THE ASSOCIATION OF SYSTEMIC LOW-GRADE INFLAMMATION WITH HEALTH-RELATED QUALITY OF LIFE IN FINNISH YOUNG MEN

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Exercise Physiology Master's thesis
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TIIVISTELMÄ

Alho, Mika. 2019. Systeemisen, matala-asteisen tulehduksen yhteys elämän laatuun nuorilla suomalaisilla miehillä. Liikuntabiologian laitos, Jyväskylän yliopisto, liikuntafysiologian pro gradu -tutkielma, 23 sivua, 2 liitettä.

Taustaa Viimeisten vuosikymmenien aikana on tullut todistetuksi, että tulehduksellisilla mekanismeilla on keskeinen rooli monien kroonisten sairauksien taudinkehityksessä. Tällaisia sairauksia ovat mm. tyypin 2 diabetes, aivohalvaus, kasvainten kehittyminen, krooninen ahtauttava keuhkosairaus ja Alzheimerin tauti. Kroonisissa sairauksissa elämänlaatu usein heikentyy. Heikentynyt elämänlaatu on liitetty lisääntyneeseen kuolleisuuteen. Useat tekijät, kuten ikä, sukupuoli, painoindeksi, tupakointi, sydänverenkiertoelimistön kunto ja sairaudet ovat olleet tutkimuksissa yhteydessä sekä tulehdusvälittäjäaineisiin että elämänlaatuun. Tutkimuksissa on ollut näyttöä siitä, että elämänlaatu on käänteisesti yhteydessä tulehdustekijöihin, mutta terveillä nuorilla aikuisilla tutkimuksellinen näyttö on hyvin rajallista.

Tutkimuksen tavoite Tutkimuksen tavoitteena on selvittää elämän laadun ja systeemisen matala-asteisen tulehduksen välistä yhteyttä nuorten, suomalaisten reserviläismiesten joukossa.

Aineisto ja menetelmät Tutkimukseen osallistui vapaaehtoisesti Suomen armeijan reserviläismiehiä (n = 777, keski-ikä 26.5 SD 6.8 vuotta) seitsemän kertausharjoituksen yhteydessä vuonna 2015. Elämänlaadun mittarina käytettiin RAND-36 kyselyn perusteella laskettuja fyysisen (PCS) ja henkisen (MCS) elämänlaadun pistemääriä. Osallistujien verinäytteistä analysoitiin plasman C-reaktiivisen proteiinin (CRP) ja interleukiini 6:n (IL-6) pitoisuudet. Osallistujien sydän-verenkiertojärjestelmän kunto sekä lihas voima ja kunto mitattiin. Mittaustuloksista suoritettiin korrelaatio- ja regressioanalyysit, ja regressioanalyysi suoritettiin myös vakioiden ikä, painoindeksi ja tupakointi.

Tulokset CRP:n, IL-6:n, PCS:n, and MCS:n keskiarvot (keskihajonta) olivat 1.15 mg/L (1.54), 1.10 pg/L (1.35), 54.8 (4.6), and 50.9 (9.4). Maksimaalisen hapenottokyvyn keskiarvo (keskihajonta) oli 41.3 (7.7) ml $\cdot$ kg$^{-1}\cdot$ min^{-1}. PCS:n ja molempien tulehduksen merkkiaineiden välillä oli tilastollisesti merkitsevä yhteys, mitä ei ollut MCS:n ja tulehduksen merkkiaineiden välillä. Sydän-verenkiertojärjestelmän kunto ja lihaskunto olivat positiivisesti yhteydessä fyysiseen elämänlaatuun ja negatiivisesti tulehduksen merkkiaineisiin. Regressioanalyysissä iän, painoindeksin ja tupakoinnin mukaan vakioidussa mallissa sekä PCS että MCS olivat merkitsevästi yhteydessä inflammaatiotekijöihin.

Johtopäätökset RAND-36 kyselyllä mitatun fyysisen elämänlaadun ja tulehduksen merkkiaineiden välillä on yhteys tutkimuksen terveiden, resilienttien, nuorten miesten aineistossa, vaikkakin sekä CRP että IL-6 selittivät vain vähän PCS:n vaihtelusta.

Asiasanat: CRP, elämänlaatu, IL-6, merkkiaineet, RAND-36, tulehdus, väestötutkimus

ABSTRACT

Alho, Mika. 2019. The associations of systemic low-grade inflammation with health-related quality of life in Finnish young men. Department of Biology of Physical Activity, University of Jyväskylä, Master's thesis in exercise physiology, 63 pages, 2 appendices.

Background During the last two decades, it has become evident that inflammatory mechanisms have central role in pathological processes of several chronic diseases such as type 2 diabetes, cardiovascular disease, stroke, tumorigenesis, chronic obstructive pulmonary disease, and Alzheimer disease. Chronic diseases tend to lower health-related quality of life (HRQoL). Low HRQoL has been associated with increased mortality risk. Several factors like age, gender, body mass index, smoking, cardiovascular fitness, and morbidities have been associated both inflammatory markers and HRQoL. There is a data that HRQoL has been associated inversely with inflammatory markers, but the data is very limited in healthy, young, adult population.

Objective To investigate associations between HRQoL and systemic low-grade inflammation in a Finnish young, men population.

Material and Methods Participants (n = 777; mean age 26.5 SD 6.8 years) were volunteered male reservists of the Finnish Defence Forces who participated in refresher courses organized in seven different garrisons around Finland during 2015. As a measure of HRQoL physical (PCS) and mental (MCS) component summary scores of the RAND-36 were calculated. Plasma concentrations of C-reactive protein (CRP) and Interleukin-6 (IL-6) were analyzed from the blood samples of participants. Cardiorespiratory fitness and muscle strength and fitness of the participants were measured. Correlation and regression analysis were performed, and in regression analysis there were also adjustments for age, BMI and smoking-status.

Results The means (SD) for CRP, IL-6, PCS, and MCS were 1.15 mg/L (1.54), 1.10 pg/L (1.35), 54.8 (4.6), and 50.9 (9.4), respectively. Mean VO_2max (ml · kg^{-1}· min^{-1}) of the participants was 41.3 SD 7.7. There were statistically significant association between PCS and both inflammatory markers (modified to natural logarithmic values), but not between MCS and inflammatory markers. Cardiorespiratory and muscle fitness were associated positively with PCS and negatively with inflammatory markers. In regression analysis after adjustments for age, BMI, and smoking-status, there were weak but significant association between both PCS and MCS and inflammatory markers.

Conclusion The present study shows that there is a relationship between PCS of the RAND-36 and inflammatory markers in a healthy, resilient, young, adult men population, despite both CRP and IL-6 explained only a little about the variance of PCS.

Key words: biomarkers, CRP, general population, health-related quality of life, IL-6, inflammation, RAND-36

ABREVIATIONS

ACTH	adrenocorticotropic hormone
BCDF	human B-cell differentiation factor
BMI	body mass index (= weight * height^{-2})
BSF-2	human B-cell differentiation factor
$CD8^+$ T-cells	subset of lymphocytes which could be identified by cell surface marker called $CD8^+$
CRP	C-reactive protein
gp130	common receptor subunit glycoprotein 130
HPA	hypothalamus-pituitary-adrenal
HRQoL	health-related quality of life
IL-1β	interleukin 1β
IL-1ra	interleukin 1 receptor antagonist
IL-6	interleukin 6
IL-6R	interleukin 6 receptor
IL-10	interleukin 10
LPS	bacterial lipopolysaccharides
QoL	quality of life
RAND-36	RAND 36-item health survey, a measure of HRQoL
SF-36	36-item short form, a measure of HRQoL
sIL-6R	soluble interleukin 6 receptor
SNS	sympathetic nervous system
sTNF-R	soluble TNF-α receptors
TNF-α	tumor necrosis factor α
VO_2max	maximal oxygen uptake

CONTENT

1 INFLAMMATION

Inflammation is traditionally described as the principal response evoked in the body when injured; it is an adaptive and reparative process following injury to the body, whether the injury is caused by microbes, trauma, heat, chemicals or any other phenomenon. Injured tissues release many substances that cause secondary changes in the surrounding uninjured tissues. Classical signs of inflammation are swelling, redness, pain, fever (tumor, rubor, dolor and calor) and impaired function. These signs can be related to (1) the vasodilation and increased flow of local blood vessels; (2) leakage of large quantities of fluid into the interstitial spaces caused by increased permeability of the capillaries; (3) (in some cases) leakage of huge amounts of fibrinogen and other proteins leaking from the capillaries and causing clotting of the fluid in the interstitial spaces; (4) migration of large numbers of granulocytes and monocytes into the tissue; and (5) swelling of the tissue cells. This adaptive and tissue repair process is normally short-term, but it is extremely complex and variable depending on, e.g., the site of injury, stimulus causing the injury, hormonal and nutritional status of the individual or genetic factors. (Larsen 1983; Gyuton & Hall 2006, 434–435).

The previously mentioned local response to tissue injury also includes the release of cytokines at the site of inflammation. In addition to playing a crucial role in the regulation of immune response, cytokines are important factors of metabolism, endocrine systems, the coagulation system and the brain function. Different cells in a wide range of organs synthesize and secrete cytokines instantly after stimulation. Most cytokines are difficult to detect in a serum because producer cells are often near the target cells and usually secrete only small amounts of cytokines at a time. Cytokines achieve their effect via specific cell surface receptors on their many target cells. The effect is mostly a combination of the additive, synergistic or antagonistic actions of many different cytokines. Several different cytokines can cause corresponding biological responses. (Heinrich et al. 1998; Foster 2001; Brüünsgaard 2005).

In order of appearance, the initial cytokines at the site of inflammation are tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1ra), soluble TNF-α receptors (sTNF-R) and interleukin-10 (IL-10). Locally produced, pro-inflammatory TNF-α and IL-1 stimulate the production of IL-6, which is considered to have primarily anti-

inflammatory effects stimulating the release of sTNF-R and the production of IL-1ra and IL-10, which all have an inhibitory role in the inflammation. A local inflammatory response is followed by a systemic response called the acute-phase response, which comprises the production of a large number of hepatocyte-derived proteins including C-reactive protein (CRP). IL-6 appears to be the primary inducer of the acute-phase response. (Brüünsgaard & Pedersen 2003; Petersen & Pedersen 2005; Mathur & Pedersen 2008).

Acute inflammation is adaptive, tissue-repairing and temporary, but when prolonged, the long-term consequences of inflammation will be deleterious (Hotamisligil 2006). During the last three decades, it has become evident that inflammatory mechanisms play a central role in the pathological processes of several chronic diseases such as type 2 diabetes (Hotamisligil 2006), cardiovascular disease (Ridker et al. 2000B; Laaksonen et al. 2005), stroke (Hallenbeck 2002), tumorigenesis (Hanahan & Weinberg 2011), chronic obstructive pulmonary disease (Gan et al. 2004), depression (Haapakoski et al. 2015) and Alzheimer's disease (Akiyama et al. 2000). Compared to acute inflammation (sepsis, trauma, surgery and so on) in which plasma levels of pro-inflammatory mediators increase even more than 100 times, chronic low-grade systemic inflammation is characterized by a twofold to fourfold elevation of circulatory inflammatory and acute-phase parameters like interleukin-6 and C-reactive protein (Ridker et al. 2000A; Bruunsgaard & Pedersen 2003; Suárez Krabbe et al. 2004).

From the point of view of inflammation, the present thesis concentrates on interleukin-6 and C-reactive protein as markers of chronic low-grade systemic inflammation. The following chapters present a review of both the previously mentioned markers of inflammation and the basic information about the meaning of chronic low-grade systemic inflammation.

1.1 Interleukin-6 (IL-6)

Interleukin-6 (IL-6) was first sequenced in the mid-1980s (Hirano et al. 1986). This 184-amino acid glycosylated protein was described as a human B-cell differentiation factor (called BCDF or BSF-2) facilitating B-cells to differentiate into immunoglobulin-secreting plasma cells (Hirano et al. 1986). Soon after, IL-6 received its current name when it was noticed that BSF-2 was identical to other factors that were active outside the immune system (Poupart et al. 1987). IL-6 is secreted by

neutrophils, monocytes, macrophages, fibroblasts, endothelial cells, smooth muscle cells and T-cells during many, if not all, inflammatory and infectious diseases (Schaper & Rose-John 2015). During septic infections, the plasma concentration of IL-6 could elevate 1000 folds from resting level and could reach 10,000 pg/ml, but mainly, IL-6 elevations are less dramatic in several infections and inflammatory diseases (Fischer 2006). In healthy individuals at rest, the circulating IL-6 is mainly produced by white blood cells and adipose tissue (Fischer 2006). Mohamed-Ali et al. (1997) estimated that, at rest, adipose tissue produces 15–35% of the circulating IL-6 depending on the time of day. Only about 10% of adipose tissue IL-6 release originates from adipocytes (Fried et al. 1998). A meta-analysis by Nilsonne et al. (2016) showed that there is a diurnal variation of circulating IL-6 levels with typical troughs in the mornings.

IL-6 binds to a specific receptor (IL-6R), which is a transmembrane protein. For signal transduction, IL-6 and its receptor complex use the common receptor subunit glycoprotein 130 (gp130), which is also used by other members of the IL-6 cytokine family. While gp130 is expressed on the surface of all cells of the body, membrane-bound IL-6R is largely found on hepatocytes and certain leucocytes (neutrophils, monocytes and CD+ T-cells). This previously mentioned “classical signaling” is seen as mainly protective and regenerative, i.e., anti-inflammatory. A proteolytic cleavage of IL-6R can construct a soluble IL-6R (sIL-6R). Binding to this soluble receptor sIL-6R prolongs the IL-6 half-life by protecting it from enzymatic degradation. The cytoplasmic portion of IL-6R is not needed for signal transduction. IL-6 and the soluble IL-6R complex can bind to gp130 and cause intracellular signaling in cells that do not have IL-6R. This “trans-signaling” may be considered to express a stress response in the body to maintain body homeostasis, which is pro-inflammatory. (Heinrich et al. 1998; Nimmo et al. 2013; Schaper & Rose-John 2015; Liu et al. 2016).

In healthy individuals at rest, the plasma concentration of IL-6 is about 1 pg/ml or even lower (Brüünsgaard et al. 1997; Ostrowski et al. 1998). In previous studies, participants were young, healthy males mean ages were 26 and 30.5 years, respectively, and a mean VO_2max 51.1 and 58.8 ml/kg/min, respectively. In Finnish young adult men with and without abdominal obesity, the mean plasma IL-6 concentrations were 1.09 ± 1.29 pg/mL (VO_2max 42.7 ± 7.6 mg/ml/kg) and 1.46 ± 1.18 pg/mL (VO_2max 32.0 ± 5.5 mg/ml/kg), respectively (Vaara et al. 2014). As shown in Figure 1, the plasma concentration of IL-6 and TNF-α tend to elevate with age (Brüünsgaard et al. 1999). In this study of

healthy young adults (aged 18–30 years, 21 females, 17 males), the plasma concentrations of IL-6 were 0.3–17.0 pg/ml). In a study by Pedersen et al. (2003), healthy elderly subjects (65–79 years) tend to have more absolute and relative truncal fat mass than the younger ones (22–33 years), and the elevation of these cytokines with age is partly explained by an increase of fat mass. Brüünsgaard et al. (2003) stated that age-related and morbidity- and mortality-associated elevations of the plasma concentration of IL-6 and TNF-α is multifactorial, caused by obesity, genetic factors, reducing function of sex hormones and many environmental factors like infections and smoking.

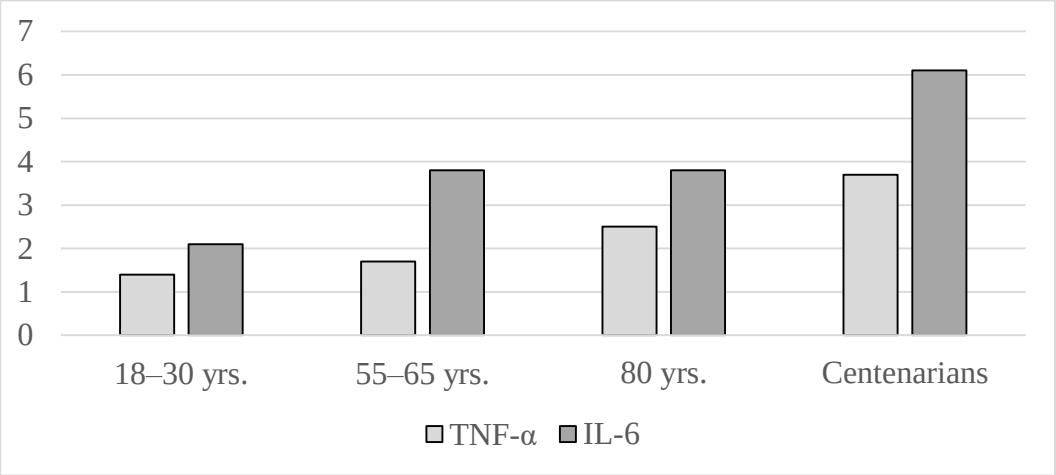

FIGURE 1. Age-associated plasma levels of TNF-α and IL-6, both concentrations in pg/ml (Adapted from Brüünsgaard et al. 1999).

During exercise, IL-6 is secreted by contracting muscle cells. The elevation of plasma IL-6 is related to contracting muscle mass, the intensity of exercise and especially the duration of exercise, which can explain more than 50% of the variance in the exercise-induced plasma levels of IL-6 (Figure 2). The main stimulus in IL-6 secretion is low skeletal muscle glycogen content, and during prolonged exercise, IL-6 levels can elevate to more than 100 times the resting levels. The accumulation of intramuscular calcium and reactive oxygen species also stimulates IL-6 secretion from contracting muscle. During prolonged exercise, one systemic effect of IL-6 is to secure fuel availability to contracting muscle via increased glycogenolysis in the liver and increased lipolysis in adipose tissue. Exercising in a glycogen-depleted state accentuates the exercise-induced IL-6 response, and instead, carbohydrate supplementation attenuates the elevation of plasma IL-6. Figure 3 presents the stimuli and the systemic effects of IL-6 secreted from contracting muscle. Endurance training makes skeletal

muscle less dependent on glucose and glycogen as energy sources and also attenuates IL-6 secretion from contracting muscle. (Phillips et al. 1996; Steensberg et al. 2003; Fischer 2006; Pedersen & Fischer 2007; Pedersen & Febbraio 2008; Pedersen & Febbraio 2008).

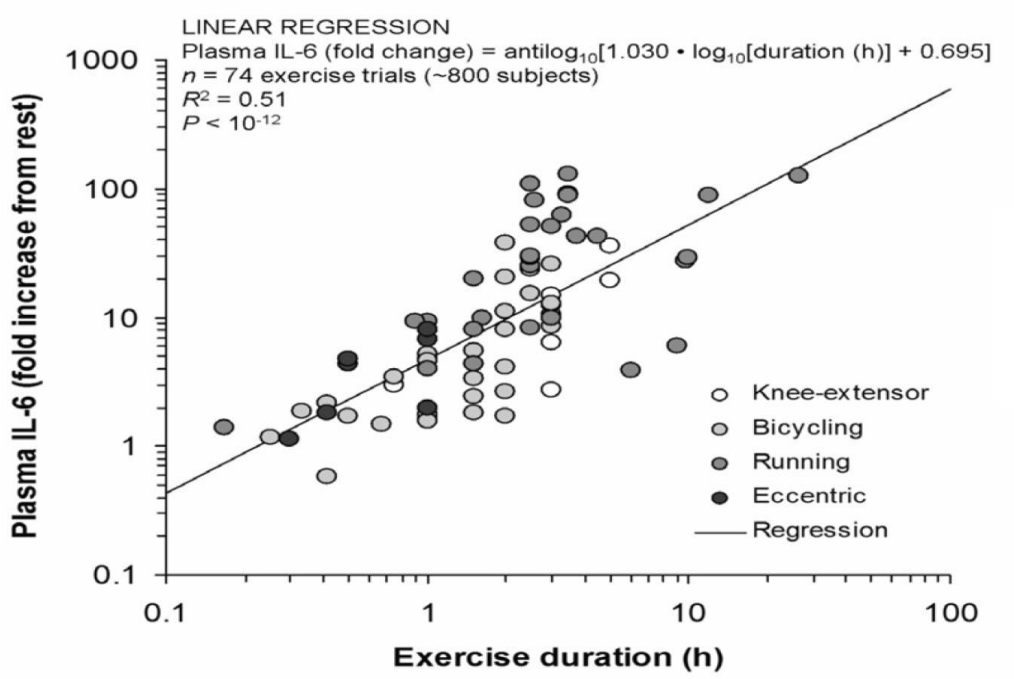

FIGURE 2. Effect of mode and duration of exercise on post-exercise plasma IL-6 (Fischer 2006).

During prolonged exercise, the plasma level of IL-6 increases, peaking at the end of the session or shortly after. During recovery, the plasma level of IL-6 rapidly declines, typically during the first few hours. Followed by the rise of IL-6 levels, there are elevations of plasma levels from other anti-inflammatory cytokines like interleukin-1 receptor antagonist (IL-1ra), soluble tumor necrosis factor receptor (sTNF-R) and interleukin-10 (IL-10). Changes in plasma cytokine levels induced by a single bout of exercise resemble sepsis-induced changes without preceded elevation of pro-inflammatory TNF-α and IL-1. As presented in Figure 4, in sepsis and during exercise, the elevation of IL-6 is most prominent, but in severe sepsis, the elevation of IL-6 can even be 100 times higher than during exercise. (Phillips et al. 1996; Steensberg et al. 2003; Fischer 2006; Pedersen & Fischer 2007; Pedersen & Febbraio 2008).

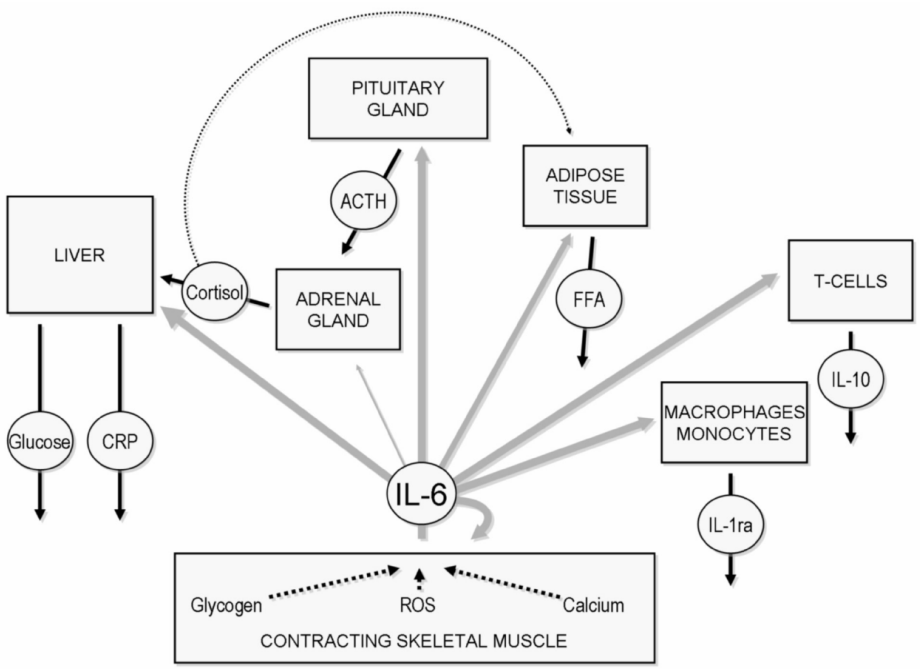

FIGURE 3. Stimulation of IL-6 secretion from contracting muscle and some IL-6 systemic targets (Fischer 2006).

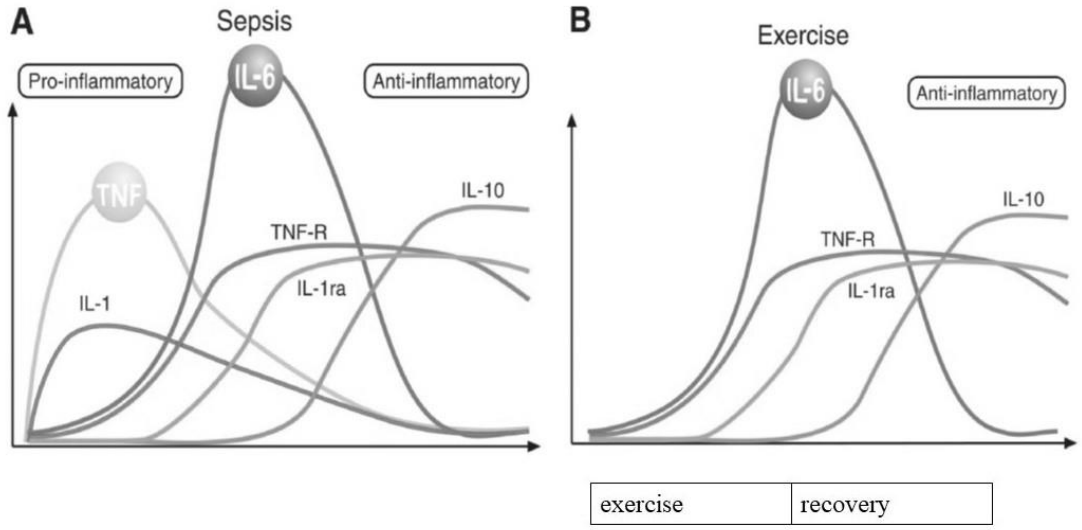

FIGURE 4. Sepsis- (A) and exercise- (B) induced plasma cytokine responses (modified from Petersen & Pedersen 2005).

