### Jani Vaara

# Associations of Physical Activity and Physical Fitness With Cardiovascular Risk Factors in Young Men



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#### ABSTRACT

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Since the 1950s, an accumulative body of research has shown the health benefits of physical activity for many health outcomes. In particular, cardiorespiratory fitness is closely linked to health indices and mortality. However, muscular fitness, an important dimension of physical fitness, has been less studied regarding health outcomes. Therefore, the aim of the present study was to investigate how muscular endurance and maximal strength are associated with cardiovascular and inflammatory risk factors independent of cardiorespiratory fitness. In addition, the associations between different physical activity dimensions and cardiovascular risk factors and physical fitness variables were studied. The present study showed an inverse association between muscular endurance and both single and clustered cardiovascular risk factors, as well as with inflammatory biomarkers independent of cardiorespiratory fitness. Although maximal strength was not associated with any of the single or clustered cardiovascular risk factors, it was inversely associated with some of the inflammatory biomarkers. In addition, commuting physical activity was inversely associated with clustered cardiovascular risk factor, however, leisuretime and occupational physical activities showed no significant associations. Leisure-time physical activity was positively associated with many of the fitness variables, whereas commuting physical activity was associated with cardiorespiratory fitness and muscular endurance, and occupational physical activity only with grip strength. The findings from the present cross-sectional study design may indicate that muscular endurance is associated with health benefits of cardiovascular risk factors and inflammatory biomarkers, whereas maximal strength may be associated with some of the inflammatory biomarkers independent of cardiorespiratory fitness. Therefore, it is conluded that aerobic type physical activity, such as active travel to work, may elicit cardioprotective health benefits. In addition, different modalities of physical fitness, especially cardiorespiratory fitness and muscular endurance, may induce cardioprotective and anti-inflammatory effects and thereby decrease the risk of developing cardiometabolic diseases.

Keywords: muscular endurance, maximal strength, cardiorespiratory fitness, cardiovascular risk factors, inflammatory biomarkers, waist circumference

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#### **ABBREVIATIONS**

%BF Percentage body fat

analysis of variance / analysis of covariance ANOVA/ANCOVA

**BETA** beta-coefficient

Bioelectrical impedance analysis **BIA** 

Body mass index **BMI** Confidence interval CI

Commuting physical activity **CPA CRF** Cardiorespiratory fitness C-reactive protein CRP

Cardiovascular CV CVD Cardiovascular disease

Diastolic blood pressure **DBP** 

FFM Fat free mass

High density lipoprotein HDL

Interleukin-6 IL-6

LDL Low density lipoprotein Leisure-time physical activity LTPA Muscular endurance index MEI Maximal strength index MSI OPA

Occupational physical activity

OR Odds ratio

Correlation coefficient r Randomized controlled trial **RCT** SBP Systolic blood pressure Standard deviation SD TG Triglycerides

TNF-alpha Tumour-necrosis factor alpha

WC Waist circumference VO<sub>2</sub>max Maximal oxygen uptake

XS Cross-sectional

#### LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original articles, which are referred to in the text by their roman numerals.

- I Vaara JP, Kyröläinen H, Fogelholm M, Santtila M, Häkkinen A, Häkkinen K, Vasankari T (2014). Associations of leisure-time, commuting and occupational physical activity with physical fitness and cardiovascular risk factors in young men. *Journal of Physical Activity and Health* 11: 1482-91.
- II Vaara JP, Fogelholm M, Vasankari T, Santtila M, Häkkinen K, Kyröläinen H (2014). Associations of maximal strength and muscular endurance with cardiovascular risk factors. *International Journal of Sports Medicine* 35: 356-60.
- III Vaara JP, Vasankari T, Fogelholm M, Santtila M, Häkkinen K, Kyröläinen H (2014). maximal strength, muscular endurance and inflammatory biomarkers in young adult men. *International Journal of Sports Medicine* 35: 1229-34.
- IV Vaara JP, Kyröläinen H, Niemi J, Ohrankämmen O, Häkkinen A, Kocay S, Häkkinen K (2012). Associations of maximal strength and muscular endurance test scores with cardiorespiratory fitness and body composition. *Journal of Strength and Conditioning Research* 26: 2078-86.

"Eating alone will not keep a man well;	; he must also take exercise" Hippocrates (460-377 BC)

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#### 1 INTRODUCTION

It is well established from observational studies that physical activity is beneficial for health. Over the last 60 years there has been an increasing number of studies reporting beneficial associations of physical activity with many health outcomes. One of the first studies by Morris et al. (1953) revealed that sedentary bus drivers had a higher rate of mortality compared to their active counterparts, conductors. Since then many large observational studies have shown physical activity to decrease the risk of mortality, cardiovascular diseases and type 2 diabetes (e.g. Paffenbarger et al. 1978, Jeon et al. 2007, Kujala et al.1998).

The present physical activity guidelines recommend that adults should do 150 minutes of moderate-intensity or 75 minutes of vigorous intensity, or an equivalent combination of both aerobic activities a week. However, the current physical activity recommendations are not specific to any physical activity domain, but simply emphasize total physical activity, which can be divided into leisure time, commuting and occupational physical activity. Physical activity can thus be defined as an activity done in leisure time, an activity related to active travel to work or study or when running errands, or an activity, that is included in work tasks and is done during working hours. Some of the previous studies have concentrated specifically on one of the dimensions of physical activity whereas fewer studies have simultaneously examined the combined information from many dimensions of physical activity. Therefore, the aim of the present dissertation was to study the associations of leisure time, commuting and occupational physical activity with cardiovascular risk factors and physical fitness variables.

