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SELF-RATED HEALTH

BIOBEHAVIORAL DETERMINANTS WITH FOCUS ON INFLAMMATORY FACTORS

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*To Mamma and Mormor
for teaching me how to knit*

ABSTRACT

Self-rated (subjective) health is an independent predictor of future mortality, but neither the mechanisms behind this relation nor the biological determinants of poor self-rated health are known. Inflammatory cytokines give rise to a sickness response which includes fatigue, malaise, anhedonia and pain, resembling factors that are known to impact negatively on self-rated health. It is therefore possible that cytokines that cause a sickness response are important mediators in subjective health perception. This thesis investigated biobehavioral determinants of self-rated health, with a primary focus on inflammatory cytokines. The study populations included women patients from a primary health care center (Study I), women from a population based study on memory and aging in Umeå (Study II), men and women from a population based prospective study in Stockholm (Study III), and men in a laboratory study on the effects of experimentally restricted sleep (Study IV). A main finding was that higher (or increased) levels of inflammation related cytokines were associated with poor (or deteriorated) self-rated health; IL-1 β , IL-1ra and TNF- α in study I, and IL-6 in study II and IV. The observed association between higher levels of cytokines and poor self-rated health was shown to be stronger with increased age. Of psychological factors, positive affect turned out to be a more important determinant of self-rated health as compared to negative affect. In study III, the relation between leptin, a cytokine-like marker for available energy in the body, and self-rated health was investigated. Higher levels of leptin were associated to poor self-rated health in men, while instead predicting better future self-rated health in women. Moreover, self-rated health was associated to further sick-leave in both men and women. In study IV, subjective health - framed to represent the prevailing day - deteriorated gradually when sleep was restricted to 4 h per night, and returned to baseline levels after two days of recovery. This decrease in subjective health was significantly correlated with increased levels of circulating IL-6. This thesis presents increased support for an immune component of subjectively perceived health. It also implies that more short-term perspectives, e.g. in relation to changes in health behaviors such as sleep, should be taken into account when understanding subjective health perception. The results are of importance for understanding the psychobiological underpinnings of self-rated health and may give clues to explain its well-established association to future health.

LIST OF PUBLICATIONS

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If they hurt you, they hurt me too.

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*I'm done, tipping on my toes,
strike an iron and attack my soul
Misty moon, you're gonna see,
I've got you blues to get on my feet
'Cause this is my life, my friend,
and this is my time to stand
'Cause this is my life, my friend,
and I can't be no one else*

Anna Bergendahl

1 PREFACE

The winter flu – a personal reflection

It started as a sensation of something being wrong as soon as I woke up. I haven't had stomach cramps in 18 years, and I felt a bit dubious about the whole thing. At the 3rd vomit, I'm still feeling rather good overall, no sickness, but the need to leave my computer to go vomiting is really disturbing. I'm pretty sure I will be recovered the following day, even though I'm not really feeling that good anymore. After a morning with no food I was drained of all energy, which made perfect sense after not eating anything since the previous day. My subjective health was unaffected. In the evening I realize that I feel cold, which makes no sense since I'm fully dressed, in a fleece coat and covered by a thermo blanket. 39 C fevers (that is a lot to be me). Now, I really feel sick. I know I'm not going to work the following day, but still believe that I will have recovered. I still thought my health was perfect, and thought that I was a bit silly asking myself about my health perception, like that would change with the flu! The shivering gives me a killing headache and I give in on the aspirin the following morning. I feel pretty confident that I will be all right by evening. My subjective health is still good (Duh!).

But after a few days of thinking that I will be fine the following day, my hope begins to fail, in spite that I'm feeling successively better. No vomiting, no headache, no fever, but totally drained of energy. All I can remember is feeling ill, I feel low, and I don't know when I will be recovered, if ever. My subjective health has worsened. It took me a few more days to recover. By then, I felt well again, and my health perception returned to normal.

2 LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
BMI	Body mass index
CRP	C-reactive protein
DHEAS	Dehydroepiandrosterone sulphate
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
ELISA	Enzyme linked immunosorbent assay
HPA	Hypothalamic pituitary adrenal
IFN	Interferon
IGF	Insulin-like growth factor
IGFBP	Insulin-like growth factor binding protein
IgG	Immunoglobulin G
IL	Interleukin
LPS	Lipopolysaccharide
mRNA	Messenger ribonucleic acid
PNI	Psychoneuroimmunology
RIA	Radioimmune assay
SF	Short form
SRH	Self-rated health
TNF	Tumor necrosis factor

3 INTRODUCTION

There are no shortcuts to any place worth going.

Beverly Sills

Poor self-rated health is an individual's own rating of her health and is proven to be an independent predictor of both mortality and morbidity [1] as well as health care use and sick leave [2-5]. The mechanisms linking poor self-rated health and morbidity and mortality, however, are largely unknown [6]. Poor self-rated health is associated with symptoms that resemble a cytokine induced sickness response, which is a coordinated set of behavioral changes that occur as consequence of activation of the immune system in response to e.g. infection. Such changes include loss of appetite, sleepiness, withdrawal from normal social activities, fever, aching joints and fatigue [7]. Diffuse and unspecific symptoms resembling those of a cytokine-induced sickness response are common in all areas of primary care as well as in specialty medicine, but are not often connected with a specific disease or a medical explanation [8-10]. The relation between poor self-rated health and symptoms of sickness behavior was the starting point for a previous study that investigated the inflammatory cytokines as determinants of self-rated health in patients at a primary health care centre in Stockholm. Higher levels of the cytokines interleukin (IL)-1 β , IL-1ra and tumor necrosis factor (TNF)- α was associated with poor self-rated health in women, but not in men [11]. Even when controlling for age, education, physical health, and diagnoses in multiple regression analyses, self-rated health was more strongly associated to cytokine levels than physician-rated health. Finding determinants of self-rated health is of importance for understanding the psychobiological underpinnings of poor self-rated health and may give clues to explain its well-established connection to future adverse health events.

4 THE AIMS OF THE THESIS

The overall aim of this PhD-project was to investigate biobehavioral determinants of self-rated health, with primary focus on inflammatory cytokines.

Specific aims

- To investigate the association between cytokines and self-rated health in primary health care patients (Study I) and in a representative sample of the population (study II).
- To investigate the impact of age on the association between cytokines and self-rated health (Study I and II)
- To investigate the relation between cytokines and positive and negative affect (study II).
- To investigate the interrelations between self-rated health, positive affect and negative affect (Study II)
- To investigate if leptin is associated with self-rated health (Study III)
- To investigate if leptin and self-rated health is associated with sick leave (Study III).
- To investigate if a working week with restricted sleep and subsequent recovery days affects self-rated health and if such a change is related to increased levels of circulating cytokines (Study IV).

5 THEORETICAL FRAMEWORKS AND CONCEPTS

When it is not in our power to follow what is true, we ought to follow what is most probable.

Rene Descartes

René Descartes (Latin name Cartesius) was a French philosopher who stated that there are two fundamental kinds of substance: mental and material. According to his philosophy, which is specifically called Cartesian dualism, the mental (mind) does not have extension in space, and the material (body) cannot think. This separation of body/brain and soul/mind has had major impact on how we talk about ourselves but also on how medical care is organized today. In the history of medical care it may have been rather practical to separate somatic illnesses from mental illnesses, but it is important to remember that mental changes are mirrored by bodily changes. However, the idea of the separation of body and soul is so profound in language and culture that it is difficult to express monistic ideas, i.e. that the human biological and mental processes are inseparable. We can now see that, however practical to separate biological and mental processes, this is probably not the way forward in research on self-rated health.

What happened to Descartes? He came to Stockholm invited by the Swedish queen Kristina, but dies in pneumonia only after a few months. He was buried at Adolph Fredrik's Church in Stockholm for more than a decade before he was sent back to France. It is told that the coffin for the transport of the corpse was too short, and instead of getting a larger coffin, the head was removed from the rest of the body. On the way back to France, the head travelling outside the coffin was stolen. It was supposedly returned after 150 years.



Descartes' monument in Adolph Fredrik's church. April 18th, 2009. From left: Bianka Karshikoff, Anna Nixon Andreasson, Susanna Jernelöv and Mats Lekander. Photo: Johan André.

5.1 SELF-RATED HEALTH

Self-rated health (SRH, subjective, self-assessed, self-perceived, self-reported, self-related health) is the answer to a question of a person's perception of his or her general health status [1, 11]. It is thus a subject's rating on a particular scale of her subjective health status. Given in an open way, with little or no information about what to include in the response, different kind of factors of both psychosocial and medical nature are shown to influence the response [12]. The subjective rating of one's health is considered to be depending on variety of factors. Beside measures of functional health such as health care and drug use, sick leave and other measures of objective health status, major correlates of poor self-rated health are lack of energy, poor appetite, disturbed sleep, low fitness, discomforts, depression/anxiety and presence of pain [12, 13].

The most commonly used version of the question is "How would you rate your general health?" (SRH-5), requiring a response on a five-point grading scale ranging from 'very good' to 'very bad' [1]. The self-rated health question is part of the short form health questionnaire (SF-12 and SF-36). In SF-36 it is part of the item "general health" together with item 2 and 11. As mentioned, the exact wording of both the question and the response scale differs, see Table 1 for examples of self-rated health questions.

Table 1. Examples of self-rated health questions.

	Included in study
How would you rate your general state of health?	I and III
Do you feel healthy?	II
Do you feel completely healthy?	
How would you rate your health for today?	IV
How would you rate your current state of health?	
How would say your general health has been during the past year?	
For someone your age, how would you rate your overall health?	
How would you rate your state of health compared to other of the same age?	

In a review from 1997, it was concluded that the exact wording of the seemed to be of less importance when it comes to the ability of predicting morbidity and mortality [14]. Nonetheless, a global measure of self-rated health, not referring to age has been found the best predictor of mortality and may emphasize that all self-rated health measures are not equivalent measures of health status [15]. The predictive capacity of poor self-rated health on mortality is independent of age [16], gender (although it is generally stronger in men than women)[17], socioeconomic status [18], country of origin [16], cognitive function [19], and is found in specific patient groups such as diabetes, cardiovascular disease [20] and cancer [21]. The predictive capacity also persists over large follow-up periods [17]. In addition, the relationship between self-rated health and mortality is surprisingly consistent between countries, despite international variations in the average health state [14]. Because of the strong relationship with future objectively verified health, self-rated health is a commonly used research tool, both nationally and internationally. For example, both the World Health Organization and the National Board of Health and Welfare in Sweden include self-rated health in their public health surveys [22, 23]. Although short, well validated and easy to administer and register, self-rated health is still sparsely used clinical settings [24]. A summary of a literature search of self-rated health is presented in Table 2.

Table 2. PubMed hits by April 30th 2010.

PubMed search key word	N
Health	1915911
Self-rated health	3441
SRH	579
Self-rated health mortality	410
Self-rated health biological	106
Self-rated health determinants	189
Self-rated health pathways	42
Self-reported health	19058
Subjective health	13437
Self-perceived health	1677
Self-assessed health	1093
Self-related health	56
Self-evaluated health	97

5.1.1 What mechanisms link self-rated health to morbidity and mortality?

It is not completely obvious which factors that will explain how self-rated health can predict mortality. The association in the pathway between poor self-rated health and biological factors can go both ways; subjectively perceived health may be considered a perceptual function recognizing low grade disease before it can be objectively verified. The opposite, poor self-rated health may be associated with stress, health behaviors, compliance, and compromising objective disease in turn associated with changes in biological factors. In the report, Self-rated health in a European perspective [25], Margareta Kristenson lists possible hypotheses for the predictive power of self-rated health: sponge, trajectory, intervening and resource hypothesis.

Sponge hypothesis: Self-rated health is a more inclusive and accurate health measure, which captures subclinical or undiagnosed disease, as well as disease severity better than the included covariates. The ability to sense underlying disease in terms of sickness behavior and related symptoms has been the starting point of this thesis.

Trajectory hypothesis: Self-ratings of health are based on expectations of future health developments as well as on changes in perceived health status. A poor self-rated health would in this case be dependent on an expected decline in health, which could be due to known high blood pressure or presence of other risk factor for future ill-health.

Intervening hypothesis: Influence of health behavior on health perception. A person who rated their own health as good may be physically active and make effort to eat healthy. In addition, health behaviors such as physical activity and a healthy diet are likely to influence metabolism, nutrition and inflammation.