1.2 C-reactive protein (CRP)

The human C-reactive protein was discovered by Tillett and Francis (1930), who found that the sera of lobar pneumonia patients are able to precipitate a somatic fraction originated from pneumococci bacteria (Fraction C). CRP was named because of the previous finding. The CRP molecule is a construct of five identical non-glycosylated polypeptide subunits. Each of these subunits contains 206 amino acids. CRP is one of the acute-phase reactants and is produced by hepatocytes mostly under the control of IL-6 in nearly all kinds of tissue damage, infection, inflammation, and malignant neoplasia as part of a non-specific acute-phase response. Human CRP binds to a variety of autologous and extrinsic ligands that bear several cellular, particulate, and molecular structures, which CRP can aggregate or precipitate. In this aggregated or bound state, CRP is recognized by C1q and powerfully activates the classical complement pathway. Under distinct circumstances, CRP could function like an antibody as a pro-inflammatory mediator. Until the mid-1990s, and the development of highly sensitive methods to measure serum concentrations below 5–10 mg/L, C-reactive protein was interpreted only as an acute-phase reactant. But with new immunoassay methods and after findings that "high-normal" values predicted elevated risk for future coronary events, there has also been interest in these lower values. (Pepys & Hirschfield 2003).

In an early study by Shine et al. (1981), the mean serum concentration of C-reactive protein was 0.8 mg/L among healthy adult volunteer blood donors (N = 468), while 90% of participants had CRP values below 3 mg/L. In a study of first-year college students (n = 177, mean age 18.1 yrs., 66.7% female, 65.5% white), the mean plasma CRP values were 1.3 mg/L (SD 1.8) and 1.4 mg/L (SD 2.4) for females and males, respectively (Fedeva et al. 2014). In Finnish young adult men with and without abdominal obesity, the mean plasma CRP concentrations were 1.34 ± 2.9 mg/L and 2.78 ± 2.38 mg/L, respectively (Vaara et al. 2014). Ballou et al. (1996) compared plasma CRP values in healthy older (≥ 65 years) to healthy younger (17–47 years) individuals and observed that CRP values of the older group were about three times higher than the younger group, with a median CRP of 3.0 µg/ml versus 0.9 µg/ml. In an adult general population study (4494 participants from Germany and 1254 participants from Scotland) by Hutchinson et al. (2000), the mean CRP values ranged from 0.75 to 2.40 mg/L. In a previous study, females tended to have higher CRP values, and the mean CRP about doubled from ~ 1 mg/L in the youngest group (25–34 years) to ~ 2 mg/L in oldest age groups of 65–

74 (German) and 55–64 years (Scotland). In a community-based prospective-longitudinal study in which participants (n = 1420) were followed from the ages of 9–13 years to the age of 21, the plasma level of CRP about doubled after age 16 in females, and 26.3% of females older than 19 years had CRP > 3 mg/L compared to 10.3% of males at the same age (See also Figure 5, Shanahan et al. 2013). Smokers tend to have higher plasma levels of CRP compared an age-matched non-smoking person (Ridker et al. 1997; Koenig et al. 1999).

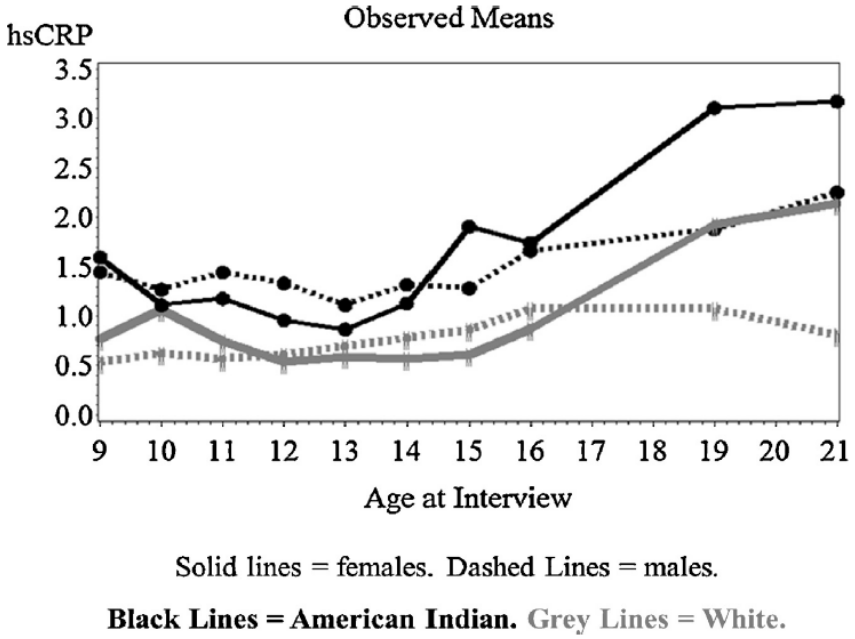

FIGURE 5. Mean plasma levels of CRP in American Indian and white females and males, ages 9–21 years (Shanahan et al. 2013).

During the acute-phase response, especially in a serious infection, plasma CRP can increase 1000-fold to the level of 500 mg/L. After a single stimulus, plasma CRP will peak in 48 hours, and the half-life of plasma CRP is constantly about 19 hours in any condition. In the general population, each person has individual and stable plasma CRP concentration, which spike during infection, inflammation and trauma. (Pepys & Hirschfielf, 2003).

In the review by Plaisance and Grandjean (2006), the authors stated that it is less likely that acute-phase reactants like CRP would increase after a single session of low to moderate intensity. Studies related to marathon running have shown that, compared to pre-exercise level, CRP seems to elevate

after strenuous exercise (Weight et al. 1991; Siegel et al. 2001). CRP was elevated four hours after the marathon (Weight et al. 1999) and peaked about 24 hours after compared to pre-exercise level, and it recovered to pre-exercise level within six days (Siegel et al. 2001).

In relatively healthy populations, CRP has been associated with age, gender, race, physical activity, oral contraceptive use and socioeconomic status (Fedewa et al. 2017). In the third National Health and Nutrition Examination Survey (NHANES III), which consisted of a large sample of adults (age ≥ 20 years, N = 13 748) in the U.S., leisure-time physical activity was inversely and dose-responsively related to CRP (Ford 2002). In the majority of large adult population cross-sectional studies, higher self-reported physical activity has been associated with lower CRP levels and has shown that more active individuals have had 19–35% lower CRP levels than less active individuals (Plaisance & Grandjean 2006). In a study of college students in the U.S. (N = 177, mean age 18.1 years, 66.7% female, 65.5% white), objectively measured body fat percentage, but not objectively measured physical activity, was statistically significantly associated with elevated CRP (Fedewa et al. 2014). In cross-sectional studies, individuals with higher fitness have had lower CRP levels than individuals with poorer fitness (Plaisance & Grandjean 2006). In a meta-analysis of exercise intervention studies (at least two weeks in duration), exercise training was associated with a statistically significant improvement in CRP regardless of sex or age, but the decrease was more prominent when there were also decreases in BMI or body fat percentage (Fedewa et al. 2017).

Improvements in CRP related to exercise training were also noticed in nearly normal-weight Finnish males. Ihalainen et al. (2017) investigated the effect of 24 weeks of combined aerobic and resistance training on plasma inflammatory markers in moderately active healthy men (N = 48, mean age 31 ± 6, BMI 25.2 ± 3.5 kg/m^2). These men were randomly divided into three groups: one group performed aerobic and resistance training consecutively in the single training session (SS) 2–3 days/week; another group performed the same amount of training on alternating days (AD) 4–6 days/week; and there was a control group that not performed exercise. After training intervention, the inflammatory status in both training groups improved: plasma concentrations of CRP, leptin and resistin decreased compared to baseline. There was no significant decrease in body mass nor fat mass, but abdominal fat mass was reduced significantly in both training groups.

1.3 Chronic low-grade systemic inflammation

The development of commercial high-sensitivity methods to measure serum concentrations of CRP and IL-6 made it possible to measure so-called high normal values, which are related to inflammation (Pepys & Hirschfield 2003). Chronic low-grade systemic inflammation is characterized and defined as 2–4 times the elevation in the plasma levels of inflammation markers such as C-reactive protein and interleukin-6 (Ballou et al. 1996; Hutchinson et al. 2000; Ridker et al. 2000A; Bruunsgaard & Pedersen 2003; Suárez Krabbe et al. 2004; Mathur & Pedersen 2008). It is estimated that chronic non-communicable diseases (CNCDs) such as cardiovascular diseases (ischemic heart disease and stroke), several cancers, type 2 diabetes, chronic obstructive pulmonary diseases and Alzheimer's disease cause about 60% of all deaths worldwide (Mathur & Pedersen 2008) and are also the leading causes of work absence and disability (de Punder & Pruimboom 2015). In recent decades, it has become evident that inflammatory mechanisms have a central role in pathological processes of previously mentioned chronic diseases (Ridker et al. 2000B; Akiyama et al. 2000; Hallenbeck 2002; Gan et al. 2004; Laaksonen et al. 2005; Hotamisligil 2006; Hanahan & Weinberg 2011).

1.3.1 Mechanisms behind chronic low-grade systemic inflammation

In the last few decades, there has been growing evidence that obesity is causally linked to inflammation, which contributes to the development of insulin resistance and metabolic dysfunction (Wellen et al. 2005; Shoelson et al. 2006; Ouchi et al. 2011). In the mid-1990s, tumor necrosis factor alpha (TNF-α) was discovered to be overexpressed in the adipose tissue of both obese rodents and obese humans, and that was the first time that inflammation, obesity and insulin resistance were linked together molecularly (Hotamisligil et al. 1993; Hotamisligil et al. 1995). Even in healthy humans, about 15–35% of plasma IL-6 is derived from adipose tissue (Mohamed-Ali et al. 1997). After that, it has been shown that, in obesity, there is an accumulation of macrophages in adipose tissue, and these macrophages are mainly responsible for adipose tissue TNF-α and IL-6 expression, which impair the insulin-signaling cascade to cause insulin resistance (Weisberg et al. 2003). Nishimura et al. (2009) found that T-cell phenotypic change precedes macrophage infiltration in obese mice, and there was an increase in $CD8^+$ T-cells in adipose tissue, which in turn promoted the recruitment and activation of macrophages in that tissue. In summary, adipose tissue hypertrophy leads to the

accumulation and phenotypic modulation of macrophages and T-cells in adipose tissue; it also leads to a growing imbalance between adipose tissue–secreted pro- and anti-inflammatory cytokines, which have both local and systemic effects and which contribute to the development of insulin resistance, non-alcoholic fatty liver disease, type 2 diabetes and cardiovascular diseases. The phenotypic modulation of adipose tissue is described in Figure 6.

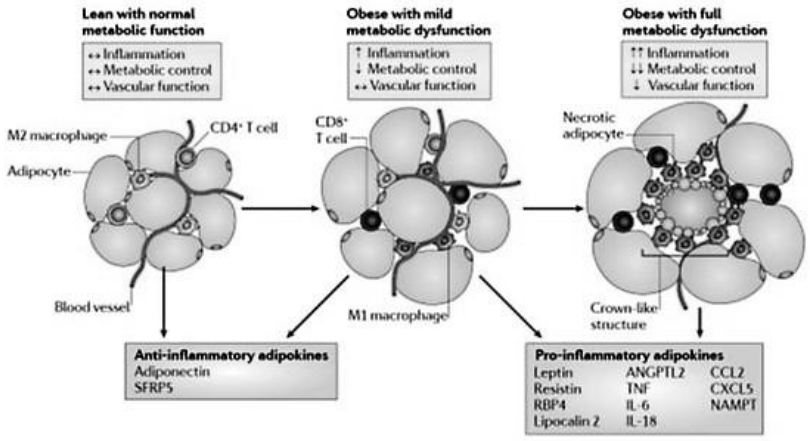

FIGURE 6. Phenotypic modulation of adipose tissue from normal metabolic function to full metabolic dysfunction. This process includes the development of pronounced inflammation and weakened metabolic control and vascular function. SFRP5 = secreted frizzled-related protein 5, RBP4 = retinol-binding protein 4, ANGPTL2 = angiopoietin-like protein 2, TNF = tumor necrosis factor, IL-6 = interleukin-6, IL-18 = interleukin-18, CCL2 = CC-chemokine ligand 2, CXCL5 = CXC-chemokine ligand 5, NAMPT = nicotinamide phosphoribosyltransferase (Ouchi et al. 2011).

In their review, Bleau et al. (2015) presented the role of the intestine in the development of systemic low-grade inflammation. They presented studies in which a high-fat diet has caused disturbances in the composition of the intestinal microbiota. These disturbances, particularly a decline in the diversity of bacteria, could lead to the "leaking" of bacterial lipopolysaccharides (LPS) and saturated fatty acids from the gut into the circulation and trigger the inflammation. Aging also leads to a decline in microbiota "richness." These changes could even precede the adipose tissue–associated inflammation and the development of metabolic diseases. Intestinal cells secrete several hormones that affect appetite and glucose metabolism, and a high-fat diet may negatively affect the secretion process.

de Punder and Pruimboom (2015) presented a theory and data on the role of stress in low-grade inflammation. Both physical and mental stress stimuli activate the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal (HPA) axis. It is evidenced that emotional stressors affect the immune response and inflammatory mediators such as IL-6, and they activate the HPA axis and cause sickness behavior and changes in energy supply. Activation of these systems enhances the availability of energy substrates, water and minerals to meet with the demand of the body. Activation of the SNS and HPA axis may mediate the increase in intestinal permeability, which may raise the amount of bacteria/LPS and/or toxins translocated from the gut into the circulation, which in turn activates both the SNS and HPA axis.

It seems that the origin of systemic low-grade inflammation remains unclear. Development of the inflammatory state involves multiple organs and complex interconnecting signals. Adipose tissue hypertrophy–related inflammatory imbalance should be preceded by an energy surplus caused by an excess of nutrients. Could a high-energy diet or chronic stress be the primary trigger and induce disturbances in gut homeostasis? There seem to be several vicious circle kinds of routes that enhance the inflammatory process.

1.3.2 Inflammation and obesity and metabolic diseases

On its website, the World Health Organization states its "WHO key facts of obesity and overweight," which shows that the worldwide prevalence of obesity (BMI $\geq$ 30 kg/m^2) has nearly tripled since 1975. In 2016, more than 1.9 billion adults (18 years and older) were overweight or obese (BMI > 25 kg/m^2), which was about 39% of the adult population. Approximately one-third of adults were obese (BMI > 30 kg/m^2). In 2015, excess body weight explained about 4 million deaths worldwide, mainly related to cardiovascular disease (The GBD 2015 Obesity Collaborators 2017). In Finland, about 60% of males 30–44 years old were overweight or obese in 2011 (Koskinen et al. 2012).

It is evident that obesity increases the risk of several diseases like asthma (Beuther et al. 2007), cardiovascular diseases (Guh et al. 2009), dementia (Loef et al. 2013), depression (Onyike et al. 2003), diabetes (Guh et al. 2009), fatty liver disease (Corey et al. 2014), gout (Puig et al. 2008), kidney disease (Wang et al. 2008), obstructive sleep apnea (Garvey et al. 2015), osteoarthritis

(Thijssen et al. 2015) and several cancers (Guh et al. 2009). Especially in the U.S., obesity is associated with more morbidity than alcoholism, poverty and smoking (Lavie et al. 2009). In a large European cohort study of almost 360,000 participants, both general and abdominal adiposity were associated with an elevated risk of death (Pischon et al. 2008).

In several cross-sectional studies, the plasma level of CRP was higher in overweight and obese subjects compared to normal-weight subjects. Even in normal-weight subjects, CRP has been positively associated with body mass index (BMI) and central obesity. Several anthropometric variables—BMI, fat mass, waist girth, sagittal diameter, visceral adipose tissue and subcutaneous adipose tissue—have been shown to correlate with plasma CRP levels. BMI and waist circumference have both explained about 30% of CRP variance. These findings have been shown in different adult and older populations in both genders, as well as in children and adolescents. Some of the comparable data are presented in Table 1 (Hak et al. 1999; Koenig et al. 1999; Visser et al. 1999; Lemieux et al. 2001; Järvisalo et al. 2002; Ford 2003; Park et al. 2005; Chaikate et al. 2006; Wärnberg et al. 2006; Wang et al. 2011; Marques-Vidal et al. 2012; Cruz et al. 2013).

In addition to plasma CRP levels, concentrations of interleukin-6 and tumor necrosis factor-α have also been positively related to BMI and central obesity in white non-diabetic subjects (Yudkin et al. 1999). In the teenage population, high BMI and waist circumference were associated with the up-regulation of pro-inflammatory cytokines (including IL-6) and the down-regulation of anti-inflammatory adiponectin (Herder et al. 2007). These findings have not been repeated in all studies. Kern et al. (2001) found in their non-diabetic adult participants that the plasma concentration of IL-6 was significantly higher in obese subjects, but the concentration of TNF-α was not. Chaikate et al. (2006) did not find a statistically significant difference in the plasma concentrations of IL-6 and TNF-α between normal and overweight adult subjects.

In a population of young Finnish males (mean age 25.1 years, n = 844), the plasma concentrations of both IL-6 and TNF-α were significantly higher in the metabolic syndrome group compared to the non-metabolic syndrome group (Kosola et al. 2013). In the 11-year follow-up study of Finnish middle-aged men (mean age 50.8–52.1 years, N = 762) free of type 2 diabetes and metabolic syndrome but with elevated CRP levels (CRP ≥ 3 mg/L) at baseline, there was more than 3 times the

risk of developing metabolic syndrome; compared to those subjects, the baseline CRP level was below 1 mg/L, but risk was attenuated after adjustment for BMI (Laaksonen et al. 2004). In that study, the risk for developing type 2 diabetes was 2.30–4.11 times higher depending on adjustments in men with elevated CRP levels compared to those with CRP < 1 mg/L. A 10-year follow-up study of younger non-diabetic adults (mean age 40.1 years, N = 2339) indicated that CRP was positively associated with the incidence of type 2 diabetes even after full adjustments (Odegaard et al. 2016). In a meta-analysis of 19 prospective studies with non-diabetic adult populations, elevated plasma levels of IL-6 and CRP were significantly associated with an increased risk of type 2 diabetes both in women and in men (Wang et al. 2013).

TABLE 1. Plasma inflammatory parameters in overweight subjects and healthy controls in different populations. Data are collected from the studies mentioned below. Statistically significant P-values are bolded.

	Overweight			Healthy controls			
	Mean	SD	N	Mean	SD	N	p
Chaikate et al. (2006), mean age 40 y, Thailand			44			46	
CRP (mg/L)	1.80	1.28		1.01	0.96		**0.000**
IL-6 (pg/mL)	1.87	1.50		1.76	1.57		0.637
Cruz et al. (2013), 11–15 y, Brazil			365			117	
CRP (mg/L)	0.63			1.08			**0.001**
Park et al. (2005), 20–60 y, South Korea			46			54	
CRP (mg/L)	1.05			0.22			**< 0.05**
IL-6 (pg/mL)	2.00			1.58			**< 0.05**
Wang et al. (2011), 15 y, U.S.			113			192	
CRP (ng/mL)	0.95	0.06		0.74	0.03		**< 0.001**
IL-6 (pg/mL)	2.2	0.1		2.5	0.2		0.11
Wärnberg et al. (2006), 13–18.5 y, Spain							
CRP (mg/L), male	1.68	1.55	74	1.17	1.62	174	**< 0.001**
CRP (mg/L), female	1.33	1.47	46	0.83	0.86	178	**< 0.001**

Weight reduction has led to a statistically significant reduction of plasma inflammatory markers in healthy overweight/obese middle-aged adults (Heilbronn et al. 2001; Ho et al. 2015; Möller et al. 2016). The changes in plasma concentrations of inflammatory parameters in the study by Möller et al. (2016) are shown in Figure 7. Meta-analysis by Fedewa et al. (2017) concluded that the reduction of CRP after exercise intervention was more prominent with weight loss. In premenopausal overweight women, weight reduction from diet, diet + aerobic training, and diet + resistance training was significantly associated with decreases in plasma levels of inflammatory markers (e.g., CRP and IL-6) (Fisher et al. 2011). Ihalainen et al. (2017) showed that a reduction in CRP could be achieved without weight loss, even in nearly normal weight males, with 24 weeks of combined aerobic and resistance training. Gondim et al. (2015) showed that a small positive change in physical activity in sedentary obese individuals could lead to an improvement in inflammation.

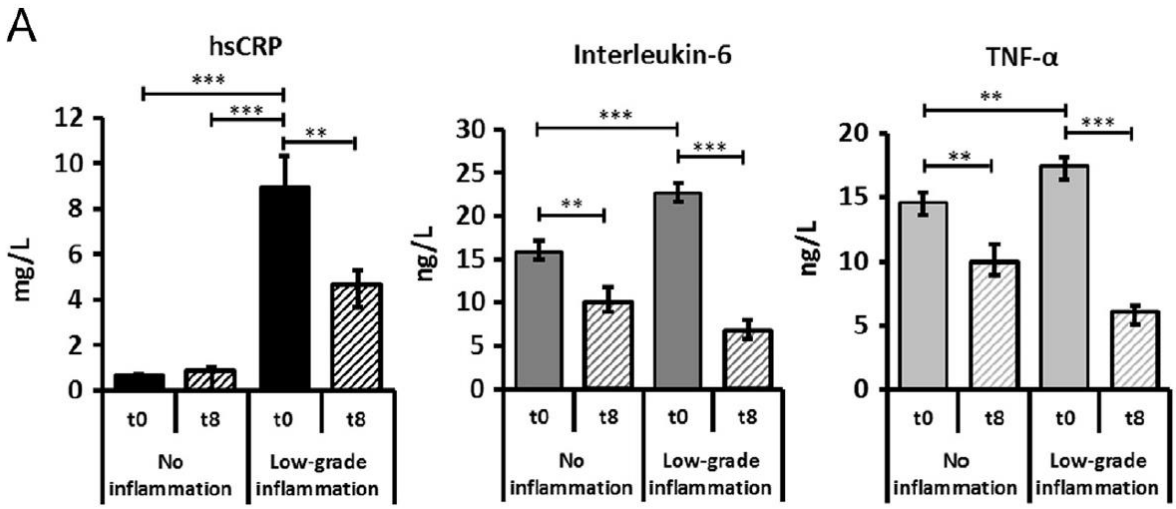

FIGURE 7. Plasma concentrations of CRP, IL-6 and TNF-α at baseline (t_0) and after eight weeks (t_8) of weight reduction in subjects with and without low-grade inflammation. Significance level between two time points and between inflammation groups: * $p \leq 0.05$, ** $p \leq 0.005$, *** $p \leq 0.001$ (Möller et al. 2016).

1.3.3 Inflammation and cardiovascular diseases

According to the "WHO Top 10 causes of death", ischemic heart disease and stroke caused over 15 million deaths altogether in 2016, being the world's biggest killer. Over 20 years, there has been unquestionable evidence that chronic inflammation of the arterial wall plays an important role in the pathogenesis of atherosclerosis. Inflammation of the arterial wall is one reason for endothelial dysfunction and structural alterations, and inflammation also predisposes one to plaque rupture, causing myocardial infarction and ischemic stroke. Elevated serum C-reactive protein levels have also been significantly associated with a decrease in endothelial vasodilatory function in a group of healthy children (Ross 1999; Järvisalo et al. 2002; Libby 2002; Moore et al. 2011; Weber et al. 2011).

In prospective studies in the late 1990s and early 2000s, modest elevations in baseline plasma concentrations of CRP and IL-6 have been demonstrated to independently predict the first future cardiovascular events in apparently healthy populations both in males (Ridker et al. 1997; Koenig et al. 1999; Ridker et al. 2000B; Sakkinen et al. 2002) and females (Ridker et al. 2000A; Pradham et al. 2002). By then, some meta-analysis showed that the value and usefulness of plasma CRP concentration as a predictor of cardiovascular events has become controversial (Danesh et al. 2004; Buckley et al. 2009; The Emerging Risk Factors Collaboration 2012; Zhou et al. 2015). Figure 8 presents the risk for coronary heart disease associated with an elevated plasma CRP level (Buckley et al. 2009). In AHA/CDC risk assessment guidelines for future cardiovascular events, an event risk has been classified into three categories according to CRP level: low (CRP < 1 mg/L), average ($1 \leq$ CRP ≤ 3), and high ($3 <$ CRP). The Emerging Risk Factors Collaboration (2012) concluded that the additional screening of plasma CRP after including classical risk factors in people at intermediate risk for a cardiovascular event could help prevent one event for approximately every 440 people during a period of 10 years.