Some studies have shown that physical fitness, namely aerobic fitness, is a stronger predictor of health outcomes compared to physical activity (Blair et al. 2001, Sassen et al. 2007). To date, there is compelling evidence from observational studies to show that aerobic fitness is inversely associated with health outcomes (Blair et al. 1995, Lakka et al. 1994, Myers et al. 2002). Nevertheless, the associations of muscular fitness and health outcomes are less studied (Artero et al. 2002). Resistance training was acknowledged to be important in the physical activity guidelines in 1995 (Pate 1995), and for the first time in 2008, the

guidelines specifically recommended resistance training for a minimum of twice a week. Muscular fitness can be divided into maximal strength, muscular endurance and maximal power. There are specifically a lack of studies, that have simultaneously investigated the relationship between health outcomes and the different dimensions of muscular fitness. Nevertheless, previous observational studies report an inverse association between engagement in resistance training and cardiovascular diseases, type 2 diabetes and cardiovascular risk factors (Tanasescu et al. 2002, Grontved et al. 2012, Grontved et al. 2014). However, many of the previous study results regarding muscular fitness have not been adjusted for cardiorespiratory fitness (CRF) in order to assess whether the relationship is additive to that of CRF.

The second aim of the present dissertation was to study whether maximal strength and muscular endurance are associated with cardiovascular risk factors and inflammatory biomarkers. Moreover, these associations were studied with adjustments for one another in order to assess whether different types of fitness, namely cardiorespiratory and muscular fitness, are associated with different magnitudes of cardiovascular risk factors.

#### 2 REVIEW OF THE LITERATURE

#### 2.1 Physical activity

#### 2.1.1 Definition of physical activity

Physical activity can be defined as any bodily movement produced by skeletal muscles that requires energy expenditure (Bouchard et al. 1994). Moreover, physical activity can further be stratified to leisure-time (LTPA), commuting (CPA), occupational (OPA) and domestic physical activity. LTPA is an activity which takes place in the individual's discretionary time that leads to any substantial increase in the total daily energy expenditure. It is characterized by actions chosen on the basis of personal needs and interests. The term exercise is also extensively used in the literature. It is defined as structured and planned bodily movement done to improve or maintain one or more components of physical fitness (Archer 2011). Therefore, it is a subset of physical activity (Caspersen 1985). OPA is an activity during the working hours at a work site, and usually includes prolonged activity or sedentary bouts with sometimes adverse circumstances (e.g. heavy loading of small muscle groups, high temperature, awkward posture). In OPA the pace of the activity is often set by external factors, such as a machine or supervisor instead of the exercising individual. OPA can consist of sitting, standing, walking and lifting (Bouchard & Shephard 1994). CPA (also referred to as active travel or active commuting) includes activities undertaken when travelling to work and back home or when running errands.

#### 2.1.2 History of physical activity and health research

The first large epidemiologic study about the association of physical activity and mortality from cardiovascular disease in 1953 by Morris et al revealed that sedentary bus drivers had a higher rate of mortality compared to their active counterparts, conductors. Thereafter, Morris et al. (1953) expanded their studies

to other occupations with civil servants and found that the prevalence of heart disease was lower in postmen who walked or cycled when delivering mail compared to postal clerks who performed more sedentary work. In 1966, Morris et al. were the first to report that occupational physical activity was not only related to CVD but also its risk factors, such as blood pressure and blood lipid concentrations. In this study, they were also the first to show a dose response of physical activity with CVD. In 1973, Morris et al. reported in a cohort of middleaged men with sedentary jobs that those who reported vigorous leisure-time physical activity reduced their risk of CVD events. This finding was complemented with the same cohort with a follow-up of eight years in 1980 to show that those who engaged in vigorous LTPA had lower incidence of fatal and non-fatal CVD events than those who were sedentary (Morris et al. 1980).

Paffenbarger and Hale (1975) complemented the above mentioned studies of Morris et al. (1953, 1973, 1980) with their prospective study of over 3000 long-shoremen. They began their data collection in 1951 and reported in 1975 that the CVD death rate was lower in the most active longshoremen compared to sedentary workers. Paffenbarger et al. (1975) also found in a cohort of over 6000 long-shoremen that when divided by workers energy expenditure per work shift, the most active workers had lower rates of CVD compared to middle and low activity groups adjusted for age. In 1978, Paffenbarger et al. reported in a cohort of college alumni prospective study (known as the Harvard cohort) an inverse association between leisure-time physical activity and CVD. The low energy-expenditure group had over 60% higher risk of CVD adjusted for age compared to the high-energy expenditure group.

Since the above mentioned seminal studies many other studies have confirmed and expanded the findings of Morris et al and Paffenbarger et al. Physical activity has been shown to protect against all-cause and CVD mortality (Leon et al. 1987, Slattery et al. 1989, Berlin et al. 1990, Rosengren et al. 1997, Sofi et al. 2008, Moore et al. 2012, Sattelmair et al. 2012, Sesso et al. 2000). Moreover, Kujala et al. (1998) showed an inverse relationship between all-cause mortality and LTPA independent of genetic and familial factors.

#### 2.1.3 Recommendations for physical activity

One of the first recommendations for exercise was introduced in the publication of "Guidelines for Graded Exercise Prescription" by the American College of Sport Medicine (ACSM) in 1975 and later ACSM introduced their first position statement of the quantity and quality of exercise to develop and maintain fitness in healthy adults in 1978. These recommendations emphasized exercise sessions of 15-60 minutes and intensity of 50-85% of the heart rate reserve (HRR) with a frequency of 3-5 times per week. The recommendations at that time aimed to develop cardiorespiratory fitness with exercise. The revision of recommendations in 1990 stated a similar frequency and intensity of exercise, but revised the duration of exercise to 20-60 minutes. These recommendations were,

however, the first step in moving away from performance-focused fitness to include both performance and health-related aspects (Blair et al. 2004). Later in 1995, ACSM and Centers for Disease Control and Prevention recommended 30 minutes or more of moderate-intensity physical activity for healthy adults aged 18-65 on most, preferably all, days of the week (Pate 1995). The recommendations gave the possibility to accumulate intermittent short bouts (8-10 min) of physical activity totalling 30 minutes or more in order to reach the recommended amount of physical activity.

