that low self-rated health is associated with higher levels of pro-inflammatory cytokines (e.g. Lekander et al., 2004; Janszky, Lekander, Blom, Georgiades, & Ahnve, 2005; Undén et al., 2007) but the association has been more convincingly shown in women than in men (see e.g. Lekander et al., 2004).

Overall, since self-rated health shows impressive predictive powers, it is a promising instrument in the screening of high-risk groups due to its cost-efficiency and simplicity of use. Moreover, the discovery of disease at early stages can reduce the risk of a progression into chronic states, potentially reduce suffering and bring important socio-economic benefits for the individual at risk as well as for society. Thus, research that further investigates the potential mechanisms between self-rated health and inflammation may be of high clinical importance in the development of preventive care.

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1 A stressor has been defined as anything that will disturb homeostasis, causing the organism to resemble its resources to meet the threat, and may be of physiological (e.g. an injury), infectious (e.g. a virus) or psychological character (e.g. losing one’s job; Maier & Watkins, 1998).
Theoretical background

Psychoneuroimmunology is a relatively new field of research. As proposed in Figure 1, it investigates the relationships between behaviour and the immune and nervous systems from a multidisciplinary perspective, presenting a holistic view of the intricate interactions of the psyche and soma. One of its main discoveries is that the immune system greatly influences behaviour, and the neural-immune link becomes particularly important when investigating the effects of chronic stress.

Figure 1. Psychoneuroimmunology is a field of research that investigates relationships between overt behaviour, the immune system and the nervous system.

The immune system and the inflammatory response

The immune system is a complex structure with the principal function of protecting the organism from invading microorganisms, such as viruses, bacteria, parasites—so-called pathogens—and to promote healing after injury and disease (Maier & Watkins, 1998). The immune defence consists of physical and chemical barriers, such as the skin or enzymes in body fluids. Other components that make up the immune defence are white blood cells, otherwise known as leukocytes, and immune organs, including the spleen, the thymus gland, and the lymph organs (Bränden & Andersson, 2004). Upon detection of an infection, the immune system initiates an inflammatory response which engages and recruits different groups of leukocytes that has widespread effects on physiology, cognition and overt behaviour (Lekander, 2002; Maier & Watkins, 1998).

Cytokines

It is known that pro-inflammatory cytokines are central to the inflammatory response. Cytokines are protein molecules that act as intercellular messengers, much like the neurotransmitters of the nervous system. Whereas neurotransmitters are synthesized by neurons (Schwartz, 2000), cytokines are produced and released by different types of white blood cells. They are also produced by several other cell types, such as muscle cells.

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2 The endocrine system is also a central part in the field of psychoneuroimmunology, but is not focused on in the present paper.
The pathways of immune-brain communication are not yet fully understood but it is known that cytokines and neurotransmitters communicate over distance, process information and have memory formation capacities. There are, for instance, direct innervations by sympathetic nerve fibres of immune-organs, such as the spleen and lymph organs and there are synaptic-like connections between axon terminals of the nervous system and some of the leukocytes. In essence, the immune system has much in common with the nervous system, functionally as well as in structural terms (Lekander, 2002; Maier & Watkins, 1998). Moreover, cytokines have the capacity of conveying information about the body, for example by reaching the nucleus tractus solitarius (NTS) in the brain through stimulation of e.g. the vagus nerve. From there, neural projections reach hippocampal, hypothalamic and other regions related to emotion, cognition and homeostatic regulation. The immune system has thus been described as a “diffuse sensory organ” providing information to the brain regarding the status of the organism (Mailer & Watkins, 1998). When information of an infection or injury reaches relevant centres in the brain, the nervous and the immune systems are activated in order to produce an adequate inflammatory response, with mentioned effects on physiology, cognition and overt behaviour. For instance, even mild bacterial challenges have been shown to have a negative effect on mood, cognition and memory in what is referred to as cytokine-associated emotional and cognitive disturbances (Reichenberg et al., 2001; Strike, Wardle, & Steptoe, 2003).

**Cytokines and sickness-behaviours**

The changes that occur during the inflammatory response are collectively called sickness-behaviours, as illustrated by Figure 2. The cognitive changes may comprise of interference with certain types of memory, a shift of attention toward potential threats, and a depressed mood (anhedonia). Behavioural adjustments include reductions in appetite (anorexia), sexual activity, social contact and motor activity. The physiological alterations may consist of increased slow-wave sleep, fever (pyrexia), and shift in protein synthesis in the liver.

![Figure 2. Sickness-behaviours are referred to as alterations of physiology, cognition and overt behaviour. Sickness-behaviours may be a motivational state, purporting to aid the organism in restoring homeostasis by energy saving behaviours, and by limiting exposure to further threats.](image-url)
Sickness-behaviours are adaptive because they promote energy saving conduct and facilitate the inflammatory response. Fever is an example of an adaptive alteration during immune activation, which involves the immune and the nervous systems in a coordinated effort to restore homeostasis, i.e. the balance of the internal physiological milieu. Orchestrated by cytokines, it is a powerful response in combating infection. At altered temperatures some parts of the immune system are more efficient and the mitochondrial activity (which provides cells with energy) of invading microorganisms is hampered even at a slightly raised body temperature. However, the production of fever entails a very high metabolic cost; therefore additional overt behaviours further help the organism to save energy and to raise body temperature. For example, cytokines alter the thermostat of the hypothalamus making the individual feel cold at previously normal temperatures which, in endotherms (organisms who regulate their body temperature through behavioural and metabolic means) such as humans, motivates covering up, staying still, and avoidance of social and physical contact—comportments which help raise core temperature at lesser cost and inhibits exposure to further threats at a point when the body is busy fighting an infection or healing from injury. Animals other than humans engage in similar conduct in response to an infection. Ectotherms (organisms that regulate their body temperature through the environment) change their overt behaviour in order to increase body temperature when infected. For instance, infected fish seek the warmer water temperatures closer to the surface (Lekander, 2002; Maier & Watkins, 1998). Jointly, the production of fever and accompanying sickness-behaviours can be described as a motivational state in which the organism reallocates its resources in order to meet a threat. Thus, seen from an evolutionary perspective, the inflammatory response is an adaptive part of an organism’s active defence strategy and not—as previously believed—a by-product of the infection itself (Lekander, 2002; Maier & Watkins, 1998).