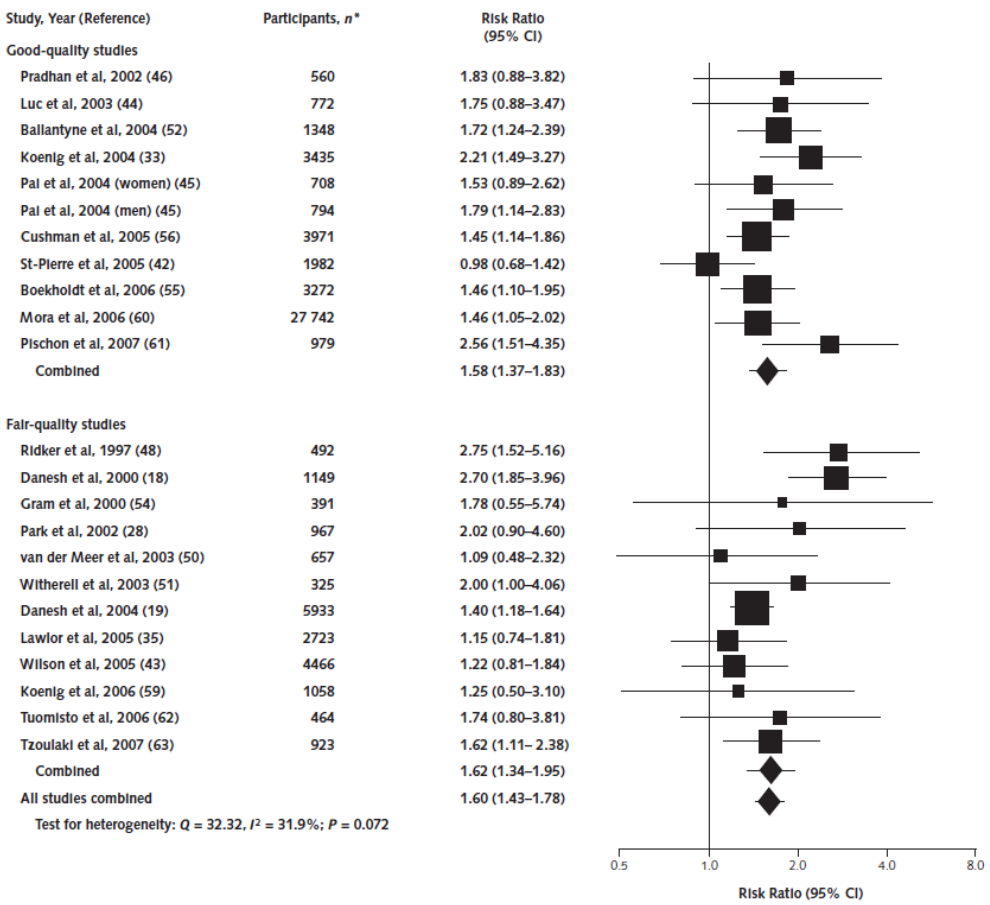

FIGURE 8. Risk ratio for coronary heart disease associated with C-reactive protein level > 3.0 versus < 1.0 mg/L (Buckley et al. 2009).

Ridker (2016) stated in his review that, in apparently healthy populations, a baseline plasma IL-6 level predicts future cardiovascular risk. Figure 9 shows the results of meta-analysis by The Emerging Risk Factors Collaboration (2012), which shows a 25% increase in risk of future vascular events for each SD increase in log IL-6.

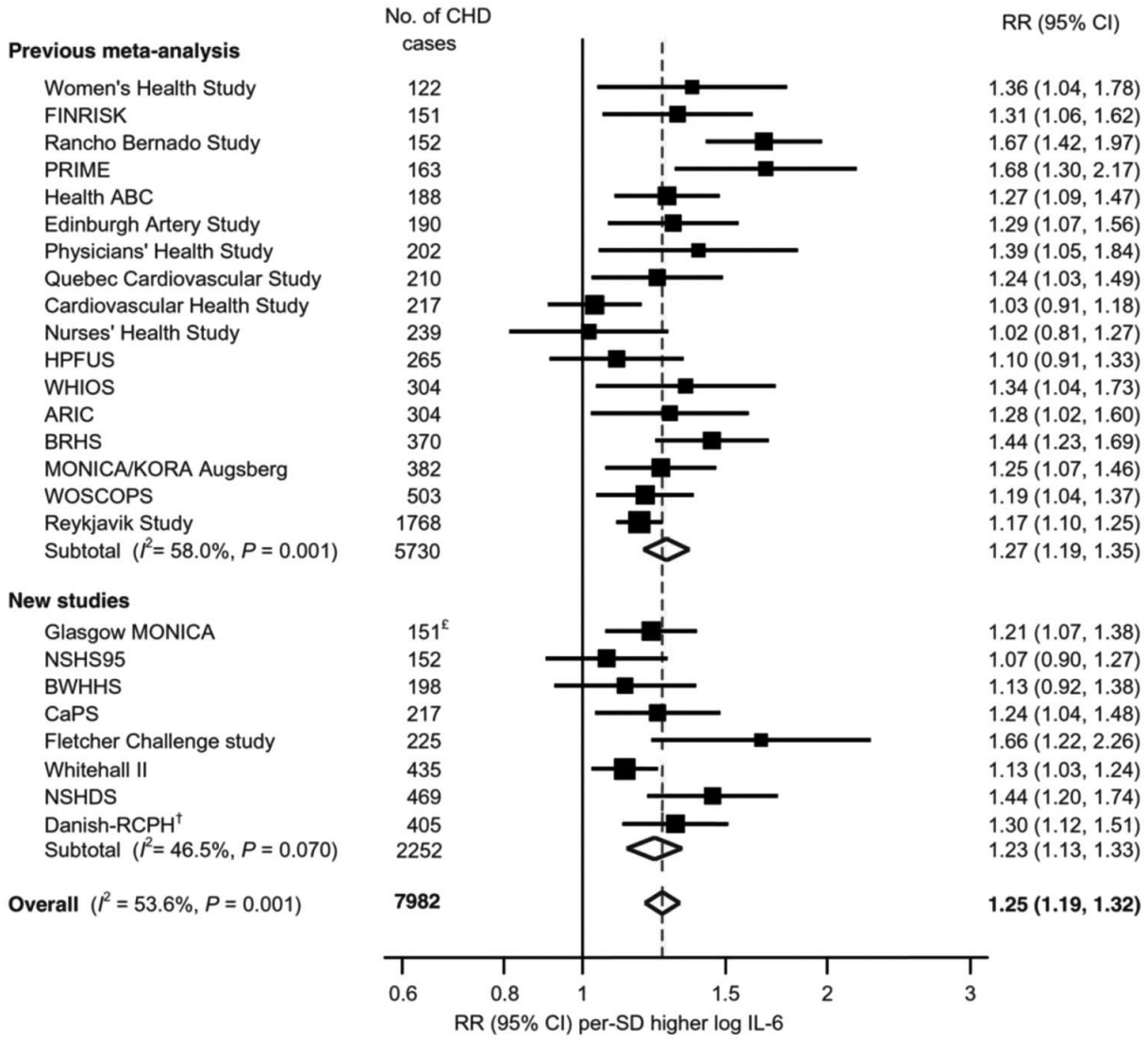

FIGURE 9. Plasma level of interleukin-6 and future risks of cardiovascular disease (Ridker 2016).

1.3.4 Anti-inflammatory effect of exercise

It seems unquestionable that physical activity and fitness have inverse associations with systemic low-grade inflammation, and the association becomes stronger with more frequent and/or more intense exercise. What could be the mechanisms behind that anti-inflammatory effect? In the following sections of this chapter, some potential mechanisms are presented that are described in reviews by Beavers et al. 2010, Gleeson et al. 2011, Nimmo et al. 2013, and You et al. 2013. These mechanisms are also presented in Figure 10.

Any other stressor exercise causes activation of the SNS and HPA axis, secretion of catecholamines (adrenaline and noradrenaline) from the adrenal medulla and secretion of cortisol from the adrenal cortex. Both catecholamines and cortisol downregulate the production of pro-inflammatory cytokines (including TNF-α and IL-1β) by immune cells.

During and after exercise, especially with prolonged exercise, active skeletal muscles secrete IL-6, and the circulating level of IL-6 can transiently increase over 100 times from the resting level. IL-6 stimulates the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland, but part of the cortisol release may occur from the direct stimulation of the adrenal cortex. A transient increase in plasma IL-6 levels seems to be mainly responsible for subsequent increases of anti-inflammatory cytokines, IL-1ra and IL-10. IL-1ra is secreted largely by macrophages and monocytes, and it has an ability to bind to the IL-1 receptor, inhibiting the pro-inflammatory actions of IL-1. IL-10 is produced by a variety of leukocytes, especially regulatory T-cells, but also by monocytes, macrophages, dendritic cells, B-cells and many T-cells, and its primary function is to downregulate adaptive inflammatory responses and minimize inflammation-induced tissue damage. IL-10 potentially promotes an anti-inflammatory state.

Regular exercise increases fat mobilization and oxidation and reduces adipocyte size. Abdominal and visceral fat can be reduced even without weight loss. Regular exercise enhances the phenotypic modulation of macrophages and T-cells in adipose tissue in such a way that a secretion of pro-inflammatory IL-6 and TNF-α decreases and a secretion of anti-inflammatory IL-10 and adiponectin increases.

Following exercise, the monocyte's Toll-like receptor-mediated downstream inflammatory signaling decreases. Regular exercise reduces the proportion of pro-inflammatory monocytes in the circulation. Exercise mobilizes IL-10–secreting regulatory T-cells. All these changes are anti-inflammatory.

Endothelial cells do not express adhesion molecules without damage. It is shown that exercise training may improve vascular regeneration capacity after endothelial cell injury. Regular exercise also reduces the expression and release of adhesion molecules in endothelial cells. Both previous

mechanisms reduce local inflammation, downregulating monocyte infiltration to vessel walls and different tissues, including adipose tissue.

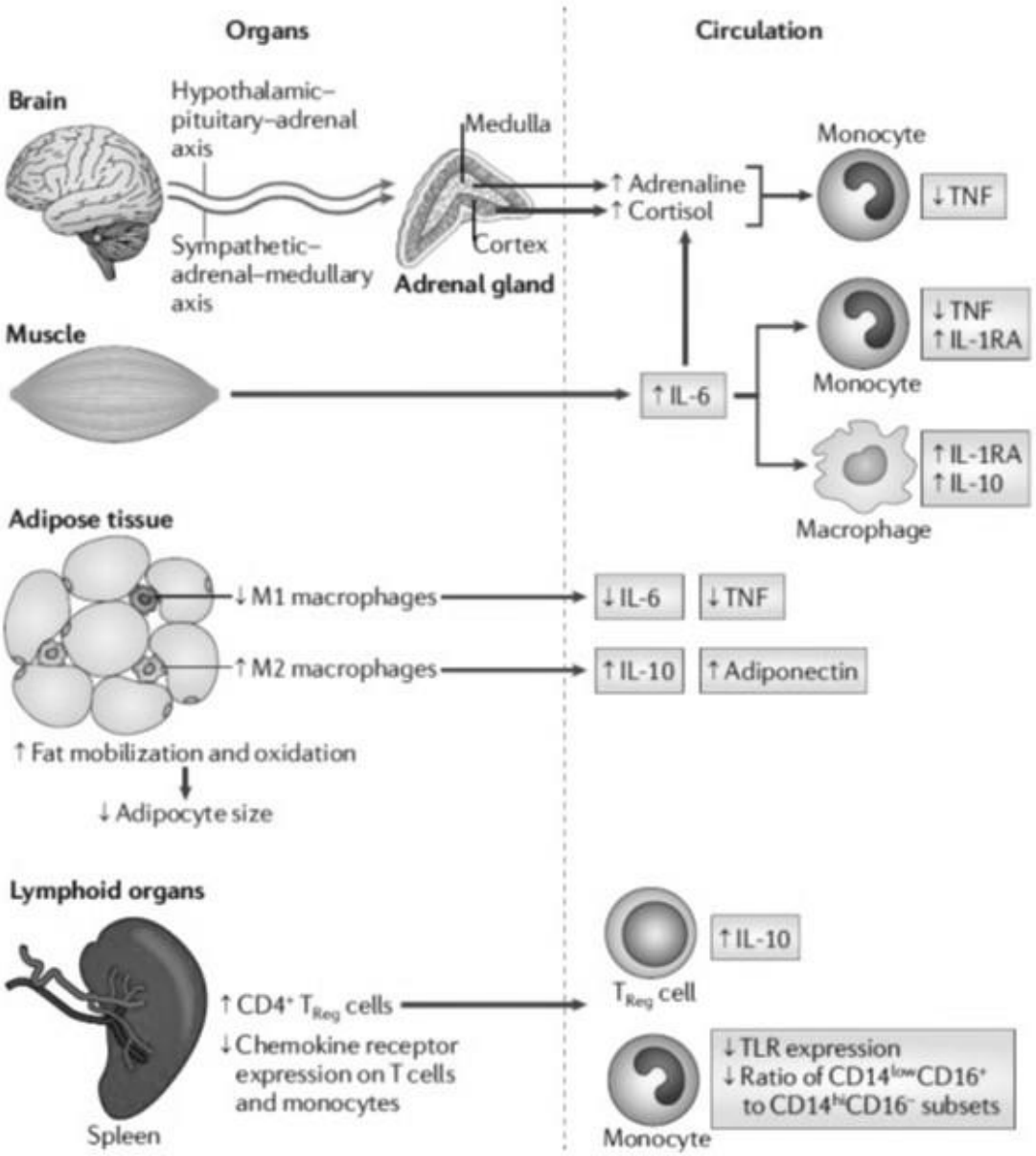

FIGURE 10. Potential mechanisms for the anti-inflammatory effect of exercise (Gleeson et al. 2011).

2. HEALTH-RELATED QUALITY OF LIFE (HRQoL)

Advances in medicine and medical technology have had a remarkable impact on the life expectancy of individuals in general, especially those affected by different chronic diseases. This has led to a situation where the number of individuals with manageable diseases has increased. There are also alternative comparable treatment techniques and remedies for one purpose. This development has created a need for measures other than morbidity and mortality numbers in health care, public health decision-making and health-related services. It has become important to evaluate the impact of treatments and interventions on individuals' functional health and well-being, as well as the relative burden of the disease. Measuring an individual's health-related quality of life may be the answer (Kaplan & Bush 1982; Brazier et al. 1992; Moons 2004; EUPATI 2016; Karimi & Brazier 2016).

In the constitution of The World Health Organization, health was defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." It also stated that "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition." This very influential definition, which includes social well-being as a component of health, is broader than earlier definitions. In the achievement of peace and security, the health of all people was seen as fundamental. The WHO constitution also states that the health of mankind is dependent on the involvement of every human and state (United Nations World Health Organization Interim Commission 1948).

In addition to the WHO's definition of health and quality of life (QoL), there are other definitions, and health-related quality of life (HRQoL) has been much more challenging. In their position paper, the WHOQOL Group (1995) described the substantial agreement about the nature of quality of life: it is subjective and multi-dimensional, including both positive and negative dimensions. The WHOQOL Group defined quality of life as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." According to this definition, quality of life is "affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment." Uutela and Aro (1993)

defined health-related quality of life as an individual's experience with his or her own state of health and health-related well-being.

2.1 Measuring HRQoL

In recent decades, it has become evident that mortality and morbidity measures were inadequate for measuring the impact of disease or disorder in an individual's life (Moons 2004). There is a need for a means to evaluate the benefit-burden ratio of equivalent therapies (Moons 2004). Feeny et al. (2013) state that "the ultimate goal of health care is to restore or preserve functioning and well-being related to health." The evaluation of health-related quality of life may be valuable for patients, clinicians, researchers, administrators, health care organizations and policy-makers (Crosby et al. 2003).

2.1.1 Concepts of quality of life and health-related quality of life

Uniform definitions of quality of life (QoL) and especially health-related quality of life (HRQoL) have been challenging to formulate, as briefly mentioned in the earlier section. Some authors have noted that the terms mentioned have been used interchangeably with functional status and health status (Revicki et al. 2000; Karimi & Brazier 2016). Revicki et al. (2000) point out that, in general, functional status refers to the capacity to perform daily activities like personal care, eating, housekeeping, occupational and social activities. They also mentioned that health status is a multidimensional construct that is usually but not always representative of an individual's subjective view of their own state of physical and mental health.

Testa and Simonson (1996) suggest that physical, psychological and social domains could be measured both objectively and subjectively (Figure 11). In this schematic representation, an objective measure defines an individual's degree of health (y-axis in Figure), but their subjective perceptions and expectations (x-axis in Figure) are needed to convert the objective assessment into the actual quality of life experienced (Q in Figure). Tolerance of limitations and disability and expectations regarding life are individual and influence a person's perception of health and life satisfaction. Each of these domains consists of several subdomains or components that should be measured. This

multidimensionality leads to a nearly unlimited number of states of health, all with varying qualities, which change during a lifetime, and all almost independent of longevity.

These several components of quality of life, which are impossible to observe directly, could be evaluated according to the classic principles of item-measurement theory. This theory suggests that there is a true quality of life value, Q, which is unmeasurable directly, but it is possible to measure indirectly by asking a series of questions. These questions, called items, measure the same true construct or concept. The respondents' answers are transformed into numerical scores, which are then combined to produce "scale scores" of the construct or concept. These scale scores could also be combined to produce summary or domain scores. (Testa & Simonson 1996).

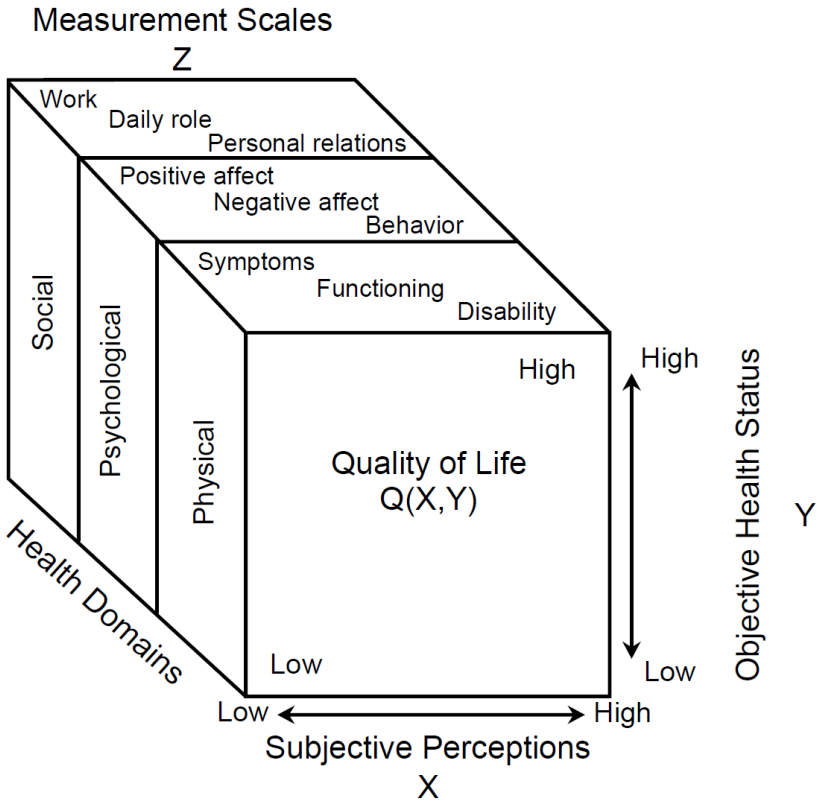

FIGURE 11. Conceptual scheme of the domain and variables involved in a Quality of Life assessment (Testa & Simonson 1996).

There is a considerable consensus about the nature of QoL consisting of at least three dimensions: physical, psychological and social (Uutela & Aro 1993; WHOQOL Group 1995; Testa & Simonson 1996; Aalto et al. 1999). There is not a uniform definition of HRQoL. In addition to the above-mentioned definitions by Uutela and Aro (1993) and EUPATI (2016), Feeny et al. (2013) state as useful a definition of HRQoL by Patrick and Erickson: "Health-related quality of life is the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy." Moons (2004) has criticized the whole concept of HRQoL because he says the terms "quality of life" and "health status" are often used interchangeably with the assumption that a perfectly healthy life indicates a high quality of life. He argued that health should be considered a determinant, not an indicator, of quality of life. He also criticized that the instruments developed primarily to measure functional status have been used as measures of HRQoL, and he emphasized the importance of a uniform definition of HRQoL.

2.1.2 Characteristics of HRQoL instruments

HRQoL instruments could be classified as disease-specific and generic. Disease-specific tools of HRQoL have been developed for several diseases and disorders and focus on their most specific and essential dimensions. Generic measures are useful when comparing differences in HRQoL in the general population or between patient groups. Some instruments have been developed for group-level comparison, and others are capable of individual-level analyses (Testa & Simonson 1996; Aalto et al. 1999; Crosby et al. 2003).

Aalto et al. (1999) presented that measures of HRQoL could be classified by the comprehensiveness of the instrument. There are global measures, one-dimension measures, multi-dimension profile measures and utility measures. Using global measures, for example, a simple question with a 5-level answering scale or a visual analog scale from 0 to 100, respondents assess their overall quality of life or health status. Despite providing limited information about HRQoL, a single question measure has been reported as practical and reliable in large population studies. For example, in a study of a North German general population, participants were asked the following: "Over the last 12 months, would you say your health has been very good, good, fair, poor, or very poor?" This single question predicted mortality risk better than a multi-biomarker panel (Haring et al. 2011).

One-dimension measures are limited to measuring only one dimension of HRQoL. There are instruments that were not originally developed to assess QoL but to describe some aspect of HRQoL, for example “Activities of daily living” instruments measuring elderly people’s ability to function, Beck’s Depression Inventory (BDI-21), the State-Trait Anxiety Inventory (STAI), the General Health Questionnaire (GHQ) developed to identify minor psychiatric disorders in the general population, and the Illness Attitude Scale (IAS), devised to assess hypochondria and abnormal illness behavior. One dimension of disease-specific measures could be used as complementary measures with multi-dimension measures (Aalto et al. 1999).

Profile measures have a multi-dimensional view of HRQoL. There are disease-specific and generic measures, and there are several widely used generic HRQoL instruments: SF-20, SF-36, the Sickness Impact Profile (SIP), and the Nottingham Health Profile (NHP). These instruments are suitable for general population studies and patient group comparison. (Aalto et al. 1999).

Utility measures are developed for health economics purposes and have been used in healthcare decision-making. Quality-Adjusted Life Year (QALY) instruments attempt to assess the impact of different therapies on the length of life while accounting for any changes in HRQoL. QALY tools represent one numeric index, which has been calculated from several individually weighted dimensions of a person’s state of health. One QALY means one year of life with perfect health. For example, the EuroQOL and 15D are instruments developed for this purpose. (Aalto et al. 1999, EUPATI 2016).

2.1.3 Requirements of measures

Feeny et al. (2013) and EUPATI (2016) have documented and defined important properties of HRQoL measures. These properties are reliability, validity and responsiveness. Cronbach’s α has been considered a satisfactory measure of internal consistency, and it should be calculated separately for each scale (Terwee et al. 2007). A low Cronbach’s α denotes a lack of correlation between items in a scale. For group-level comparison, a criterion for good internal consistency of Cronbach’s α has been proposed to be between 0.70 and 0.90 (Gandek et al. 1998) or between 0.70 and 0.95 (Terwee et al. 2007). Cronbach’s $\alpha \geq 0.90$ has been suggested for individual-level comparisons (Gandek et al.

1998). Revicki et al. (2000) state that for group comparisons, a test-retest reliability should exceed 0.70 in subjects with no change in health over two weeks. Convergent validity is considered satisfactory if an item correlation was at least 0.40 on its hypothesized scale (Roberts et al. 1997; Aalto et al. 1999). The HRQoL instrument should have low floor and ceiling effects (< 5% of respondents with the lowest or highest possible score) to detect the differences between groups and during time (Aalto et al. 1999; Revicki et al. 2000). Terwee et al. (2007) mentioned that floor and ceiling effects are thought to be present if over 15% of respondents achieved the lowest/highest possible score. In the validation of multi-item questionnaires, factor analysis is a significant phase: "Factor analysis is a statistical technique which is designed to reveal whether or not the pattern of responses on a number of items can be explained by a smaller number of underlying factors" (de Vet et al. 2005).

2.2 36-item short form (SF-36)/RAND 36-item health survey

The beginning of this chapter describes the history and development of the SF-36 and RAND-36 instruments. The tiny difference between SF-36 and RAND-36 is also explained. Then the construction of this measure is explained.

2.2.1 History and development of the SF-36/RAND-36

The RAND Corporation is a nonprofit research and analysis institution in the United States. The Medical Outcome Study (MOS) was one of the institution's research projects. The goal of the MOS was to develop tools for outcome measures in health care, and the premise of the project was to underline the patient's view in the evaluation of health status. MOS researchers developed the Functioning and Well-Being Profile (FWBP), a 149-item general health survey that was intended to be comprehensive and psychometrically sound. For this instrument, researchers also selected and adapted items and concepts from instruments that were already proven useful in the 1970s and 1980s. At the end of the 1980s, based on the FWBP items, MOS researchers developed shortened versions, like the 20-item Short Form Survey (SF-20); after that, they created the 36-item Short Form Survey (SF-36), which measures the concept of health more broadly than the SF-20. The SF-36 was intended to be a generic, multipurpose measure of health-related quality of life in contrast to age, disease or

treatment group–specific measures. The SF-36 has also been published in the name of The RAND 36-Item Health Survey (RAND-36). The question-and-answer possibilities of both questionnaires are identical, but in two scales of eight—bodily pain and general health—there are minor differences in how to compute scale scores, but this difference has minimal impact in practice. Hays et al. (1993) report a range of difference from -8 to +10 and from -3.58 to +0.08 in bodily pain and general health scales, respectively. (Brazier et al. 1992; Ware & Gandek 1998; Aalto et al. 1999).