Resource hypothesis: External resources such as social support and socioeconomic status, and within person resources such as perceived control and trust associated to self-rated health can prevent health decline. Factors such as stress, psychosocial support and work load are also likely to influence health behavior and to be associated with changes in metabolism, nutrition and inflammation.

All these hypotheses are likely to interact, since for example, a smoker is likely to experience both a larger inflammatory load as well as carrying the knowledge of the adverse health effects of smoking. In addition, all of these hypotheses are likely to involve psychoneuroimmunological interactions.

5.2 PSYCHONEUROIMMUNOLOGY

Psychoneuroimmunology (PNI), which should perhaps rather be called psychoneuroimmunoendocrinology, is the research area of the connections and communication between the nervous, immune and endocrine systems and behavior. It is common knowledge that the nervous system regulates the endocrine system centrally via the pituitary and peripherally via the autonomic nervous system branches of the sympathetic and parasympathetic nervous system. The endocrine system in turn has several ways of communicating back to the brain, by hormones binding to receptors in the central nervous system. Through this communication, we can wake up every day, maintain our homeostasis and react physiologically to our environment. In spite of the known interactions between the central nervous system and other systems, the neuroimmune interactions, with the immune system signaling to the brain and the brain modulating the immune system, have previously had a hard time integrating in the fields of both immunology and neuroscience, as well as in other areas of medicine [26]. However, the presence of a bidirectional communication between the immune and the nervous system is beyond doubt. In below I first describe how the immune system signals to the nervous system and in turn how the nervous system modulates the immune system. Thereafter, some key areas in psychoneuroimmunology of relevance for the present thesis are presented.

5.2.1 Immune to brain communication and cytokines

The major explanatory factor investigated in relation to self-rated health in this thesis is cytokines. Cytokines are small proteins originally characterized in the intra regulation of the immune system. They have names such as interleukins, tumor necrotic factors, and interferons. Many cytokines have partially overlapping effects, and every cytokine has more than one effect [27], which makes the study of cytokines

both complex and interesting. In general, cytokines can be seen through the divisions of the immune system. First, we have the innate immune system with which we are born. Through this system, the body can respond with macrophages and natural killer cells to foreign substances, such as lipopolysaccharides (LPS) from the gram negative bacteria cell wall or unmethylated DNA that differs from the methylated human DNA. When triggered, the innate immune system releases proinflammatory cytokines such as IL-1 β and TNF- α , which in turn trigger the release of IL-6 that regulates the release of acute phase proteins such as C-reactive protein (CRP) and fibrinogen from the liver. As I will describe below, behavioral changes are also seen. Secondly, we have the acquired immune system with T-cells and B-cells that is involved in the advanced fight against viruses, bacteria and parasites. The acquired immunity evolves during our lifetime, gaining memories of e.g. pathogens through infections or vaccinations, in order to make a faster response to future challenge. This system is carefully regulated as, if it is too non-selective, allergies and autoimmune diseases might evolve, and if too selective, cancer and infections may go unbattled. In my studies I mostly include cytokines from the innate immune system. One important cytokine from the adaptive immune system that I use is the soluble receptor for IL-2, which regulates the T-cell response [26]. Although first described as regulators of immune function, cytokines serve important physiological roles. For example, moderate levels of IL-1 β are needed for memory formation [28] and IL-6 is of importance for regulating glucose synthesis in the liver and for the energy balance [29].

Cytokine receptors are found on neurons, both in the periphery and centrally [30]. Even though cytokines are small proteins, they are still too large to passively diffuse through the blood brain barrier. Instead, cytokines signal to the central nervous system through other pathways, for example by assisted transport through the blood brain barrier or by signaling through the blood brain barrier by binding to the vascular tissue, releasing second messengers such as prostaglandin E2. Another possibility is passing into the brain via circumventricular organs, which lack the tight junctions of the blood brain barrier, either from the blood stream or from the cerebrospinal fluid. Also, cytokines can signal through visceral or peripheral autonomic nerves such as the vagus nerve [30, 31]. Thus, there are redundant pathways by which cytokines can communicate with the central nervous system (Figure 1).

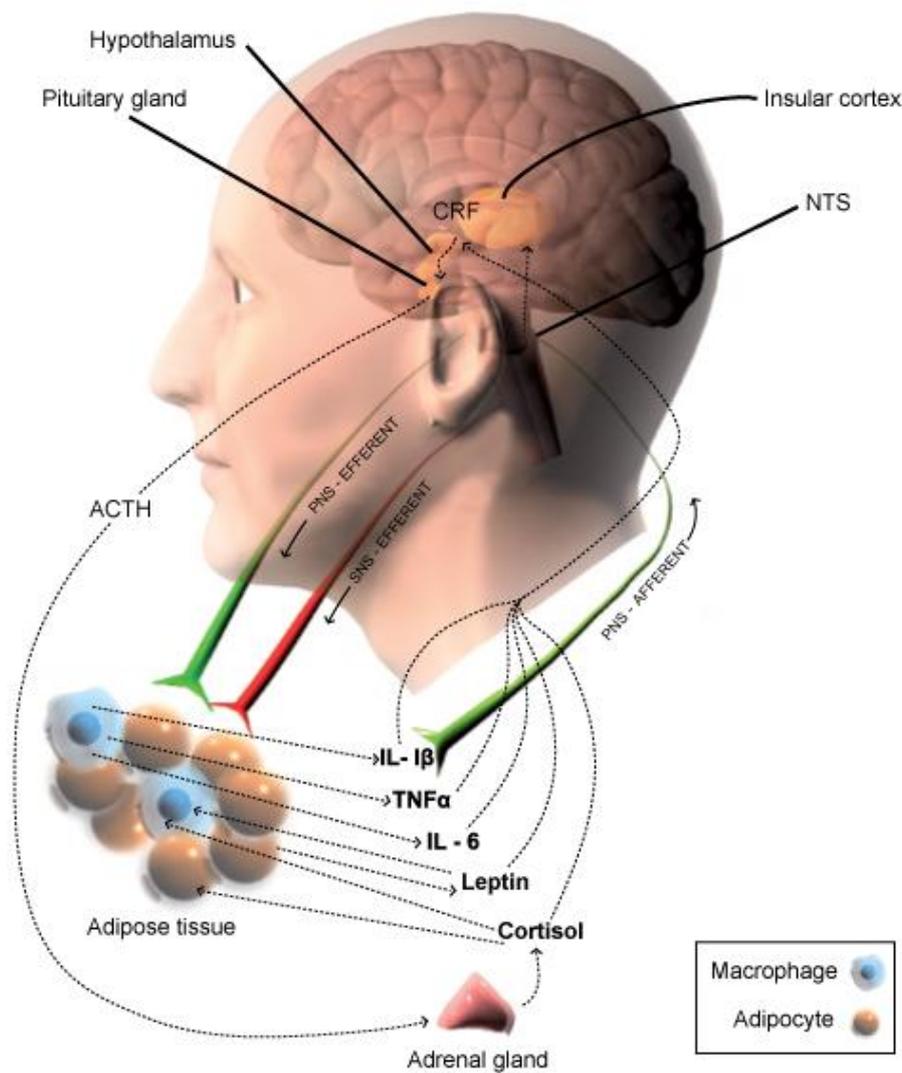


Figure 1. Interactions between the immune, neural, and endocrine systems. The proinflammatory cytokines IL-1 β , IL-6 and TNF- α are produced by activated immune cells such as macrophages and adipocytes produce the cytokine-like peptide leptin. Cytokines signal to the central nervous system through redundant pathways and activate the HPA axis which originates in the paraventricular nucleus (PVN). In turn, the autonomic nervous system (PNS and SNS) and the HPA axis regulate the immune response as well as the activity in the adipose tissue. The interoceptive pathway, which mediates the subjective perceptions of the bodily state, acts through sympathetic and parasympathetic afferent nerves, such as the vagus nerve, passes brainstem nuclei such as the NTS and reaches the insular cortex (not visible in a medial view of the brain)(Craig, 2002). We have hypothesized that the immune system, through cytokines, uses a similar pathway to inform the brain about the inflammatory state of the body, constituting an important and integrated part of the interoceptive system [29]. This pathway could be tonically activated in poor self-rated health. ACTH, adrenocorticotrop hormone; CRF, corticotropin releasing factor; HPA, hypothalamic–pituitary–adrenal; IL, interleukin; PNS, parasympathetic nervous system; NTS, nucleus tractus solitarius of the brainstem; PVN, paraventricular nucleus of the hypothalamus; SNS, sympathetic nervous system; TNF, tumor necrosis factor.) Adapted from Andreasson et al. [29]. Illustration: Thomas Nixon

5.2.2 Brain to immune communication and modulation of the immune response

The central nervous system can, as for the neuromuscular and neuroendocrine interactions of the autonomic nervous system (SNS and PNS) and the HPA axis, signal to the immune system as well (Figure 1). These pathways constitute an important route for negative feedback of inflammation and immune activation [32]. Immune cells bear receptors for neurotransmitters, neuropeptides as well as hormones, and the lymphoid organs are innervated just as muscles and endocrine glands [26]. The immune system can be classically conditioned, a function which has to include the nervous system. This was first shown convincingly demonstrated by Ader and Cohen in the seventies when they found that pairing saccharin with cyclophosphamide, an immunosuppressive agent, conditioned rats so that when they were re-exposed to saccharin, they were significantly immunosuppressed [33, 34].

5.3 KEY AREAS IN PSYCHONEUROIMMUNOLOGY

5.3.1 Sickness behavior

Why investigate cytokines in relation to self-rated health? When proinflammatory cytokines such as IL-1 β and TNF- α are injected into the body or directly into the brain, they give rise to a collection of central nervous system symptoms that together may be referred to as sickness behavior. Sickness behavior includes fever, fatigue, malaise, numbness, coldness, muscle and joint aches and anorexia [35, 36] and includes factors that resemble those that have previously been associated with poor self-rated health, see [11]. As described below, some cytokines also promotes sleep, likely to increase slow wave sleep during infection [37].

In a large body of studies, cytokine-induced sickness behavior has been studied in animals. If a female rat is injected with LPS, the bacterial endotoxin described above that provokes the innate immune system, she will experience sickness behavior and at 24°C she rests without doing the nesting she would normally do. However, lowering the temperature in the cage to 8°C will make her nest to protect her pups from hypothermia [38]. Obviously, she is not simply weak since she can work if she needs

to. Nevertheless she needs more incentives than normally to actually do so and to overrun the motivation to be still. A much earlier experiment showed that a LPS injection will reduce the bar pressing for water, food and intracranial self-stimulation in the lateral hypothalamus (one of the brain areas associated with reward)[7]. However, when the bar pressing will stop a rotating drum in which the rat is placed, the pressing rate is increased in response to LPS. The general conclusion of these and other experiments is that sickness behavior is a motivational state that organizes behavior towards a certain goal, and not simply a state of weakness [7].

5.3.2 Interoception

Interoception is generally described as the sense of the physiological state of the entire body, and constitutes a basis for the subjective evaluation of one's condition and 'how you feel' [39]. To be informed about bodily conditions, the brain depends on signals that convey relevant information through designated afferent pathways, and this information is used to regulate physiological processes as well as behavior [40]. We have suggested that interoceptive processing is likely to include inflammatory activity [29], partly because the hypothesized interoceptive pathways overlap with those implicated in the signaling of cytokines to the central nervous system (Figure 1). For example, this includes the afferent nerves of the autonomic nervous system implicated in the signaling of cytokines to the central nervous system (Figure 1).

Reasonably, the provision of input for the regulation of energy balance should be a crucial component in the interoceptive system. Leptin is produced by the adipocytes as a marker of the amount of adipose tissue and thus the available energy in the body (Figure 1)[29, 41]. As a marker of the amount of available energy, leptin is one important mediator in body-to-brain signalling to motivate behavior [42], similarly to cytokines, acting on central nervous system energy regulatory and reward circuitry [29, 43]. Leptin is a cytokine-like peptide and its receptor belongs to the IL-6 receptor family with stimulating effect of pro-inflammatory cytokines on leptin and vice versa [44, 45]. However, there are discrepancies in the associations between leptin and health, since low levels of leptin has been associated to both less depression in women [46] and high levels have been associated to better cognitive function [47]. On

the other hand, leptin has also been suggested as a link between obesity and cardiovascular disease [48-51], similarly to IL-6 [52].