The recommendations were revised again in 2007 by the ACSM and American Heart Association (AHA) to include 30 minutes of moderate intensity physical activity on five days per week or vigorous physical activity for a minimum of 20 minutes on three days a week. For the first time, muscle strengthening activity was specifically recommended for a minimum of twice a week. In previous recommendations (Pate 1995) the inclusion of muscle strengthening was acknowledge to be important, however, no specific declaration was made. It was underlined in the recommendations in 2007 that by exercising more than the minimum, would promote additional health benefits and improve physical fitness. Furthermore, a series of short bouts of physical activity lasting at least 10 minutes of duration could account for the total amount of physical activity (Haskell et al. 2007). In 2007, physical activity recommendations were also targeted to older adults (>65 years old). These recommendations were similar to those of the ACSM/AHA recommendation for adults regarding the amount and intensity of aerobic physical activity and muscle strengthening activity. Nevertheless, the following differences existed: the intensity of aerobic activity took into account the older adult's aerobic fitness and activities that maintain or increase flexibility (two days a week for at least 10 minutes) and balance were recommended.

In 2008, Physical Activity Guidelines for Americans were introduced. The recommendations stated that adults should do 150 minutes of moderate-intensity or 75 minutes of vigorous intensity, or an equivalent combination of both aerobic activities a week. The activity can be performed in short bouts of at least 10 minutes, and preferably, throughout the week. For additional health benefits the aerobic activity should be increased to 300 minutes of moderate intensity a week or 150 minutes of vigorous aerobic activity a week, or their combination. Muscle strengthening activity was recommended twice a week at moderate or high intensity and to involve all major muscle groups. For older adults, the recommendations were similar to the previous ones by Nelson et al. (2007). For children (6-17 years), at least 60 minutes of daily moderate to vigorous physical activity was recommended.

Nowadays, there are many national physical activity recommendations. Nevertheless, they are based on the recommendations by ACSM/AHA in 2007 and Physical Activity Guidelines Advisory Committee in 2008. The Finnish national recommendations for physical activity for adults and older adults (UKK-instituutti, Käypä-hoito suositus 2010) are similar to the physical activity guidelines for Americans (2008). Nevertheless, the recommendation for children (7-18

years old) aims at a slightly higher amount (1-2 hours a day) and includes emphasis on avoiding sedentary periods of more than two hours, as well as restricting screen time (e.g. watching television) to a maximum of two hours a day (Lasten ja Nuorten Liikunnan Asiantuntijaryhmä 2008). In 2010, the World Health Organisation (WHO) also launched Global Recommendations on Physical activity for Health. The recommendations do not differ from those introduced by ACSM/AHA in 2007.

In other countries, new guidelines have been introduced during recent years. Canadian guidelines for physical activity were released in 2011 (Tremblay et al. 2011). The recommendations were stratified for children (aged 5-11 years), youths (aged 12-17 years), adults (18-64 years) and older adults (aged ≥ 65 years). The guidelines recommend for children and youths at least 60 minutes of moderate- to vigorous-intensity physical activity per day so that vigorous-intensity activities and muscle strengthening activies should both be done at least 3 days per week. Recommendations for adults and older adults did not differ from those of the previous recommendations (Haskell et al. 2007, Nelson et al. 2007). The recent national recommendations in Australia (2014) categorized physical activity recommendations for children aged 0-5 years, and, physical activity and sedentary behaviour guidelines for 5-12 years olds, young people (13-17 years old), adults (18-65) and for older adults (>65 years). The recommended amount of physical activity for adults was doubled compared to previous guidelines, now suggested to consist of 150-300 minutes moderate or 75-150 minutes vigorous intensity physical activity. Australia was also one of the first nations to include avoidance of sedentary behaviour in their guidelines (Australia's Physical Activity and Sedentary Behaviour Guidelines 2014).

#### 2.2 Physical fitness

#### 2.2.1 Definition of physical fitness

Physical fitness is defined as a set of attributes that individuals have and/or achieve (Caspersen et al. 1985). Physical fitness is primarily determined by physical activity behaviour, especially activity done in recent weeks or months (Blair et al. 2001). There is also a genetic contribution to physical fitness, however, genetics is likely to account for less variation than lifestyle behaviour (Bouchard et al. 1997). The components of physical fitness are either health- or skill-related. Health-related physical fitness can be categorized into cardiorespiratory fitness, muscular endurance, maximal strength, body composition and flexibility (Caspersen et al. 1985).

Cardiorespiratory fitness is an ability of the circulatory and respiratory systems to supply the fuel during sustained physical activity and to eliminate fatigue products after supplying fuel. Muscular fitness can be stratified to muscular endurance, maximal strength and muscle power (explosive strength).

Muscular endurance is an ability of muscle groups to exert external force for many repetitions or successive exertions, whereas maximal strength is defined as the amount of external force that muscle can exert. Muscle power refers to an ability to produce maximal, dynamic contraction of a single muscle or muscle group in a short period of time (Caspersen 1985, Artero et al. 2012.)

#### 2.2.2 History of physical fitness and health research

A major contribution to the field of physical fitness and health research has been made by the Cooper Clinic, USA in the Aerobics Center Longitudinal studies (ACLS). One of the first cross sectional (Cooper et al. 1976, Gibbons et al. 1983) and prospective (Blair et al. 1983) studies from the Cooper Clinic revealed that physical fitness, notably cardiorespiratory fitness, was inversely associated with selected cardiovascular risk factors. Similarly, low physical fitness increased the risk of hypertension compared to high fitness individuals (Blair et al. 1984). In the same decade other study groups expanded knowledge about the inverse association between CRF and cardiovascular as well as all-cause mortality (Bruce et al. 1983, Degre et al. 1987, Ekelund et al. 1988, Lie et al. 1985, Peters et al. 1983, Slattery et al. 1987, Sobolski et al. 1987, Wilhelmsen et al. 1981). Further prospective ACLS study results showed that cardiorespiratory fitness was inversely associated with all-cause mortality in men and women (Blair et al. 1989), hypertensive (Blair et al. 1991), hyperglycaemic (Kohl et al. 1992), individuals with metabolic syndrome (Katzmarzyk et al. 2004) and in healthy and unhealthy individuals (Blair et al. 1995, Blair et al. 1996). From the time of these early study findings these results have been replicated by many other studies (e.g. Lakka et al. 1994, Myers et al. 2002, Laukkanen et al. 2001, Gupta et al. 2011).