The SF-36 is a self-administered questionnaire that takes less than 10 minutes to complete. The SF-36 was developed for group-level comparison, satisfying the psychometric standards for this purpose. The questionnaire was planned for usage in clinical practice and research, health policy evaluations and general population surveys. In the 1990s, the SF-36 was published in several translations, including German, French, Spanish, Italian, Dutch, Japanese, Swedish, Danish, Norwegian and Finnish. (Brazier et al. 1992; Ware & Gandek 1998; Aalto et al. 1999).

2.2.2 Construction of the SF-36

Of the 36 questions on the SF-36, 35 are included in the three-level model structure, which is described in Figure 12. The health transition question is not included in this structure. These 35 questions form the first-level items. In the second level, there are eight scales or concepts of health, each of which includes 2–10 items. Each item is used to score only one dimension. These eight concepts or dimensions of health are: 1) physical functioning (PF), indicating to limitations in physical activities because of health problems; 2) social functioning (SF), indicating to limitations in social activities because of physical or emotional problems; 3) role-physical (RP), indicating to limitations in usual role activities because of physical health problems; 4) bodily pain (BP); 5) mental health (MH), indicating to psychological distress and well-being; 6) role-emotional (RE), indicating to limitations in usual role activities because of emotional problems; 7) vitality (VT), indicating to energy and fatigue; and 8) general health (GH) perceptions. In the third level, these eight dimensions form two different summary scores: Physical (PCS) and Mental (MCS) component summary. There are several content areas not included in the SF-36, for example, sleep adequacy, cognitive functioning, sexual functioning, health distress, family functioning, spirituality and recreation/hobbies (Brazier et al. 1992; Ware & Gandek 1998; Aalto et al. 1999).

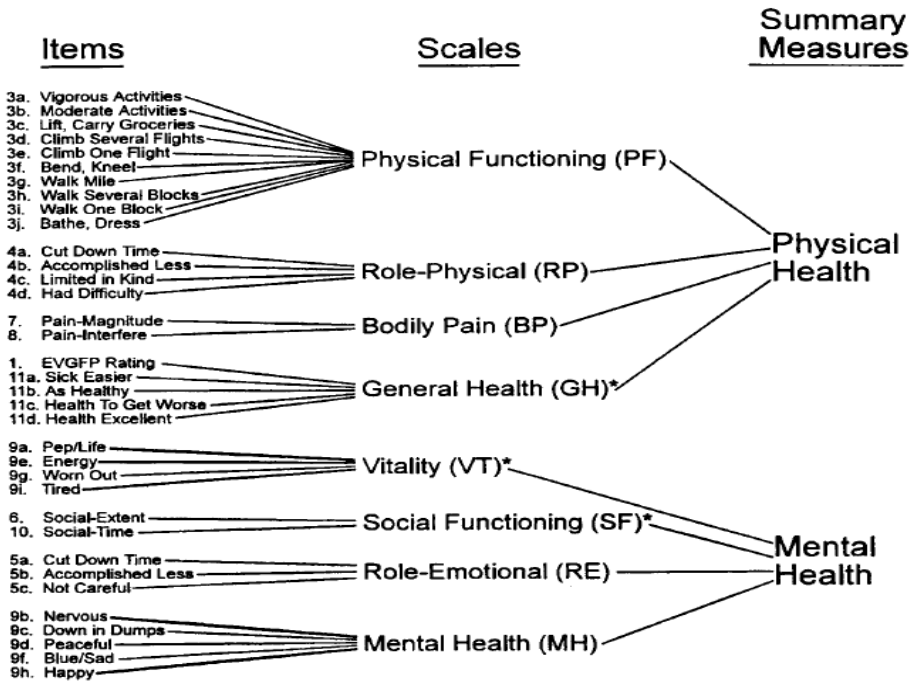

FIGURE 12. Construction of the SF-36 (Ware & Gandek 1998).

2.3 HRQoL in the general population

In a Finnish general population study (n = 2175), measured HRQoL in RAND-36 dimensions were generally lower in older and less educated participants, in those with chronic diseases and in those who used more health care services (Aalto et al. 1999). In this study, females tended to have lower HRQoL, especially in physical functioning, vitality, bodily pain and both role dimensions. In a cohort of young adults from Northern Finland (n = 874, age 19–20 years), musculoskeletal pains were associated with lower HRQoL (Paananen et al. 2011). Figure 13 presents age- and gender-weighted frequency distributions of the scale scores of the RAND-36 in the Finnish general population study. There were definite floor effects in both role dimensions and ceiling effects in all dimensions except general health, mental health and vitality. Previous findings related to floor and ceiling effects were equivalent in 11 western countries with minor exceptions (Gandek et al. 1998; Garratt & Stavern 2017). In a Norwegian general population study (N = 5936), physical (PCS) and mental (MCS) component summary scores were also calculated, and there were linear reduction in PCS by age in

females and after 40 years of age in males, but as shown in Figure 14, there was no detectable decline by age in MCS (Garratt & Stavern 2017).

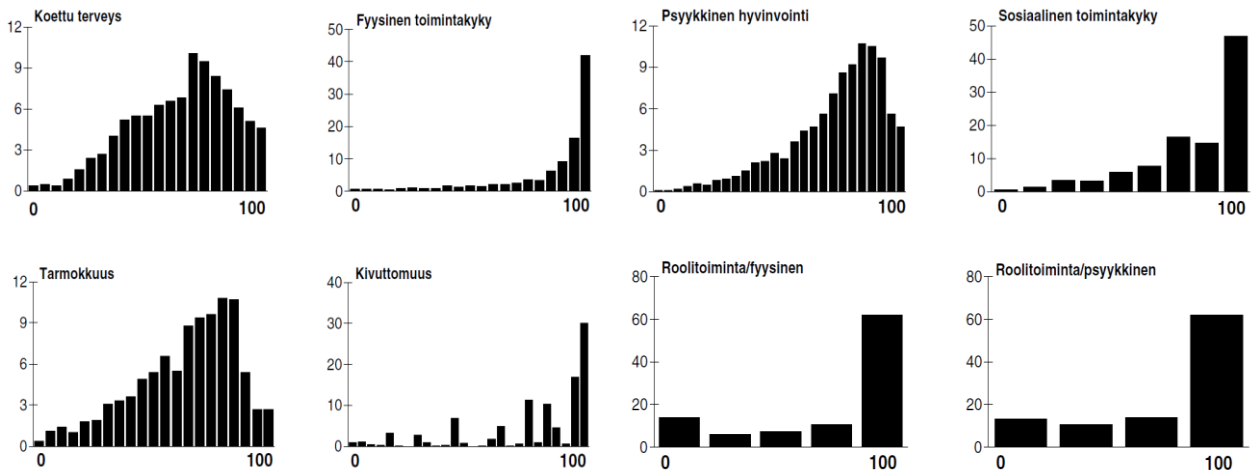

FIGURE 13. Age- and gender-weighted frequency distributions of the scale scores of the RAND-36. All distributions were skewed to the direction of good HRQoL.
Top row from left to right: general health, physical functioning, mental health and social functioning. Down from left to right: vitality, bodily pain, role limitations physical and role limitations emotional (Aalto et al. 1999).

In prospective studies of the Finnish Twin Cohort, relations of life satisfaction and mortality and morbidity have been investigated. The participants evaluated their life satisfaction in 1975. The life satisfaction scale included 4 items: happiness, easiness, interest in life and feelings of loneliness. The score ranged from 4 to 20 and was classified into three categories: satisfied (4–6), intermediate (7–11) and dissatisfied (12–20). In the male population of this cohort, self-reported dissatisfaction was linearly associated with increased all-cause, disease and injury mortality at the 20-year follow-up, but women did not show similar associations. At the 20-year follow-up, dissatisfaction was associated with a higher risk of suicide, which was more likely in the first decade of follow-up. In this cohort, the baseline life dissatisfaction was associated with increased risk of moderate/severe depression 15 years later. (Koivumaa-Honkanen et al. 2000; Koivumaa-Honkanen et al. 2001; Koivumaa-Honkanen et al. 2004).

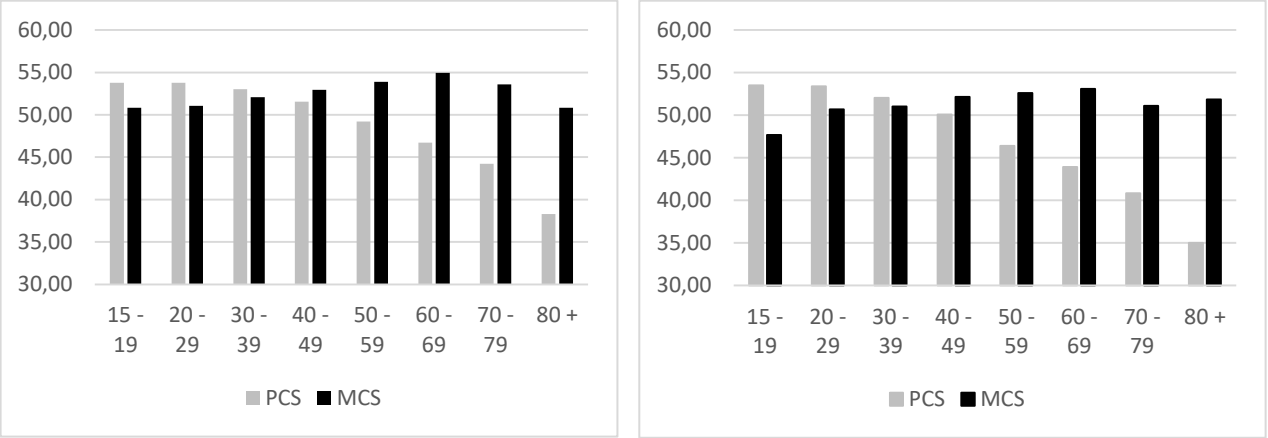

FIGURE 14. Physical and mental component summary scores by age group in the Norwegian male (left) and female (right) populations (Garratt & Stavern 2017).

Both low self-rated health and low HRQoL, especially the physical component, are associated with increased mortality. In a meta-analysis performed by DeSalvo et al. (2006) that included 22 cohorts, individuals with "poor" SRH had two times the mortality risk than individuals with "excellent" SRH. In a German adult population follow-up study of individuals aged 20–79 years with an average follow-up of 9.7 years (n = 4359), both low SRH and low PCS of SF-12 were associated with an elevated risk of all-cause mortality (Haring et al. 2011). In a prospective study of 17,777 adult participants (aged 41–80 years) without previous cardiovascular disease or cancer with an average 6.5 years' follow-up, a low PCS score of the SF-36 predicted all-cause and cardiovascular mortality in men and women independently of known risk factors (Myint et al. 2006). Low SF-36 scores have been associated with increased mortality in different populations and patient groups: in male COPD patients (Domingo-Salvany et al. 2002), in community-dwelling older persons (Tsai et al. 2007), in treated localized prostate cancer patients (Sadetsky et al. 2009) and in young adults with cerebral infarction (Naess & Nyland 2013).

2.4 HRQoL and obesity/BMI

In a Swedish population study (N = 5633 men and women aged 16–64 years), males and females aged 16–34 years showed a trend toward a reduced physical quality of life as the participant's weight increased; older obese females reported a lowered HRQoL in all eight dimensions, but older obese

males only reported it in dimensions of physical functioning and general health (Larsson et al. 2002). In the Canadian Multicentre Osteoporosis Study (CaMos) of 9423 randomly selected adult (age ≥ 25 years) men and women, deviations from normal weight, especially underweight and the three levels of obesity, were related to impaired HRQoL with the exception that overweight men tend to report slightly better HRQoL than normal-weight men (Hopman et al. 2007). Among Swiss young males (N = 5387, mean age 19.99 ± 1.24 years), deviations from normal weight predicted below-average physical HRQoL, and underweight predicted below-average mental health, but in contrast, obese participants reported better mental HRQoL (Dey et al. 2013). In Finnish healthy adults (N = 1.187, mean age 57 ± 7 years), a PCS of the SF-36 statistically significantly decreases by increasing BMI both in females and males, but in relation to MCS in the SF-36, there was no difference between BMI categories (Korhonen et al. 2014). Weight gain during the follow-up has been associated with reduced scores in physical functioning, vitality and bodily pain dimensions of the SF-36 in adult women (Fine et al. 1999) and a reduced PCS of the SF-36 in young adults (Kozak et al. 2011).

In a meta-analysis by Ul-Haq et al. (2013), the association between BMI and HRQoL assessed by the SF-36 was studied. They included eight cross-sectional studies that had reported a physical component score, a mental component score or both. Studies were performed between 2000 and 2011 and included 43,086 adult (age > 16 years) participants, of which 54% were overweight or obese. In this meta-analysis, participants were classified as overweight, class I obese, class II obese or class III obese when a BMI was 25.0–29.9 kg/m^2, 30.0–34.9 kg/m^2, 35.0–39.9 kg/m^2 or ≥ 40.0 kg/m^2, respectively. Physical HRQoL was reduced in overweight and obese participants with a clear dose response manner compared to normal-weight participants. Compared to normal-weight participants, mental HRQoL was reduced only among class III obese participants and was even better in overweight participants. In this meta-analysis, no results were presented by sex.

In a German general population cross-sectional study performed in 2008–2011, the association of physical HRQoL (SF-36 physical component summary, PCS) with metabolic health and obesity were investigated. Participants were classified in four categories according to body mass index (non-obese BMI < 30 kg/m^2 and obese BMI ≥ 30 kg/m^2) and the ATP III criteria for metabolic syndrome: metabolically healthy non-obese (MHNO, n = 1900), metabolically unhealthy non-obese (MUNO, n = 608), metabolically healthy obese (MHO, n = 196), and metabolically unhealthy obese (MUO, n =

578). In this study, obesity was significantly associated with reduced PCS independent of metabolic health status. This finding was more pronounced in women. (Truthmann et al. 2017).

2.5 HRQoL and physical activity or fitness

The majority of studies concerning HRQoL and physical activity available in the literature research were related to diseases or some disorder. Most general population studies were cross-sectional. A focus in the literature review was to find studies that used the SF-36/RAND-36 or a shorter form of previous questionnaires to measure HRQoL. Only a couple of participants in these studies were young adults. The next paragraph presents studies in which the evaluation of HRQoL was based on a tool other than the SF-36. The following paragraphs present studies related to the SF-36 family and physical activity and in the end studies, which have measured fitness and HRQoL.

In a study of U.S. adults (n = 9173), inactive individuals reported lower HRQoL regardless of their BMI status when HRQoL was measured by four CDC-developed questions (Kruger et al. 2007). In a large U.S. population study (n = 263,879), self-reported physical activity was positively associated with HRQoL when both physical and mental quality of life were assessed as the number of unhealthy days (Brown et al. 2014). In a systematic review by Bize et al. (2007), in the general adult population, physical activity was constantly and positively associated with HRQoL in cross-sectional studies, but there was limited evidence from cohort studies and randomized controlled trials.

In Finnish subjects at high risk for type 2 diabetes (n = 132, aged 26–73), the more physically active the participants were, the better the HRQoL was in all dimensions of the SF-36 (Häkkinen et al. 2009). In a cross-sectional study of type 2 diabetics (n = 98, mean age 56.9 SD 5.9), a higher level of fitness attenuated the negative impact of diabetes on physical dimensions of HRQoL better than reduced weight (Bennett et al. 2008).

In a random sample of Italian university students (72 males and 81 females, mean age 22.66 ± 3.55), the highest physical activity level was related to more beneficial scores in the SF-36 dimensions both in females and males (Massida et al. 2015). In an Australian randomized controlled trial of casino employees (n = 20, control group n = 24), a 24-week exercise program statistically significantly

improved the dimensions of mental health, vitality, general health, bodily pain, and physical functioning of the SF-36 (Atlantis et al. 2004).

In a follow-up study among middle-aged employees of the City of Helsinki (n = 5475, mean BMI 25.4 kg/m^2, 80% women), an increase in physical activity was positively related to PCS during the follow-up, and reduction of physical activity was related to lower PCS. An increase in physical activity from a low to a moderate level was beneficial for mental health, but an increase from low or moderate to a vigorous level was not. Lowering physical activity from moderate or vigorous to a low level was related to reduced MCS, but from vigorous to moderate, it was not. (Holstila et al. 2017).

In a study of 104 middle-aged Finnish male workers (mean age 50.2 ± 2.8 years, mean BMI 28 ± 1.2 kg/m^2) participating in an occupational-oriented program promoting health and work ability, a 2-km walking test time and an estimated VO_2max correlated significantly with PCS of the RAND-36 and all other physical dimensions except bodily pain, but there were no significant correlations between measured physical fitness parameters and mental health dimensions or MCS (Sörensen et al. 2007). In apparently healthy male United States Navy service members (n = 709, age 18–49 years), subjects in higher fitness quartiles tended to have better PCS and MCS scores of the SF-12v2 comparing to the subjects in the lowest fitness quartile (Sloan et al. 2009). Among Finnish young men (n = 727, mean age 25 ± 5 years), a higher physical fitness index was related to higher scores in the general health, physical functioning, mental health and vitality dimensions of the RAND-36, and leisure-time physical activity was associated with the dimensions of general health, physical functioning and vitality (Häkkinen et al. 2010).

3. HEALTH-RELATED QUALITY OF LIFE AND SYSTEMIC INFLAMMATION

In reviewing the literature, there were only a few studies that investigated the relationship of health-related quality of life and plasma inflammatory markers in the general population. For the present study, the Scopus database was used to search articles that were published before 2018. Using the keywords "health-related quality of life" and "inflammation," 47 articles were found. Using these phrases and selecting "article title, abstract, keywords," the result was 520 articles. In both cases, nearly all the articles were disease- or disorder-oriented or related to a specific population (women, adolescents, older…). Using the search query KEY (SF-36 AND [CRP or "C-reactive protein"] AND [IL-6 or interleukin-6]), five (5) articles were found, three of which were related to Zumba, hemodialysis or osteoarthritis. The previous search result included articles by Garvin et al. (2015) and Nicklas et al. (2016), which are referred to in the following paragraphs. Using the search query KEY ("RAND 36" AND [CRP or "C-reactive protein"] AND [IL-6 or interleukin-6]) returned no articles. Extending the search to title, abstract and keywords resulted in 33 studies, and the majority of these were disease- or disorder-oriented. The following paragraph presents some articles related to SRH/life satisfaction/"positive affect" and plasma inflammatory parameters, as well as articles related to vitality/HRQoL and plasma inflammatory parameters.

3.1 Self-rated health, positive affect, life satisfaction and inflammation

In the Stockholm Area primary health care consecutive patients (174 women and 91 men, aged 19–90 years), poorer SRH was associated with higher levels of circulating IL-1β, IL-1ra and TNF-α in women but not in men (Lekander et al. 2004). Among London civil service workers (N = 2873, aged 50–74 years), low "positive affect" was inversely associated with the risk of elevated plasma levels of CRP and IL-6 in women but not in men (Steptoe et al. 2008). In the Scottish general population (369 men and 428 women, mean age 52.1 ± 16.8 years), the life satisfaction score was statistically significantly, linearly and inversely associated with plasma levels of CRP and fibrinogen after adjustments for age, sex, education, smoking, body mass index and anxious and depressive symptoms (Hamer et al. 2011). Among the U.S. older adults (N = 250, mean age 63.8 years [SD 13.7.], 74.0% females), poorly rated general health (first question of the RAND-36) was associated with significantly elevated IL-6 and CRP, even taking into account health diagnosis, medication and health

behaviors (Christian et al. 2001). In the National Longitudinal Study of Adolescent Health (N = 13,236, age 24–34 years, 54.3% females), poor SRH (first question of the RAND-36) was associated with elevated CRP even after taking into account health conditions, medication, health behaviors and psychological characteristics (Shanahan et al. 2014). Among Israeli relatively healthy adults (N = 13,773, mean age 44 SD 11, 35.7% females), lower SRH was significantly associated with higher plasma CRP level in both genders, even after adjustments to potential confounding factors (Leshem-Rubinow et al. 2015). Mean plasma CRP levels according to SRH class for females and males are presented in Table 2 (Leshem-Rubinow et al. 2015).

TABLE 2. Mean plasma CRP levels (mg/L) with standard deviations according to SRH class for males and females (n = 13,773, mean age 44 ± 11 years) (Leshem-Rubinow et al. 2015).

	average	good	excellent
females	2.4 (3.3)	1.6 (3.2)	1.4 (3.2)
males	2.0 (2.8)	1.4 (2.8)	1.1 (2.8)

3.2 Vitality/HRQoL (SF-36) and inflammation

In the longitudinal CARDIA (Coronary Artery Risk Development in Young Adults) Study (N = 2983, 56.1% females, aged 33–45 years), a high baseline CRP and persistently elevated CRP (> 3 mg/L) predicted fatigue (low score in the vitality dimension of the SF-12) five years later; a high baseline fatigue score predicted high CRP at follow-up, and this relationship was mediated in part by physical activity level (Cho et al. 2009). Among London Area civil servants (N = 7509, aged 39–63 years), high CRP or IL-6 levels increased the risk for developing fatigue (low score in the vitality dimension of the SF-36) during the 3.1-year follow-up, and the risk was highest among those whose inflammatory markers were both high at baseline (Cho et al. 2013). In the 18-month weight loss intervention study of overweight or obese tibiofemoral osteoarthritic adults (N = 167, aged ≥ 55 years, 70% females, BMI 27–45 kg/m^2), there was an inverse association between changes in both CRP and IL-6 and a vitality score of the SF-36, and participants who experienced greater decline in IL-6 had higher improvement in the vitality scores (less fatigue) and greater increases in physical activity (Nicklas et al. 2016).

Among the older U.S. adults (N = 250, mean age 63.8 SD 13.7 years, 74.0% females), the physical functioning dimension of the RAND-36 associated statistically significantly with IL-6, but there were no other associations between inflammatory markers (CRP and IL-6) and the RAND-36 (Christian et al. 2001). In the Dutch LifeLines Cohort Study of obese adults (N = 13,686, BMI ≥ 30 kg/m^2, mean age 48 ± 11 years, 62% females), individuals with higher CRP tended to have increased probability of poor HRQoL, especially in the dimensions of physical health and vitality of the SF-36, and individuals with more pronounced obesity, metabolic syndrome and diabetes tend to have poorer physical health (Slagter et al. 2015). In a weight loss intervention study of 52 females (aged 23–59 years, mean baseline BMI 33.14 kg/m^2), among those who succeeded in weight loss, the reduction in leptin levels was associated with improvement in BMI and PCS of the SF-36 (Linkov et al. 2014).

Garvin et al. (2015) evaluated the associations between health-related quality of life and low-grade inflammation in a randomly selected sample of middle-aged Swedish subjects (n = 905, aged 45–69 years, 50% women). HRQoL was measured by the SF-36. The mean plasma concentrations of CRP and IL-6 were 1.7 (SD 2.0) mg/L and 1.9 (SD 2.5) pg/ml, respectively. To investigate the combined effect of CRP and IL-6, a composite variable was created. This variable had four categories: low CRP and low IL-6, low CRP and high IL-6, high CRP and low IL-6 and high CRP and high IL-6. The cut points for low and high CRP values were < 1 ml/L and > 3 mg/L. To determine the high and low cut points of IL-6, the researchers used the same proportion of study participants as in the high and low category of CRP. The cut points for low and high IL-6 values were 0.57 and 3.25 pg/ml, respectively. In this sample, after adjusting for sex and age, there were significant negative correlations for all dimensions of SF-36 to plasma levels of IL-6 and CRP except the mental health dimension for CRP. The combination of high IL-6 and high CRP was associated with substantially lower SF scores than the other combinations of IL-6 and CRP (Figure 15).

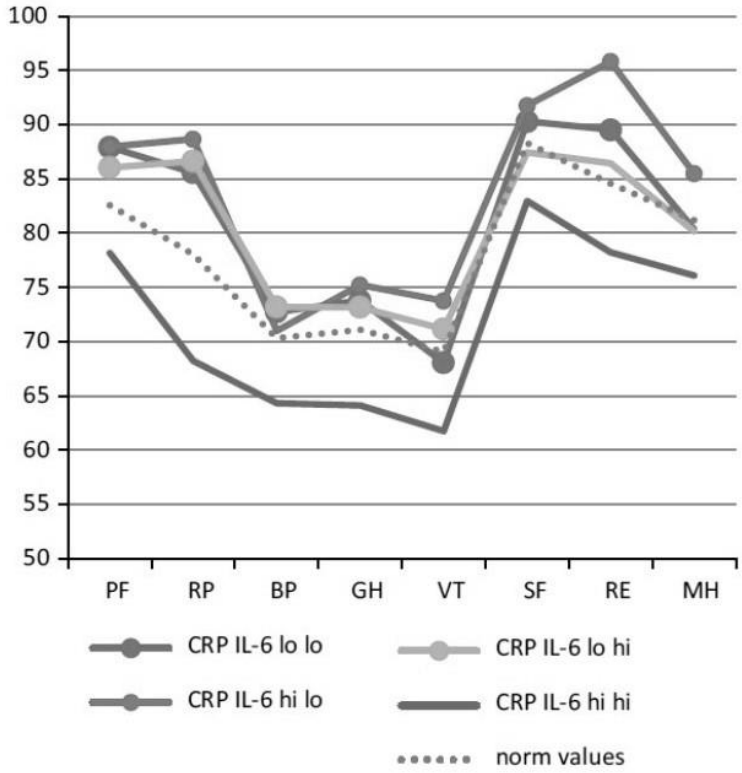

FIGURE 15. The mean SF scores and different combinations of IL-6 and CRP. Adjusted for age, sex, presence of disease, lifestyle factors and psychological factors. PF = physical functioning, RP = role-physical, BP = bodily pain, GH = general health, VT = vitality, SF = social functioning, RE = role-emotional, MH = mental health. (Garvin et al. 2015).