5.3.3 Sleep

Why we sleep remains a big mystery. What is definitely known is that sleep is essential to health. Short sleep has been associated with both higher levels of cytokines [53], poor self-rated health [54], and increased mortality [55, 56], and sleep deprivation leads to sickness behavior resembling symptoms such as fatigue and pain [57, 58]. The immune system is involved in the regulation of sleep. Several specific immunological active peptides influence the sleep–waking cycle of the brain, either promoting or inhibiting sleep. For example, IL-1 β and TNF- α have been determined to be important sleep-promoting factors and are major mediators of somnolence and fatigue seen in sickness behavior [37]. Sleep disturbances also influence the levels of circulating cytokines per se and is thus a major confounder in the studies of affective disorders and inflammation [59].

5.3.4 Stress

The relation between psychosocial stress and immune function has been investigated in a vast literature. In very short, differential effects have been shown between e.g. acute laboratory stressors (largely stimulating innate immunity), brief naturalistic stressors such as academic exams (favoring humoral over cellular immunity), and chronic stress (generally suppressing effects)[60]. For example, acute stress can induce a release of pro-inflammatory cytokines such as IL-1 β and TNF- α , e.g. [61]. Stress, or adrenergic stimulation, have been shown to result in activation of the transcription factor nuclear factor- κ B in peripheral blood mononuclear cells in mice and in humans, and lead to increased activation of IL-6 at the mRNA level, at least in mice [62]. This suggests that activation of nuclear factor- κ B may represent one mediator that links stressful psychosocial events to the cellular response. The interpretation of these results have been that hormones released during an acute stress response may help prepare the immune system for potential challenges (e.g., wounding or infection) for which stress perception by the brain may serve as an early warning signal [63].

5.3.5 Affect

Similarly to poor self-rated health, both low positive affect and high negative affect has been associated with mortality [64]. Positive affect includes happiness and joy, while negative affect includes sadness and hostility. In general, positive and negative affect may be seen as the opposites of the same dimension. A happy person is not sad and vice versa, but it is quite possible to experience both positive and negative affect, also in a shorter time frame and they may rather be seen as parallel factors that not overlap completely [64].

I believe that robots, how they are designed to communicate - both in reality and motion pictures, are interesting when trying to understand emotions. Robots have quite simple means of communicating emotion. Some have voice and/or sound to use, and some can use body language like small children. Either way it is efficient enough to communicate emotion. However, communicating emotion is one thing. Experiencing emotion is another, and that is what Data needs in his quest to become human. Data is a humanoid robot (i.e. he is a robot that looks and talks as a human) that is part of the crew on Star Trek Next Generation that puts a lot of effort in understanding humans. Watching Data, although a fictional character, gives interesting perspectives on both emotion regulation and humanity. His builder never installed the emotional chip, so Data is thought not to be able to experience emotion. In the episode "Descent", Data and some of the other crew members are attacked by "Borgs" (evil cyborgs) when Data turns furious and strangles one of the attackers. After the incident, Data tries to figure out what happened together with his friend Geordi.

DATA: Geordi, I believe I experienced my first emotion.

GEORDI: Data... no offense, but how would you know an actual flash of anger from some kind of odd power surge?

DATA: You are correct in that I have no frame of reference to confirm my hypothesis. In fact, I find myself unable to provide a verbal description of the experience. Perhaps you could describe what it feels like when you get angry... I could then use that as a reference.

GEORDI: Well... when I get angry, first I... begin to feel... hostile...

DATA: Could you describe feeling hostile?

GEORDI: It's feeling... belligerent... combative...

DATA: Can you describe feeling angry without referring to other feelings?

GEORDI: No... I guess I can't. I just ... feel angry.

DATA: That was my experience as well. I simply ... felt angry.

Emotions can be analyzed through 3 different compartments: physiological activation, expressive behavior, conscious experience and feelings (i.e. physiologically, behaviorally, and cognitively) [65]. Another way of describing emotions without using other emotions as a reference would have been to refer to bodily reactions such as arousal, increased heart rate, flushing, trembling, etc., but that would probably not be possible for the robot Data.

Some of the compartments are similar between positive and negative affect, such as arousal, but positive and negative affect have also been associated with different autonomic nervous system patterns [66]. Coherently, the biological mechanisms behind positive and negative affect seem to differ, with the right frontal lobes more activated in negative affect and a relative activation of left frontal lobe is associated with positive affect [67], and it is quite possible that the associations with cytokines at least partially would differ. Negative affect and possible association with different cytokines has been investigated for many years, with the general finding of higher levels of proinflammatory cytokines in depressed patients compared to healthy controls [68]. Positive affect on the other hand have, with few exceptions, only been investigated as associations between mood changes and cytokine production of monocytes [69], infection-induced local cytokine production and changes in mood [70] or reactions to hypersensitivity tests [71].

5.4 ADAPTIVITY IS THE KEY

As described above, affect is often divided into positive and negative affect, with positive affect being happiness, joy, pleasure and negative affect anger, depression, hostility etc. Both more positive and less negative affect have been shown to predict survival. However, this division into positive and negative is not always enlightening. After Data concluded that he actually did get angry at the attack, he visits Counselor Troi.

DATA: For the past six hours, I have attempted to produce an emotional response by subjecting myself to various stimuli.

TROI: Like what?

DATA: I listened to several operas known to be uplifting, I watched three Holodeck programs designed to be humorous, and I made four attempts to induce sexual desire by subjecting myself to erotic imagery.

TROI: What happened?

DATA: Nothing.

TROI: I'm curious... why are you ignoring the one emotion you've already experienced? Why aren't you trying to make yourself angry again?

DATA: Anger is a negative emotion. I wanted to concentrate on something more positive.

TROI: Feelings aren't positive or negative Data, they simply exist. It's what we do with those feelings that becomes good or bad. For example, feeling angry about an injustice could lead someone to take a positive action to correct it.

DATA: But my study of humanity indicates there are some emotions that are harmful, such as jealousy or hatred.

TROI: Those are very... strong emotions, and you're right -- there's very little good that can come from them. But, I don't think that an exploration of anger would necessarily lead to feelings of hate or malice.

DATA: But what if it does, Counselor? What if it turns out that those are the only emotions I am capable of experiencing? Would that not make me a... bad person?

TROI: Data, we've served together a long time... and I've gotten to know you pretty well... I have to believe if you ever do reach your goal of becoming human... you won't become a bad one.

DATA: I wish I were as confident as you are, Counselor. When I was fighting the Borg, I felt angry... but as I think back on that incident, I realize that I also experienced another sensation. It was not the same as anger, but I think it was an emotion.

TROI: Exactly when did you feel this... other emotion?

DATA: It was just after I had killed the Borg. I looked down at his body and I.... felt something.

TROI: If you had to put a name to this... feeling, what would you call it?

DATA: I believe it was pleasure.

So it seems that it is the adaptivity of the emotion that shows whether it is positive or negative. If your friends are going to be killed it might be a good thing to get angry to get the power to do something about it, even though anger in general is considered to be a negative emotion. And indeed, pleasure is in general regarded as a positive emotion, but perhaps not in adjunction to killing somebody, or something, not even an evil Borg.

Similarly to the anger Data felt at the attack, depression and hostility, and grief after a loved one is lost, may serve its purpose. It is when it is prolonged it may take out its toll, similarly to sickness behavior. Probably, sickness behavior has given the animal advantages for survival. Keeping still due to fatigue, anorexia or pain would decrease the risk of exposure to predators and saves energy for the immune system, which is a high consumer of energy. Anorexia evolves despite the need for energy, but this could be due to the fact that, during bacterial infection, accessible iron has to be removed

from the bloodstream in order not to nurture any bacterial growth. Thus, eating during infection might feed the pathogen more than the body [31]. As mentioned previously, Sickness behavior has been described as a motivational state, to increase survival during infection, by a behavioral change that leads to the conservation of energy and less exposure to danger. However, the long term effect of inflammation may lead to a reduced quality of life in patients with chronic inflammatory diseases. Poor short term subjective health may also lead to a patient seeking health care, and thus, poor self-rated health may be adaptive as well.

DATA: Captain, I believe I am feeling... anxiety. It is an intriguing sensation. A most distracting...

CAPTAIN PICARD: Data, I'm sure it's a fascinating experience, but perhaps you should deactivate your emotion chip for now.

DATA: Good idea, sir.

[beep]

DATA: Done.

CAPTAIN PICARD: Data, there are times that I envy you.

STAR TREK - First Contact

6 PRIOR RESEARCH ON SELF-RATED HEALTH AND BIOLOGICAL FACTORS

It wasn't what I expected. But facts are facts, and if one is proved to be wrong, one must just be humble about it and start again.

Miss Marple

In total, 41 articles reporting findings of associations between self-rated health and biological factors have been found. Relevant findings for this thesis are presented below. All presented associations are statistically significant if not stated otherwise. The remaining studies (all summarized in Appendix) have focused on factors such as metabolic and cardiovascular risk factors.

6.1 INFLAMMATORY FACTORS

As previously described, immune activation with the release of inflammatory cytokines such as IL-1 β , IL-6 and TNF- α leads to sickness behavior, which includes symptoms that frequently are associated with poor self-rated health, such as fatigue and pain [7]. In general, thus, the motive to study inflammatory cytokines lies in the fact that these mediators cause changes in symptoms which may be pivotal in forming a "hypothesis" about ones current health status.

IL-6 is the cytokine most widely investigated in relation to self-rated health [11, 72-75]. IL-6 is a sickness inducing cytokine, and the circulating levels of IL-6 increases with higher age [76]. Both facts have been used as rationales for analyzing the association between IL-6 and self-rated health [73]. In general, higher levels of IL-6 have been associated with poor self-rated health, independent of background factors. One of the samples consisted of only women [72], and in several studies, men and women were analyzed together [73-75]. In two cases, the samples consisted of two thirds women, why it is plausible that the association between self-rated health and IL-6 was dependent on women only. In the third study however, a little more than half of the subjects were men [75]. One study found no association between self-rated health and IL-6 in either men or women [11]. Other cytokines that have been investigated in

relation to self-rated health are IL-1 β , IL-1ra, TNF- α and interferon (IFN)- γ . An association between higher levels of both IL-1 β and IL-1ra, and poor self-rated health has also been found in women but not men [11]. However, one study found no association between IL-1ra and self-rated health [72]. Higher levels of TNF- α has been associated to poor self-rated health in women but not men [11], and a similar trend of association to self-rated health have been found in one [74], but not another [75] study in men and women analyzed together. This association was not found when men and women were analyzed together. One study has investigated, but not found, an association between IFN- γ and self-rated health [75].

CRP is an acute phase reactant induced by proinflammatory cytokines, such as IL-6, and thus a marker of inflammatory activity even though a direct relation to brain function, to my knowledge, is not known. CRP has been associated with poor self-rated health in women with coronary heart disease [72] and in a sample of diabetics patients, but was in the latter study explained by background factors and disease burden [77]. However, only 86 patients, including both men and women on different medications, were included [77], suggesting that the lack of significant independent association were due to lack of power. Interestingly, the authors wanted to investigate if the type of anti-inflammatory treatment would affect the association. No such effect was shown, but this might have been due to an all too low power. Poor self-rated health has also been associated with higher levels of fibrinogen [78], a factor increased in inflammation that affect blood clotting. In the Betula study, poor self-rated health was associated with higher levels of haptoglobin, another acute phase reactant, and a higher erythrocyte sedimentation rate indicative of higher levels of fibrinogen [79]. Poor self-rated health has also been associated with a higher count of white blood cells in men and women analyzed together [80] but not in the Betula study [79]. Two studies have investigated the association of signs of infection and self assessments of health. Pathogen burden (Chlamydia pneumonia, cytomegalovirus, HSC-1) was not related to self-rated health [Whitehall II 81]. In addition, seropositivity for anti-Borrelia immunoglobulin (Ig) G antibodies was not associated with an increase in self-rated mental or physical complaints or impairments [82]. Thus, even though there seems to be an inflammatory component of self-rated health, so far no association has been found between poor self-rated health and a measure of infectious burden.

6.2 ENDOCRINE FACTORS

Endocrine factors, as well as cytokines, have receptors on neurons and can signal to the central nervous system, and affect mood and well being. In addition, the endocrine systems are regulated by central nervous system and are thus affected by psychological factors such as stress. Dysregulation of endocrine factors and many endocrine disorders are associated with psychiatric symptoms such as anxiety, depression and fatigue, some of which have been linked to poor self-rated health [83].