How is inflammation measured?
The present study will investigate the association between self-rated health and erythrocyte sedimentation rate (ESR)—a relatively fast and cost-effective, although unspecific, way of measuring inflammation. The sedimentation rate reveals how fast red blood cells, erythrocytes, sink in a tube during an hour, indicating the serum level of fibrinogen, a protein which is produced during the initial states of an inflammatory response, referred to as the acute phase response (Brändén & Andersson, 2004). During this shift of metabolism, pro-inflammatory cytokines initiate the production of proteins, so-called acute phase reactants that facilitate blood clotting (i.e. making the blood thicker), which is necessary for wound-healing (Maier & Watkins, 1998) in case of injury. Fibrinogen causes the erythrocytes to clot together in so-called ‘rouleaux’ (rolls), which causes the erythrocytes to sink faster than when inflammation is absent. A non-specific inflammation marker, an elevated sedimentation rate is indicative of many different types of illnesses; for instance viral, parasitical and bacterial infection, malignancies (Ganrot, Grubb, & Stenflo, 1997), and active stages of autoimmune disease (Rashid & Ebringer, 2006). Another way of measuring inflammatory activity is through C-reactive protein (CRP), a substance that is produced in the liver during the aforementioned acute phase response. Cytokine-levels can also be measured through antibody analysis, a so-called enzyme-linked immunosorbent assay (ELISA; Brändén & Andersson, 2004).

Why acute psychological stress can cause inflammation
To repeat, it is known that animals and humans alike demonstrate similar inflammatory responses to infection: pathogens or an injury can trigger an inflammatory response in the immune system which results in a number of symptoms referred to as sickness-behaviours. But how about other stressors—can psychological stress trigger an immune response as well?
Animal studies have revealed that simply placing rats in a novel environment elicits fever (LeMay, Vander, & Kluger, 1990, referred in Maier & Watkins, 1998). In another experiment, a mother and infant squirrel monkey were separated for 24 hours which resulted in primed leukocyte activity long after they were reunited (Coe, Rosenberg, & Levine, 1988, referred in Maier & Watkins, 1998) and rats who were subject to an experiment called “inescapable tail shock” displayed increased core body temperature 45 hours after the end of the session compared to controls (Maier & Watkins, 1998). In humans, too, psychological stress is known to induce a mild rise in body temperature, referred to as psychogenic fever (see e.g. Oka, Oka, & Hori, 2001) or stress-induced hyperthermia (Vinkers et al., 2009). By way of illustration, in medical students, an academic examination caused a significant increase in the production of pro-inflammatory cytokines (Maes et al., 1998). Furthermore, speaking in front of an audience has been shown to cause an increase of a pro-inflammatory cytokines (Goebel, Mills, Irwin, & Ziegler, 2000) and a laboratory experiment in which participants were exposed to the Trier Social Stress Test—a standardized psychological procedure designed to provoke stress in humans—resulted in an activation of intracellular transcription factors, which enable cytokine production (Bierhaus et al., 2003).

It may seem maladaptive that psychological stressors would trigger a metabolically costly inflammatory response with the ensuing allostatic load. As we have seen, fever is part of an adaptive defence strategy in combating invading microorganisms, such as viruses or bacteria. So why would making a speech be associated with psychogenic fever (Oka et al., 2000)? Also, how come the production of fibrinogen increases in individuals who experience acute psychological stress (von Känel, Bellingrath, & Kudielka, 2009) despite the apparent lack of danger of contracting a physical injury? Buss (2009), an evolutionary psychologist, has drawn attention to the common misconception that all of our mechanisms are optimally designed: ultimately, optimal design is hindered by evolutionary time lags, meaning that change happens over thousands of generations of humans, thus creating gaps between the effectiveness of adaptations and the triggering factors in the environment. From an evolutionary perspective, it is probable that our organisms developed in an environment in which the threats that humans faced were largely of infectious or violent character, rather than the psychological stress that is ubiquitous in every-day life in the industrialized world, leaving us exposed to the modern world stressors with suboptimal response mechanisms of an ancient origin. However, it is important to note that psychological stress probably activates the neural-immune pathways from a different entry-point than physiological stress (i.e. infection, trauma or injury), but the mechanisms are not yet fully understood (Maier & Watkins, 1998).

In conclusion, acute mental strain potentially elicits cytokine-induced alterations because the immune system responds to stress in a similar—though not identical—fashion, regardless of whether the threat is of psychological, infectious or a physical nature (Figure 3).