In a cross-sectional study by Dür et al. (2016), the main focus was to investigate the possible associations between occupational balance, functioning, cytokines (IL-6, IL-8, INF-α, TNF- α) and CRP in patients of rheumatoid arthritis (RA) and healthy people. Both groups were divided into employed and unemployed subgroups. The study sample included 132 RA patients (median age 59 years, 88% female, 32% employed) and 76 healthy persons (median age 38, 63% female, 86% employed). HRQoL was measured using the SF-36 (version 2.0) questionnaire. In RA patients, the plasma levels of all cytokines and CRP were statistically significantly higher than in healthy participants. The median plasma levels of IL-6 and CRP were 2.9 pg/ml (CI 95% 1.2–8.2) and 2.5 mg/L (1.0–6.0) in RA patients, and 1.3 pg/ml (0.8–2.1) and 0.8 mg/L (0.5–2.0) in healthy participants, respectively. Among healthy unemployed participants, median CRP was significantly higher than in healthy employed participants, but cytokine levels did not differ significantly. There were positive

associations between CRP levels and scores in the dimensions of vitality and mental health in healthy employed participants and between CRP levels and scores of bodily pain (higher score, less pain) in healthy unemployed participants. In addition, there were inverse associations between CRP levels and general health in healthy unemployed participants. Among healthy participants, there were no significant associations between IL-6 and HRQoL. In addition, better occupational balance associated with favorable HRQoL. There were also few and weak associations between occupational balance and cytokines and CRP.

3.3 Conclusions of SRH/Vitality/HRQoL and inflammation

Low SRH, low life satisfaction and low level of "positive affect" were consistently associated with higher levels of plasma inflammatory markers. In prospective studies (Cho et al. 2009, 2013), high baseline plasma levels of CRP or IL-6 predicted lower vitality scores in the future, i.e., fatigue. The relationship between inflammation and fatigue proved to be bidirectional (Cho et al. 2009). Successful weight loss in overweight/obese participants resulted in a decline of inflammatory markers and an improvement of vitality (Nicklas et al. 2016).

The results of studies using the SF-36/RAND-36 as a measure of HRQoL have been inconsistent. It is possible that the inconsistency has been related to different study populations. However, it gives the impression that there is an inverse relationship between inflammation and HRQoL, especially in physical dimensions and vitality.

4 RESEARCH QUESTIONS AND HYPOTHESIS

The purpose of this study is to answer the following questions related to inflammation, health-related quality of life, fitness and body composition.

Question 1: Is there an association between the systemic low-grade inflammation markers IL-6 and CRP and HRQoL in the Finnish young male population?
Hypothesis 1: I am not aware of any previous studies exploring the association between IL-6 and CRP and RAND-36 in a young adult population. I suppose that there is a negative association between these inflammatory markers and HRQoL. Garvin et al. (2015) observed that higher inflammatory markers were negatively associated with HRQoL in the middle-aged population. Häkkinen et al. (2010) and Vaara et al. (2014) used an identical young male population in their studies. Häkkinen et al. (2010) found associations between physical fitness and HRQoL, and Vaara et al. (2014) found associations between inflammatory markers and cardiorespiratory fitness, muscle strength, and muscle fitness.

Question 2: How is cardiorespiratory fitness related to inflammatory markers and HRQoL?
Hypothesis 2: Cardiorespiratory fitness is negatively associated with inflammatory markers and positively associated with HRQoL. There is much evidence that physical activity and cardiorespiratory fitness are inversely associated with inflammatory markers (Ford 2002; Plaisance & Grandjean 2006; Vaara et al. 2014; Fedewa et al. 2017). It is also demonstrated in different populations that physical activity and cardiorespiratory fitness are positively related to HRQoL (Bize et al. 2007; Bennett et al. 2008; Sloan et al. 2009; Häkkinen et al. 2010; Massida et al. 2015).

Question 3: How are muscle fitness and strength related to inflammatory markers and HRQoL?
Hypothesis 3: Both muscle fitness and strength are negatively associated with inflammation and positively associated with HRQoL. In the Finnish young male population, Vaara et al. (2014) showed that there were negative associations between inflammation and muscle fitness and strength. In an identical population, Häkkinen et al. (2010) found that muscle fitness was associated with general health and physical functioning.

Question 4: How is body composition related to inflammatory markers and HRQoL?

Hypothesis 4: Higher BMI, waist circumference, fat mass and fat percentage are related to higher inflammatory markers and poorer physical HRQoL. Table 1 shows a comparison of inflammatory markers between normal and overweight subjects. In a meta-analysis of Ul-Haq et al. (2013), physical HRQoL was reduced in overweight and obese participants.

5 MATERIAL AND METHODS

5.1 Material

In Finland, a compulsory military service is in place for males older than 18 years. Conscripts serve 6, 9 or 12 months, and after serving, reservists are invited to the refresher courses. The measurements of this study were performed during seven separate refresher courses organized in different garrisons around Finland in 2015. Of the 1106 invited reservists, 823 took part in the refresher courses, and 792 volunteered (including 15 women) in the main research, of which this study was a part. Women were not included in this study.

The reservists arrived to the county garrison one day before physical measurements were performed. On arrival day, reservists ate at about 4 p.m. and then participated in the information session about the study at 6 p.m. After that session, the volunteers signed a written consent form related to the risks and benefits of the study and filled out general health questionnaires for the physical tests and the main study. Questionnaires included the RAND-36. Eating was not allowed after the information session; fasting for the blood tests the following morning was at least 12 hours. In every refresher course, volunteers were separated into groups of 10.

5.2 Schedule of measurements and methods

At 6 a.m., the measurements of the first group of 10 participants began. At first, blood pressure was measured three times in a sitting position from the left arm in intervals of one minute using the Omron M3 Comfort instrument, which is an automatic blood pressure meter. After measuring blood pressure, blood samples were drawn and anthropometric measurements were performed.

Blood samples were drawn from the antecubital vein using the Terumon VenoSafe^{TM} method when participants were in the supine position. Blood count (leucocytes, erythrocytes, thrombocytes, hematocrit, hemoglobin and erythrocyte indexes) was analyzed instantly from EDTA blood using the Sysmex co-analyzer. Blood glucose and serum tubes were centrifuged after sampling. Serum concentrations of CRP and IL-6 were measured using commercial high-sensitivity ELISA kits

according to the manufacturer's instructions (Quantikine HS, R&D Systems, Minneapolis, USA). Assay specifications were for CRP sensitivity of 0.10 mg/L and IL-6 0.11 pg/mL. The maximum intra- and inter-assay CV percentages were 4.8% and 6.1% for CRP, and 5.9% and 9.8% for IL-6, respectively.

After blood samples were taken, height, weight, waist circumference and body composition were measured. Waist circumference was measured using Seca measuring tape from the midpoint of the lowest rib and iliac bone of volunteers. The InBody 720 instrument was used to measure body composition. Body mass index (BMI) was recorded after the measurement of body composition and was classified as underweight (BMI < 18.5), normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 29.9), and obese (30.0 ≤ BMI). A waist circumference wider than 40 inches (= 102 cm) is one criterion for the metabolic syndrome according to the ATP III definition (Huang 2009). After their measurements were taken, participants had their breakfast, but they were instructed to eat lightly.

Before the physical performance tests, participants took part in a 10-minute warm-up organized by test personnel. A standing long jump was the first physical performance test and was performed on a base designed for the purpose, and starting and landing areas were at the same level. To perform the jump, the participant stood at the starting area with the feet shoulder-width apart, and then they bent their knees and hips and jumped as far forward as possible. The length of the jump was measured with one-centimeter accuracy from the landing point of the participant's heels. Participants performed some practice jumps, and three jumps with about a one-minute interval were measured and the best result counted in the analysis.

Next measurements were taken for maximal bilateral isometric force tests of the extensor muscles of lower and upper limbs. Participants performed the horizontal leg press and vertical bench press, and the forces were measured using a dynamometer. In the leg press test, the knee angle was set to 107 degrees with a goniometer, and the hands hold a handle grip (Häkkinen & Häkkinen 1995). The bench press participants performed the exercise in a supine position, keeping their back flat on the bench and feet flat on the floor with shoulder and elbow joints positioned at 90 degrees. Both isometric tests preceded at least two submaximal sets. In both tests, participants performed the exercise three times

with a 30-second recovery period, and the best result was included in the analysis. Test personnel advised each participant to produce maximal force as fast as possible and to sustain it for at least three seconds. Test personnel also verbally spurred participants during maximal efforts. Maximal force was recorded with a 16-bit AD-converter (CED power 1401, Cambridge Electronic Design Ltd., England) at the frequency of 1 kHz on a computer. A barbell weight (6 kg) was added to the results of upper limb force.

After isometric force tests, participants performed a bicycle ergometer test (Ergoline 800S, Ergoselect 100K or 200K, Bitz, Germany) to indirectly measure the maximal rate of oxygen consumption (VO_2max). Participants had the possibility to adjust the handlebars and seats individually. After a five-minute warm-up, the test began with an initial power output of 50 watts (W), and the load was progressively increased with 25 W every other minute until volitional exhaustion or until pedaling cadence decreased to under 60 rpm/min. During the test, heart rate (HR) was measured continuously using HR monitors (Polar T-31, Polar Vantage, Kempele, Finland). Predicted VO_2max was assessed from HR and maximal power (MilFit5/Fitware, Finland) using the following equation: VO_2max (ml $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$) = (11.016 * P_{max}) * body mass^{-1} + 7.0, where P_{max} is maximal power in watts and body mass is in kilograms. The Milfit test is rather reliable in measuring VO_2max on a group level (intracorrelation coefficients between r = 0.85 and r = 0.94), but in the accuracy of the predicted VO_2max values, there have been high interindividual differences (Santtila et al. 2013). VO_2max was classified by the reference values measured by the Finnish Defence Forces (age group 25–29 years) (Pihlainen et al. 2011).

The muscle fitness tests—push-ups and sit-ups—were scheduled for one hour after beginning the maximal fitness test. Before both tests, test personnel demonstrated the correct performance technique and also controlled the technique of each participant. Both tests were performed in pairs so that one performed and the other counted the number of repetitions in 60 seconds with correct technique. In the sit-up test, the performing participant lay supine on the floor with hands behind the neck and elbows directed forward. The knees were flexed at an angle of 90 degrees with legs slightly apart, and the assisting participant supported the ankles. During one movement, the participant lifted their upper body until the elbows touched the knees and then straightened back until the shoulder plates touched the floor for the next repetition. In the push-up test, participants started the movement face-

down with the torso straight, hands shoulder-width and level with the fingers pointed forward, elbows extended, and legs hip-width and parallel. To complete one repetition, the participant lowered their torso down to an elbow angle of 90 degrees and then pushed the torso back to the starting position (ACSM 2000; Viljanen et al. 1991).

On the grounds of isometric muscle tests and muscle fitness tests, a muscle strength index (MSI) and muscle fitness index (MFI) were calculated, respectively. The results of muscle test scores were transformed to z-scores. The average of a participant's isometric muscle test z-scores created an MSI, and the average of muscle fitness test z-scores created an MFI.

As mentioned in chapter 2.2.1, the SF-36/RAND-36 is a self-administered questionnaire that takes less than 10 minutes to fill out (Aalto et al. 1999). On the basis of responses, scale scores for eight dimensions and both physical and mental summary scores were counted. Depending on the item-level data completeness, dimension scores could be counted for 713–729 participants. PCS and MCS scores could be counted for 705 participants. On the basis of the studies presented in the following sections, the SF-36 has at least reasonable reliability and validity for group-level comparison.

The reliability of the SF-36 has been shown as satisfactory for group-level comparison in general population studies because, with a couple exceptions, each scale separately calculated Cronbach's $\alpha > 0.70$ (Gandek et al. 1998; Aalto et al. 1999; Garratt & Stavern 2017). In their general population study ($n = 1582$), Brazier et al. (1992) evaluated that the test-retest reliability of the SF-36 was excellent. It can be thought that the time interval between the tests may affect the test-retest reliability because, in longer time, changes in health can appear.

Convergent validity refers to the extent to which an item is related to its own scale when it is excluded, and the correlation coefficient should be greater than 0.40 between items of the same scale (Failde et al. 2000). In large general population studies, a minimum standard of item-scale correlation was met with only one exception, in Italy, in one item of the general health scale (Gandek et al. 1998; Aalto et al. 1999; Garratt & Stavern 2017). An item should have a stronger relationship to its own scale than to the other scales (Failde et al. 2000). A scaling success rate describes the item-discriminant validity of a scale, and scaling success is definite if an item has a higher correlation with its

hypothesized scale than with all the other scales (Gandek et al. 1998). In the Finnish general population study, the scaling success rate was perfect, with the exception of two items, which had a higher correlation to the other scale than to their hypothesized one (Aalto et al. 1998). In a Norwegian general population study, scaling success was 100% for all the other items except the physical functioning item related to most vigorous activities (Garrett & Stavern 2017).

It is hypothesized that the eight scales form two distinct higher-ordered clusters: physical and mental health. Factor analysis has been used in the evaluation of the SF-36 construct validity, and these studies have been performed in several countries, including Finland. These studies have revealed that summary components of physical and mental health were to account for 76–85% (10 countries) and 80–85% (the U.S.) of the reliable variance in the eight scales. Studies in Finland, the U.S. and in 10 other countries, the physical functioning, role-limitations physical and bodily pain scales correlated most highly with the physical component summary (PCS), while the mental health, role-limitations emotional, and social functioning scales correlated most highly with the mental component summary (MCS). The general health and vitality scales had notable correlations with both the PCS and the MCS in Finland and in 10 other countries. In Finland, the role-limitations emotional scale had a weaker correlation with the MCS and a stronger correlation with the PCS as expected. These results supported the success of translations and the two-dimensional model of the SF-36. (See Figure 16) (Ware et al. 1998; Ware & Gandek 1998; Aalto et al. 1999).

De Vet et al. (2005) published a critical review of 28 different factor analysis studies of the SF-36. They reported that, in nearly half the studies (15/28), exploratory factor analysis was performed instead of the more appropriate confirmatory analysis. They found that the interpretation of the final factor solution was inadequate, and cross-validation was rarely performed. They concluded that "the quality of factor analysis in exploring or confirming the factor structure of the SF-36 leaves much to be desired."

Of most concern was the floor and ceiling effects of the SF-36, which probably indicates the lack of the lower or upper end of the scale and limitations in content validity. Also, reliability and sensitivity are reduced because it is impossible to distinguish respondents by their lowest or highest scores or changes in HRQoL over time. This problem was nicely presented in a study of Finnish young males

(mean age 25 years), in which it was difficult to find a clear difference between fitness groups in dimensions of HRQoL other than general health and physical functioning (Häkkinen et al. 2010). In all dimensions, distributions were skewed to the direction of good HRQoL. In addition to the general population, there has been a definite ceiling effect for most dimensions of the SF-36 in several patient populations, even in stroke patients (Anderson et al. 1996), brain tumor patients (Bunevicius et al. 2017) and coronary artery disease patients (Failde et al. 2000). Does this indicate a good level of health care or problems with the instrument? Especially in general population studies, the role limitations scales were most polarized, having both floor and ceiling effects. One reason for the polarity could be that, for items of role limitations scales, there were only two response choices: YES or NO. The updated international version 2.0 of the SF-36 was published in 1996. In this version, there are five response choices for items of role limitations scales, reducing the floor and ceiling effects in these scales (Ware 2000).

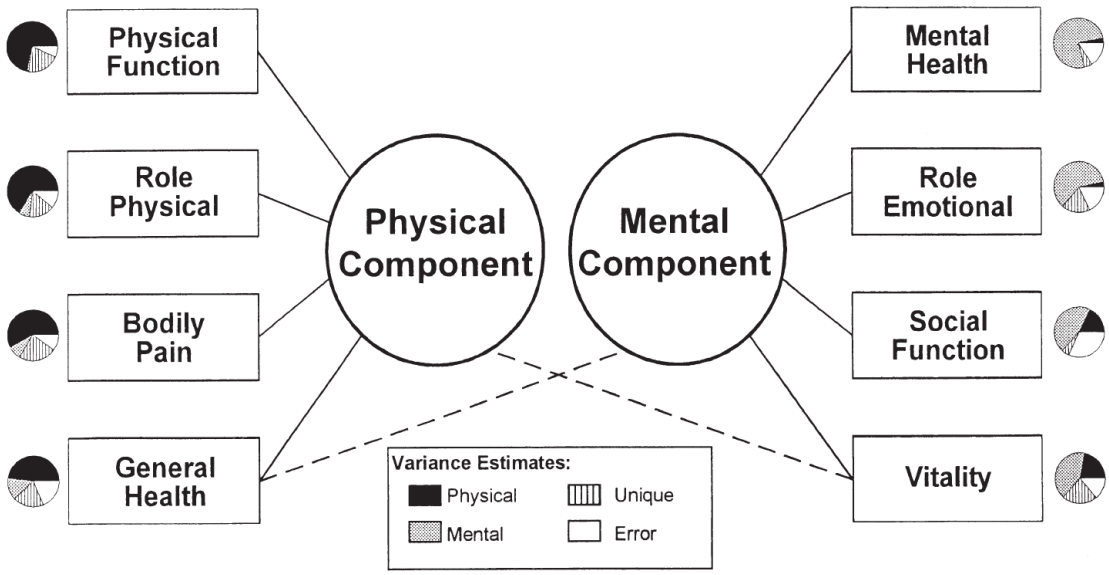

FIGURE 16. Construct validation of the SF-36 two-component model (Ware & Gandek 1998).

5.3 Statistical analysis

Prior to statistical analysis, participants with CRP ≥ 10 mg/L were excluded because of an acute inflammatory response due to, for example, ongoing infections. Mental and physical summary scores of the SF-36 could be counted for 705 participants.

Descriptive data include the number of participants and means with standard deviations (SD), a 95% confidence interval (CI) and the range of values. Because the distributions of CRP and IL-6 values were not normal, they were modified to natural logarithmic values for analysis of associations between variables. Before natural logarithmic modification, IL-6 values below 0.2 pg/ml (the lowest reliable concentration) were modified to zero.

The associations of mental and physical summary scores of the SF-36 with age, demographic measures, blood pressure, physical performance results and inflammatory markers were examined with Pearson correlation coefficients (2-tailed). Linear regression analysis was used to explore the explanatory factors for MCS and PCS. Before analysis related to MCS, participants were sorted according to their MCS scores, from the lowest to the largest, so that participants with the lowest value got an MCS-RANK value of 1 and so on. After this modification, regression standardized residual distributions were normal. In the regression analysis, model 1 was unadjusted and model 2 was adjusted for age, smoking and BMI. The level of significance was set at $p < 0.05$.

Statistical analyses were performed using IBM SPSS Statistics 22.0.0.0 for Windows, RStudio 0.98.932 (RStudio Team 2015) and R 3.2.2 (R Core Team 2015) software package *survey* (Lumley 2004; Lumley 2014).

6 RESULTS

The demographic data of the study participants are shown in Table 3. The mean age of the 741 participants was 26.5 (SD 6.8) years. The mean height, body mass and body mass index (BMI) were 179.4 (SD 6.3) cm, 80.8 (SD 14.0) kg and 25.0 (SD 3.9), respectively. Of the participants, 51.8% were in the normal range and 45.9 were overweight or obese; the distribution of the participants in the BMI groups are presented in Figure 17. The mean waist circumference was 87.0 (SD 11) cm, and 10.5% of the participants had a waist circumference of at least 102 cm. The mean fat mass was 14.8 (SD 8.5) kg, the mean fat-free mass was 37.7 (SD 5.1) kg and the fat percentage was 17.5 (SD 7.7). The mean systolic and diastolic blood pressures were 123 (SD 12) mmHg and 74 (SD 9) mmHg, respectively.

TABLE 3. Detailed descriptive data regarding the study sample

	N	mean (SD)	95% CI for mean	min–max
Age (years)	741	26.5 (6.8)	26.0–27.0	20–55
Height (cm)	727	179.4 (6.3)	179.0–179.9	157–198
Body mass (kg)	731	80.8 (14.0)	79.8–81.8	49.2–134.1
BMI	731	25.1 (3.9)	24.8–25.3	15.8–37.5
Waist circumference (cm)	727	87 (11)	86–88	66–123
Lean body mass (kg)	731	37.7 (5.1)	37.3–38.0	24.2–54.4
Fat mass (kg)	730	14.8 (8.5)	14.1–15.4	1.8–48.1
Fat %	731	17.5 (7.7)	17.0–18.1	3.0–43.5
Systolic BP (mmHg)	727	123 (12)	123–124	91–171
Diastolic BP (mmHg)	727	74 (9)	74–75	43–113

For leisure time, 29.2% of the participants were physically inactive, 30.0% took part in vigorous physical activities once or twice per week and 40.9% were physically active at least three times per week. The percentages of participants who were sober and did not smoke or use snuff were 18.7%, 67.8%, and 80.9%, respectively.

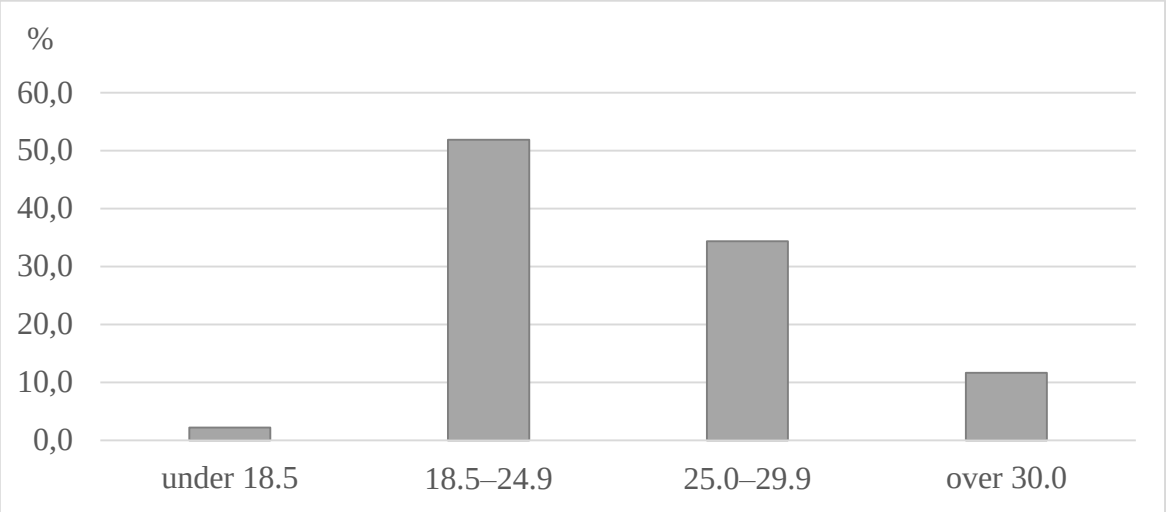

FIGURE 17. Distribution of the participants in the BMI groups.

Figure 18 shows the classification of the mean maximal oxygen uptake (VO_2max) of the participants. The mean (SD) VO_2max was 41.3 (7.7) ml · kg^{-1}· min^{-1}. The VO_2max results of the 231 participants (32.1%) were satisfying or better. The mean (SD) length of the standing long jump was 227 (25) cm, the mean (SD) sit-up count was 35 (12), the mean (SD) push-up count was 29 (14), the mean (SD) maximal isometric leg press was 339.2 (93.2) kg and the mean (SD) maximal isometric bench press was 87.1 (21.4) kg.

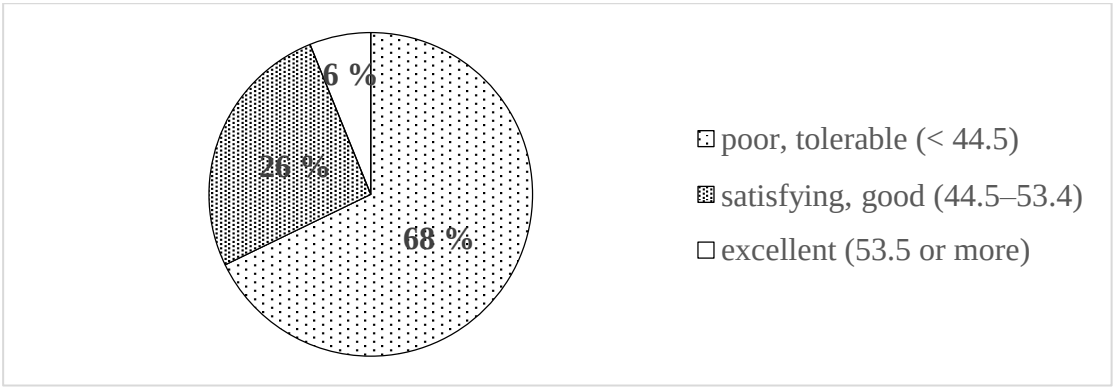

FIGURE 18. Classification of maximal oxygen uptake (ml · kg^{-1}· min^{-1}) of the participants.