There is now a convincing body of evidence from observational studies showing the beneficial association between cardiorespiratory fitness and different health outcomes. Kodama et al. (2009) showed in their meta-analysis that cardiorespiratory fitness was inversely associated with all-cause mortality and CVD events. They executed a dose-response analysis and found that 1-metabolic equivivalent (MET) higher aerobic capacity was related to 13-15% lowered risk of all-cause mortality and CVD events (Kodama et al. 2009). In addition, Kokkinos et al. (2010) found an inverse relationship between cardiorespiratory fitness and all-cause mortality in older men in their prospective study. Studies have also shown cardiorespiratory fitness to be inversely associated with incidence of type 2 diabetes (Carnethon et al. 2009) and prevalence of cardiovascular risk factors (Sassen et al. 2009). Moreover, cardiorespiratory fitness has been shown to be more strongly associated with CVD than physical activity (Blair et al. 1989, Lakka et al. 1994).

There is now compelling evidence from observational studies for the beneficial effect of cardiorespiratory fitness with health outcomes across gender, age, healthy individuals and different patient groups, as well as for normal-, overweight and obese individuals. Conversely, the association between muscular

fitness and health outcomes is less well established. However, within the last decade, there have been an increasing number of prospective studies, which have shown an inverse association between maximal strength and mortality. Nevertheless, most of them have been conducted with elderly subjects (Phillips et al. 1986, Laukkanen et al. 1995, Al Snih et al. 2002, Rantanen et al. 2003, Newman et al. 2006, Rolland et al. 2006, Gale et al. 2007, Swallow et al. 2007, Buchman et al. 2008) and only a few with middle-aged (Ruiz et al. 2008, Ruiz et al. 2009), younger study populations (Ortega et al. 2013, Silventoinen et al. 2009), or with different patient groups (Artero et al. 2011, Hulsmann et al. 2004). Moreover, most of these studies have assessed maximal strength using grip strength and only a few have used tests with the involvement of larger muscle groups (e.g. leg press or knee torque and bench press) (Swallow et al. 2007, Silventoinen et al. 2009, Ortega et al. 2012).

In addition, regarding mortality as an outcome, only the study by Katzmarzyk et al. (2002) have used cardiorespiratory fitness as a confounding factor to establish whether the association is independent of aerobic fitness. In their study, the number of sit-ups that could be performed was inversely related to mortality, whereas grip strength and number of push-ups were not, after adjustment for aerobic fitness. There are only a few cross sectional and prospective studies about the association between strength and prevalence or incidence of cardiovascular disease risk factors (Jurca et al. 2004, Jurca et al. 2005, Wijndaele et al. 2007, Maslow et al. 2010).

#### 2.3 Cardiovascular risk factors and inflammatory biomarkers

Cardiovascular risk factors that increase the risk of deveploping cardiovascular diseases can be classified as behavioral and metabolic risk factors. Behavioral risk factors include physical inactivity, smoking, alcohol use and unhealthy diet. Metabolic risk factors include hypertension, raised blood glucose and lipids (cholesterol, triglycerides), and obesity as well as inflammatory biomarkers. The conventional and clinically used metabolic cardiovascular risk factors most often include total cholesterol, LDL, HDL, triglycerides, blood pressure and fasting glucose. Besides behavioral and metabolic risk factors there are other risk factors such as inherited genetic disposition, age and psychological factors (e.g. stress, depression) (Mendis et al. 2011).

LDL is a major risk factor for the development of atherosclerosis (Nicholls & Young 2009) The majority of the cholesterol is bound to LDL in the blood, and when there is an excessive amount of LDL, it starts to accumulate. Further, in the arterial wall, there may be an interaction with cells, where accumulated LDL is oxidized and further transformed in the foam cells formed in atherosclerotic plaque (Nicholls & Young 2009). HDL lipoproteins are the most dense and smallest lipid particles, which bring cholesterol from arterial walls and transport it to the liver to be further metabolized. HDL lipoproteins are also

anti-inflammatory, antithrombotic and antioxidant. In addition, HDL may stabilize endothelial function. Therefore, a high concentration of HDL has been considered to be cardioprotective, whereas a low concentration is potentially atherogenic (Nicholls & Young 2009). Triglycerides are formed of glycerol with three fatty acids. Triglycerides may only be weakly atherogenic independently but when they co-exist with high levels of LDL or low levels of HDL, they increase the risk substantially (Nicholls & Young 2009). In general, the clustering of CVD risk factors increases the risk of CVD (Berenson et al. 1998).

Blood pressure refers to the pressure in the arterial walls resulting from the cardiac output, which acts in a pulsatile manner. Systolic blood pressure refers to the highest and diastolic blood pressure to the lowest pressure during the contraction-cycle of the heart muscle. Hypertension refers to a condition where blood pressure is chronically elevated. The elevated arterial pressure is associated with total peripheral resistance. Hypertension is a major risk factor for the development of atherosclerotis, and therefore poses a risk of premature CV mortality as well. In hypertension, the increased risk for CVD is associated with endothelial dysfunction and altered function of the autonomic nervous and renin-angiotensin-aldosterone systems (Frohlich & Venture 2009).