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3 The term allostatic refers to the physiological changes that occur in an organism as a reaction to stress, such as the inflammatory response which purports at restoral of homeostasis. Allostatic load can be described as the “costs imposed by frequent and prolonged stress” and importantly, lack of time to recover between stressors (Gunnar & Quevedo, 1997; McEwen, 1998).
The inflammatory response may be induced by psychological, infectious or physiological stressors.

The immune response to chronic psychological stress

If, as discussed, acute psychological stress can activate the immune system, the exposure to chronic stress should have an effect on immune parameters as well. Pioneering stress as a concept in the 1930ies, Hans Selye was the first to recognize that psychological stressors have physiological implications; and that long-term stress may eventually lead to disease (McEwen, 1998). For instance, there is a well established link between health and socioeconomic status which can partially be explained by immune activity (Wright & Steptoe, 2005). An increasing body of research has demonstrated that psychological factors (see e.g. Janszky et al., 2005) and low socioeconomic status are linked to the development and progression of coronary heart disease (CHD), to the cause of death by CHD and to many types of cancer (Owen, Poulton, Hay, Mohamed-Ali, & Steptoe, 2003). In addition, low socioeconomic status has shown to be related to infectious illnesses, autoimmune and affective disorders (Owen et al., 2003). This relationship may to some extent be explained by higher exposure to frequent psychological pressures in lower socioeconomic status groups compared to more privileged groups, due to lacking social support, higher levels of financial strain, lower job control and lacking psychological resources, such as functional coping strategies4 (Marmot, Bosma, Hemingway, Brunner, & Stansfeld, 1997; Owen et al., 2003; Taylor & Seeman, 1999).

In an experiment designed to investigate the link between socioeconomic status—as defined by annual income, education and job-position—and inflammatory activity, it was expected that low socioeconomic status would correspond to elevated CRP-levels reflecting a cytokine-associated inflammatory response caused by prolonged exposure to stress, and that the recovery from experiment-induced psychological stress would be delayed for those with low socioeconomic status compared to more privileged controls. After correcting for confounding variables, such as smoking and alcohol consumption, the results showed that lower socioeconomic status was associated with increased CRP regardless of gender, although no difference in responsiveness to acute stress between participants of low and high

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4 Coping strategy has been defined as "the way in which stressors are appraised and dealt with" (Kiecolt-Glaser et al., 2002).
socioeconomic status was discovered. However, independent of socioeconomic status, the study revealed that men and women respond differently to stress; women responded stronger in terms of immune-activated leukocyte count and were slower to recover from acute stress (Owen et al., 2003). Strike et al. (2003) investigated the mild inflammatory response as an effect of administration of harmless bacteria products on mood, and the potentially modifying effect of chronic stress. The results indicate that the infection led to a transitory negative mood in those who received an injection with bacteria compared to placebo, with a greater effect for those reporting financial strain. This suggests that an underlying psychological stressor either magnified the inflammatory response to a challenge, in this case bacterial infection, or that it enhanced the change of mood following an inflammatory response. Other studies have confirmed these results (see e.g. Kiecolt-Glaser et al., 2002; see e.g. Maier & Watkins, 1998).

Inflammation and the connection to morbidity
There is growing evidence that many illnesses that are associated with premature death—such as cardiovascular disease or cancer—have among other factors the immune-related inflammatory activity in common, as reflected by elevated levels of pro-inflammatory cytokines and CRP-levels (Brotman et al., 2007; Kiecolt-Glaser et al. 2002; Toker, Shirom, Shapira, Berliner, & Melamed, 2005). These links are not yet fully understood but an increasing body of evidence points at the presence of low-grade inflammation as indicative of a disrupted balance of pro-and anti-inflammatory responses of the immune, endocrine and sympathetic nervous systems (Melamed, Shirom, Toker, Berliner, & Shapira, 2006). In addition, psychological factors have been shown to affect the outcome of disease since chronic stress may cause pathological increases of the production of pro-inflammatory cytokines which enhances risk of mortality in individuals with cardiovascular disease (Brotman et al., 2007; Kiecolt-Glaser et al., 2002). Also, studies have shown that inflammatory cytokines are increased in patients with anxiety and mood disorders (Dantzer, Connor, Freund, Johnson, & Kelley, 2008), and depression has been associated with elevated levels of CRP and fibrinogen in men (Toker et al., 2005). In women, burnout and vital exhaustion have been associated to increased levels of pro-inflammatory cytokines (Grossi, Perski, Evengård, Blomkvist, & Orth-Gomér, 2003; Janszky et al., 2005), fibrinogen and CRP (Toker et al., 2005).

Self-rated health—previous research
As previously mentioned, an association between the levels of circulating cytokines and self-rated health has been demonstrated (Janszky et al., 2005; Lekander et al., 2004; Undén et al., 2007). When it comes to ESR, a previous study of 3,000 men and women, revealed a significant correlation (r=0.15, p<0.01) between high ESR-values and poor self-rated health, but no analyses of gender differences were performed (Nilsson et al., 1997). However, as demonstrated in further detail below, previous research has revealed differences in the way health is subjectively perceived which relates to factors such as functional health, psychosocial factors, gender and age (Gerber et al., 2009; Lekander et al., 2004; Molarsus et al., 2006; Undén & Elofsson, 1998). Moreover, self-rated health has been found to be a stable predictor of mortality in men and women (Benyamini & Idler, 1999; DeSalvo et al., 2005; Gerber et al., 2009; Larsson, Hemmingsson, Allebeck, & Lundberg, 2002).