The mean plasma levels of CRP and IL-6 were 1.15 mg/L (SD 1.54) and 1.10 pg/ml (SD 1.35), respectively. From the viewpoint of inflammation, a future risk of cardiovascular events was low (CRP < 1 mg/L) in 67.6% (N = 510) of the participants. Physical fitness results and indexes and

inflammatory parameters are shown in Table 4. The means for health-related quality of life dimension and summary scores (RAND-36) are presented in Table 5.

TABLE 4. Physical fitness measures and inflammatory parameters

	N	mean (SD)	95% CI for mean	min–max
VO_2max (ml · kg^{-1}· min^{-1})	718	41.3 (7.7)	40.7–41.8	21.8–67.1
Standing long jump (cm)	719	227 (25)	226–229	145–294
Sit-up (number)	718	35 (12)	34–36	0–66
Push-up (number)	716	29 (14)	28–30	0–78
Isometric leg press (kg)	721	339 (93)	332–346	115–738
Isometric bench press (kg)	722	87 (21)	86–89	36–164
Muscular Fitness Index	713	0.015 (0.900)	-0.051–0.081	-2.49–2.42
Muscular Strength Index	719	0.001 (0.882)	-0.064–0.065	-2.22–3.66
CRP (mg/L)	754	1.148 (1.541)	1.038–1.258	0.006–9.870
IL-6 (pg/ml)	750	1.099 (1.351)	1.002–1.196	0.010–16.800

TABLE 5. Health-related quality of life dimensions, physical and mental component summary scores (SF-36) and inflammatory parameters

	N	mean (SD)	95% CI for mean	min–max
Physical Functioning (PF)	729	97.4 (6.6)	96.9–97.9	0–100
Role-Physical (RP)	713	95.7 (15.5)	94.6–96.9	0–100
Role-Emotional (RE)	714	87.5 (28.2)	85.4–89.5	0–100
Vitality (VT)	729	67.8 (17.5)	66.5–69.1	0–100
Mental Health (MH)	729	77.6 (15.1)	76.5–78.7	8–100
Social Functioning (SF)	725	89.3 (16.5)	88.1–90.5	12.5–100
Bodily Pain (BP)	728	84.0 (15.0)	82.9–85.1	22.5–100
General Health (GH)	729	75.4 (15.9)	74.3–76.6	20–100
PCS	705	54.8 (4.6)	54.5–55.2	30.5–67.0
MCS	705	50.9 (9.4)	50.2–51.6	12.9–66.9

There were statistically significant negative associations between CRP and physical functioning, general health and physical components, and also between IL-6 and general health and physical summary (Table 6). The inflammatory biomarkers were positively associated with age, blood pressure and all anthropometric and body composition measures except CRP with height and IL-6 with height, lean body mass and systolic blood pressure (Table 7). There were negative associations between inflammatory biomarkers and maximal oxygen uptake, dynamic muscle tests and muscle fitness index, and CRP with isometric bench press (Table 8).

TABLE 6. Parametric correlations (Pearson correlation coefficient) between health-related quality of life dimensions and summary scores and inflammatory biomarkers

	CRP(ln)		IL-6(ln)	
	R	p	r	p
PH, Physical Functioning	-0.153 **	< 0.001	-0.059	0.112
RP, Role-Physical	0.012	0.744	-0.019	0.865
RE, Role-Emotional	0.013	0.735	-0.001	0.979
VT, Vitality	-0.016	0.666	0.007	0.854
MH, Mental Health	0.030	0.425	0.046	0.213
SF, Social Functioning	0.017	0.648	0.024	0.516
BP, Bodily Pain	-0.058	0.120	-0.040	0.278
GH, General Health	-0.146 **	< 0.001	-0.115 **	0.002
PCS, Physical Component Summary	-0.136 **	< 0.001	-0.113 **	0.003
MCS, Mental Component Summary	0.045	0.231	0.041	0.279

Correlation is significant at the 0.01 level (2-tailed) **

PCS was positively associated with maximal oxygen uptake, dynamic muscle tests and muscle fitness index, and it was negatively associated with weight, body fat measures and diastolic blood pressure at level $p < 0.01$ and with age at level $p < 0.05$. PCS was negatively associated with age, weight, body fat mass, body fat percentage, BMI, waist circumference and diastolic blood pressure. MCS was positively associated with the standing long jump, number of push-ups and muscular fitness index and negatively associated with systolic blood pressure. Results are presented in Tables 9 and 10.

TABLE 7. Parametric correlations (Pearson's correlation coefficient) between inflammatory biomarkers and age, anthropometric measures and blood pressure

	CRP(ln)		IL-6(ln)	
	R	P	r	p
Age	0.138 **	< 0.001	0.115 **	0.002
Height	-0.046	0.212	-0.003	0.931
Weight	0.343 **	< 0.001	0.170 **	< 0.001
Lean body mass	0.077 *	0.038	0.076	0.040
Body fat mass	0.479 **	< 0.001	0.196 **	< 0.001
Body fat %	0.476 **	< 0.001	0.181 **	< 0.001
BMI	0.403 **	< 0.001	0.182 **	< 0.001
Waist circumference	0.446 **	< 0.001	0.175 **	< 0.001
Systolic BP	0.123 **	0.001	0.046	0.218
Diastolic BP	0.209 **	< 0.001	0.148 **	< 0.001

Correlation is significant at the 0.01 level (2-tailed) ** and at the 0.05 level (2-tailed) *

TABLE 8. Parametric correlations (Pearson's correlation coefficient) between inflammatory biomarkers and fitness and strength measures

	CRP(ln)		IL-6(ln)	
	R	p	r	p
VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)	-0.426 **	< 0.001	-0.175 **	< 0.001
Standing long jump (cm)	-0.337 **	< 0.001	-0.149 **	< 0.001
Sit-up (number)	-0.290 **	< 0.001	-0.138 **	< 0.001
Push-up (number)	-0.299 **	< 0.001	-0.125 **	< 0.001
Isometric leg press (kg)	-0.019	0.614	0.013	0.726
Isometric bench press (kg)	-0.110 **	0.003	-0.039	0.291
Muscular Fitness Index	-0.323 **	< 0.001	-0.143 **	< 0.001
Muscular Strength Index	-0.072	0.054	-0.017	0.657

Correlation is significant at the 0.01 level (2-tailed) **

TABLE 9. Parametric correlations (Pearson's correlation coefficient) between the PCS and MCS scores of the SF-36 and age, anthropometric measures and blood pressure

	PCS		MCS	
	r	P	r	p
Age	-0.092 *	< 0.015	0.047	0.211
Height	0.004	0.910	0.026	0.489
Weight	-0.119 **	0.002	0.041	0.284
Lean body mass	-0.041	0.281	0.041	0.286
Body fat mass	-0.163 **	< 0.001	0.043	0.255
Body fat %	-0.149 **	< 0.001	0.034	0.371
BMI	-0.138 **	< 0.001	0.048	0.206
Waist circumference	-0.158 **	< 0.001	0.036	0.339
Systolic BP	-0.038	0.315	-0.096 *	0.011
Diastolic BP	-0.100 **	0.008	0.053	0.164

Correlation is significant at the 0.01 level (2-tailed) ** and at the 0.05 level (2-tailed) *

Regression analysis was performed without (model 1) and with (model 2) adjustments for age, BMI and smoking status. In models 1 and 2, the maximal oxygen uptake was the most powerful explanatory variable for the variance of PCS, $r^2 = 0.052$ ($p = 0.001$) and $r^2 = 0.067$ ($p < 0.001$), respectively. For all other variables, r^2 was below 0.030 in model 1. In model 2, all measured variables were related to PCS, but all relations between explanatory variables and PCS were weak. In model 2, the explanatory power of inflammatory markers for the variance of PCS was low because the adjusted R^2 values for CRP and IL-6 were 0.049 ($p < 0.001$) and 0.048 ($p < 0.001$), respectively. The regression analysis for the mental component summary was performed after the RANK modification of MCS. In model 1, only systolic blood pressure explained more than 1% of the variance of MCS. In model 2, all measured variables were statistically significantly related to MCS, but the explanatory power was weak ($r^2 < 0.020$). Also in model 2, CRP and IL-6 explained 1.2% and 1.0% for the variance of MCS, respectively. Results are presented more accurately in the Appendix in Tables 1 and 2.

TABLE 10. Parametric correlations (Pearson's correlation coefficient) between the PCS and MCS scores of the SF-36 and fitness and strength measures and inflammatory biomarkers

	PCS		MCS	
	r	P	r	P
VO_2max (ml · kg^{-1}· min^{-1})	0.225 **	< 0.001	0.037	0.329
Standing long jump (cm)	0.112 **	0.003	0.096 *	0.012
Sit-up (number)	0.156 **	< 0.001	0.068	0.077
Push-up (number)	0.144 **	< 0.001	0.088 *	0.022
Isometric leg press (kg)	0.053	0.169	0.046	0.232
Isometric bench press (kg)	0.031	0.422	0.049	0.200
Muscular Fitness Index	0.162 **	< 0.001	0.087 *	0.024
Muscular Strength Index	0.043	0.256	0.055	0.149
CRP (ln)	-0.136 **	< 0.001	0.045	0.231
IL-6 (ln)	-0.113 **	0.003	0.041	0.279

Correlation is significant at the 0.01 level (2-tailed) ** and at the 0.05 level (2-tailed) *

7 DISCUSSION

The present study results showed that in a sample of young Finnish men, there were only a few associations between measured inflammatory markers and health-related quality of life measured by the RAND 36-item health survey version 1.0 (RAND-36). The plasma level of C-reactive protein (CRP) was negatively associated with dimensions of physical functioning and general health and a physical component summary score. The plasma level of Interleukin-6 (IL-6) was negatively associated with the general health and physical component summary scores (PCS). In the regression analysis, CRP explained 1.6% of the variance of PCS (model 1), and after adjusting for age, BMI and smoking, the power of explanation increased to 4.9% (model 2). In models 1 and 2, IL-6 explained 1.0% and 4.8% of the variance of PCS, accordingly. Regarding model 2, the findings were statistically significant ($p < 0.001$). The regression analysis for the mental component summary was performed after the RANK modification of MCS. In model 1, CRP explained 0.4% ($p = 0.046$) of the variance of MCS, and in model 2, the power of explanation increased to 1.2% ($p = 0.015$). Also in model 2, IL-6 explained 1.0% ($p = 0.025$) of the variance of MCS.

As expected, the plasma levels of CRP and IL-6 were low in the present population of young men but were at the same level as in the referred studies (Shine et al. 1981; Brüünsgaard et al. 1997; Ostrowski et al. 1998; Fedeva et al. 2014; Vaara et al. 2014). Inflammatory markers were positively associated with age- and weight-related measures (weight, body fat mass, body fat percentage, BMI and waist circumference) as expected. These associations are presumably because central obesity induces the imbalance between the pro- and anti-inflammatory properties of adipose tissue and the development of systemic inflammation (Hotamisligil 1995; Nishimura et al. 2009; Ouchi et al. 2011). In intervention studies, a diet-based weight reduction has been an effective means to lower inflammation, especially in overweight and obese subjects (Heilbronn et al. 2001; Ho et al. 2015; Möller et al. 2016), and regular exercise could have an independent effect on reducing systemic inflammation (Gondim et al. 2015; Fedewa et al. 2017; Ihalainen et al. 2017).

There were negative associations between inflammatory markers and maximal oxygen uptake, muscle fitness measures (sit-ups, push-ups), muscle fitness index (MFI) and standing long jump results. CRP level was also negatively associated with isometric bench press results. The Pearson's

correlation coefficient for CRP and cardiorespiratory fitness was -0.426, which is comparable to Vaara et al. (2014) (r = -0.46). The present inflammatory markers were not associated with the muscular strength index, which was contradictory to the results of Vaara et al. (2014), who found a statistically significant negative association in the same kind of sample of Finnish males.

As expected, in the present population of young men, there were clear ceiling effects in several dimensions of the RAND-36, including physical functioning, role limitations physical, role limitations emotional, social functioning and bodily pain (Aalto et al. 1999; Häkkinen et al. 2010). All other dimensions of the RAND-36 were also skewed to the direction of good health. Figure 21 presents the comparison of the means of scale scores of the present study population to the normal values of young male age groups (Aalto et al. 1999). In the present study, scores in both role limitations dimensions were clearly better than in Aalto et al. (1999) in the 25–29 age group. As shown in Figure 19, HRQoL tends to decline with age, even in young adults. PCS and MCS scores of the present study were at the same level than in Norwegian men aged 20–29 (Garrett & Stavern 2017).

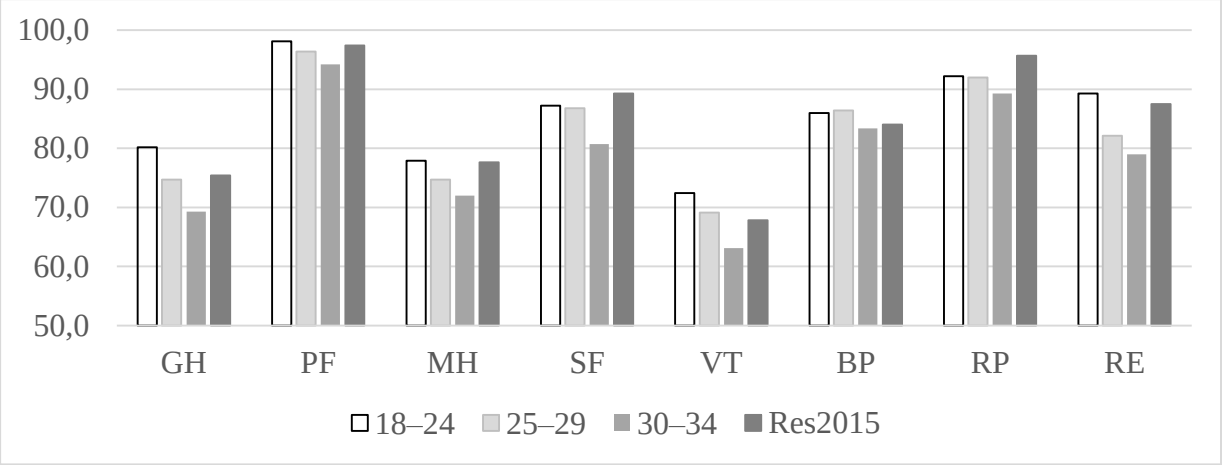

FIGURE 19. Means of the RAND-36 dimensions by age group (Aalto et al. 1999) and Res2015 (= present study). GH = general health, PF = physical functioning, MH = mental health, SF = social functioning, VT = vitality, BP = bodily pain, RP = role limitations physical, RE = role limitations emotional.

In the present study, PCS was negatively associated with age ($p < 0.015$), weight ($p = 0.002$), obesity-related variables such as body fat mass, body fat percentage, BMI, waist circumference ($p < 0.001$) and diastolic blood pressure ($p < 0.001$). MCS was associated only with systolic blood pressure ($r = -0.096$, $p = 0.011$). In the general population studies, especially physical HRQoL has been weakened by age (Aalto et al. 1999; Garratt & Stavern 2017). The associations between HRQoL and BMI have been controversial. The present finding of negative associations between BMI and the physical part of HRQoL is in accordance with the meta-analysis by Ul-Haq et al. (2013), who found that physical HRQoL was reduced in overweight and obese participants with a clear dose response manner compared with normal weight participants. However, mental HRQoL was not so clearly affected by an increase in BMI (Ul-Haq et al. 2013). In Swiss young males, variation in normal weight predicted below-average physical HRQoL, and underweight predicted below-average mental HRQoL, but in contrast, obese participants reported better mental health (Dey et al. 2013).

In the present study, PCS was positively associated with fitness-related measures (VO_2max, sit-ups, push-ups and MFI) at level $p < 0.001$ and standing long jump results ($p = 0.003$). MCS was positively associated with standing long jump ($p = 0.012$), push-ups ($p = 0.022$) and MFI ($p = 0.024$). These results are in accordance with the findings of the reviewed studies using exercise tests to estimate cardiorespiratory/muscle fitness. In the reviewed studies, fitness has at least been associated with PCS (Sloan et al. 2007; Sörensen et al. 2007) or some dimensions of a physical component of HRQoL (Häkkinen et al. 2010). Sloan et al. (2007) found that cardiorespiratory fitness also associated with MCS, and Häkkinen et al. (2010) found that the physical fitness index associated with dimensions of vitality and mental health. In the present regression analysis, after adjusting for age, BMI and smoking, cardiorespiratory fitness (VO_2max) was the most powerful explanatory variable for PCS ($r^2 = 0.067$, $p < 0.001$) while standing long jump explained most of the variance for MCS ($r^2 = 0.018$, $p < 0.003$).

I have not heard of any previous studies exploring the association between IL-6 and CRP and RAND-36 in a young adult population. In the reviewed studies, only Garvin et al. (2015) used the same inflammatory markers and a measure of HRQoL in a sample of the general population. They found that low-grade inflammation was negatively and widely associated with HRQoL. What is the difference compared to the present study? Garvin et al. (2015) studied the middle-aged population,

which included females, and their finding was particularly related to a composite variable of CRP and IL-6. Both inflammatory markers tend to elevate with age (Ballou et al. 1996; Brüünsgaard et al. 1999). Females tend to have higher CRP levels than males (Hutchinson et al. 2000). In the Finnish general population study, both age and female gender were negatively associated with HRQoL (Aalto et al. 1999). There are also other variables related to inflammation and HRQoL, like BMI, fitness level, smoking, number of medical conditions and pain. Table 11 demonstrates some comparable variables of the present study and the study by Garvin et al. (2015). A higher proportion of overweight and obese participants and participants with pain could elevate inflammatory markers and lower at least the physical dimensions of HRQoL in Garvin's study compared to the present study. A higher proportion of participants in the present study were smokers and were physically inactive compared to Garvin's study. Both smoking and physical inactivity are related to lower HRQoL and elevated inflammatory markers (Koenig et al. 1999; Bize et al. 2007; Beavers et al. 2010; Vogl et al. 2012).

TABLE 11. Comparable variables of the present study and Garvin et al. (2015)

Variable	Garvin et al. (2015)	present study
age (years)	45–69	20–55
gender (females %)	50%	0%
BMI < 25 kg/m^2 (%)	38%	54%
smokers (at least 1/day)	21%	32%
back pain vs. low back pain	41%	26%
physically inactive	4%	21%
mean CRP (SD), mg/L	1.7 (2.0)	1.15 (1.54)
mean IL-6 (SD), ng/ml	1.9 (2.5)	1.10 (1.35)

There were two main differences in the previously mentioned studies. In the present study, inflammatory markers were dealt with separately; Garvin et al.'s (2015) study presented CRP and IL-6 as a composite variable. Secondly, in the present study, HRQoL was assessed using two component summary scores, and Garvin used all eight dimensions of the SF-36. It would have been interesting to investigate the association between the composite inflammatory variable and the component summary scores of the RAND-36. However, grouping participants as in Garvin et al. (2015) into low and high inflammatory marker groups, the number of participants in the high-CRP, high-IL-6 group

could have been too small for statistical analysis. In the present study, the proportion of "high-CRP" (> 3 mg/L) was only 9.4% (n = 71). Garvin et al. (2015) set the cut-point to "high-IL-6" to the level above when there was the same proportion of participants as in the "high-CRP" group. Garvin speculated that a combination of high-IL-6 and high-CRP reflects a true measure of longstanding subclinical inflammation instead of elevation in one of the two indicating a more acute reaction.

In the present study, there was not a negative association between inflammatory markers and vitality, which was demonstrated in a study of obese middle-aged adults (Slagter et al. 2015), in general population studies (Cho et al. 2009, Cho et al. 2013), and in a weight loss intervention study of knee osteoarthritis patients (Nicklas et al. 2016). Subjects were older in these studies, and in a study by Nicklas et al. (2016), all subjects had health-related conditions that could lower vitality. The vitality score was higher and inflammatory markers lower in the present study than in previous studies, as expected. Also, the variance of inflammatory markers was lower. It is possible that previously mentioned differences explain why an association between inflammatory markers and vitality was not found in the present study.

The strength of this study is that the sample represents the population of Finnish young men quite well. However, reservists who did not enter into the refresher courses and males who had not participated in military service at all are not represented. Cardiorespiratory fitness and muscle fitness and strength were measured objectively by experienced test personnel instead of being the participants' subjective perspectives.

One of the major limitations of the present study is related to the measure of HRQoL, the RAND 36-item health survey. The strong ceiling effect of several dimensions of HRQoL was not a surprise. The ceiling effect indicates the lack of scale at the upper end of the RAND-36 and has been shown in many populations. It diminishes validity, reliability and sensitivity because it is impossible to distinguish respondents with the highest scores from each other (Gandek et al. 1998; Aalto et al. 1999; Garrett & Stavern 2017). Despite the two-summary score model of the SF-36 having been largely accepted (Ware et al. 1998; Ware & Gandek 1998; Aalto et al. 1999), the construct validity of the SF-36 has also been criticized (de Vet et al. 2005).

In the present population, the distribution of the MCS was not normal, and thus, it had to be modified before regression analysis. The ranking modification always leads to a loss of information and affects the results. In this case, beta coefficients inform only the ordering of the MCS, not the change per unit.

One weakness of the present study was that the morbidities of participants were not included in the analysis. In a similar sample of Finnish young males, morbidities did not differ between fitness level groups (Häkkinen et al. 2010). In a Finnish general population study, a number of diseases were inversely associated with all dimensions of the RAND-36 (Aalto et al. 1999).

Several factors like age, gender, body mass index, smoking, cardiovascular fitness and morbidities have been associated with both inflammatory markers and HRQoL. It has been verified that pro-inflammatory cytokines induce sickness behavior, especially in acute infections (Dantzer 2001). It is possible that long-term subclinical inflammation affects an individual's perception of their own health and quality of life even before there are any signs of disease. The present study cannot answer the question does the inflammatory markers influence independently to the HRQoL or do they mediate some of the influence of age, BMI, smoking, fitness, and morbidities. This challenge is related to all cross-sectional studies because these cannot show the causality.

In the present study, both CRP and IL-6 were negatively associated with the PCS of the RAND-36. Despite CRP/IL-6 having explained only a little about the variance of the PCS, it is interesting that these associations exist in a healthy, resilient, young, adult male population. It could be speculated that the skewness of inflammatory markers and most scale scores of the RAND-36 weaken the associations between these variables. It is debatable whether the associations between inflammatory markers and HRQoL would have been different if the participants with the lowest quartile inflammatory markers were compared with participants with the highest quartile. It would be interesting to investigate whether inflammatory markers like CRP and IL-6 predict future HRQoL in the young adult population. It would also be interesting to know whether there would be a difference in the HRQoL of persons with persistent elevated inflammatory markers compared to those with low values.

REFERENCES

Aalto, A-M., Aro, A. R., & Teperi, J. 1999. RAND-36 terveyteen liittyvän elämänlaadun mittarina. Mittarin luotettavuus ja suomalaiset väestöarvot. STAKES. Sosiaali- ja terveysalan tutkimus- ja kehittaämiskeskus. Tutkimuksia 101.

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G. M., Cooper, N. R., Eikelenboom, P., Emmerling, M., Fiebich, B. L., Finch, C. E., Frautschy, S., Griffin, W. S., Hampel, H., Hull, M., Landreth, G., Lue, L., Mrak, R., Mackenzie, I. R., McGeer, P. L., O'Banion, M. K., Pachter, J., Pasinetti, G., Plata-Salaman, C., Rogers, J., Rydel, R., Shen, Y., Streit, W., Strohmeyer, R., Tooyoma, I., Van Muiswinkel, F. L., Veerhuis, R., Walker, D., Webster, S., Wegrzyniak, B., Wenk, G. & Wyss-Coray, T. 2000. Inflammation and Alzheimer's disease. Neurobiology of Aging 21: 383 – 421.

American College of Sport Medicine. 2000. ACSM`s Guidelines for Exercise Testing and Prescription. Philadelphia: Lippincott Williams & Wilkins, pp. 84–85.

Anderson, C., Laubscher, S. & Burns. R. 1996. Validation of the Short Form 36 (SF-36) Health Survey Questionnaire Among Stroke Patients. Stroke 27 (10): 1812 – 6.

Atlantis, E., Chin-Moi, C., Kirby, A., & Singh, F. 2004. An effective exercise-based intervention for improving mental health and quality of life measures: a randomized controlled trial. Preventive Medicine 39 (2): 424 – 434.

Ballou, S. P., Lozanski, F. B., Hodder, S., Rzewnicki, D. L., Mion, L. C., Sipe, J. D., Ford, A. B., & Kushner, I. 1996. Quantitative and qualitative alterations of acute-phase proteins in healthy elderly persons. Age and ageing 25 (3): 224 – 230.