Fasting plasma glucose is also widely clinically used in the assessment of CV health. Abnormal glucose regulation and function exist in type 2 diabetes. However, between normal glucose homeostasis and type 2 diabetes, there are, defined metabolic conditions such as impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT), also referred to as prediabetes. IFG and IGT are not clinical entities by themselves but rather risk categories for the development of type 2 diabetes. IFG, IGT and type 2 diabetes are diagnosed based on values of fasting glucose and, when possible, with 2-hour post glucose load in an oral glucose tolerance test. IFG and IGT increase the risk of CVD and type 2 diabetes. Among other severe complications, type 2 diabetics are at increased risk of cardiovascular, peripheral vascular and cerebrovascular diseases. (Alberti et al. 1999).

Inflammation is a protective physiological response to an acute infectious stimulus. Furthermore, a low-grade inflammation, which refers to chronically but modestly elevated levels of inflammation in the circulation or in other tissues, is suggested to be associated with the development of CVD (Libby et al. 2002, Ridker et al. 2000, The Emerging Risk Factor Collaboration 2012). Low-grade inflammation has shown to be positively associated with age, smoking, obesity and type 2 diabetes, and inversely with physical activity and fitness (Pedersen 2006). There are several inflammatory factors, among them the most frequently measured C-reactive protein (CRP) and interleukin-6 (IL-6), which have been suggested to add to prognostic information provided by traditional cardiovascular risk factors (Licastro et al. 2005). C-reactive protein is an acute phase reactant, which is mainly produced by hepatocytes in the liver. The production of CRP is mainly exhibited by IL-6, but also by IL-1 and TNF-alpha (Casas et al. 2008). IL-6 is produced by activated T helper cells, fibroblasts and macrophages (Gleeson & Bosch 2013), but it is also considered to be a myokine

(cytokine produced by muscle contractions), which has anti-inflammatory effects (Pedersen 2006). TNF-alpha is produced by monocytes, T-cells, B-cells and natural killer cells (Gleeson & Bosch 2013). However, it has been suggested that the circulating TNF-alpha is produced by adipose tissue. TNF-alpha may be an important mediator linking insulin resistance to CV diseases. Furthermore, TNF-alpha and IL-6 induce lipolysis but only IL-6 may induces fat oxidation. (Pedersen 2006).

#### 2.4 Physical activity and health

#### 2.4.1 Leisure-time physical activity

As discussed earlier, there is a convincing body of evidence to show from observational studies that LTPA is inversely related to different health outcomes. Recent reviews of prospective studies concluded that LTPA reduces the risk of CVD (Li & Siegrist 2012), metabolic syndrome (He et al. 2013) and type 2 diabetes (Jeon et al. 2007). Cross-sectional studies have also shown that high LTPA is associated with reduced likelihood for the clustered CVD risk factors (Ekblom-Bak et al. 2010, DuBose et al. 2005, Churilla et al. 2012), however a lack of association has also been observed (Ford et al. 2005).

Physical activity and blood pressure. Kaul et al. (1966) observed for the first time that acute aerobic exercise induced decreases in systolic and diastolic blood pressure. The reduction in blood pressure may continue up to 12-16 hours after exercise. This postexercise hypotension has been detected in a variety of study samples with the largest reductions in hypertensive individuals (Thompson et al. 2001.) In cross-sectional studies, a linear trend for lower blood pressure was observed for regularly physically active middle aged to older women after adjustments for age, BMI and insulin levels (Reaven et al. 1991). Melby et al. (1991) found among middle-aged African Americans that those who exercised two or more times per week had lower (8 mmHg) systolic blood pressure compared to those exercising once or less, adjusted for age, sex, and waist-to-hip ratio. Moreover, more recent cross-sectional studies have also shown an inverse association of LTPA with blood pressure (Barengo et al. 2006, Jakes et al. 2003), however there are some studies that have observed no association (Kronenberg et al. 2000, O`Donovan et al. 2005, Dubose et al. 2005).

In prospective studies, Paffenbarger et al. (1983) found that those individuals consuming less than 2000 kcal in their LTPA per week were 30% more likely to develop hypertension (defined in their study as 160/90 mmHg) compared to those exceeding 2000 kcal. The study sample consisted of 15 000 male graduates with a follow-up of 6-10 years. Furthermore, individuals who did not participate in vigorous LTPA had a 35% higher risk of developing hypertension independent of age. A further analysis with a follow-up of 15 years revealed an inverse association between engagement in vigorous LTPA and the risk of de-

veloping hypertension. This association was independent of age and BMI (Paffenbarger et al. 1991). In a later study, Paffenbarger et al. (1997) found that moderately vigorous LTPA reduced the risk of hypertension, whereas low intensity activity (e.g. stair climbing, walking) did not. Therefore, the intensity reduced the risk more than total energy expenditure of physical activity.

In more recent studies, Barengo et al. (2005) showed in a Finnish adult sample that with a follow-up of 11 years, men with high LTPA levels were less likely (20%) to develop hypertension. This result was independent of several confounders, e.g. age, education, smoking, alcohol intake, BMI, baseline blood pressure and other dimensions of physical activity. In another Finnish prospective study, Hu et al. (2004) showed that moderate and high physical activity were inversely associated with the risk of hypertension independent of baseline blood pressure and BMI in women. Chase et al. (2009) found in a study of ACLS a linear inverse association between LTPA and incidence of hypertension in a follow-up lasting an average of 18 years, after adjustments for smoking, alcohol intake, resting systolic pressure, BMI, baseline health status and family history of diseases.

Furthermore, previous meta-analyses of randomized controlled trials have mostly shown aerobic exercise to induce reductions in resting systolic (-3.0 - -3.8 mmHg) and diastolic (-1.5 - -2.6 mmHg) blood pressure (Cornelissen & Fagard 2005, Whelton et al. 2002, Cornelissen et al. 2013, Murtagh et al. 2015, Murphy et al. 2007). Furthermore, reduction in blood pressure has found to be pronounced among hypertensive individuals (-6.9/-4.9 mmHg) (Cornelissen & Fagard 2005). Moreover, aerobic exercise has been shown to elicit a decrease in blood pressure, almost to the same extent as improvements in diet, and to a higher extent than alcohol and sodium restriction (Dickinson et al. 2006).