Self-rated health and functional health
Perhaps not surprisingly, in a cross-sectional survey study of 1,045 men and women, low functional health—as indicated by disability, chronic disease and chronic pain—strongly
correlated with poor self-rated health, as did certain manifestations of low physiological health. These included variables such as the number of times of seeking medical consultation, the amount of sick-leave and musculoskeletal symptoms as well as measures of chronic pain (Undén & Elofsson, 1998).

**Self-rated health and psychosocial factors**

Results from meta-analyses and longitudinal studies show that some psychosocial measures, too, are stable predictors of self-rated health. Molarius et al. (2006) found that low socioeconomic status has been associated with poor self-rated health: in a Swedish survey study with 36,048 participants, those with poor self-rated health experienced low job control, fear of losing one’s job, dissatisfaction with work, economic hardship, together with the lack of social support and the feeling of recently having been belittled. For men, but not women, a low educational level was associated to poor self-rated health. Moreover, Undén and Elofsson (1998) found that satisfaction with work and leisure time and the feeling of being appreciated in and outside of home was positively related to good self-rated health. Self-rated health was also found to relate to the mental health indicators ‘mood’ and ‘level of energy’. With regard to socio-demographic situation and lifestyle, satisfaction with the economic and domestic situation and the level of physical activity in the spare time, revealed positive correlations to high self-rated health. In a longitudinal study by Gerber et al. (2009), self-rated health among patients following a myocardial infarction (MI) was examined. It was shown that self-rated health at baseline was associated with physiological as well as social and psychological factors. Apart from cardiovascular disease severity, post-MI complications and the presence of co-morbid disorders, it was also shown that life-style related factors such as diabetes, physical inactivity, smoking and obesity were strong predictors of low self-rated health. Additionally, low family income was significantly related to poor self-rated health, as was being of immigrant or minority status. In conclusion, self-rated health among post-MI patients was related to basically the same socio-economic, demographic and life-style factors in addition to factors involving physical and functional health as in non-clinical populations, and was of prognostic importance for post-MI recovery.

**Demographic variance in inflammation and self-rated health**

When it comes to self-rated health, the results from several studies have concluded that women tend to assess their health as slightly poorer than men (Molarius et al., 2006). Again, there is strong evidence that self-rated health is inversely related to elevated levels of inflammation in women—a relation that becomes more evident with age (Undén et al., 2007); but the connection between inflammation and self-rated health is insufficiently examined in men, although a weaker and non-significant connection was observed in one study (Lekander et al., 2004). It has been proposed that a greater female interoceptive sensibility to inflammatory cytokines may explain the stronger association between inflammatory activity and self-rated health in women (Lekander et al., 2004). As to age as a factor, it has been shown that poor self-rated health is two to three times more common among 50-79 year old men and women than among 18-34 year olds (Molarius et al., 2006). It has also been shown that aging is associated with increased inflammatory activity (Krabbe, Pedersen, & Bruunsgard, 2004); for instance, stress has a more pronounced effect on the immune system in elder subjects compared with younger subjects (Segerstrom & Miller, 2004). In addition to poorer objective health in elder as compared to younger people, the sensitivity to inflammatory cytokines appears to increase with age (Undén et al., 2007).
**Self-rated health and mortality**

A systemic review of 19 studies published between 1985 and 1998 revealed a two- to fourfold increased risk of mortality among those with the poorest self-rated health compared to those with the best self-rated health (Benyamini & Idler, 1999) and a meta-analysis by DeSalvo et al. (2005) found that there was a two-fold increased risk of mortality for individuals with poor self-rated health compared to those with excellent self-rated health. There has been several different explanations offered to this phenomenon; it has been suggested that self-rated health captures debuting illness at subclinical level (Undén et al., 2007). But—as pointed out by Idler and Benyamini (1997)—if self-rated health would only reflect debuting morbidity and increased inflammatory activity, whatever the aetiology may be, the association with mortality would likely diminish over time. This is, however, not the case. Although the pattern of death changes over time, self-rated health remains a stable predictor of mortality long after the initial assessment (Idler & Benyamini, 1997; Larsson et al., 2002). It seems that the predictive power of self-rated health remains also after controlling for symptoms of disease and dysfunction (Idler & Benyamini, 1997). These findings have led Gerber et al. (2009) to propose that self-rated health is a measure that “reflects a variety of health-related aspects and spans the entire wellness-illness continuum” thus including aspects of mental and physiological health that are most salient to an individual.

**Study aim**

The primary aim of this study was to investigate whether ESR, a non-specific marker of inflammation, is related to self-rated health among young men. In reference to previous studies which has linked self-rated health with inflammatory activity as reflected by pro-inflammatory activity (Janszky et al., 2005; Lekander et al., 2004; Undén et al., 2007), it was expected that poor self-rated health would be associated with high ESR. A secondary objective was to investigate whether self-rated health is related to mortality. Drawing upon data from previous research (Benyamini & Idler, 1999; DeSalvo et al., 2005; Gerber et al., 2009; Larsson et al., 2002) which has shown that self-rated health is a stable predictor of mortality, it was hypothesized that poor self-rated health would predict premature death at follow-up 37 years after the collection of data began. To our best knowledge, this is the first study with follow-up data covering a time period this long. Thirdly, since it has been shown that inflammation is associated with a number of disorders and illnesses, which are in turn predictors of mortality (Brotman et al., 2007; Kiecolt-Glaser et al., 2002; Toker et al., 2005), it was hypothesized that ESR would predict mortality.