Cortisol is known for its immunomodulating effects. Higher levels of cortisol and a disturbed HPA axis have been associated to depression and fatigue and may be a indicator of psychosocial stress that is in turn related to poor self-rated health [83]. In a study on healthy men and women, poor self-rated health has been associated to higher basal levels of salivary cortisol, but not cortisol awakening response [84]. In a study on men only, in addition to the association to higher basal levels of salivary cortisol, poor self-rated health were associated to a lower cortisol response to acute stress [83]. In a small sample of office workers, low salivary cortisol levels in the morning and high evening levels of salivary cortisol have been associated with poor self-rated health [85].

A number of studies have investigated the association between levels of dehydroepiandrosterone sulfate (DHEAS) and self-rated health. DHEAS is a steroid secreted from the adrenals that seem to affect bioavailability of insulin-like growth factor (IGF)-I and may partially transform into sex steroids and have effects on neurotransmitter receptors [86]. Thus, DHEAS may be interpreted as a signal of physiological health and anabolism (e.g. growth, mineralization of bone and increases in muscle mass). Since DHEAS decreases with age, the hypothesis has been that low levels of DHEAS would be associated with physiological and pathological manifestations of aging, and thus poor self-rated health [87]. An association between low levels of DHEAS and poor self-rate health has been found, generally only in men and not in women [86, 88, 89]. However, most of these studies included fewer women than men in the samples, and one of the studies reported similar magnitude of

association in women, even though not reaching statistical significance [90]. Still others report an association between low levels of DHEAS and poor self-rated health in women, but not in men [87]. In all samples, the age was above 54 years, making menstrual divergences during menstrual cycle an unlikely explanation for the lack of association in women. In a prospective study, low levels of DHEAS predicted poor self-rated health [88] in men, but not women. Consequently, the general health item of SF-36 that includes self-rated health did not improve with DHEAS supplementation in 41 prednisolone treated women with systemic lupus erythematosus [91].

IGF-I is a cytokine like protein that is produced in response to growth hormone that has important actions on cell division, apoptosis, differentiation and metabolism, as well as on cell proliferation in vascular smooth muscle [92]. IGF-I levels have been related to cognitive function in older individuals [92]. Lower levels of IGF-I and poor self-rated health have been associated in younger, but not at older ages, in men and women combined [92]. No association has been found between self-rated health and IGF-I binding protein (IGFBP)-1 in men and women [93].

Aging is accompanied by a decline of serum sex hormones in men and women [94, 95] and symptoms of menopause have been associated to poor self-rated health [96]. After adjustment for age, higher levels of both total and free testosterone were associated with better self-rated health in men [97], but after additional adjustment for BMI, no statistically significant association remained [97]. A decrease in SRH has been associated with decreased serum levels of testosterone in men [98]. Estradiol but not follicle-stimulating hormone has been associated with self-rated health [94].

6.3 COMMENTS TO PREVIOUS STUDIES ON BIOLOGICAL DETERMINANTS FOR SELF-RATED HEALTH

One of the main rationales given for investigating the association between self-rated health and biological factors has been to find a mediator for the predictive capacity of self-rated health [86, 99-101]. Other studies have aimed to validate the use of poor self-rated health as an indicator to measure testosterone [97] and to start hormone replacements at lower levels than the present cut-off scores [102]. Self-rated health has also been used as an evaluation tool to measure clinical effects and to identify

biological factors that can be given to increase self-rated health and promote longevity. Another rationale has been to investigate a factor in a population in relation to other measures as well because of its association with age, such as IL-6 [73, 87]. Quite common has been that no hypothesis attached for the presented association between self-rated health and biological factors. In some of these cases, the findings have been reported as secondary, e.g. as associations between risk factors included in a mortality model.

In general, more studies have investigated and found associations between immunological factors and self-rated health in women [11, 72], while there seem to be more evidence for associations between self-rated health and endocrine or metabolic factors in men [83, 86, 88, 89]. The co-analysis of men and women, e.g. [73-75] complicates the interpretations of the results. However, most associations are adjusted for age and other background factors such as BMI.

There is generally a lack of theoretical frameworks on the pathway for the association between the investigated factor and self-rated health. Only a few longitudinal studies investigating the predictive capacity of the investigated factor on self-rated health and vice versa. Interventional studies are scarce, consequently, the causality in the associations between biological factors and self-rated health are far from elucidated. As written by Marja Jylhä in a recent review on self-rated health [6]: “most empirical studies on self-rated health come from the epidemiological tradition that focuses on the statistical associations of variables rather than on the processes from which the variables emerge. There is an obvious need for more comprehensive approaches.”

7 METHODS

I think the thing to do is enjoy the ride while you're on it.

Johnny Depp

7.1 DESIGN, INCLUSION CRITERIA, RECRUITMENT, AND PARTICIPANTS

As different samples are used for each included study, descriptive statistics of populations and key variables for studies I-IV are presented in Table 3.

Table 3. Descriptive statistics of populations and key variables for studies I-IV.

	Study I	Study II	Study III	Study IV
	Consecutive patients at a primary health care center	Randomized population based sample from Umeå	Randomized population based sample from Stockholm county	Healthy volunteers
N	174	347	285 baseline 209 follow-up	9
Age	56.8 (19-100)	66.4 (45-90)	49.7 (23-76)	23-26
% Women	100	100	51.2	0
Health variable	How would you rate your general health status? Very good (1) to very poor (5)	Do you feel healthy? Yes/No	How would you rate your general health status? Very good (1) to very poor (5)	How would you rate your health for the day? excellent (1) to very poor (7)
SRH: median (point scale)	2 (5)	70,5 % healthy	2 (5)	2 (7)
BMI	25.9	26.3	25.4	
Included cytokines	IL-1 β , IL-1ra, IL-6, TNF- α	IL-1 β , IL-1ra, sIL-1rii, sIL-2r, IL-6,		IL-6, TNF- α
Other included biological determinants	IGF-I/IGFBP-1		Leptin Sex hormones	
Other factors	Sickness behavior (energy, sleep, appetite, fitness, memory, pain) Physical health Age	Positive and negative affect Age	Sick leave Age	Fatigue

7.1.1 Study I

In study I, the participants were recruited at a primary health care unit in a suburban area of Stockholm. No exclusion criterion was used, other than the need of the participants to be able to communicate in Swedish and to be above 18 years. The material consisted of 174 women, age 18 to 75 years.

7.1.2 Study II

In study II, the material consists of cross-sectional data of 357 randomly selected women of the normal population in Umeå, from the Betula Prospective Cohort Study, which is a population-based longitudinal study on health, ageing and memory [79, 103]. The exclusion criteria were dementia, mental retardation, severe sensory handicap, and a native tongue other than Swedish.

7.1.3 Study III

Study III was performed within a prospective cohort on health and ill-health from the normal population of Stockholm County. There were no exclusion criteria, other than by language - the mailed questionnaire was in Swedish only. The study was prospective, with the participants attending health controls and filling out questionnaires in 1995 and 1998, with a questionnaire follow-up in 2001. In this study, the cytokine-like peptide leptin measured from the 1998 blood sample was investigated in relation to self-rated health as rated in 1998 and 2000. 287 randomly selected men and women ages 22 to 76 years attended the health control in 1998 and were included in the study.

7.1.4 Study IV

The participants in study IV were recruited through advertisement at Karolinska Institutet, Royal Institute of Technology and Stockholm University, at both student and personnel areas. Included in the study were 9 healthy young men. These 9 participant followed a strict 6-week sleep protocol, in which participants slept in the sleep laboratory for 12 days, one habituation day (sleep 23-07 h), two baseline days (23-07 h), five days with restricted sleep (03-07 h) and four recovery days (23-07 h). For 9 of those days, blood was drawn every hour 23-08 h and every 3rd hour 08-23h.

7.2 ASSESSMENTS

7.2.1 Self-rated health

The most common self-rated health question “How would you rate your general health status?” answered on a 5 point scale (SRH-5) is used in study I and III. The self-rated health question in study II is worded “do you feel healthy?” answered as “yes” or “no”, thus differing from the most common wording. This question has no time reference, not even general, which makes it probable that the response refers to the present time, right here and right now. In that case, this question is closer to a state marker, rather than the trait component of the general health question, and similar to the question used in study IV. The question used in study IV, worded “How would you rate your health for the day” answered on a 7 grade Likert scale from very poor to very good, is limited to the present day and not in general. Thus, self-rated health in studies I and III are closer to the trait of how a person in general experiences their health, while in study IV, and probably also in study II, the present health experience is reflected. We have therefore chose to refer to SRH-5 used in paper I and III as self-rated health, while “subjective health” was used as a more general expression for subjectively perceived health in paper II and IV. In other words, we chose to use “subjective health”, closer to the psychological construct of interest as an alternative to “self-rated health”, which we feel refers more to how the measurement is made, where a global health question without a given time reference is often implied. Without any doubt, subjectively perceived health is at the core of these questions, even though they are framed and worded in different ways.

7.2.2 Sickness behavior

In article I, sickness behavior was operationalized by using a sum score of rating of the different components: energy, sleep, appetite, fitness, memory and pain derived from the Gothenburg Quality of Life Instrument [104]. The instrument comprises ratings of social wellbeing (home and family, housing, work situation, economy and leisure), physical wellbeing (vision, hearing, memory, appetite and fitness) and mental wellbeing (endurance, mood, energy, self confidence and sleeping). All of the areas are rated on Likert scales ranging from ‘very poor’ (1) to ‘excellent, could not be better’ (7). Pain was assessed by the following questions: have you during the last 3 months been troubled by pain in the neck and shoulder; back pain; pain in the legs;

joint aches; and/or pain in the body? These five items were answered with yes, every day; yes, often; yes, occasionally; and never, and were coded 1–4. The weighted mean score of the pain questions together with the ratings of energy, sleep, appetite, fitness and memory, was used to form a provisional variable to reflect sickness behavior. The operationalization was based on sickness theory rather than empirical findings.

7.2.3 Affect

Affect is often measured as components of sadness, hostility, happiness and joy, over the last week or month. In study II, affect is derived from the Center of Epidemiological studies Depression scale (CES-D)[105]. The scale consist of 16 statements, referring to the last week with 4 different response alternatives 0=“Rarely or none of the time (<1 day)”, 1=“Some or a little of the time (1-2 days)”, 2=“Occasionally or a moderate amount of the time (3-4 days)”, 3=“Most or all of the time (5-7 days)”. A sum score of above 16 for the entire scale has been used in epidemiological studies as a cut off for minor depression [106]. The test consists of four subscales as found in factor analyses: positive affect, negative affect, somatic symptoms and interpersonal problems. The positive affect subscale consists of 4 items; 4 Feel as good as others, 8 Hopeful about future, 12 Felt happy, 16 Enjoyed life. Item 12 and item 16 are considered to be true positive affect measures (happiness and joy), while item 4 and 8 reflects self-esteem and optimism, respectively [64]. The positive affect items are mirrored before calculating the total CES-D score. This was not done in study II, as sum CES-D score was not analyzed. The negative affect scale consists of 7 items; 3 Could not shake blues, 6 Felt depressed, 9 Life is a failure, 10 Felt fearful, 14 Felt lonely, 17 Crying spells, 18 Felt sad. The negative affect items of CES-D only includes depressed affect, and not other negative affects, such as hostility.

7.2.4 Sick leave

At the beginning, we aimed to investigate the relation between biobehavioral factors, self-rated health and sick-leave. Sick leave is not only associated to high costs for the society, but also for the individual, with lower socioeconomic status and lower psychosocial support. In addition, sick leave is associated to increased mortality [2].

In Study I, sick leave was assessed with the question: “Have you been on sick leave or disability pension for the last 3 month?” The proportion of participants on sick leave were 28 (27 %) of 105 responders of the question.

In study II, sick leave was assessed using the question: “What did you do last week?” 6 of 168 responders were on sick leave last week. Two (33 %) of them rated themselves as healthy, as compared to 75 % in the rest of the participants. There were too few participants on sick-leave for any further analyses.

In study III, sick leave was included using the question: “How much have you been on sick leave during the last year?” No sick leave = 54 %, One day=27 %, more than one day=10 %, more than one week= 8 %. Sick leave from study 3 is included in the article.

In study IV, sick leave was not applicable to investigated.

The general conclusion was that larger studies are needed to investigate sick leave in relation to self-rated health and biobehavioral factors.