Physical activity and triglycerides. A seminal study by Holloszy et al. (1964) showed for the first time that triglyceride concentration acutely decreased in response to aerobic exercise in hypertriglyceridemic men. The reduction in triglycerides occurred 18-24 hours post exercise and was maintained up to 72 hours post exercise. The reduction is largest in those with higher baseline values (Thompson et al. 2001). Previous cross-sectional studies have shown an inverse association between regular LTPA and triglycerides (Jakes et al. 2003, Kronenberg et al. 2000), whereas some have not detected associations (O`Donovan et al. 2005, Panagiotakos et al. 2003, DuBose et al. 2005, Fung et al. 2000). Most of the meta-analyses of intervention studies show reductions in triglycerides (Durstine et al. 2001, Halbert et al. 1999, Kelley et al. 2004, Kelley et al. 2005, Leon & Sanchez 2001, Lokey & Tran 1989), however not all meta-analyses support this finding (Tambalis et al. 2009). Durstine et al. (2001) report in their review based on observational findings that physically active individuals have lower triglyceride levels compared to their inactive counterparts. The range of differences in triglycerides between active and inactive participants in over the half of the studies in the review was 0.2-0.9 mmol/L and 19-50 % in relative terms (Durstine et al. 2001).

Physical activity and lipoproteins. Among lipoproteins, high-density lipoprotein cholesterol (HDL) has most consistently been shown to be associated with LTPA (Kokkinos et al. 2010). Cross-sectional studies in runners have shown an inverse relationship between HDL and running kilometres (Kokkinos et al. 1995, Williams et al. 1996). More recent cross-sectional studies have reported a similar association (Barengo et al. 2006, Jakes et al. 2003, Kronenberg et al. 2000, Panagiotakos et al. 2003, Fung et al. 2000), although contradictory findings have also been reported between LTPA and HDL (Dubose et al. 2005). Durstine et al. (2001) reported in their review that observational studies indicate 0.10-0.62 mmol/L higher HDL-concentrations and 9-59 % relative difference in those who engage in physical activity compared to their less active counterparts.

Furthermore, the evidence from intervention studies has confirmed a positive impact of aerobic exercise on HDL level in previous meta-analyses (Halbert et al. 1999, Kelley et al. 2004, Kodama et al. 2007, Leon et al. 2001, Tambalis et al. 2009, Durstine et al. 2001). However, not all meta-analyses support these findings (Kelley et al. 2005, Lokey et al. 1989). Kodama et al. (2007) reported that aerobic exercise induced a modest but significant net change (0.065 Mmol/L) in HDL concentration. They further estimated the threshold for increase in HDL level to be 900 kcal energy expenditure or 120 minutes of aerobic exercise per week. They also found that a higher increase in HDL levels was observed in those individuals with high cholesterol and low body mass index (Kodama et al. 2007). The mechanisms by which physical activity reduces HDL are not yet well defined. However, physical activity acutely increases HDL in the same time frame as the reduction of triglycerides (18-72 hours after exercise) (Thompson et al. 2001).

The evidence for a decreasing effect of physical activity on LDL levels is more controversial than the effects on HDL. There are controversial results from cross-sectional studies to support an inverse relationship between LTPA and LDL independent of body fat and other confounders (Durstine et al. 2001). Durstine et al. (2001) also concluded in their review that the evidence shows a tendency towards no effect rather than an effect of physical activity on LDL. Furthermore, if an effect is observed, it is in most cases small (4-7 %). In newer cross sectional studies, LTPA has been controversially shown either to be inversely associated with LDL-cholesterol (Jakes et al. 2003, Kronenberg et al. 2000, O'Donovan et al. 2005) or to show no association (Panagiotakos et al. 2003, Fung et al. 2000. The results from meta-analyses of intervention studies also conclude controversial results showing either a reduction (Halbert et al. 1999, Leon et al. 2001, Kelley et al. 2004) or no change (Kelley et al. 2005, Lokey et al. 1989, Murphy et al. 2015, Tambalis et al. 2009, Durstine et al. 2001). An acute bout of physical activity may decrease LDL by 5-8% in men with hypercholesterolemia, however, small reductions are mainly observed following prolonged exercise in trained men. Furthermore, the changes in LDL after prolonged physical activity such as a marathon may be mediated by an acute expansion of plasma volume (Thompson et al. 2001).

Physical activity and glucose homeostasis. Exercise acutely decreases insulin resistance and improves glucose control in type 2 diabetic patients for a period of several days, however the mechanisms responsible are not well known. In non-diabetic individuals blood glucose are well pertained after an acute bout of exercise (Thompson et al. 2001). Healy et al. (2007) observed in a study sample of over 9000 Australian men and women that LTPA was inversely associated with 2-hour plasma glucose in an oral glucose tolerance test. Nevertheless, they found no association between LTPA and fasting plasma glucose levels. In prospective studies LTPA has been shown to be inversely related to the risk of diabetes (Heimrich et al. 1991, Lynch et al. 1996, Hu et al. 1999). Heimrich et al. (1991) reported in middle-aged men that LTPA was negatively related to incidence of type 2 diabetes after adjustments for age, obesity, history of hypertension, and parental history of diabetes. They further observed that the relationship was more pronounced in individuals with the highest risk of diabetes. During an 8 year follow-up, Manson et al. (1991) found in nearly 90 000 middleaged women that vigorous LTPA was inversely associated with the incidence of type 2 diabetes after adjustments for age, BMI, and family history of diabetes. Manson et al. (1992) also found in another prospective study in male physicians that vigorous LTPA was inversely associated with incidence of type 2 diabetes after controlling for age, BMI, smoking, hypertension and other cardiovascular risk factors. Moreover, Hu et al. (1999) observed that moderate intensity LTPA was inversely related to a reduced risk of type 2 diabetes.