**Method**

**Study population**

This study is based on data, which was collected in 1969-70 when 49,321 Swedish men underwent military conscription. At that time, the military service was compulsory in Sweden, and the study population represents 97-98 per cent of all Swedish men born in 1949-51. In this cohort, 97.7 per cent of the men were born in 1949-51, the remaining 2.3 per cent were born before 1949. Mainly due to congenital disorders or severe disabilities, 2 to 3 per cent of the male population were exempted from military conscription. The regional ethics examination board at Karolinska Institutet in Stockholm approved the study.
Data collection
At the time of conscription, the study subjects answered questionnaires concerning social background, habits, psychological factors, social adjustment and health. The conscripts also met with a psychologist for a structured interview. Additionally, a physician examined all conscripts, and any physical disorders were diagnosed according to the Swedish version of international classification of disorders, version 8 (ICD-8).

Self-rated health
The conscripts were asked to subjectively assess their health, answering the question: “In general, would you say your health right now is: very good, rather good, neither good nor poor, rather poor or very poor”? The ratings were coded on a 5-point scale where 1=very good, 2=rather good, 3=neither good nor bad, 4=rather poor and 5=very poor.

Erythrocyte sedimentation rate
During the physical examination at conscription, samples of blood were drawn and ESR was analysed according to standard clinical laboratory procedures. Erythrocyte sedimentation rate is stated in mm/h.

Body mass index
At conscription, the study subjects were weighed and measured. According to Adolfsson (2004) there is an inverse association between self-related health and body mass index (BMI)—the ratio of weight to height squared (kg/m2). Body mass index is a factor that can affect connections between certain biological mechanisms and self-rated health. For instance, cytokines are to a certain extent produced in the adipose (fat) tissue (Andreasson, Arborelius, Erlanson-Albertsson, & Lekander, 2007). Therefore BMI was controlled for in the analysis.

Emotional control
The combined questionnaire and interview data made up the basis for a rating of emotional control by a psychologist. Individuals who suffered from self-reported psychosomatic symptoms, anxiety, low stress-tolerance, nervous problems, whom had difficulties with emotional commitment and with uncontrolled aggression, were given a score of 1 or 2. On the opposite, a score of 4 or 5 were given those conscripts who were judged as well-adapted and showed high stress-tolerance, whom had good control over aggression and nervousness and who were not anxious. Those in between were allocated a score of 3 (see Larsson et al., 2002).

Psychiatric diagnosis, past or present
Individuals who reported of current or prior psychiatric or neurologic disorder or showed symptoms thereof during the interview with the psychologist were assessed by a psychiatrist and diagnosed according to ICD-8.

Smoking
Smoking has been associated with inflammatory markers, such as CRP and fibrinogen (Toker et al., 2005). Therefore smoking was controlled for in the analysis. The self-reported amount of cigarettes smoked per day were coded on a 5-point scale where 1=>20, 2=11-20, 3=6-10, 4=1-5 and 5=non-smoker.
Follow-up information
This study contains longitudinal data available in 2006, including time of death and cause of mortality. The data was obtained through the national cause of death register based on the personal identification number that is assigned to Swedish residents.

Data analyses
First, a Pearson correlation analysis of the eventual association between self-rated health and ESR was calculated. Thereafter, Pearson correlation analyses between potential explanatory variables of relevance for self-rated health and inflammation (BMI, emotional control psychiatric diagnosis and smoking) were performed. The univariate relations found in the first analyses were further analysed with a multiple regression analysis, adjusting for BMI, emotional control, psychiatric diagnosis and smoking. Last, Cox regression analyses of self-rated health and mortality and of ESR and mortality were performed. Due to missing values, the numbers of participants (N) in each analysis vary slightly. All analyses were performed using SPSS.

Inclusion and exclusion criteria
A normal ESR-value for men under 50 years of age, is ESR equal to or below 20 mm/h (Ganrot et al., 1997). As mentioned, elevated ESR-values are an indication of an ongoing infection or pathology. Among the 49,321 men, 1 per cent had an ESR-level that exceeded 20 mm/h. However, according to Ganrot et al. (1997), values less than 2 mm/h may be pathological as well, or an indication of a technical error in handling the blood samples. Because levels less than 2 may indicate an error in handling, and since the aim was to look for linear correlations between variables, values less than 2 were excluded from further analyses leaving 32,236 study subjects, or 65.3 per cent of the original cohort. This did not significantly affect the first results. Thus, all analyses presented hereafter were made using data of those with ESR values 2 mm/h or higher.

Results
Self-rated health
Out of 31,967 study subjects, 132 subjects rated their health as “very poor”, and 1,210 rated their health as “rather poor”. In between, 4,527 subjects rated their health as “neither good nor poor” while 13,436 and 12,662 rated their health as “rather good”, and “very good”, respectively (Diagram 1).
Diagram 1. Distribution of self-rated health

**ESR**
As presented in Table 1, after exclusion of ESR-values 0 and 1, the most frequent ESR-value was 2 mm/h. The majority of the participants had ESR-values within the normal range (ESR-value 2-20).