7.2.5 Sleep

Sleep can be measured in different ways. In study IV, diaries, actiwatches and EEG were used. The participants filled out bedtime and rising time in diaries and wore actiwatches when sleeping at home. Actiwatches measure arm movement during sleep that can be used as indicators of sleep time and depth. EEG records brain waves and is a more accurate measure of sleep stages, but was only used when the participants slept in the laboratory.

7.2.6 Measures of objective disease

In study I, physical health was rated by the physician at the primary health care visit after the consultation, strictly based on medical criteria. The alternatives were: “Healthy”, “Healthy with slight problems”, “Fair”, “Rather poor”, and “Poor” [107].

In study II, the reported use of aspirin, anti-inflammatory and antireumatic drugs including non-steroid anti-inflammatory drugs and glucocorticoids, heart drugs, diabetes drugs, antidepressants and sedatives were used.

In study III, self-reported disease included indicated disorders in the question “Do you suffer from the following disorders?": “Heart disease”, “High blood pressure”, “Diabetes”, “Allergy”, “Asthma” and “Kidney disease”.

Study IV, only included healthy participants.

7.2.7 Blood sample analyses

Cytokines, IGF-I, IGFBP-1 and leptin has been analyzed from plasma or serum donated by the participants, using either ELISA, RIA or biochip array (Randox) methodology. All of these methods are based on antibodies and some kind of detection device as described below. Sex hormones, i.e. estradiol and testosterone, were analyzed using standard methods at a clinical laboratory.

7.2.7.1 Radioimmunoassay (RIA)

RIA was used for analyses of IGF-1 and IGFBP1 in Study I and for leptin in Study III. To perform a radioimmunoassay, a known quantity of an antigen (in this case, IGF-I, IGFBP1 or leptin) is made radioactive, frequently by labeling it with gamma-radioactive isotopes of iodine attached to the amino acid tyrosine. This unknown amount of radio labeled antigen is then mixed with a known amount of antibody for that antigen, and as a result, the two chemically bind to one another. A sample of serum from a patient containing an unknown quantity of that same antigen is added. The unlabeled antigen from the serum will compete with the radio labeled antigen for antibody binding sites. As the concentration of antigen in the serum is increased, more of it binds to the antibody, displacing the radio labeled variant. The bound antigens are then separated from the unbound ones, and the radioactivity of the unbound antigen is measured. The amount of radioactivity is translated using a binding curve constructed with known standards to determine the serum amount of antigen.

4.2.6.2. Enzyme-linked immunosorbent assay (ELISA)

Enzyme-linked immunosorbent assay (ELISA) was used for cytokine analysis in study I and II. In ELISA, an antigen specific antibody (in this case specific for the cytokine) is affixed to a surface, and then an unknown amount of antigen (cytokine) from a plasma or serum sample is washed over the surface so that it can bind to the antibodies. The more antigen present, the more antigen will bind to the antibodies. A second detecting antibody is added that will bind to the bound antigen. This antibody is linked to an enzyme, and in the final step a substance is added that the enzyme can convert to some detectable signal, often using magnitude of fluorescence. The amount of fluorescence is translated using a standard curve constructed with known concentration to determine the serum amount of antigen.

4.2.6.3. High-sensitivity cytokine biochip array (Randox)

The high-sensitivity cytokine biochip array used for cytokine analysis in study IV is very similar to ELISA described above, with the general exception of antibodies being bound and stabilized in predefined positions on a preactivated biochip surface [108].

7.3 DATA ANALYSES AND STATISTICAL METHODS

In this thesis, both parametric and non-parametric tests are used, depending on the hypothesis, the sample and the included data. Cytokines are rarely normally distributed and it is quite common in the literature to transform the data to obtain normality, to be able to use parametric testing. This may be a relevant approach, since it is not often the absolute cytokine values per se that are of interest in this area but rather directions of the associations. However, it may be difficult to interpret findings with inversed, logarithmic, squared, inversed squared etc values. In those cases, non parametric methods, i.e. methods that don't require normally distributed data, may be preferred. Self-rated health as well as other questionnaire data is ordinal in nature. That is, it is an ordered scale but the distance between each step does not need to be equal, in contrast to e.g. weight where there is 1 kg difference between each step of the scale. Quite often, the ratings are also skewed, and because of the few steps, it is hard to obtain normality by transformation. The option is then to dichotomize the data with associated loss of information, to categorize in other ways with less loss of information and use ordinal logistic regression, or to use non-parametric tests. Dichotomous variables have seldom been used in this thesis.

When investigating the relation between biological factors and self-rated health, there are many factors that may be influencing the relation, as confounders, as mediators and as interacting with other factors. A major factor in this thesis has been to decide what factors that should be included in the analyses or not. Including too few or the wrong background factors could lead to confounded results [109]. On the other hand, including too many variables in relation to sample size increases the risk for invalid results due to over fitting [110, 111].

In paper 1, the cytokine levels were transformed and we used Pearson correlation for the univariate associations. When categorizing the cytokines, there were no indications of non-linear associations between cytokines and self-rated health. Since higher age has been indicated to be connected with increased sensitivity to

inflammation [112, 113], the impact of age was investigated using age stratification in the analyses. Multiple linear regression models were built to investigate the influence of the IGF-I/IGFBP-1 ratio and sickness behavior on the associations between self-rated health and the included cytokines: IL-1 β , IL-1ra, IL-6 and TNF- α . Partial correlations were used to build a theoretical model of the associative pattern between physical health, IGF-I/IGFBP1 ratio, cytokines, sickness behavior and self-rated health.

In paper 2, univariate associations between cytokines, self-rated health, affect and background variables were investigated using spearman correlations and Mann-Whitney test. The methods use ranks instead of actual numbers to calculate the coefficient or group differences, respectively. We could not exclude non-linear associations between self-rated health, affect and cytokines. Since it was difficult to find a regular adapting model such as square or cubic approximation, cubic splines with knots [114] were used. Cubic splines would have been a suitable choice for the other samples as well would they have been somewhat larger. The relation between self-rated health, positive and negative affect were investigated using logistic regression and ordinal logistic regression.

In paper 3, we wanted to look at the relation between a skewed variable, leptin, with the ordinal outcomes, self-rated health and sick-leave, adjusted for background factors, and spearman and partial spearman coefficients were calculated.

In paper 4, we needed to compare self-rated health and cytokines before and after sleep restriction. Since the sample consisted of all healthy young men, and smoking and alcohol consumption were not allowed during the experiment, there was little need of adjustment of background factors. Due to the small sample, Kendall's tau was calculated to investigate relation between changes in cytokine levels, self-rated health and fatigue. Repeated measures ANOVA was used to calculate change over and within days. When significant differences were found, they were further investigated using T-tests.

7.3.1 Power

Post-hoc power calculations for the included studies are presented below. The Type I error probability associated with this test of this null hypothesis is 0.05.

Study I: T-test good vs. poor self-rated health and logarithmic values of IL-1 β . With 77 participants with poor self-rated health (neither good nor poor, poor and very poor) and 93 participants with good self-rated health (good or very good), IL-1 β log transformed and normally distributed with standard deviation 0.097, and the true difference in the experimental and control means is 0.31, the null hypothesis (that the mean between those with good and poor health are equal) will be rejected with probability (power) 1,000.

Study II: T-test IL-6 and good vs. poor subjective health. With 102 participants with poor self-rated health and 244 participants with good subjective health, IL-6 log transformed and normally distributed with standard deviation 0.14 and the true difference in the experimental and control means is 0.07, the null hypothesis (that the mean between those with good and poor health are equal) will be rejected with probability 0.99.

Study III: T-test leptin and good vs. poor self-rated health. With 18 participants with poor self-rated health and 80 participants with good self-rated health with leptin normally distributed, standard deviation 5.5 and the true difference in the experimental and control means is 4, the probability that the null hypothesis (that the mean between those with good and poor health are equal will) be rejected is 0.78.

Study IV: T-test change in self-rated health with sleep restriction. The difference in self-rated health of matched pairs is normally distributed with standard deviation 1.1. If the true difference in the mean response of matched pairs is 1.3, the probability that the null hypothesis that this change is zero will be rejected is 0.875.

8 RESULTS

Many of the truths we cling to depend greatly on our own point of view.

Obi-Wan Kenobi

8.1 PAPER I. INFLAMMATORY CYTOKINES, BEHAVIOR AND AGE AS DETERMINANTS OF SELF-RATED HEALTH IN WOMEN

The aim of Study I was to increase the understanding of the association between cytokines and different markers of health and wellbeing in women and to investigate the impact of age on these associations.

The hypothesis that the association between higher levels of cytokines and poor self-rated health was age dependent, with a stronger association with higher age, was largely confirmed. Poor self-rated health was significantly associated with higher levels of TNF- α in all of the age groups. For IL-1 β and IL-1ra, the correlations with self-rated health were significant only in the oldest age group. Thus, the strength of the association between inflammatory cytokines and poor health perception increased with advanced age, indicating an increased vulnerability for inflammatory activity during aging.

Sickness behavior, measured as combination of energy, sleep, appetite, fitness, memory and pain, was investigated as a possible mediator between higher levels of inflammatory cytokines and poor self-rated health, so that high levels of cytokines induce symptoms of sickness behavior making the subjects rate their health as lower. Sickness behavior was implicated to be associated with lower self-rated health, but did not fully explain the association between higher levels of cytokines and poor self-rated health. However, the pathway between TNF- α , sickness behavior and self-rated health was significant in the oldest age group, suggesting that higher levels of TNF- α are connected to a sickness response that, in turn, is connected to self-rated health.

An additional analysis, not included in the article, was performed to analyze the relation between self-rated health and sick leave. Those who were on sick-leave had significantly lower self-rated health ($p < 0.001$).

8.2 PAPER II. ASSOCIATIONS BETWEEN SUBJECTIVE HEALTH, AFFECT AND CYTOKINES IN WOMEN

The aim of study II was to investigate the relation between subjective health, positive and negative affect and an array of cytokines known to interact with brain function, in a representative sample of the population. In addition, the interrelations between self-rated health, positive affect and negative affect were studied.

Among the main findings, an association between higher levels of IL-6 and poor self-rated health was found in the univariate analysis. This association was stronger at older age. An association between higher levels of IL-6 and worse subjective health was also shown in multivariate non-linear analyses, when age and other factors were controlled for. Concerning positive affect, while no univariate linear association with cytokines were found, a non-linear association between positive affect and sIL-2r was observed. Hence, both lower and higher levels of sIL-2r, as compared to median levels were associated with lower positive affect. Less negative affect was associated to higher levels of sIL-2r in the univariate analyses and also reflected in the multivariate analysis as more negative affect in those with mid-low levels of sIL-2r as compared to those with median levels.

As presented in figure 2, subjective health was more associated to positive than negative affect, suggesting that positive affect, at least in the normal population, could be of higher importance for health perception as compared to negative affect.

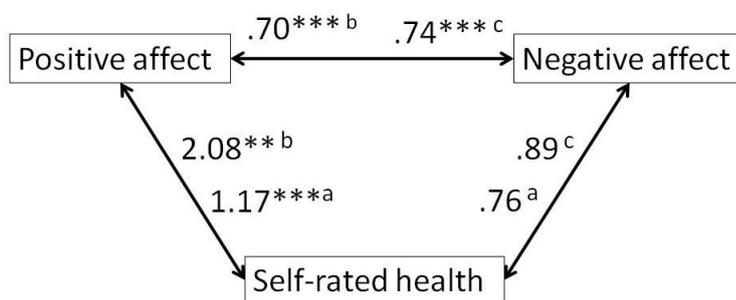


Figure 2. Associations between self-rated health, positive and negative affect investigated using logistic (health) and ordinal logistic (positive and negative affect) regression. Each association adjusted for age, BMI medication and smoking. Poor self-rated health associated with less positive affect, but not with negative affect. Positive affect associated with lower negative affect. a. Odds ratio self-rated health dependent variable; b. Odds ratio positive affect dependent variable; c. Odds ratio negative affect dependent variable.

8.3 PAPER III. DIFFERENTIAL RELATIONS BETWEEN LEPTIN AND SELF-RATED HEALTH IN MEN AND WOMEN?

The aim of the present study was to investigate cross-sectional and prospective associations between leptin and self-rated health, a strong predictor of future morbidity and mortality, in a random population sample. An additional aim was to investigate if leptin and poor self-rated health were associated to sick leave.

In sum, the result of this study showed that higher levels of leptin predicts better self-rated health in women, but is associated to poor self-rated health in men.