These observational studies are supported by intervention studies (Tuomilehto et al. 2001, Knowler et al. 2002). In middle-aged overweight subjects who were to follow counselled diet, Tuomilehto et al. (2001) observed, a reduction in weight and an increase in physical activity, as well as decreased risk of diabetes of 58% compared to control group after 3 years follow-up. Knowler et al. (2002) found that in an intervention group where diet and physical activity (150min/w) were modified, the risk of diabetes decreased by 58% compared to control group. Boule et al. (2005) observed improvements in glucose metabolism after 20-weeks of endurance training independent of weight loss in nearly 600 previously untrained individuals.

In conclusion, observational and meta-analyses from RCT studies clearly show a beneficial association and effect of physical activity on blood pressure. In addition, there are several studies that report a beneficial association between physical activity and triglycerides, however, controversial findings exist as well, so the overall effect is less clear compared to e.g. blood pressure. Collectively, among lipoproteins, the most consistent association and effect of physical activity has been shown with HDL, whereas less consistent findings have been reported with LDL. Collectively, studies show a beneficial effect of physical activity on glucose homeostasis. The effect is likely more pronounced in those with perturbed glucose metabolism.

Muscular strengthening physical activity and health outcomes. There are not many observational studies that have concentrated specifically on muscular strengthening physical activity and health outcomes. One of the first studies by Tanasescu et al. (2002) showed prospectively an inverse association between resistance training and coronary heart disease. They showed in a study sample of nearly 45 000 middle-aged to older men that self-reported engagement in resistance training decreased mortality risk to a similar extent to brisk walking and rowing activities. However, the risk decreased by only half of the risk reduction compared to running (Tanasescu et al. 2002). Those individuals who reported resistance training more than 30 minutes per week had a 23% lower risk of CHD compared to those who reported no resistance training after adjustment for other types of physical activity. Previously, in a cross-sectional study of over 8000 adult men, Tucker & Silvester (1996) reported self-reported resistance training to be inversely associated with total cholesterol. However, after multiple adjustments, the association was significant only for those who engaged in resistance training for more than 4 hours per week.

Grontved et al. (2012) observed in 32 000 middle-aged to older men that selfreported engagement in resistance training was associated with a lower risk (34%) of diabetes compared to those reporting no resistance training after multiple adjustments including aerobic physical activity. Grontved et al. (2014) observed in their prospective study an inverse association between self-reported engagement in resistance training and incidence of type 2 diabetes in over 90 000 middle-aged and older women after adjustment for aerobic physical activity. They also reported a similar association for lower intensity muscular conditioning (yoga, stretching). Nevertheless, after further adjustments for aerobic physical activity and mutual adjustments for resistance training and lower intensity muscular conditioning, the association disappeared for lower intensity muscular conditioning, but not for resistance training. In addition, Grontved et al. (2012) found that self-reported engagement in resistance training was inversely associated with CVD mortality and all-cause mortality. However, further adjustment for either aerobic physical activity or BMI attenuated the associations to non-significant levels. In addition, Zhao et al. (2013) observed no association between self-reported engagement in resistance training and CVD mortality and all-cause mortality after adjustments for body weight and aerobic physical activity.

Cheng et al. (2007) showed an inverse association between muscle-strengthening activities and insulin sensitivity, but no association was observed for fasting plasma glucose. Similarly, Minges et al. (2013) observed in their cross-sectional study of nearly 6000 middle-aged that self-reported engagement in resistance training (2 times/week or < 40 min/week) was associated with reduced risk of impaired glucose tolerance by 27-31%. Moreover, they found that at least one resistance exercise session per week of short duration (10-39 min) was also inversely associated with impaired glucose tolerance. These associations were found after adjusting for age, smoking, family history of diabetes and aerobic physical activity. Magyari & Churilla (2012) and Churilla et al.

(2012) reported in their cross-sectional studies that those individuals with self-reported engagement in resistance training had lower likelihood of developing metabolic syndrome compared to those without training. Nevertheless, further adjustment for aerobic physical activity attenuated the association in one of these studies (Magyari & Churilla, 2012). Drenowatz et al. (2014) found self-reported resistance training to be inversely associated with triglycerides, total cholesterol and blood glucose even after controlling for CRF and LTPA in over 7000 adult women.

Previous meta-analyses of randomized controlled trials have confirmed the beneficial associations between muscle strengthening physical activity and blood pressure. Cornelissen & Fagard (2005) have shown resistance exercise to induce net change reductions in systolic (-3.2 mmHg) and diastolic (-3.5 mmHg) blood pressure. Moreover, in a meta-analysis of RCT studies, it was found that resistance training reduced diastolic (-2.2 mmHg) but not systolic blood pressure (Rossi et al. 2013). In addition, resistance training has been reported to decrease systolic (-3.9) and diastolic (-3.9 mmHg) blood pressure in normotensive and prehypertensive but not hypertensive individuals (Cornelissen et al. 2011). Furthermore, in a meta-analysis of RCT studies in participants with abnormal glucose regulation, resistance exercise has been shown to reduce systolic blood pressure by 6.2 mmHg (Strasser et al. 2010).

Moreover, isometric handgrip training has been shown to result in larger decreases in blood pressure than dynamic resistance training (Cornelissen et al. 2011). Dynamic resistance training led to reductions in systolic (-1.8 mmHg) and diastolic (-3.2) blood pressure, as did isometric resistance training (-10.9 mmHg and -6.2 mmHg, respectively) (Cornelissen & Smart 2013). In another meta-analysis, the potential of isometric training for blood pressure was also confirmed (Carlson et al. 2014). Furthermore, combined resistance and aerobic training decreased diastolic (-2.2 mmHg) but not in systolic blood pressure. (Cornelissen & Smart 2013). A meta-analysis by Kelley & Kelley (2009) suggested no effect of resistance training on lipids and lipoprotein (triglycerides, HDL, LDL, total cholesterol). In another meta-analysis of RCTs resistance training was found to decrease triglyceride concentration but not for lipoproteins or plasma glucose (Cornelissen et al. 2011).