Beavers, K. M., Brinkley, T. E., & Nicklas, B. J. 2010. Effect of exercise training on chronic inflammation. Clinica Chimica Acta 411 (11 – 12): 785 – 793.

Bennett, W. L., Ouyang, P., Wu, A. W., Barone, B. B., & Stewart, K.J. 2008. Fatness and fitness: How do they influence health-related quality of life in type 2 diabetes mellitus? Health and quality of life outcomes 6: 110.

Beuther, D. A. & Sutherland, R. 2007. Overweight, Obesity, and Incident Asthma: A Meta-analysis of prospective epidemiologic studies. American Journal of Respiratory and Critical Care Medicine 175: 661 – 666.

Bize, R., Johnson, J. A., & Plotnikoff, R. C. 2007. Physical activity level and health-related quality of life in the general adult population: A systematic review. Preventive Medicine 45 (6): 401 – 415.

Bleau, C., Karelis, A. D., St-Pierrre, D. H., & Lamontagne, L. 2015. Crosstalk between intestinal microbiota, adipose tissue and skeletal muscle as an early event in systemic low-grade inflammation and the development of obesity and diabetes. Diabetes/metabolism research and reviews 31 (6): 545 – 561.

Brazier, J. E., Harper, R., Jones, N. M., O'Cathain, A., Thomas, K. J., Usherwood, T., & Westlake, L. 1992. Validating the SF-36 health survey questionnaire: New outcome measure for primary care. The British Medical Journal 305 (6846): 160 – 164.

Brown, D. R., Carroll, D. D., Workman, L. M., Carlson, S. A., & Brown, D. W. 2014. Physical activity and health-related quality of life: US adults with and without limitations. Quality of life research 23 (10): 2673 – 2680.

Brüünsgaard, H., Galbo, H., Halkjaer-Kristensen, J., Johansen, T. L., MacLEan, D. A., & Pedersen, B. K. 1997. Exercise-induced increase in resum interleukin-6 in humans is related to muscle damage. Journal of Physiology 499 (Pt 3): 833 – 841.

Brüünsgaard, H., Andersen-Randberg, K., Jeune, B., Pedersen, A. N., Skinhøj, & Pedersen, B. K. 1999. A high plasma concentration of TNF-α is associated with dementia in centenarians. The journals of gerontology. Series A, Biological sciences and medical sciences 54 (7): M357 – M364.

Brüünsgaard, H. & Pedersen, B. K. 2003. Age-related inflammatory cytokines and disease. Immunology and Allergy Clinics of North America 23 (1): 15 – 39.

Brüünsgaard, H. 2005. Physical activity and modulation of systemic low-level inflammation. Journal of Leukocyte Biology 78 (4): 819–835.

Buckley, D. I., Fu, R., Freeman, M., Rogers, K., & Helfand, M. 2009. C-reactive protein as a risk factor for coronary heart disease: A systematic review and meta-analyses for the U.S. preventive services task force. Annals of Internal medicine 151 (7): 483 – 495.

Bunevicius, A. 2017. Reliability and validity of the SF-36 Health Survey Questionnaire in patients with brain tumors: a cross-sectional study. Health and quality of life outcomes 17 (92): 1 – 7.

Chaikate, S., Harnroongroj, T., Chantaranipapong, Y., Puduang, S., Mahaisiriyodom, A., Viroonudomphol, D., Singhasivanon, P., Schelp, F. P., Tornee, S., Tribunyatkui, S. & Changbumrung, S. 2006. C-reactive protein, interleukin-6, and tumor necrosis factor-α levels in overweight and healthy adults. Southeast Asian Journal of Tropical Medicine and Public Health 37 (2): 374 – 381.

Cho, H. J., Seeman, T. E., Bower, J. E., Kiefe, C. I., & Irwin, M. R. 2009. Prospective Association Between C-Reactive Protein and Fatigue in the Coronary Artery Risk Development in Young Adults Study. Biological Psychiatry 66 (9): 871 – 878.

Cho, H. J., Kivimäkin, M., Bower, J. E. & Irwin, M. R. 2013. Associations of C-reactive protein and interleukin-6 with new-onser fatigue in the Whitehall II prospective cohort study. Psychological Medicine 43 (8): 1773 – 1783.

Christian, L. M., Glaser, R., Porter, K., Malarkey, W. B., Bevensdorf, D., & Kiecolt-Glaser, K. K. 2011. Poorer self-rated health is associated with elevated inflammatory markers among older adults. Psychoneuroendocrinology 36 (10): 1495- 1504.

Corey, K. E. & Kaplan, L. M. 2014. Obesity and liver disease: the epidemic of the twenty-first century. Clinics in Liver Disease 18 (1): 1 – 18.

Crosby, R. D., Kolotkin, R. L., & Williams, G. R. 2003. Defining clinically meaningful change in health-related quality of life. Journal of Clinical Epidemiology 56 (5): 395 – 407.

da Cruz, L. L., Cardoso, L. D., Pala, D., de Paula, H., Lamounier, J. A., Silva, C. A. M., Volp, A. C. P. & Nascimento de Freitas, R. 2013. Metabolic syndrome components can predict C reactive protein concentration in adolescents. Nutricion Hospitalaria 28 (5): 1580 – 1586.

Danesh, J., Wheeler, J. G., Hirchfield, G. M., Eda, S., Eiriksdottir, G., Rumley, A., Lowe, G. D. O., Pepys, M. B., & Gudnason, V. 2004. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. The New England journal of medicine 350 (14): 1387 – 1397.

Dantzer. R. 2001. Cytokine-Induced Sickness Behavior: Where Do We Stand? Brain, Behavior, and Immunity 15 (1): 7 – 24.

de Punder, K. & Pruimboom, L. 2015. Stress induces endotoxemia and low-grade inflammation by increasing barrier permeability. Frontiers in immunology 6 (223): 1 – 12.

DeSalvo, K. B., Bloser, N., Reynolds, K., He, J., & Munther, P. 2006. Mortality prediction with a single general self-rated health question. Journal of general internal medicine 21 (3): 267 – 275.

de Vet, H. C. W., Herman, J. A., Terwee, C. B., & Pouwer, F. 2005. Are factor analytical techniques used appropriately in the validation of health status questionnaires? A systematic review on the quality of factor analysis of the SF-36. Quality of Life Research 14 (5): 1203 – 18.

Dey, M., Gmel, G., & Mohler-Kuo, M. 2013. Body mass index and health-related quality of life among young Swiss men. BMC public health 13: 1028

Domingo-Salvany, A., Lamarca, R., Ferrer, M., Garcia-Aymerich, J., Alonso, J., Félez, M., Khalaf, A., Marrades, R. M., Monsó, E., Serra-Batles, J., & Antó, J. M. 2002. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. American Journal of respiratory and critical care medicine 165 (5): 680 – 685.

Dür, M., Steiner, G., Stoffer, M. A., Fialka-Moser, V., Kautzky-Willer, A., Dejeco, C., Ekmekcioglu, C., Prodinger, B., Binder, A., Smolen, J., & Stamm T. A. 2016. Initial evidence for the link between activities and health: Associations between a balance of activities, functioning and serum levels of cytokines and C-reactive protein. Psychoneuroendocrinology 65: 138 – 148.

European Patients' Academy (EUPATI). 2016. Measuring Health-related quality of life (HRQoL). 1 – 10. https://www.eupati.eu/health-technology-assessment/measuring-health-related-quality-life-hrqol/

Failde, I., & Ramos, I. 2000. Validity and reliability of the SF-36 Health Survey Questionnaire in patients with coronary artery disease. Journal of clinical epidemiology 53 (4): 359 – 365.

Fedewa, M. V., Bhibha, M., Forehand, R. L., & Evans, E. M. 2014. Area-level socioeconomic status, adiposity, physical activity, and inflammation in young adults, 2013. Preventing Chronic Disease 11, 140090.

Fedewa, M. V., Hathaway, E. D., & Ward-Ritacco, C. L. 2017. Effect of exercise training on C reactive protein - a systematic review and meta-analysis of randomised and non-randomised controlled trials. British Journal of Sports Medicine 51 (8): 670 – 676.

Feeny, D. H., Eckström, E., Whitlock, E. P., & Perdue, L. A. 2013 A Primer for Systematic Reviewers on the Measurement of Functional Status and Health-Related Quality of Life in Older Adults. Agency for Healthcare Research and Quality.

Fine, J. T., Colditz, G. A., Coakley, E. H., Moseley, G., Manson, J. E., Willett, W. C., & Kawachi, I. 1999. A prospective study of weight change and health-related quality of life in women. JAMA 282 (22): 2136 – 2142.

Fischer, C. P. 2006. Interleukin-6 in cute exercise and training: What is the biological relevance? Exercise immunology review 12: 6- 33.

Fisher, G., Hyatt, T. C., Humter, G. R., Oster, R. A., Desmond, R. A., & Gower, B. A. 2011. Effect of diet with and without exercise training on markers of inflammation and fat distribution in overweight women. Obesity 19 (6): 1131 – 1136.

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

Ford, E. S. 2003. C-reactive protein concentrations and cardiovascular risk factors in children. Findings from the National Health and Nutrition Examination Survey 1999 – 2000. Circulation 108 (9): 1053 – 1058.

Foster J. R. 2001. The functions of cytokines and their uses in toxicology. International Journal of Experimental Pathology 82: 171-192.

Fried, S. K., Bunkin, D. A., & Greenberg, A. S. 1998. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: Depot differense and regulation by glycocorticoid. Journal of Clinical Endocrinology and Metabolism 83 (3): 847 – 850.

Gan, W. Q., Man, S. F., Senthilselvan, A., Sin, D. D. 2004. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 59: 574–580.

Gandek, B., Ware, J. E. Jr, Aaronson, N. K., Alonso, J., Apolone, G., Bjorner, J., Brazier, J., Bullinger, M., Fukuhara, S., Kaasa, S., Leplège, A., & Sullilvan, M. 1998. Tests of Data Quality, Scaling Assumptions, and Reliability of the SF-36 in Eleven Countries: Results from the IQOLA Project. Journal of Clinical Epidemiology 51 (11): 1149 – 1158.

Garrat, A. M., & Stavern, K. 2017. Measurement properties and normative data for the Norwegian SF-36: results from a general population survey. Health and quality of life outcomes 15(51): 1 – 10.

Garvey, J. E., Pengo, M. F., Drakatos, P. & Kent, B. D. 2015. Epidemiological aspects of obstructive sleep apnea. Journal of Thoracic Disease 7 (5): 920 – 929.

Garvin, P., Nilsson, E., Ernerudh, J. & Kristenson, M. 2015. The joint subclinical elevation of CRP and IL-6 is associated with lower health-related quality of life in comparison with no elevation or elevation of only one of the biomarker. Quality of Life Research 25: 213 – 221.

Gleeson, M., Bishop, N., C., Stensel, D. J., Lindley, M. R., Mastana, S. S., & Nimmo, M. A. 2011. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nature reviews. Immunology 11 (9): 607 – 615.

Gondim, O. S., de Camargo, V. T. N., Gutierrez, F. A., de Oliveira Martins, P. F., Pereira Passos, M. E., Momesso, C. M., Santos, V. C., Gorjäo, R., Pithon-Curi, T. C., & Cury-Boaventura, M. F. 2015. Benefits of regular exercise on inflammatory and cardiovascular risk markers in normal weight, overweight and obese adults. PLos One 10 (10): 1 – 14.

Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham. C. L. & Anis, A.H. 2009. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health 9 (88): 1 – 20.

Gyuton, A. C. & Hall, J. E. 2006. Textbook of Medical Physiology. 11th edition. 434-435.

Haapakoski, R., Mathie, J., Ebmeier, K. P., Alenius, H., & Kivimäki, M. 2015. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. Brain, behavior, and immunology 49 : 206 – 215.

Hak, A. E., Stehouwer, C. D. A., Bots, M. K., Polderman, K. H., Schalkwijk, C. G., Westendorp, I. C. D., Hofman, A. & Witterman, J. C. M. 1999. Associations of C-reactive protein with measures of obesity, insulin resistence, and subclinical atherosclerosis in healthy, middle-aged women. Arteriosclerosis, thrombosis, and vascular biology 19 (8): 1986 – 1991.

Hallenbeck, J. M. 2002. The many faces of tumor necrosis factor in stroke. Nature Medicine 8: 1363–1368.

Hanahan, D., Weinberg, RA. 2011. Hallmarks of cancer: the next generation. Cell 144: 646-74.

Hamer, M. & Chida, Y. 2011. Life satisfaction and inflammatory biomarkers - The 2008 Scottish Health Survey. Japanese Psychological Research 53 (2): 133 – 139.

Haring, R., You-Shan, F., Moock, J., Völzke, H., Dörr, M., Nauck, M., Wallaschofski, H., & Kohlmann, T. 2011. Self-perceived quality of life predicts mortality risk better than a multi-biomarker panel, but the combination of both does best. BMC Medical Research Methodology 11 (103): 1 – 10.

Hays, R. D., Sherbourne, C. D., & Mazel, R. M. 1993. The RAND 36-item health survey 1.0. Health economics 2 (3): 217 – 227.

Heilbronn, L.K., Noakes, M. & Clifton, P. M. 2001. Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. Arteriosclerosis, Thrombosis, and Vascular Biology 21 (6): 968 – 970.

Heinich, P. C., Behrmann, I., Müller-Newen, G., Schaper, F., & Graeve, L. 1998. Interleukin-6-type cytokine signalling through the gp130-Jak-STAT pathway. The Biochemical journal 334 (Pt 2): 297 – 314.

Herder, C., Schneitler, S., Rathmann, W., Haastert, B., Schneitler, H., Winkler, H., Bredahl, R., Hahnloser, E. & Martin, S. 2007. Low-grade inflammation, obesity, and insulin resistance in adolescents. The Journal of Clinical Endocrinology & Metabolism 92 (2): 4569 – 4574.

Hirano, T., Yasukawa, K., Harada, H., Taga, T., Watanabe, Y., Matsuda, T., Kashiwamura, S., Nakajima, K., Koyama, K. & Iwamatsu, A. 1986. Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. Nature 324: 73-76.

Ho, T. P., Zhao, X., Courville, A. B., Linderma, J. D., Smith, S., Sebring, N., Della Valle, D. M., Fitzpatrick, B., Simchowitz, L. & Celi F.S.2015. Effects of a 12-Month Moderate Weight Loss Intervention on Insulin Sensitivity and Inflammation Status in Nondiabetic Overweight and Obese Subjects. Hormone and metabolic research 47 (4): 289 – 296.

Holstila, A., Mänty, M., Rahkonen, O. Lahelma, E., & Lahti, J. 2017. Changes in leisure-time physical activity and physical and mentalhealth functioning - a follow-up study. Scandinavian Journal of Medicine and Science in Sports 27 (12): 1785 – 1792.

Hopman, W. M., Berger, C., Joseph, L., Barr, S. I., Gao, Y., Prior, J. C. Poliquin, S. Towheed, T., Anastassiades, T., & CaMos Research Group. 2007. The association between body mass index and health-related quality of life: data from CaMos, a stratified population study. Quality of life research 16 (10): 1595 – 1603.

Hotamisligil, G. S., Shargill, N.S. & Spiegelman, B.M. 1993. Adipose expression of tumor necrosis factor-α: Direct role in obesity-linked insulin resistance. Science 259 (5091): 87 – 91.

Hotamisligil, G. S., Arner, P., Caro, J. F., Atkinson, R. L. & Spiegelman, B. M. 1995. Increased adipose tissue expression of tumor necrosis factor-α in human obesity and insulin resistance. Journal of Clinical Investigation 5: 2409 – 2415.

Hotamisligil, GS. Inflammation and metabolic disorders. 2006. Nature 444: 860-7.

Huang, P. L. 2009. A comprehensive definition for metabolic syndrome. Disease models & mechanisms 2 (5 – 6): 231 – 237.

Hutchinson, W. L., Koenig, W., Fröhlich, M., Sund, M., Lowe, G., D., O., & Pepys, M. B. 2000 Immunoradiometric assay of airculating C-reactive protein: age-related values in the adult general population. Clinical chemistry 46 (7): 934 – 938.

Häkkinen, A., Kukka, A., Onatsu, T., Järvenpää, S., Heinonen, A., Kyröläinen, H., Tomas-Carus, P., & Kallinen, M. 2009. Health related quality of life and physical activity in persons at high risk for type 2 diabetes. Disability and rehabilitation 31 (10): 799 – 805.

Häkkinen, A., Rinne, M., Vasankari, T., Santtila, M., Häkkinen, K., & Kyröläinen, H. 2010. Association of physical fitness with health-related quality of life in Finnish young men. Health and quality of life outcomes 8 (15): 1 – 8.

Häkkinen, K., & Häkkinen, A. 1995. Neuromuscular adaptation during intensive strength training in middle-aged and elderly males and females. Electromyography and clinical neurophysiology 35 (3): 137 – 147.

Ihalainen, J. K., Schumann, M., Eklund, D., Hämäläinen, M., Moilanne, E., Paulsen, G., Häkkinen, K., & Mero, A. A. 2017. Combined aerobic and resistance training decreases inflammation markers in healthy men. Scandinavian journal of medicine & science in sports 28 (1): 40 – 47.

Järvisalo, M. J., Harmoinen, A., Hakanen, M., Paakkurnainen, U., Viikari, J., Hartiala, J., Lehtimäki, T., Simell, O. & Raitakari, O. T. 2002. Elevated serum C-reactive protein levels and arterial changes in healthy children. Arteriosclerosis, thrombosis, and vascular biology 22 (8): 1323 – 1328.

Kaplan, R. M., & Bush, J. W. 1982. Health-related quality of life measurement for evaluation research and policy analysis. *Health Psychology 1*(1): 61 – 80.

Karimi, M. & Brazier, J. 2016. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? Pharmacoeconomics 34 (7): 645 – 649.

Kern, P. A., Ranganathan, S., Li, C., Wood, L. & Ranganathan, G. 2001. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. American Journal of physiology: endocrinology and metabolism 280 (5): E745 – E751.

Koenig, W., Sund, M., Fröhlich, M., Fischer, H.-G., Löwel, H., Döring, A., Hutchinson, W. L., & Pepys, M. B. 1999. C-reactive protein, a sensitive marker of inflammation, predicts future risk

of coronary heart disease in initially healthy middle-aged men. Results for the MONICA (Monitoring Trends and Determinants in Cardiovascular disease) Augsburg cohort study, 1984 to 1992. Circulation 99 (2): 237 – 242.

Koivumaa-Honkanen, H., Honkanen, R., Viinamäki, H., Heikkilä, K., Kaprio, J., & Koskenvuo, M. 2000. Self-reported Life Satisfaction and 20-Year Mortality in Healthy Finnish Adults. The American Journal of Epidemiology 152 (10): 983 – 991.

Koivumaa-Honkanen, H., Honkanen, R., Viinamäki, H., Heikkilä, K., Kaprio, J., & Koskenvuo, M. 2001. Life satisfaction and suicide: A 20-year follow-up study. The American Journal of Psychiatry 158 (3): 433 – 439.

Koivumaa-Honkanen, H., Kaprio, J., Honkanen, R., Viinamäki, H., Heikkilä, & Koskenvuo, M. 2004. Life satisfaction and depression in a15-year follow-up study of healthy adults. The American Journal of Psychiatry 158 (3): 433 – 439.

Korhonen, P.E., Seppala, T., Jarvenpaa, S., Kautiainen, H. 2014. Body mass index and health-related quality of life in apparently healthy individuals. Quality of Life Research 23 (1): 67 – 74.

Koskinen, S., Lundqvist, A., & Ristiluoma, N. 2012. Terveys, toimintakyky ja hyvinvointi Suomessa 2011. Terveyden ja hyvinvoinnin laitos, raportti 68 / 2012.

Kosola, J., Vaara, J. P., Ahotupa, M., Kyröläinen, H., Santtila, M., Oksala, N., Atalay, M. & Vasankari, T. 2013. Elevated concentrations of oxidized LDL together with poor cardiorespiratory and abdominal muscle fitness predicts metabolic syndrome in young men. Metabolism: Clinical and Experimental 62 (7): 992 – 999.

Kozak, A. T., Daviglus, M. L, Chan, C., Kiefe, C. I., Jacobs Jr, D. R., & Liu, K. 2011. Relationship of body mass index in young adulthood and health-related quality of life two decades later: the Coronary Artery Risk Development in Young Adults study. International Journal of Obesity 35 (1): 134 – 141.

Kruger, J., Bowles, H. R., Jones, D. A., Ainsworth, B. E., & Kohl III, H. W. 2007. Health-related quality of life, BMI and physical activity among US adults (≥ 18 years): National Physical Activity and Weight Loss Survey. International Journal of Obesity 31 (2): 321 – 327.

Laaksonen, D. E., Niskanen, L., Nyyssönen, K., Punnonen, K., Tuomainen, T.-P., Valkonen, V.-P., Salonen, R. & Salonen, J. T. 2004. C-reactive protein and the development if the metabolic syndrome and diabetes in meddle-aged men. Diabetologia 47 (8): 1403 – 1410.

Laaksonen, D. E., Niskanen, L., Nyyssönen, K., Punnonen, K., Tuomainen, T., & Salonen, J. 2005. C-reactive protein in the prediction of cardiovascular and overall mortality in middle-aged men: a population-based cohort study. European Heart Journal 26 (17): 1783 – 1789.

Larsen, G. L. & Henson, P. M. 1983. Mediators of inflammation. Annual Review of Immunology 1: 335–359.

Larsson, U., Karlsson, J., & Sullivan, M. 2002. Impact of overweight and obesity on health-related quality of life - A Swedish population study. International Journal of Obesity 26 (3): 417 – 424.

Lavie, C. J., Milani, R. V., & Ventura, H. O. 2009. Obesity and cardiovascular disease. Risk factor, Paradox, and inpact of weight loss. Journal of the American College af Cardiology 53 (21): 1925 – 1932.

Lekander, M., Elofsson, S., Neve, I.-M., Hansson, L.-O., & Unden, A.-L- 2004. Self-rated health is related to levels of circulating cytokines. Psychosomatic medicine 66 (4): 559 – 563.

Lemieux, I., Pascot, A., Prud'homme, D., Alméras, N., Bogaty, P., Nadeau, A., Bergoren, J., & Després, J-P. 2001. Elevated C-reactive protein. Another component of the athrethrombotic profile of abdominal obesity. Arteriosclerosis, thrombosis, and vascular biology 21 (6): 961 – 967.

Leshem-Rubinow, E., Shenhar-Tsarfaty, S., Milwidsky, A., Toker, S., Shapira, I., Berliner, S., Benyamini, Y., Melamed, S., & Rogowski, O. 2015. Self-rated health is associated with elevated C-reactive protein even among apparently healthy individuals. The Israel medical association journal 17 (4): 213 – 218.

Libby, P. 2002. Inflammation in atherosclerosis. Nature 420: 868 – 874.

Linkov, F., Burke, L. E., Komaroff, M., Edwards, R. P., Lokshin, A., Styn, M. A., Tseytlin, E., Freese, E., & Bovbjerg, D. H. 2014. An exploratory investigation of links between changes in adipokines and quality of life in individuals undergoing weight loss interventions possible implications for cancer research. Gynecologic Oncology 133 (1): 67 – 72.

Liu, X., Jones, G. W., Choy, E. H., & Jones, S. A. 2016. The biology behind interleukin-6 targeted interventions. Current opinion if rheumatology 28 (2): 152 – 160.

Loef, M. & Walach, H. 2013. Midlife obesity and dementia: Meta-analysis and adjusted forecast of dementia prevalence in the United States and China. Obesity 21 (1): E51 – E55.

Lumley, T. 2004. Analysis of complex survey samples. Journal of Statistical software 9(1): 1 – 19.

Lumley, T. 2014. Survey: analysis of complex survey sampless. R package version 3.30.

Marques-Vidal, P., Bochud, M., Bastardot, F., Lüscher, T., Ferrero, F., Gaspoz, J.-M., Paccaud, F., Urwyler, A., von Känel, R., Hock, C., Waeber, G., Preisig, M., & Vollenweider, P. 2012. Association between Inflammatory and Obesity Markers in Swiss population based sample. Obesity Facts 5 (5): 734 – 744.

Massida, M., Cugusi, L., & Mathieu, A. 2015. Physical activity levels and Health-related quality of life in young Italian population. The Journal of sports medicine and physical fitness 55 (5): 506 – 512.

Mathur, N. & Pedersen, B. K. 2008. Exercise as a mean to control low-grade systemic inflammation. Hindawi Publishing Corporation. Mediators of Inflammation: 1 – 6.

Mohamed-Ali, V., Goodrick, S., Rawesh, A., Katz, D. R., Miles, J. M., Yudkin, J. S., Klein, S., & Coppack, S. W. 1997. Subcutaneous Adipose Tissue Releases Interleukin-6, But not tumor necrosis factor α, in vivo. Journal of clinical endocrinology and metabolism 82 (12): 4196 – 4200.

Moons, P. 2004. Why call it health-related quality of life when you mean perceived health status? European Journal of Cardiovascular Nursing 3 (4): 275 – 277.