Table 1. Distribution of ESR

<table>
<thead>
<tr>
<th>ESR-value</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Percent</th>
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<tr>
<td>2</td>
<td>13,528</td>
<td>42.0</td>
<td>42.0</td>
</tr>
<tr>
<td>3</td>
<td>6,351</td>
<td>19.7</td>
<td>61.7</td>
</tr>
<tr>
<td>4</td>
<td>3,577</td>
<td>11.1</td>
<td>72.8</td>
</tr>
<tr>
<td>5</td>
<td>2,249</td>
<td>7.0</td>
<td>79.7</td>
</tr>
<tr>
<td>6</td>
<td>1,494</td>
<td>4.6</td>
<td>84.4</td>
</tr>
<tr>
<td>7</td>
<td>1,048</td>
<td>3.3</td>
<td>87.6</td>
</tr>
<tr>
<td>8</td>
<td>765</td>
<td>2.4</td>
<td>90.0</td>
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<td>9</td>
<td>482</td>
<td>1.5</td>
<td>91.5</td>
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<tr>
<td>10</td>
<td>492</td>
<td>1.5</td>
<td>93.0</td>
</tr>
<tr>
<td>11</td>
<td>305</td>
<td>0.9</td>
<td>94.0</td>
</tr>
<tr>
<td>12</td>
<td>308</td>
<td>1.0</td>
<td>94.9</td>
</tr>
<tr>
<td>13</td>
<td>233</td>
<td>0.7</td>
<td>95.6</td>
</tr>
<tr>
<td>14</td>
<td>225</td>
<td>0.7</td>
<td>96.3</td>
</tr>
<tr>
<td>15</td>
<td>224</td>
<td>0.7</td>
<td>97.0</td>
</tr>
<tr>
<td>16</td>
<td>109</td>
<td>0.3</td>
<td>97.4</td>
</tr>
<tr>
<td>17</td>
<td>122</td>
<td>0.4</td>
<td>97.8</td>
</tr>
<tr>
<td>18</td>
<td>97</td>
<td>0.3</td>
<td>98.1</td>
</tr>
<tr>
<td>19</td>
<td>62</td>
<td>0.2</td>
<td>98.2</td>
</tr>
<tr>
<td>20</td>
<td>60</td>
<td>0.2</td>
<td>98.4</td>
</tr>
<tr>
<td>21-99</td>
<td>505</td>
<td>1.6</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Background variables
Table 2 shows the proportion of exposure to the background variables in total and across each level of self-rated health. In comparison to subjects with very good self-rated health, those with very poor self-rated health were 4.7 times more likely to have low or very low emotional control. Moreover, a current or prior psychiatric diagnosis was 8.5 times more common and there were 1.4 times as many smokers in this group of self-rated health. There were little or no differences in BMI across the 5 categories of self-rated health.

Table 2. Proportion (%) exposed to the potential explanatory variables, in total, and across the 5 levels of self-rated health

<table>
<thead>
<tr>
<th>Background variable</th>
<th>Very good</th>
<th>Rather good</th>
<th>Ngnp</th>
<th>Rather poor</th>
<th>Very poor</th>
<th>Total</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI mean (SD)</td>
<td>21.0 (2.5)</td>
<td>21.0 (2.6)</td>
<td>20.8 (2.9)</td>
<td>20.6 (2.8)</td>
<td>20.7 (2.5)</td>
<td>20.9 (2.6)</td>
<td>32,044</td>
</tr>
<tr>
<td>Very low &amp; Low emotional control</td>
<td>17.0</td>
<td>32.1</td>
<td>52.0</td>
<td>67.5</td>
<td>79.4</td>
<td>30.6</td>
<td>9,797</td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td>5.9</td>
<td>11.9</td>
<td>24.2</td>
<td>37.7</td>
<td>50.0</td>
<td>12.6</td>
<td>4,027</td>
</tr>
<tr>
<td>Smoking</td>
<td>52.4</td>
<td>59.6</td>
<td>64.7</td>
<td>68.3</td>
<td>71.2</td>
<td>57.5</td>
<td>18,372</td>
</tr>
</tbody>
</table>

SD= standard deviation, SRH=self-rated health, Ngnp = neither good nor poor

Relations between self-rated health, ESR and background variables
The Pearson correlation analysis revealed a significant correlation between self-rated health and ESR among the study population (r= 0.08, p<0.001). The univariate correlations between self-rated health and ESR on the one hand, and background factors on the other, are presented in Table 3. Self-rated health was significantly correlated to all of the background variables, but correlated most strongly to emotional control and psychiatric diagnosis. ESR was significantly and negatively correlated with BMI, emotional control and smoking, and positively and significantly correlated to psychiatric diagnosis.

Table 3. Univariate relations between self-rated health and ESR with background factors

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Self-rated health</th>
<th>ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>-0.036***</td>
<td>-0.023***</td>
</tr>
<tr>
<td>Emotional control</td>
<td>-0.348***</td>
<td>-0.054***</td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td>0.240***</td>
<td>0.097***</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.150***</td>
<td>-0.017***</td>
</tr>
</tbody>
</table>

*** p<0.001
Multivariate regression analyses between self-rated health and ESR adjusted for background factors

As Table 4 shows, multiple regression analyses showed that the effect of ESR on self-rated health remained largely unaffected after adjustment for psychiatric diagnosis, emotional control, BMI and smoking. Emotional control showed the strongest independent relation with self-rated health. With ESR as the dependent variable, self-rated health was the most important contributing factor. Also, emotional control and BMI showed significant, albeit small, independent relations to ESR.

Table 4. Multivariate associations between self-rated health and ESR adjusted for background factors (beta coefficient)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Self-rated health</th>
<th>ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-rated health</td>
<td>-</td>
<td>0.080***</td>
</tr>
<tr>
<td>ESR</td>
<td>0.069***</td>
<td>-</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.014**</td>
<td>-0.021***</td>
</tr>
<tr>
<td>Emotional control</td>
<td>-0.284***</td>
<td>0.013*</td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td>0.093***</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.087***</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*=p < 0.1, **=p < 0.01, ***=p < 0.001

The relations between self-rated health, ESR and mortality

The Cox regression analysis showed that in 2006, the increased risk of premature death was almost two-fold for those with very poor self-rated health. Five point three per cent of those with very good self-rated health had deceased, compared to 9.8 per cent of those with very poor self-rated health. Furthermore, ESR significantly predicted mortality (beta=0.051, p<0.002), i.e. the higher the ESR the greater the odds for mortality.