In men, higher levels of leptin were prospectively associated with poor self-rated health, but the relationship was not significant in the cross-sectional analysis. This association was not found in women. When controlling for age, BMI, presence of diagnosis, and testosterone, higher levels of leptin were associated with poor self-rated health in men in cross-sectional analysis, but not prospectively. In women, leptin was not associated with self-rated health in cross-sectional analysis, but higher levels predicted better self-rated health when adjusted for background factors and estradiol. An association between lower levels of estradiol and poor self-rated health in women above 50 years was reported as a secondary finding.

Self-rated health was independently associated to future sick leave in both men and women, whereas no association between leptin and future sick leave was found. A possible, however not consistent, association between leptin and sick leave mediated by self-rated health was found in men, with higher levels of leptin associated with poor self-rated health, that in turn predicted higher sick leave. In women, higher levels of leptin predicted better self-rated health that in turn was associated with fewer sick leaves during the last year.

Further analyses not presented in the article showed that all men that rated their health as very good had leptin levels <9 ng/ml even though there were individuals with low levels that also rated their health as bad. All women who rated their health as bad at follow-up had leptin levels below median, even though there were women with good self-rated health with low levels of leptin. In sum, the highest quartile of leptin in men was not compatible with good self-rated health, while in women, levels of leptin below median was predictive of poor self-rated health.

Even though individuals with sick leave the last year were more likely to rate their health as low, a high proportion (4 out of 12) of those on sick leave for more than 3 months rated their health as good (Table 4). Similar result has been found in a larger study on sick leave and health [5].

Table 4. Self-rated health and sick-leave.

Sick-leave during last year	Self-rated health				
	Very good	Good	Neither good nor poor	Poor	Very poor
No sick leave	22	48	7	2	0
1-7 days	15	21	4	0	0
8-30 days	5	9	1	0	0
> 30 days	1	3	4	3	1

8.4 PAPER IV. SUBJECTIVE HEALTH IS AFFECTED BY EXPERIMENTALLY RESTRICTED SLEEP AND SUBSEQUENT RECOVERY SLEEP

In study IV we investigated whether a working week with restricted sleep and subsequent recovery days affects variations in subjective health and if such a change is related to increased levels of circulating IL-6 and TNF- α .

The participants slept in the sleep laboratory for 12 days, with one habituation day (sleep 23-07 h), two baseline days (23-07 h), five days with restricted sleep (03-07 h) and four recovery days (23-07 h). Baseline day 2 and sleep restriction day 5 were compared to investigate changes in cytokines, self-rated health and fatigue.

Subjective health deteriorated gradually when sleep was restricted to 4 h per night and returned to baseline levels after two days of recovery. This decrease in subjective health was significantly correlated with increased levels of circulating IL-6 (baseline day 2 compared to restricted sleep day 5 averaged through samples over the day), but not with changes in TNF- α . No association between higher levels of cytokines and fatigue was found.

9 DISCUSSION

If we knew what it was we were doing, it wouldn't have been called research, would it?

Albert Einstein

In this thesis, the association between inflammatory cytokines and self-rated health has been investigated in relation to age, metabolic factors, affect, and restricted sleep.

9.1 MAIN FINDINGS

An association between higher levels of inflammatory cytokines and poor self-rated health was generally confirmed (study I and II), also in a population based sample (study II). However, the cytokines showing significant relations to self-rated health were not entirely consistent across studies (IL-1 β , IL-1ra and TNF- α in study I and IL-6 in study II and IV). The association between inflammatory cytokines and self-rated health was stronger at higher age (study I and II), consonant with notions of increased sensitivity to inflammatory cytokines with higher age [28, 112]. Both positive affect and negative affect were associated to cytokines, in a partly inverted pattern (Study II). In addition, self-rated health was more strongly associated to positive than to negative affect (study II). Leptin was associated with self-rated health in a gender specific way (study III), with higher levels largely associated with poor self-rated health in men but to good self-rated health in women. With experimentally restricted sleep, self-rated health decreased gradually, a change which was associated with increased levels of IL-6 (study IV). In large, the thesis supports a relation between inflammatory cytokines and how an individual perceives and denotes her health status. This finding is consistent with an impact on the brain from inflammatory mediators as in a cytokine induced sickness response and the notion that cytokines released in response to challenge are interpreted by the brain as "sickness signals". However, it should be noted that the causal relations behind the connections observed in the present study are not clear. Because very little is known about biological aspects of self-rated

health, this knowledge may increase the understanding of how and why an individual's subjective perceptions about health issues are connected to future health in ways that complement and sometimes surpass objective assessments as known today.

9.2 ADDED KNOWLEDGE FROM THE CURRENT STUDIES

The general association between higher levels of one or more inflammatory cytokines and poor subjective health observed in study I, II and IV is coherent with known effects of IL-1 β , TNF- α and IL-6 on behavioral factors of relevance for subjective health perception [7]. In spite of some difference in the implicated cytokines between the studies, it thus lends preliminary support to a view on inflammatory cytokines as factors that impact on the brain and that can be "sensed" in a way that has bearing on how the bodily state of the organism is interpreted, in concordance with the sponge hypothesis of self-rated health [25]. In study I, a construct made from ratings of satisfaction with factors (energy, sleep, appetite, fitness, memory and pain) that resemble sickness behavior was associated with lower self-rated health. It is possible that the attempt to estimate sickness behavior was not up to the mark, since sickness was measured ad hoc with selected factors from a general questionnaire, thus with unknown psychometric properties. Another explanation is that, besides the association between cytokines and sickness behavior, cytokines have an independent association with self-rated health. However, in spite of possible flaws in the sickness behavior construct from study I, the pathway between TNF- α , sickness behavior and self-rated health was significant in the oldest age group, suggesting that higher levels of TNF- α were connected to a sickness response that, in turn, is connected to worse self-rated health. Future models of inflammatory determinants of self-rated health would benefit both from improved measures of low-grade inflammatory products and sickness behavior.

In study I, we examined the association between circulating levels of IL-1 β , IL-1ra, IL-6 and TNF- α and self-rated health in three age groups. Poor self-rated health was significantly associated with higher levels of TNF- α in all of the age groups, but with increasingly stronger correlation coefficients displayed with older age. For IL-1 β and IL-

1ra, the correlations with self-rated health were significant only in the oldest age group. Thus, the strength of the association between higher levels of inflammatory cytokines and poor health perception increased with advanced age, indicating an increased vulnerability for inflammatory activity during aging. This notion is further supported by the results from the age stratified analysis in study II, which demonstrated a stronger univariate association between the cytokines sIL-1 β and IL-6 and self-rated health in the older age group. The associations between leptin and self-rated health in study III did not change with age stratification, even though they largely turned insignificant. Instead, the age stratification revealed an association between lower levels of estradiol and poor self-rated health in women above 50 years. These observed age effects, with more associations between biological determinants and self-rated health in women might partly be explained by interference of the menstrual cycle in premenopausal women.

In study II, lower self-rated health was found in those with the lowest levels of IL-1 β as compared to the median, which is in contrast to the results from study I where higher levels of IL-1 β were connected with poorer self-rated health. The reason for this difference between study I and study II is not clear, but could be related to the fact that study I was performed in primary health care patients from a psychosocially burdened area, while study II was performed in a sample of the normal population. As described earlier, cytokines are involved in maintaining physiological function. The association between low levels of IL-1 β and poor self-rated health in study II, together with the association between below median levels of sIL-2r and both less positive and more negative affect, may suggest that there is a limit for how low cytokine levels could be without negative impact on health perception and affect due to their physiological properties. Such findings emphasize the importance of investigating linearity in relations between biological factors and self-rated health and affect, to increase the possibility to estimate true biological effects of mediators of interest.

The result from study II suggests that positive affect, at least in the normal population, could be of higher importance for health perception as compared to negative affect. Thus, positive affect is generally connected with favorable health outcomes, and interestingly, its influences on psychobiological processes are indicated to be

independent of negative affect [115]. Because the mechanisms behind the predictive powers of subjective health on long-term objective health are unknown, research on positive affect and its behavioral (e.g. health protective behaviors) and biological (e.g. cardiovascular or immune) sequelae in relation to long term health outcomes are clearly warranted.

Leptin has previously not been investigated in relation to self-rated health. In study III, leptin was found to have sex-specific differences in its association with self-rated health. When controlling for age, BMI, presence of diagnosis, and testosterone, higher levels of leptin were associated with poor self-rated health in men in cross-sectional analysis but not prospectively. In women, leptin was not associated with self-rated health in cross-sectional analysis, but relatively higher levels were prospectively associated with better self-rated health when adjusted for age and BMI. Based on our findings, together with some support from recent studies on leptin and physical and mental health, we proposed that leptin may serve different psychobiological functions in men compared with women.

Self-rated health can obviously be affected in a short term perspective, here shown through sleep restriction to build up a cumulative sleep debt, which was mirrored in subjective health ratings. Even though the question was stated differently as compared to other studies, framed to represent the prevailing day, the worsened subjective health in the sleep restricted participants in study IV suggests that self-ratings of health could be used in experimental situations to study changes over short term periods. This notion is in agreement with a view on self-rated health as a dynamic evaluation of health, incorporating past health experience with current health conditions and future health expectations [116], and in concordance with the trajectory hypothesis of self-rated health [25].

9.3 LIMITATIONS AND STRENGTHS

A general limitation in studies on the relations between cytokines and behavior is the measures of systemic levels of cytokines as a proxy for their putative impact within the central nervous system. Cytokines produced in the periphery are known to signal

to the brain but the exact nature between systemic and local concentrations, signal properties and impact on brain areas of relevance are (not surprisingly) unknown. However, strong associations between circulating cytokine levels and behavioral changes in response to acute stimulation with endotoxin have been demonstrated [117, 118], supporting the relevance of systemic cytokine analysis. Despite methodological challenges in analysis of cytokines, measurement in the periphery rather than in the nervous system, use of single blood samples with only partial control over diurnal rhythms (except study IV), our underlying hypothesis of cytokines as a class of biological mediators of subjective health was generally confirmed.

From cross-sectional studies, we are little informed about possible causal relations. For example, even though there is an association between higher circulating levels of inflammatory cytokines and poor self-rated health, it is not possible to know whether higher inflammatory cytokines leads to poor self-rated health or vice versa. Possibly, the association could be related to other phenomena beyond our control. In study III, low levels of leptin predicted poor self-rated health 2 years later in women. Thus, it is known that the levels of leptin preceded the health perception, but it is still not possible to state that the low levels of leptin caused the poor self-rated health. Again, a parallel phenomenon may explain both the low levels of leptin as well as the health decline. However, in study IV, sleep restriction appears to have caused a decline in perceived health in the participating subjects. Still, it should be acknowledged that no control group was included, even if participants were closely monitored in a rigorous multi-night sleep protocol. Investigating epidemiological relations between biological determinants for self-rated health may give clues on the mechanisms behind the predictive capacities of self-rated health, but further interventional and experimental studies are needed to understand the causality in the association between biobehavioral factors and self-rated health.

9.4 CLINICAL IMPLICATIONS

As mentioned, poor self-rated health is a good predictor of health care use, sick leave, morbidity and mortality [1-5], thus factors of great personal significance for the

afflicted individual but also of importance for society. For this reason, self-rated health is a commonly used research tool. The use of self-rated health may also help towards a patient centered treatment, but it is still scarcely used in clinical settings. It has been suggested to be due to a lack of understanding of the definition of health status, a lack of familiarity with health status surveys, a perception that these measures are “soft,” and a lack of acceptance that health status measures may be useful in clinical practice [24].

However, measuring self-rated health in a clinical setting may be compared with measuring blood pressure, as previously discussed in an editorial in the journal *Circulation* [24]. First, neither self-rated health nor blood pressure can be inferred from observation without formal measurement. Second, self-rated health is as reproducible as blood pressure measurement. Finally, self-rated health is an independent predictor of outcome on par with blood pressure [24]. However, when a patient has high blood pressure, the patient is treated with blood pressure lowering drugs, at least according to the Swedish National Board of Health and Welfare care program for hypertension. But how do you treat a patient with poor self-rated health? With knowledge of what systems are most likely to be involved in poor health perception, they can be specifically investigated and targeted. Inclusion of self-rated health in medical records together with recent development in health informatics will make it easier to monitor patients with poor subjective health and to detect changes for the worst.