Moore, K. J. & Tabas. I. 2011. Magrophages in the pathogenesis of atherosclerosis. Cell 145 (3); 341 – 355.

Myint, P. K., Luben, R. N., Surtees, P. G., Wainwright, N. W., Welch, A. A., Bingham, S. A., Day, N. E., Wareham, N. J., & Khaw, K. T. 2006. Relation between self-reported physical functional health and chronic disease mortality in men and women in the European Prospective Investigation into Cancer (EPIC-Norfolk) a prospective study. Annals of epidemiology 16 (6): 492 – 500.

Möller, K., Ostermann, A. I., Rund, K., Thoms, S., Blume, C., Stahl, F., Hahn, A., Schebb, H. & Schuchardt, J. P. 2016. Influence of weight reduction on blood levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and oxylipins in obese subjects. Prostaglandins, Leukotrienes and Essential Fatty Acids 106: 39 – 49.

Naess, H, & Nylund, H. 2013. Poor health-related quality of life is associated with long-term mortality in young adults with cerebral infarction. Journal of Stroke and cerebrovascular diseases 22 (7): e79 – e83.

Nicklas, B. J., Beavers, D. P., Mihalko, S. L., Miller, G. D., Loeser, R. F., & Messier, S. P. 2016. Relationship of Objectively-Measured Habitual Physical Activity to Chronic Inflammation and Fatigue in middle-aged and older adults. Journals of Gerontology: Medical Sciences 71 (11): 1437 – 1443.

Nilsonne, G., Lekander, M., Åkerstedt, T., Axelsson, J., & Ingre, M. 2016. Diurnal Variation of Circulating Interleukin-6 in humans: A meta-analysis. PLoS One 11 (11): e0165799.

Nimmo, M. A., Leggate, M, Viana, J. L., & King, A. 2013_The effect of physical activity on mediators of inflammation. Diabetes, Obesity and Metabolism 15 (suppl. 3): 51 – 60.

Nishimura, S., Manabe, I., Nagasaki, M., Eto, K., Yamashita, H., Ohsugi, M., Otsu, M., Hara, K., Ueki., K., Sugiura, S., Yoshimura, K., Kadowaki., T. & Nagai, R. 2009. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nature Medicine 15: 914 – 920.

Odegaard, A. O., Jacobs Jr, D. R., Sanchez, O. A., Goff Jr, D. C., Reiner, A. P. & Gross, M. D. 2016. Oxidative stress, inflammation, endothelial dysfunction and incidence of type 2 diabetes. Cardiovascular Diabetology 15 (51): 1 – 12.

Onyike, C. U., Crum, R. M., Lee, H. B., Lyketsos, C. G. & Eaton, W. W. 2003. Is obesity associated with major depression? Results from the third National Health and Nutrition examination survey. American Journal of Epidemiology 158: 1139 – 1147.

Ostrowski, K., Rohde, T., Zacho, M., Asp, S., & Pedersen, B. K. 1998. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. Journal of Physiology 508 (3): 949 – 953.

Ouchi, N., Parker, J. L., Lugus, J. J. & Walsh, K. 2011. Adipokines in inflammation and metabolic disease. Nature Reviews Immunology 11 (2): 85 – 97.

Paananen, M., Taimela, S., Auvinen, J., Tammelin, T., Zitting, P., & Karppinen J. 2011. Impact of self-reported musculoskeletal pain on health-related quality of life among young adults. Pain medicine 12 (1): 9 – 17.

Park, H. S., Park, J. Y., & Yu, R. 2005. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-α and IL-6. Diabetes Research and Clinical Practice 69 (1): 29 – 35.

Pedersen, B. K., & Febbraio, M. A. 2008. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiological reviews 88(4): 1379 – 1406.

Pedersen, B. K., & Fischer, C. P. 2007. Beneficial health effects of exercise – the role of IL-6 as a myokine. Trends in pharmacological science 28(4): 152 – 156.

Pedersen, M., Bruunsgaard, H., Weis, N., Hendel, H. W., Andreassen, B. U., Eldrup, E., Dela, F., & Pedersen, B. K. 2003. Circulating levels of TNF-alpha and IL-6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes. Mechanisms of ageing and development 124 (4): 495 – 502.

Pepys, M. B., & Hirschfield, G. M. 2003. C-reactive protein: a critical update. The Journal of Clinical Investigation 111 (12): 1805 – 1812.

Petersen, A. M. W., & Pedersen, B. K. 2005. The anti-inflammatory effect of exercise. Journal of applied physiology 98 (4): 1154 – 1162.

Phillips, S.M., Green, H.J., Tarnopolsky, M. A., Hill, R.E., & Grant, S. M. 1996. Effects of training duration on substrate turnover and oxidation during exercise. Journal of applied physiology 81(5): 2182 – 2191.

Pihlainen, K., Santtila, M., Ohrankämmen, O., Ilomäki, J., Rintakoski, M., & Tiainen, S. 2011. Puolustusvoimien kuntotestaajan käsikirja. Edita Prima Oy 2. painos.

Pischon, T., Boeing, H., Hoffman, K., Bergmann, M., Schulze, M. B., Overvad, K., et al. 2008. General and abdominal adiposity and risk of death in Europe. The New England Journal of Medicine 359 (20): 2105 – 2120.

Plaisance, E. P., & Grandjean, P. W. 2006. Physical Activity and High-Sensitivity C-reactive protein. Sports Medicine 36 (5): 443 – 458.

Pradhan, A. D., Manson, J. E., Rossouw J. E., Siscovick, D. S., Mouton, C . P., Rifai, N., Wallace, R. B., Jackson, R. D., Pettinger, M. B. & Ridker, P. M. 2002. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease. Prospective analysis from the Women's Health Initiative Observational Study. JAMA 288: 980 – 987.

Poupart, P., Vandenabeele, P., Cayphas, S., Van Snick, J., Haegeman, G., Kruys, V,, Fiers, W. & Content, J. 1987. B cell growth modulating and differentiating activity of recombinant human 26-kd protein (BSF-2, HuIFN-beta 2, HPGF). The EMBO Journal 6 (5): 1219-1224.

Puig, J. G. & Martinez, M. A. 2008. Hyperuricemia, gout and metabolic syndrome. Current Opinion in Rheumatology 20: 187 – 191.

R Core Team. 2015. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/

Revicki, D. A., Osoba, D., Fairclough, D., Barofsky, I., Berzon, R., Leidy, N. K., & Rothman, M. 2000. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. Quality of Life Research 9 ((): 887 – 900.

Ridker, P. M., Cushman, M., Stampfer, M. J., Tracy, R. P. & Hennekens, C. H. 1997. Inflammation, Aspirin, and the risk of cardiovascular disease in apparently healthy men. The New England Journal of Medicine 336: 973 – 979.

Ridker, P. M., Hennekens, C. H., Buring, J. E. & Rifai, N. 2000A. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in Women. The New England Journal of Medicine 342: 836 - 43.

Ridker, P. M., Rifai, N., Stampfer, M. J. & Hennekens, C. H. 2000B. Plasma Concentration of Interleukin-6 and the Risk of Future Myocardial Infarction Among Apparently Healthy Men. Circulation 101: 1767-1772).

Ridker, P. M. 2016. From C-reactive protein to Interleukin-6 to Interleukin-1. Circulation Research 118: 145 – 156.

Roberts, R., Hemingway, H., & Marmot, M. 1997. Psychometric and clinical validity of the SF-36 General Health Survey in the Whitehall II Study. British Journal of Health Psychology 2 (4): 285 – 300.

Ross, R. 1999. Atherosclerosis - an inflammatory disease. The New England journal of medicine 340 (2): 115 – 126.

Sadetsky, N., Hubbard, A., Carroll, P. R., & Satariano, W. 2009. Predictive value of serial measurements of quality of life on all-cause mortality in prostate cancer patients: data from CaPSURE^{TM} (cancer of the prostate strategic urologic research endeavor) database. Quality of life research 18 (8): 1019 – 1027.

Sakkinen, P., Abbott, R. D., Curb, J. D., Rodriguez, B. L., Yano, K., & Russell, P. T. 2002. C-reactive protein and myocardial infarction. Journal of clinical epidemiology 55 (5): 445 – 451.

Santtila, M., Häkkinen, K., Pihlainen, K., & Kyröläinen H. 2013. Comparison between direct and predicted maximal oxygen uptake measurement during cycling. Military medicine 178 (2): 234 – 238.

Schaper, F., & Rose-John, S. 2015. Interleukin-6 Biology, signaling and strategies of blockade. Cytokine & growth factor reviews 26(5) : 475 – 487.

Shanahan, L., Copeland, W. E., Worthman, C. M., Erkanli, A., Angold, A., & Costello, E. J. 2013. Sex-differentiated changes in C-reactive protein from ages 9 to 21: The contributions of BMI and physical/sexual maturation. Psychoneuroendocrinology 38 (10): 2209 – 2217.

Shanahan, L., Bauldry, S., Freeman, J., & Bondy, C. L. 2014. Self-rated health and C-reactive protein in young adults. Brain, behavior, and immunity 36: 139 – 146.

Shine, B., de Beer, F. C., & Pepys, M. B. 1981. Clinica chimica acta; international journal of clinical chemistry 117 (1): 12 – 23.

Shoelson, S. E., Lee, J. & Goldfine, A. B. 2006. Inflammation and insulin resistance. The Journal of Clinical Investigation 116: 1793 – 1801.

Siegel, A. J., Stec, J. J., Lipinska, I., Van Cott, E. M., Lewandrowski, K. B., Ridker, P. M., & Tofler, G. H. 2001. Effect of marathon running on inflammatory and hemostatic markers. The American Journal of Cardiology 88 (8): 918 – 920.

Slagter, S. N., van Vliet-Ostaptchouk, J. V., van Beek, A. P., Keers, J. C., Lutgers, H. L., van der Klauw, M. M-, & Wolffenbuttel, B. H. 2015. Health-Related Quality of Life in Relation to Obesity Grade, Type 2 Diabetes, Metabolic Syndrome and Inflammation. PLoS One 10 (10): 1 – 17.

Sloan, R. A., Sawada, S. S., Martin, C. K., Church, T., & Blair, S. N. 2009. Associations between cardiorespiratory fitness and health-related quality of life. Health and Quality of life outcomes 7 (47): 1 – 5.

Steensberg, A., Fischer, C. P., Keller, C., Møller, K., & Pedersen, B.K. 2003. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. American journal of physiology – endocrinology and metabolism 285(2 48-2), pp. E433 – E437.

Steptoe, A., O'Donnell, K., Badrick, E., Kumari, M. & Marmot, M. 2008. Neuroendoctine and inflammatory factors associated with positive affect in healthy men and women. American Journal of Epidemiology 167 (1): 96 - 102.

Suárez Krabbe, K., Pedersen, M., & Bruunsgaard, H. 2004_Inflammatory mediators in the elderly. Experimental gerontology 39 (5): 687 – 99.

Sörensen, L., Honkalehto, S., Kallinen, M., Pekkonen, M., Louhevaara, V., Smolander, J, & Alén, M. 2007. Are Cardiorespiratory Fitness and Walking Performance Associated with Self-Reported Quality of Life and Work Ability. International journal of occupational medicine and environmental health 20 (3): 257 – 264.

Terwee, C. B., Bot, S. D. M., de Boer, M. R., van der Windt, D. A. W, M., Knol, D. L., Dekker, J., Bouter, L. M., & de Vet, H, C, W. 2007. Quality criteria were proposed for measurement properties of health status questionnaires. Journal of Clinical Epidemiology 60 (1): 34 – 42.

Testa, N. A., & Simonson, D. C. 1996. Assessment of Quality-of-Life Outcomes. The New England Journal of Medicine 334 (13): 835 – 40.

The Emerging Risk Factors Collaboration. 2012. C-reactive protein, fibrinogen, and cardiovascular disease prediction. The New England Journal of Medicine 367 (14): 1310 – 1320.

The GBD 2015 Obesity Collaborators. 2017. Health effects of overweight and obesity in 195 countries over 25 years. The New England Journal of Medicine 367 (1): 13 – 27.

The WHOQOL Group. 1995. The World Health Organization quality of life assessment (WHOQOL) - Position paper from the World Health Organization. Social science and medicine 41 (10): 1403 – 1409.

Thijssen, E., vaan Caam, A. & van der Kraan, P.M. 2015. Obesity and osteoarthritis, more than just wear and tear - pivotal roles for inflamed adipose tissue and dyslipidemia in obesity-induced osteoarthritis. Rheumatology 54: 588 – 600.

Tillett, W. S., & Francis, T. Jr, 1930. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. Journal of Experimental Medicine 52 (4): 561 – 571.

Tsai, S. Y., Chi, L. Y., Lee, C. H., & Chu, P. 2007. Health-related quality of life as a predictor of mortality among community-dwelling older persons. European journal of epidemiology 22 (1): 19 – 26.

Truthmann, J., Mensink, G. B. M., Bosy-Westphal, A., Hapke, U., Scheidt-Nave, C., & Schienkiewitz, A. 2017. Physical health-related quality of life in relation to metabolic health

and obesity among men and women in Germany. Health and Quality of Life Outcomes 15 (1): 122.

Ul-Haq, Z., Mackay, D. F., Fenwick, E., & Pell, J. P. 2013. Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. Obesity (Silver Spring, Md.) 21 (3): E322 – E327.

United Nations World Health Organization Interim Commission. 1948. Summary report on proceedings minutes and final acts of the International Health Conference held in New York from 19 June to 22 July 1946.

Uutela, A., & Aro, A. R. 1993. Koettu ja havaittu elämänlaatu – toisiaan täydentävät näkökulmat. Duodecim 109 (17): 1507 – 1511.

Vaara, J. P., Vasankari, T., Fogelholm, M., Häkkinen, K., Santila, M., & Kymäläinen, H. 2014. Maximal Strength, Muscular Endurance and Inflammatory Biomarkers in Young Adult Men. International Journal of Sports Medicine 35 (14): 1229 – 1234.

Viljanen, T., Viitasalo J. T., & Kujala U. M. 1991. Strength characteristics of a healthy urban adult population. European Journal of Applied Physiology and occupational physiology 63 (1): 43 – 47.

Visser, M., Bouter, L. M. McQuillan, G. M., Wener, M. H. & Harris, T. B. 1999. Elevated C-reactive protein levels in overweight and obese adults. JAMA 282 (22): 2131 – 2135.

Vogl, :, Wenig, C. M., Leidl, R., & Pokhrel, S. 2012. Smoking and health-related quality of life in English general population: implications for economic evaluations. BMC Public Health 12:203.

Wang, H., Steffen, L. M., Vessby, B., Basu, S., Steinberger, J., Moran, A., Jacobs Jr, D. R., Hong, C.-P. & Sinaiko, A, R. 2011. Obesity Modifies the Relations Between Serum Markers of Dairy Fats and Inflammation and Oxidative Stress Among Adolescents. Obesity 19 (12): 2404 – 2410.

Wang, X., Bao, W., Liu, J., OuYang, Y.-Y., Wang, D., Rong, S., Xiao, X., Shan, Z.-L., Zhang, Y., Yao, P. & Liu, L.-G. 2013. Inflammatory markers and risk of type 2 diabetes. Diabetes Care 36: 166 – 175.

Wang, Y., Chen, X., Song, Y, Caballero, B. & Cheskin, L. J. 2008. Association between obesity and kidney disease - A systematic review and meta-analysis. Kidney International 73: 19 – 33.

Ware, J. E. Jr, & Gandek, B. 1998. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. Journal of Clinical Epidemiology 51 (11): 903 – 912.

Ware, J. E. Jr, Kosinski, M., Gandek, B., Aaronson, N. K., Apolone, G., Bech, P., Brazier, J., Bullinger, M., Kaasa, S., Leplége, A., Prieto, L., & Sullivan, M. 1998. The Factor Structure of the SF-36 Health Survey in 10 Countries: Results from the IQOLA Project. Journal of Clinical Epidemiology 51 (11): 1159 – 1165.

Ware, J. E. 2000. SF-36 Health Survey Update. Spine 25 (24): 3130 – 3139.

Weber, C. & Noels, H. 2011. Atherosclerosis: current pathogenesis and therapeutic options. Nature Medicine 17: 1410 – 1422.

Weight, L. M., Alexander, D., & Jacobs, P. 1991. Strenuous exercise: analogous to the acute-phase response? Clinical Science 81 (5): 677 – 683.

Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L. & Ferrante, A. W. jr. 2003. Obesity is associated with macrophage accumulation in adipose tissue. The Journal of Clinical Investigation 112: 1796 – 1808.

Wellen, K. E. & Hotamisligil, G. S. 2005. Inflammation, stress, and diabetes. The Journal of Clinical Investigation 115: 1111 – 1119.

WHO key facts of obesity and overweight (http://www.who.int/mediacentre/factsheets/fs311/en/)

WHO Top 10 causes of death website (http://www.who.int/mediacentre/factsheets/fs310/en/)

Wärnberg, J., Nova, E., Moreno, L. A., Romeo, J., Mesana, M. I., Ruiz, J. R., Ortega, F. B., Sjöström, M., Bueno, M., Marcos, A. & the AVENA study group. 2006. Inflammatory proteins are related to total and abdominal adiposity in a healthy adolescent population: the AVENA Study1’2’3. The American Journal of Clinical Nutrition 84 (3): 505 – 512.

You, T., Arsenis, N. C., Disanzo, B. I., & LaMonte, M. J. 2013. Effects of Exercise Training on Chronic Inflammation in Obesity. Sports Medicine 43 (4): 243 – 256.

Yudkin, J. S., Stehouwer, C. D. A., Emeis, J. J. & Coppack S. W. 1999. C-reactive protein in healthy subjects: Association with obesity, insulin resistance, and endothelial dysfunction: A potential role for cytokines originating from adipose tissue? Arteriosclerosis, thrombosis, and vascular biology 19 (4): 972 – 978.

Zhou, Y., Han, W., Gong, D., Man, C., & Fan, Y. 2016. Hs-CRP in stroke: A meta-analysis. Clinica chimica acta; international journal of clinical chemistry 453: 21 – 27.

APPENDICES

APPENDIX TABLE 1. Physical Component Summary in relation to explanatory variables.

	Physical Component Summary				model	
	beta	SE	st.beta	p	r^2	p
Age						
- model 1	-0.070	0.027	-0.098	**0.010**	0.008	**0.010**
- model 2	-0.048	0.027	-0.067	0.082	0.045	< **0.001**
CRP						
- model 1	-0.413	0.120	-0.130	**0.001**	0.016	**0.001**
- model 2	-0.253	0.125	-0.080	**0.044**	0.049	< **0.001**
IL-6						
- model 1	-0.362	0.127	-0.108	**0.004**	0.010	**0.004**
- model 2	-0.247	0.126	-0.074	0.051	0.048	<**0.001**
Body composition						
Weight						
- model 1	-0.039	0.012	-0.117	**0.002**	0.012	**0.002**
- model 2	0.014	0.029	0.041	0.647	0.044	<**0.001**
Muscle mass						
- model 1	-0.035	0.034	-0.039	0.305	0.000	0.305
- model 2	0.060	0.041	0.064	0.145	0.046	<**0.001**
Fat mass						
- model 1	-0.087	0.020	-0.162	<**0.001**	0.025	<**0.001**
- model 2	-0.105	0.045	-0.194	**0.020**	0.052	<**0.001**
Fat %						
- model 1	-0.089	0.023	-0.149	<**0.001**	0.021	<**0.001**
- model 2	-0.075	0.036	-0.124	**0.037**	0.055	<**0.001**
Waist circumference						
- model 1	-0.070	0.017	-0.159	<**0.001**	0.024	<**0.001**
- model 2	-0.056	0.041	-0.127	0.172	0.045	<**0.001**
Blood pressure						
Systolic						
- model 1	-0.015	0.015	-0.037	0.339	0.000	0.339
- model 2	0.014	0.017	0.034	0.416	0,044	<**0.001**
Diastolic						
- model 1	-0.051	0.020	-0.099	**0.010**	0.008	**0.010**
- model 2	-0.018	0.021	-0.036	0.391	0.044	<**0.001**
Muscle fitness tests						
Maximal oxygen uptake						
- model 1	0.138	0.022	0.231	<**0.001**	0.052	**0.010**
- model 2	0.114	0.027	0.191	<**0.001**	0.067	< **0.001**
Standing long jump						
- model 1	0.022	0.007	0.121	**0.002**	0.013	**0.002**
- model 2	0.012	0.007	0.069	0.095	0.041	< **0.001**
Sit up number						
- model 1	0.062	0.015	0.161	<**0.001**	0.024	<**0.001**
- model 2	0.038	0.016	0.100	**0.015**	0.050	<**0.001**

Push up number						
- model 1	0.052	0.013	0.154	**<0.001**	0.022	**<0.001**
- model 2	0.038	0.013	0.113	**0.004**	0.054	**<0.001**
Muscle strength tests						
Leg press						
- model 1	0.003	0.002	0.057	0.140	0.002	0.140
- model 2	0.005	0.002	0.103	**0.012**	0.048	**<0.001**
Bench press						
- model 1	0.008	0.008	0.038	0.326	0.000	0.326
- model 2	0.015	0.009	0.069	0.084	0.048	**<0.001**
Muscle fitness index						
- model 1	0.851	0.191	0.171	**<0.001**	0.028	**<0.001**
- model 2	0.596	0.203	0.119	**0.003**	0.052	**<0.001**
Muscle strength index						
- model 1	0.258	0.199	0.050	0.196	0.001	0.196
- model 2	0.495	0.212	0.096	**0.020**	0.048	**<0.001**

model 1 – non adjusted
model 2 – adjusted for age, smoking status and body mass index
Statistically significant p-values are shown in bold.
SE = standard error, st.beta = standardized beta, r^2 = adjusted r^2

APPENDIX TABLE 2. Mental Component Summary (MCS-RANK) in relation to explanatory variables.

	Mental Component Summary				model	
	beta	SE	st.beta	p	r^2	p
Age						
- model 1	3.141	1.185	0.101	**0.008**	0.009	**0.008**
- model 2	2.525	1.231	0.081	**0.041**	0.011	**0.013**
CRP						
- model 1	10.591	5.305	0.076	**0.046**	0.004	**0.046**
- model 2	6.915	5.611	0.050	0.218	0.012	**0.015**
IL-6						
- model 1	-1.205	5.607	-0-008	0.830	-0.001	0.830
- model 2	-4.087	5.655	-0.028	0.470	0.010	**0.025**
Body composition						
Weight						
- model 1	1.291	0.549	0.089	**0.019**	0.007	**0.019**
- model 2	0.221	1.320	0.015	0.867	0.010	**0.029**
Muscle mass						
- model 1	2.345	1.496	0.060	0.117	0.002	0.117
- model 2	-0.053	1.845	-0.001	0.977	0.010	**0.029**
Fat mass						
- model 1	2.192	0.901	0.092	**0.015**	0.007	**0.015**
- model 2	1.127	2.014	0.048	**0.035**	0.011	**0.021**
Fat %						
- model 1	2.403	1.004	0.091	**0.017**	0.007	**0.017**
- model 2	1.475	1.609	0.056	0.359	0.011	**0.020**
Waist circumference						
- model 1	1.847	0.739	0.096	**0.013**	0.008	**0.013**
- model 2	-0.691	1.823	-0.036	0.705	0.013	**0.012**
Blood pressure						
Systolic						
- model 1	2.021	0.675	0.114	**0.003**	0.012	**0.003**
- model 2	1.373	0.745	0.078	0.066	0,018	**0.003**
Diastolic						
- model 1	2.305	0.862	0.102	**0.008**	0.009	**0.008**
- model 2	1.224	0.950	0.054	0.198	0.015	**0.006**
Muscle fitness tests						
Maximal oxygen uptake						
- model 1	-0.387	1.031	-0.015	0.707	-0.001	0.707
- model 2	1.531	1.244	0.058	0.219	0.012	**0.016**
Standing long jump						
- model 1	0.316	0.308	0.040	0.306	0.000	0.306
- model 2	0.728	0.331	0.091	**0.028**	0.018	**0.003**
Sit up number						
- model 1	0.446	0.668	0.026	0.505	-0.001	0.505
- model 2	1.294	0.719	0.075	0.073	0.017	**0.004**

Push up number						
- model 1	0.666	0.578	0.045	0.250	0.000	0.250
- model 2	0.999	0.599	0.067	0.096	0.016	**0.006**
Muscle strength tests						
Leg press						
- model 1	0.056	0.084	0.026	0.503	-0.001	0.503
- model 2	-0.015	0.091	-0.007	0.868	0.010	**0.027**
Bench press						
- model 1	0.122	0.370	0.013	0.741	-0.001	0.741
- model 2	-0.178	0.388	-0.019	0.647	0.013	**0.012**
Muscle fitness index						
- model 1	8.755	8.767	0.039	0318	0.008	0.318
- model 2	17.592	9.331	0.078	0.060	0.017	**0.005**
Muscle strength index						
- model 1	5.509	8.919	0.024	0.530	-0.001	0.530
- model 2	-2.684	9.684	-0.012	0.782	0.011	**0.025**

model 1 – non adjusted
model 2 – adjusted for age, smoking status and body mass index
Statistically significant p-values are shown in bold.
SE = standard error, st.beta = standardized beta, r^2 = adjusted r^2