Discussion

The aim of this study was to investigate the associations between self-rated health and ESR, and the associations between self-rated health, ESR and mortality, controlling for background factors. There were three main findings. Firstly, a significant correlation between poor self-rated health and elevated levels of ESR was observed. Secondly, the association between self-rated health and ESR was not explained by BMI, emotional control, psychiatric diagnosis or smoking. Thirdly, both self-rated health and ESR were significant predictors of premature death.

The association between self-rated health and ESR

In the present study, poor self-rated health was significantly associated with elevated levels of ESR, but the correlation was in the low range. Consisting of young, apparently healthy men, the study sample represents a population that has been insufficiently examined in terms of
gender and age, and one in which a strong association between self-rated health and inflammation has not yet been demonstrated. So far, as previously discussed, researchers have been able to demonstrate a strong association between self-rated health and inflammation only in women. The results of the present study suggest that there is an inconsistent link between self-rated health and inflammation among men, thus pointing at a gender difference in the way health is subjectively perceived in relation to markers of inflammation.

Several notions may be related to this divergence. For one thing, it is well-known that the prevalence of allergies and autoimmune disease is manifold in women compared to men (Kavelaars & Heijnen, 1999; Shames, 2002) although the basis of this divergence is not clear. In addition, there is evidence of an enhanced inflammatory response to acute stress in women (Toker et al., 2005) and Owen et al. (2003) demonstrated that there is a difference in the way men and women respond to stress; immune-related changes in response to a stressful event may take longer to retrieve base-line levels in women. According to Lundberg (2005), rather than being the result of biologically predisposed gender difference, the divergence could stem from cultural influence of gender roles, which exposes women to a heavier allostatic load than men. Essential for the restoral of homeostasis is time to recover, and studies have shown that women generally take on greater responsibilities concerning household and childcare tasks compared to men thus putting women at risk of an increasing allostatic load (Luecken et al., 1997; Lundberg, 2005). It should be noted however, that animal studies have revealed a gender difference in the stress-response: e.g. female rodents react differently than males under acute stress, leading some researchers to implicate the role of sex hormones in the stress-response (Wood & Shors, 1998). Obviously, the above mentioned findings might point towards a greater overall inflammatory activity in women, but do not explain why there seem to be a greater female interoceptive sensibility to inflammatory cytokines that may explain the stronger association between inflammatory activity and self-rated health in women, as reported by Lekander et al. (2004). Notably, in the present study 81.5 per cent of the participants, rated their health as rather good or very good and only 4.2 per cent rated their health as rather poor or very poor. Thus, statistically, the weak correlation that was found between self-rated health and ESR may be the result of limited variance in the variables. Moreover, there was a relatively low prevalence of inflammation among the participants in the present study. Only 1.6 per cent had above normal ESR levels which could possibly be attributed to the study participants’ young age, since it has been shown that aging is associated with higher levels of pro-inflammatory cytokines (Krabbe et al., 2004) and that the sensitivity to inflammatory cytokines increases with age (Undén et al., 2007).

In sum, the modest correlation between self-rated health and ESR that was observed in the cohort of the present study may be due to gender related differences in immune function, and to the young age of the participants which may further limit bodily sensitivity for inflammation.

Associations between background factors and self-rated health

In the present study, the inclusion of background factors in the multivariate analyses did not explain the association between self-rated health and ESR, although there were significant correlations between all background factors that were included in the analysis (BMI, emotional control, psychiatric diagnosis and smoking) and self-rated health, as well as between background factors and ESR. When comparing exposure to background factors between those with very good self-rated health to those with very poor self-rated health it appeared that low and very low emotional control was almost 5 times as common among those in the latter category; and a prior or current psychiatric or neurological diagnosis was
8.5 times as common among those with very poor self-rated health compared to those with very good self-rated health.

Among the available background variables, emotional control had by far the strongest independent correlation to self-rated health, followed by psychiatric diagnosis. Emotional control is a measure that encompasses expressions of anxiety, low stress-tolerance, nervousness, psychosomatic symptomatology, difficulties with emotional commitment and uncontrolled aggression; behaviours that may be symptomatic of lack of functional coping style. Thus, Kristenson, Olsson, and Kucinskiene's (2005) hypothesis that self-rated health covers “psychological and physiological measures of stress and resilience to stress”; could be consistent with the finding of the present study, possibly suggesting that the perception of not having mental resources to face psychological challenges may result in poor self-rated health. Conversely, it has been proposed that having access to functional coping strategies may have protective properties to the tear and wear of life’s stress (Kristenson et al., 2005), and that an optimistic coping style may have a positive influence on recovery after serious illness (Fayers & Sprangers, 2002). A fairly restricted amount of potential background variables were included, thus limiting the possibility to draw conclusions based upon our results. It should be kept in mind, however, that inclusion of too many statistical controls also carries a downside, most importantly in terms of decreased construct validity (Segerstrom, 2009), referring to the degree of legitimacy between the theoretical construct upon which the operationalizations of a study are based.