9.5 FUTURE RESEARCH

There is a great need for longitudinal studies that follow changes in variables of interest to capture the dynamics of self-rated health. Also, the area of biological and behavioral determinants for self-rated health lacks experimental and interventional studies.

Interventional studies should aim to improve self-rated health by targeting factors of importance for subjective health, such as sleep quality and fitness. Methods to reduce circulating levels of cytokines could also include weight reduction or medication with

statins. Physical activity on prescription has previously been associated with improvement of the general health component of SF-36 [119]. By reducing visceral fat, physical activity is likely to reduce inflammatory load that may be mirrored in an improved self-rated health. While better self-rated health may be a goal in itself, interventions to improve self-rated health have to be investigated in relation to reduced health care use, sick leave, morbidity and mortality. Finally, more experimental studies on factors that may affect subjective health perception are needed to elucidate causality in the associations between biological determinants and self-rated health.

9.6 CONCLUSION

This thesis presents increased support for the hypothesis of an inflammatory component in subjectively perceived health, which appears valid also in normal population samples. The association between cytokines and self-rated health was found to be stronger with increasing age, consistent with the notion of an increased effect of inflammatory factors on e.g. behavior at older age. Markers related to energy balance may be interesting to investigate further as determinants of self-rated health, and could possibly shed light on the differences that have been observed in the relation between self-rated health and mortality in men and women, respectively. Finally, aspects of subjective health seem to vary in a short term perspective and may be affected by behavioral factors such as sleep debt.

10 SAMMANFATTNING PÅ SVENSKA

Bakgrund

Dålig självskattad hälsa kan förutsäga framtida sjuklighet och död, oberoende av objektiv ohälsa, men mekanismerna bakom sambandet är mer eller mindre okända. Aktivering av inflammatoriska cytokiner har visats ge symtom av en sjukdomsrespons med energilöshet, smärta, trötthet och nedstämdhet. Alla dessa symtom är kopplade till dålig självskattad hälsa. Därför är det möjligt att cytokiner som orsakar en sjukdomsrespons är viktiga signaler för hur man upplever sin hälsa. Målsättning med avhandlingen var att undersöka sambandet mellan självskattad hälsa och möjliga förklaringsfaktorer, med fokus på inflammatoriska cytokiner.

Metod

Fyra studier på fyra olika material är inkluderade i avhandlingen, kvinnor från primärvården (Studie I), kvinnor från en befolkningsstudie från Umeå (Studie II), kvinnor och män från en befolkningsstudie från Stockholm (Studie III), och män från en experimentell studie på sömnbrist (Studie IV).

Resultat

Högre nivåer av inflammatoriska cytokiner var associerat till sämre självskattad hälsa, även om delvis olika cytokiner var involverade i de olika studierna. Sambandet mellan högre nivåer av vissa cytokiner och sämre självskattad hälsa var starkare vid högre ålder. Självskattad hälsa var starkare associerat med positiv än med negativ affekt. I studie III undersöktes sambandet mellan leptin, ett cytokinliknande ämne som fettväven producerar för att signalera hur mycket lagrad energi som finns i kroppen, och självskattad hälsa. Högre nivåer av leptin var associerat till sämre självskattad hälsa hos män, medan höga nivåer av leptin hängde samman med bättre framtida självskattad hälsa hos kvinnor. Sämre självskattad hälsa var kopplat till ökad framtida sjukskrivning hos både män och kvinnor. Hälsa skattad för att gälla den aktuella dagen sjönk successivt vid sömnbrist, en sänkning som kunde kopplas till en ökning av en inflammatorisk cytokin.

Slutsats

De aktuella studierna ger ett ökat stöd för att inflammationsrelaterade signaler bidrar till hur den egna hälsolivån upplevs. Positiv affekt tycks ha större tyngd än negativ affekt för hur individer skattar sin hälsa och tyder på att faktorer som positivt påverkar självskattad hälsa borde undersökas vidare. Avhandlingen visar också att subjektiva hälsobedömningar kan variera på mycket kort sikt och att de påverkas av mängden sömn en individ får. Det finns ett behov av longitudinella och experimentella studier för att bättre förstå de orsaksfaktorer som är viktigast för den självskattade hälsan.

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APPENDIX

Previous studies on self-rated health and biological factors, sorted by first author

Authors Titel Reference	Self-rated health measure	Sample	Findings
af Sillén U, Nilsson JÅ, Månsson NO, Nilsson PM <i>Self-rated health in relation to age and gender; Influences on mortality risk in the Malmö Preventive Project.</i> Scand J Public Health 2005;33:183-189	"Do you feel completely healthy?" "Yes/no"	15590 men 10089 women	Poor SRH associated to higher BMI, higher systolic blood pressure, higher diastolic blood pressure (men only), higher heart rate, higher cholesterol (women only), higher levels of triglycerides, higher fasting glucose (women only), adjusted for age
Almeida OP, Lautenschlager N, Vasikaram S, Leedman P, Flicker L. <i>Association between physiological serum concentration of estrogen and the mental health of community-dwelling postmenopausal women age 70 years and over.</i> Am J Geriatr Psychiatry. 2005;13(2):142-9	SF-36	265 postmenopausal women above 70 yrs (mean age: 74.6 yrs)	Higher levels of estron and estradiol borderline significantly associated to better SRH.
Blaum CS, Velez L, Hiss RG, Halter JB. <i>Characteristics related to poor glycemic control in NIDDM patients in community practice.</i> Diabetes Care. 1997 Jan;20(1):7-11.	Not stated	393 non insulin dependent diabetes patients mean 63 yrs, 54 % women	High proportion of glycated hemoglobin associated to poor SRH.
Berr, C., Lafont, S., Debuire, B., Dartigues, J.F., Baulieu, E.E., <i>Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: a French community-based study.</i> Proc. Natl Acad. Sci. USA 93, 13410–13415.	SRH-5	622 men and women older than 65 yrs.	Lower levels of DHEAS associated with poor SRH in women but not in men.
Brunner E, Smith GD, Marmot M, Canner R, Beksinska M, O'Brien J. <i>Childhood social circumstances and</i>	SRH-5 previous year	Whitehall II 6895 men 3413 women 35-55	Higher levels of fibrinogen associated with poor SRH in both men and women.

psychosocial and behavioral factors as determinants of plasma fibrinogen Lancet 1996;347:1008-13		yrs.	
Cohen HJ, Pieper CF, Harris T, KMK Rao, MS Currie The association of plasma IL-6 levels with functional disability in community-dwelling elderly. J Gerontol A Biol Sci Med Sci. 1997;52(4):M201-8.	Not stated, refer to reference within.	Population sample age>70 yrs 605 men and 1122 women analyzed together	Higher levels of IL-6 associated with poor SRH
Cummings DM, King DE, Mainous AG 3rd. C-Reactive Protein, Antiinflammatory Drugs, and Quality of Life in Diabetes Ann Pharmacother. 2003;37(11):1593-7.	SF-12	There were 86 subjects in the study, with mean age 63.6 yrs, 71% African American, and 68% women.	Poor SRH associated with higher levels of CRP in those used statins or nothing, but not in those who used ASA/NSAID. Similar findings were observed using SRH-5 as an outcome variable.
Dahlgren A, Kecklund G, Theorell T, Åkerstedt T. Day-to-day variation in saliva cortisol – Relation with sleep, stress and self-rated health Biological Psychology 2009;82:149-55	“How have your day been in regard to health?”, 7-graded scale.	14 office workers recruited at Karolinska University Hospital	Low salivary cortisol levels in the morning and high evening levels of salivary cortisol were associated with poor SRH.
Delpierre C, Lauwers-Cances V, Datta GD, Berkman L, Lang T. Impact of social position on the effect of cardiovascular risk factors on self-rated health. Am J Public Health. 2009 Jul;99(7):1278-84.	SRH-5	4015 men and 4066 women	Poor SRH associated with higher blood pressure (men and highly educated women), Higher HbA1c (both men and women), higher cholesterol (highly educated women), but not triglycerides. Adjusted for background factors.
Dennerstein L, Lehert P, Burger HG, Guthrie JR. New findings from non-linear longitudinal modelling of menopausal hormone changes. Hum Reprod Update. 2007;13(6):551-7.	SRH was asked as bad or worse than others; reasonable or same as others; good or better than others.	Age 45-55 yrs at first examination. 204 women who completed a 13-year prospective study	SRH were highly significantly associated with estradiol. Higher estradiol change was associated with lower SRH. Follicle stimulating hormone did not affect any of the health outcomes analyzed.
Eskelinen SI, Vahlberg TJ, Isoaho RE,		The study	After adjustment for age,

<p>Kivelä SL, Irjala KM. Associations of sex hormone concentrations with health and life satisfaction in elderly men. Endocr Pract. 2007 Nov-Dec;13(7):743-9.</p>		<p>subjects were men from the community-based Lieto Study (N = 517).</p>	<p>higher levels of testosterone and free testosterone were associated with better SRH, but after adjustment for age and BMI, no statistically significant associations were found between sex hormone levels and SRH</p>
<p>Eskelinen SI, Vahlberg TJ, Isoaho RE, Löppönen MK, Kivelä SL, Irjala KM. Associations of thyroid-stimulating hormone and free thyroxine concentrations with health and life satisfaction in elderly adults. Endocr Pract. 2007 Sep;13(5):451-7.</p>	<p>SRH-5 dichotomized 1=very good, good or fair; 2=poor and very poor.</p>	<p>thyroid disease-free population 502 men (median 71 yrs) 584 women (median 73 yrs); primary hypothyroidism stable thyroxine treatment: 49 women (median 75 yrs)</p>	<p>After age adjustment, there were no associations between TSH levels and SRH, life satisfaction, or most symptoms in the thyroid disease-free population.</p>
<p>Fylkesnes K, Foerde OH The Tromsø study: Predictors of Self-Evaluated health - has society adopted the expanded health concept? Soc sci med 1991;32(2):141-6</p>	<p>SRH-5</p>	<p>Randomized population sample 9408 men 20-61 years 9152 Women 20-56 years</p>	<p>Poor SRH associated with higher heart rate.</p>
<p>Glei DA N Goldman M Weinstein and IW Liu Dehydroepiandrosterone sulfate (DHEAS) and health: does the relationship differ by sex? Exp Gerontol. 2004 Mar;39(3):321-31. [90] Erratum in: Exp Gerontol. 2006 Mar;41(3):337.</p>	<p>SRH-5 (Current)</p>	<p>Population based sample from Taiwan 967 participants, 42.6 % kvinnor, age 54 yrs and older</p>	<p>Poor SRH associated with lower levels of DHEAS and higher levels of cortisol. Significant in men only, but similar magnitude of association in women. The association is stronger between SRH and DHEAS than between SRH and cortisol.</p>
<p>Goldman N, DA Gleib Sex differences in the relationship between DHEAS and health Experimental Gerontology 2007;42:979–987</p>	<p>SRH-5 (Current)</p>	<p>835 men and women, approx 40 % women</p>	<p>Poor SRH predicts lower levels of DHEAS in men but not women.</p>
<p>Goldman N, Gleib D, Chang MC The role of clinical risk factors in</p>	<p>SRH-5 (Current)</p>	<p>Population based sample from</p>	<p>Poor SRH associated with higher BMI, larger waist-hip</p>

<p>understanding self-rated health. Ann Epidemiol 2004;14:49-59</p>		<p>Taiwan 928 participants, 42.6 % women, 54 years and older</p>	<p>ratio, higher total to HDL-cholesterol-ratio (in men), presence of ApoE in women. Higher cholesterol to DHEAS ratio (in women), more adrenaline, higher HbA1c, waist-hip ratio. But not blood pressure or noradrenaline. Plenty more factors investigated.</p>
<p>Grabe HJ, Spitzer C, Lüdemann J, Guertler L, Kramer A, John U, Freyberger HJ, Völzke H. No association of seropositivity for anti-Borrelia IgG antibody with mental and physical complaints. Nord J Psychiatry. 2008;62(5):386-91.</p>	<p>Self-reported health complaints</p>	<p>4264 men and women</p>	<p>seropositivity for anti-Borrelia IgG antibodies not associated with an increase of self-rated mental or physical complaints or impairments.</p>
<p>Halford C, Anderzén I, Arnetz B. Endocrine measures of stress and self-rated health: a longitudinal study. J Psychosom Res. 2003;55(4):317-20.</p>	<p>How would you say your general health has been during the past year? Bad-poor-fair-good-excellent.</p>	<p>Longitudinal study 102 healthy men mean age 37.8. Written questionnaires and blood samples were collected at baseline and at follow-up 1 year later.</p>	<p>A decrease in SRH below the level of good at follow-up was associated with increased s-prolactin and decreased s-testosterone. There were no consistent, associations found at baseline or at follow-up between endocrine hormone profile or specific hormone levels and SRH. Similarly, there were no significant differences in hormone levels found among men with SRH that improved or remained unchanged during the study period.</p>
<p>Hampson SE, Goldberg LR, Vogt TM, Hillier TA, Dubanoski JP. Using physiological dysregulation to assess global health status: associations with self-rated health and health behaviors. J Health Psychol. 2009;14(2):232-41.</p>	<p>SRH-5 age</p>	<p>Hawaii Personality and Health cohort (N = 470)</p>	<p>Six measures of physiological dysregulation (allostatic load) were derived from 11 clinically assessed biomarkers, and related to health outcomes and health behaviors. Dysregulation and health behaviors predicted SRH for both men and women.</p>
<p>Hasson D, Von Thiele Schwarz U, Lindfors P.</p>	<p>SRH-5 alt SRH VAS-</p>	<p>241 employees from the health</p>	<p>Lower SRH associated with higher systolic blood</p>