In conclusion, according to results of this study, the association between self-rated health and ESR was weaker than those between self-rated health and low emotional control and psychiatric diagnosis, respectively, suggesting that inflammatory activity is modestly associated to self-rated health among young males and that measures of mental resources are more important to how overall health is perceived in this population.

**Associations between background factors, ESR and mortality**

The results of this study revealed that a diagnosis of psychiatric or neurologic dysfunction most strongly correlated to elevated levels of inflammation as measured by ESR. Assuming that having or having had a psychiatric diagnosis would be indicative of psychological vulnerability; this association may be explained by inflammatory responses caused by psychological stress (Owen et al., 2003) since it has been shown that psychological stress may adversely impact the time of restoral of homeostasis after an inflammatory response to a mild challenge of the immune system (Strike et al., 2003). Additionally, individuals who experience chronic psychological stress may take longer to recover after illness, injury or negative emotional reactions, and are subsequently at higher risk of chronic inflammation, which ultimately may progress into disease and mortality (Wright & Steptoe. 2005), possibly in part mediated through risk behaviours and unhealthy life style choices (see e.g. Molarius et al., 2006). For instance, in this study, smoking and ESR were positively correlated in the univariate analysis. Speculatively, this correlation could be explained by the fact that smoking has in itself a pro-inflammatory effect (Lao et al., 2008) and smoking has also been shown to enhance the physiological reaction to stress (Robinson & Cinciripini, 2006), thus causing an accumulative effect on the total allostatic load, which might explain an increase of inflammatory activity.

The results of the present study show that after adjustment for BMI, emotional control, psychiatric diagnosis and smoking, the multivariate analysis of the relation between self-rated health and ESR remain largely unaffected. To conclude, the background factors that were
included in the analyses were not confounders for the association between self-rated health and ESR, although they did, to various extents, explain the variance of self-rated health and of ESR: emotional control had by far the strongest independent association to self-rated health, whereas ESR was explained by self-rated health to a modest degree.

*The relations between self-rated health, ESR and mortality*

Drawing upon the results from e.g. the study by Larsson (2002), which examined the same cohort that was used in the present study but from follow-up in 1996, it was expected that self-rated health would predict mortality. In 2006, more than three and a half decades after collection of data, those with very poor self-rated health still had an almost two-fold risk of premature death compared to those whose self-rated health was very good at the time of conscription. Thus, the results of the present study show that self-rated health remains a stable predictor of mortality long after the initial assessment.

In the present study, a significant association between ESR and mortality, i.e. the higher the ESR, the greater the risk of premature death, could be observed. These results are in line with the results from previous studies which have found that elevated levels of inflammatory cytokines in the blood is associated with a number of disorders that, in turn, are linked to mortality (Brotman et al., 2007; Kiecolt-Glaser et al., 2002; Toker et al., 2005). Remarkably, our results show relatively strong associations between self-rated health and mortality, and between ESR and mortality, but a modestly significant association between self-rated health and ESR. Hypothetically, among the conscripts who reported poor and very poor self-rated health, but did not have elevated levels of inflammatory activity at the time of conscription nevertheless had lowered resilience to stress in the years that followed, thus explaining the link to morbidity.

*Study strengths and study weaknesses*

Our study sample consisted of 49,321 male 18-20 year olds, which, at conscription in 1969-70, represented 97 per cent of all Swedish men born in 1949-51. On the one hand, having a study sample that represents such a large percentage of the population minimizes the risk of a selection bias (Borg & Westerlund, 2006). On the other hand, the confined age span of this study sample may limit the possibility to generalize the results (Borg & Westerlund, 2006) as regards the association between self-rated health, ESR and background variables to other age groups. Based upon previous research (Undén et al., 2007) it is also possible that a link between self-rated health and inflammation is not as obvious in study subjects of this young age as it possibly would have been in older subjects. Also, concerning the external validity, it cannot be excluded that the setting in which information was collected may have affected the data. For instance, as demonstrated, psychological stress may affect physiology, cognition and overt behaviour. Theoretically, if the study subjects perceived the conscription as stressful, may have caused increased ESR-levels, or alter the way in which memories were recalled during the interview or when answering questionnaires. Regarding causality, it is not possible to draw conclusions based upon cross-sectional data in a correlation study design (Borg & Westerlund, 2006); it is impossible to know if ESR affects self-rated health, or vice versa. Regarding the longitudinal data used in this study, the results indicate that self-rated health and ESR may predict mortality but attempts in explaining the underlying mechanisms will remain speculative.
Conclusion
The aim of the present study was to investigate the relation between self-rated health and inflammation in men. The present study confirms an association between poor self-rated health and higher levels of inflammation, here measured by ESR, even after controlling for potential confounding variables. Although highly significant in this large study population, ESR explains relatively little variance in self-rated health. This fact may be due to gender (a putative weaker relation between inflammation and subjective health in males), age (a lower sensitivity for inflammatory activity in younger people) and the fact that both ESR and self-rated health showed restricted variance. In order to further elucidate the mechanisms behind the observed gender and age related differences, research that investigates relations between self-rated health and inflammation in middle-aged and older men, is warranted. Adding to a growing body of evidence, it was also shown that inflammation and in particular self-rated health predict mortality. Finally, in the cohort of the present study, and drawing upon data from previous studies, measures of mental health were important factors in how overall health was perceived, and was significantly associated with inflammatory activity. Therefore, investigating the variations of coping styles seems a promising avenue in understanding the underlying mechanisms of the powerfully predictive qualities of self-rated health.

References