<p>Self-rated health and allostatic load in women working in two occupational sectors. J Health Psychol. 2009;14(4):568-77.</p>	scale.	care sector and 98 employees from the IT/media sector. Women	pressure, higher HDL, lower LDL/HDL ratio, lower waist-hip ratio, lower prolactin, but not with diastolic blood pressure, heart rate, HbA1c, total cholesterol, LDL, triglycerides, DHEAS. Poor SRH was significantly associated with a high allostatic load.
<p>Hu P, Wagle N, Goldman N, Weinstein M, Seeman TE. The associations between socioeconomic status, allostatic load and measures of health in older Taiwanese persons: Taiwan social environment and biomarkers of aging study. J Biosoc Sci. 2007;39(4):545-56.</p>	SRH-5 (Current)	national representative sample of 1023 elderly and near-elderly Taiwanese non-Western population	Poor SRH associated with higher allostatic load level. There were significant associations of lower education or less income with worse SRH and more difficulties with physical functioning.
<p>Janszky I, Lekander M, Blom M, Georgiades A, Ahnve S. Self-rated health and vital exhaustion, but not depression is related to inflammation in women with coronary heart disease Brain Behav Immun, 2005;19(6): 555-63.</p>	SRH-5	Women cardiovascular event 235 women below 75 years	Poor SRH associated with higher levels of IL-6 and CRP
<p>Jylhä M, S Volpato, JM Guralnik Self-rated health showed a graded association with frequently used biomarkers in a large population sample J clin epidem 2006;59:465-471</p>	Different versions of SRH-5.	Population based sample 4065 men and women analyzed together 71 years and older.	Poor SRH associated with higher HBG* higher white cell count*, lower albumin and creatinin and higher blood pressure, but not HDL-C. *independent
<p>Kristenson M, Olsson AG, Kucinskiene Z. Good Self-rated health is related to psychosocial resources and a strong cortisol response to acute stress: the LiVicordia study of middle-aged men International j of behavioural Medicine 2005;12(3)153-160.</p>	SRH-5	185 men	Poor SRH associated with higher basal levels of salivary cortisol and larger cortisol response to acute stress.
<p>Lekander M, Elofsson S, Neve IM, Hansson LO, Unden AL. Self-rated health is related to levels of circulating cytokines Psych Med 2004;66(4): 559-63.</p>	SRH-5	Consecutive patients at a primary health care center 91 men and 174	Poor SRH associated with higher levels of IL-1 β , IL-1ra and TNF- α , but not IL-6, in women but not in men. Independent of physician

		women 19-90 years	rated health.
<p>Matsunaga M, Tokiko Isowa, Hiroki Murakami, Kunio Kasugai, Masashi Yoneda, Hiroshi Kaneko and Hideki Ohira</p> <p>Association of polymorphism in the human μ-opioid receptor OPRM1 gene with proinflammatory cytokine levels and health perception</p> <p>Brain, Behavior, and Immunity. 2009;23(7): 931-935.</p>	SF-36	123 healthy volunteers (65 males and 58 females; age range: 20–38 years) for the study.	General health score was significantly higher in the opioid receptor gene OPRM1 AG and GG genotypes than in the AA genotype. The general health score was negatively correlated with the IL-6 serum concentration. The correlations between general health score and serum concentrations of TNF- α and IFN- γ were not observed.
<p>Mazat, L., Lafont, S., Berr, C., Debuire, B., Tessier, J.F., Dartigues, J.F., Baulieu, E.E.,</p> <p>Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality.</p> <p>Proc. Natl Acad. Sci. USA 2001;98(14):8145-50.</p>	SRH-5 (current)	Randomized population cohort 119 men and 171 women at follow-up	DHEAS from baseline associated with SRH at follow-up in men, but no association between SRH and DHEAS at follow-up. Reports earlier study association between DHEAS-SRH in both men and women.
<p>Nilsson LG, L Bäckman, K Erngrund, L Nyberg, R Adolfsson, G Bucht, S Karolsson, M Widing, B Winblad</p> <p>The Betula Prospective Cohort Study: Memory, Health and Aging</p> <p>Aging, neuropsych, cogn 1997;4(1):1-32</p>	“Do you feel healthy?” “yes/No”	Randomized population sample 500 men 500 women, 25-80 yrs Men and women analyzed together	Poor SRH was associated with higher levels of haptoglobin and higher erythrocyte sedimentation rate, but not to HbA1c, hemoglobin, EC, EVF, EMCV, leukocytes, platelet, neutrophils, eosinophiles, lymphocytes, monocytes, TSH, T4, T3, cortisol, B12, folic acid, cholesterol, TG, glucose, a-1-antitrypsin, albumin, orosmuroid, IgG, prealbumin, ALAT, ALP, ASAT, GT, LD, bilirubin, NA, K, Cl, CO2, Ca, kreatinin, P, leucocytes, glucose, protein, erythrocytes hemoglobin, blood pressure, heart rate
<p>Nordmark G, Bengtsson C, Larsson A, Karlsson FA, Sturfelt G, Rönnblom L.</p> <p>Effects of dehydroepiandrosterone</p>	General health from SF-36		DHEAS treatment did not improve general health (sf-36) in glucocorticoid treated

<p>supplement on health-related quality of life in glucocorticoid treated female patients with systemic lupus erythematosus.</p> <p>Autoimmunity. 2005;38(7):531-40. [91]</p>			women.
<p>O'Donnell K, Badrick E, Kumari M, Steptoe A.</p> <p>Psychological coping styles and cortisol over the day in healthy older adults</p> <p>Psychoneuroendocrinology. 2008;33(5):601-11. [84]</p>	SRH-5	350 men 192 women average 60.9 yrs analyzed together adjusted for sex.	Poor SRH associated with higher basal level (but not awakening level) of cortisol. Participants with greater BMIs and poorer SRH had higher cortisol outputs over the day.
<p>Shankar A, Wang JJ, Rohtchina E, Mitchell P.</p> <p>Association between self-rated health and incident severe hypertension among men: a population-based cohort study.</p> <p>Singapore Med J. 2008;49(11):860-7.</p>	“For someone your age, how would you rate your overall health – would you say it is excellent, good, fair, or poor?”	N=1,298 (62.5, range 49-84 years), at baseline (1992-1994) re-examined after five years (1997-1999).	Poor SRH predicted hypertension in men but not women.
<p>Skjelbakken T, Langbakk B, Dahl IM, Løchen ML; Tromsø Study.</p> <p>Haemoglobin and anaemia in a gender perspective: the Tromsø Study.</p> <p>Eur J Haematol. 2005;74(5):381-8.</p>	“How is your current state of health? Poor, not so good, good, or very good”	Tromsø, Norway. All >24 yr invited. 26 530 (75%) Hb analysed.	Poor SRH associated to lower Hb in men but not women in some age groups
<p>Steptoe A, Gylfe A, Shamaei-Tousi A, Bergstrom S, Henderson B.</p> <p>Pathogen burden and cortisol profiles over the day.</p> <p>Epidemiol Infect. 2009 May 19:1-9</p>		Whitehall II study. 237 men and 124 women 51-72 years	Pathogen burden (Chlamydia pneumonia, cytomegalovirus, HSC-1) was not related to SRH. Cortisol not investigated in relation to SRH.
<p>Söndergaard HP LO Hansson T Theorell</p> <p>Elevated Blood Levels of Dehydroepiandrosterone Sulphate Vary with Symptom Load in Posttraumatic Stress Disorder: Findings from a</p>	not stated	32 women 54 men of who 32 suffered from post-traumatic stress syndrome (58 finished the study)	Poor SRH associated with lower levels of DHEAS, however not significantly, in non post-traumatic stress syndrome subjects. Only referred to in the abstract, no

<p>Longitudinal Study of Refugees in Sweden</p> <p>Psychother Psychosom 2002;71:298–303</p>		Mean 34.6 yrs.	data presented.
<p>Tomten SE, AT Hoestmark</p> <p>Self-rated health showed a consistent association with serum HDL-cholesterol in the cross-sectional Oslo Health Study</p> <p>Int J Med Sci 2007;4(5):278-287.</p>	<p>“How would you describe your present state of health? Poor, not very good, good, very good?”</p>	Population based sample 8404 men and 10366 women 30-76 years	Poor SRH associated with lower HDL-C for both men and women, independent of age.
<p>Undén A-L, A Andréasson, S Elofsson, K Brismar, L Mathsson, J Rönnelid, M Lekander</p> <p>Inflammatory cytokines, behaviour and age as determinants of self-rated health in women</p> <p>Clinical Science. 2007;112:363–373.</p>	SRH-5	174 women consecutive primary health care patients	Stronger association with higher age between SRH and cytokines. SRH not associated to IGF-I/IGFBP1 ratio when adjusted for physical health, cytokines, sickness behavior. Further analysis of Lekander 2004.
<p>Undén AL, Elofsson S, Andréasson A, Hillered E, Eriksson I, Brismar K.</p> <p>Gender differences in self-rated health, quality of life, quality of care, and metabolic control in patients with diabetes.</p> <p>Gend Med. 2008;5(2):162-80.</p>	SRH-5	169 men and 167 women 20-60 yrs, registered at the Dep Endocrinology, Metabolism, and Diabetes at Karolinska University Hospital, Sweden	Poor SRH associated to higher HbA1c in both men and women when analyzing the age groups together (P < 0.05). This association was most prominent in young women, in whom having more diabetes-related worries was also related to higher HbA1c (P < 0.01).
<p>Undén AL, Elofsson S, Brismar K.</p> <p>Gender differences in the relation of insulin-like growth factor binding protein-1 to cardiovascular risk factors: a population-based study.</p> <p>Clin Endocrinol (Oxf). 2005;63(1):94-102.</p>	SRH-5	Population based sample 408 randomly selected people from 4200 people over age 17	SRH was not associated to IGFBP1
<p>Uden AL, Elofsson S, Knox S, Lewitt MS, Brismar K.</p> <p>IGF-I in a normal population: relation to psychosocial factors.</p>	SRH-5	Cross-sectional study. 135 men and 137 women aged 18-74 years	Self rated health was not associated to IGF-I other than in the younger age group (18-44 yrs) with men and women

Clin Endocrinol (Oxf). 2002 Dec;57(6):793-803.			combined with control for age.
Wexler T, Gunnell L, Omer Z, Kuhlthau K, Beaugard C, Graham G, Utz AL, Biller B, Nachtigall L, Loeffler J, Swearingen B, Klibanski A, Miller KK. <i>Growth hormone deficiency is associated with decreased quality of life in patients with prior acromegaly.</i> J Clin Endocrinol Metab. 2009;94(7):2471-7.	Sf-36	Forty-five patients with prior acromegaly participated: 26 with GH deficiency and 19 with GH insufficiency.	Sf-36 general health lower in GH insufficient acromegaly patients compared to acromegaly jämfört med de med normalt GH
Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, Launer L, Kuller L, Rubin S, Harris T. <i>Inflammatory markers and cognition in well-functioning African-American and white elders</i> Neurology, 2003. 61(1):76-80.	SRH-5 compared to others	3031 African-American and white men and women (mean age 74 yrs).	Higher prevalence of fair/poor SRH was found in those in the lowest tertile of IL-6 as compared to those in the higher tertiles. Were also more likely to be African-American, male, and older.