Taken together, muscular strengthening physical activity shows a beneficial association and effect, especially on blood pressure, whereas the evidence is less convincing for lipids and lipoproteins. The strongest evidence comes from systematic reviews and meta-analysis from RCT studies. In addition, there are controversial results regarding whether significant results remain after adjusting for aerobic physical activity in observational studies. The controversial results in observational studies may be related to e.g. measurement error in assessing muscular strengthening physical activity and potentially some confounders. Nevertheless, there is evidence to indicate that muscular strengthening physical activity has beneficial effects on glucose homeostasis, especially in obese and type 2 diabetic patients.

#### 2.4.2 Commuting physical activity

Previous studies have shown that CPA modes, namely walking and cycling are associated with health outcomes (Murphy et al. 2015, Oja et al. 2011). However, there are less of those studies, which have aimed to assess specificially CPA including walking and cycling to work or study place. Within the last few decades the number of these studies has, however, been increasing (Saunders et al. 2012, Hamer & Chida 2008). One of the first studies that prospectively studied CPA and running errands was a study by Paffenbarger et al. (1978). They reported in the Harvard Alumni study population that walking fewer than 5 blocks daily was associated with a 23% higher risk of a first heart attack, adjusted for age. Later on, however, they found no association between these two groups for the risk of hypertension (Paffenbarger et al. 1983). Moreover, some prospective studies have assessed the association between CPA and mortality. Andersen et al. (2000) have reported a 28 % lower risk of all-cause mortality in individuals who cycle compared to non-cyclists after multiple adjustments including LTPA. Neverthless, Barengo et al. (2004) reported in a sample of Finnish middle-aged adults that CPA was not associated with CVD or all-cause mortality after adjustments including other dimensions of physical activity. Similarly, Batty et al. (2001) found no association between CPA and all-cause mortality or CHD in their prospective cohort study of nearly 12000 middle-aged subjects. Matthews et al. (2007) found no association between CPA (either walking or cycling) and all-cause or CVD or other cause mortality in a study population of Chinese women (n=67 000). Besson et al. (2008) also reported no association between CPA (either walking or cycling) with all-cause or CVD mortality in an English cohort of nearly 15 000 subjects. Furthermore, Hayashi et al. (1999) reported that high CPA (> 20 min/day) to reduced the risk of hypertension, whereas Barengo et al. (2005) reported no association of CPA with hypertension. Additionally, Autenrieth et al. (2011) reported no association of CPA with allcause, CVD or cancer mortality. However, one of the largest meta-analyses (Samitz et al. 2011) including over 1 300 000 participants concluded that there was an inverse association between CPA and all-cause mortality in the overall analyses but not for sex-specific analyses.

However, Hamer & Chida (2008) reported an inverse association between CPA and CVD risk in their meta-analysis of prospective studies. The review included seven cohort studies from Europe and one from Japan. The authors concluded an overall reduction of 11% in cardiovascular risk with CPA. The association was more robust for women. In a recent systematic review of prospective and intervention studies by Saunders et al. (2013) a small positive health effect of active commuting was reported on all cause mortality, hypertension and type 2 diabetes. Moreover, the association between active travel to school and health outcomes has been studied more widely in children and adolescents during the recent years. Some of these studies have shown active travel to be inversely associated with a better cardiovascular risk factor profile (e.g. Andersen et al. 2011)

Laverty et al. (2013) reported in their cross-sectional study of 20 000 adult participants that CPA was inversely related to self-reported diabetes and hypertension. However, these results were not adjusted for other dimensions of PA. Furie et al. (2013) showed a lower likelihood of diabetes and hypertension in active travellers compared to passive travellers adjusted for other PA. Millet et al. (2013) showed in an Indian adult study population that walking to work was inversely associated with HOMA-index and cycling to work with prevalence of hypertension and diabetes, after adjusting with multiple covariates including LTPA. A Finnish study reported an inverse association between CPA and incidence of type 2 diabetes in middle-aged men and women (Hu et al. 2003).

Previous cross-sectional studies regarding single CVD risk factors and CPA have shown an inverse associations of CPA with triglycerides and blood pressure (von Huth et al. 2007, Gordon-Larsen et al. 2009). Conversely, a lack of association has been observed with LDL-cholesterol (Furie et al. 2013, von Huth et al. 2007, Gordon-Larsen et al. 2009, Kwasniewska et al. 2010), fasting glucose (Gordon-Larsen et al. 2009, Kwasniewska et al. 2010) and blood pressure (Hu et al. 2002, Barengo et al. 2006, von Huth et al. 2007, Gordon-Larsen et al. 2009, Kwasniewska et al. 2010). In addition, a positive relationship has been observed between HDL-cholesterol and CPA in some (Barengo et al. 2006, von Huth et al. 2007, Kwasniewska et al. 2010) but not all studies (Gordon-Larsen et al. 2009). It is noteworthy that in some of these studies (Hu et al. 2002, Barengo et al. 2006) body mass index was adjusted for in the analysis whereas in others it was not (von Huth et al. 2007, Gordon-Larsen et al. 2009). Although Kwasniewska et al. (2010) reported no association between CPA and most of the single CVD risk factors, they did observe a higher prevalence of metabolic syndrome in the low CPA group compared to high CPA group in men.

There are only very few intervention studies investigating CPA and cardiovascular health outcomes in an experimental setting in adults. Oja et al. (1991) assessed a short-term 10-week intervention in 68 adults. They were divided into active and passive commuting groups. The active commuting group improved their HDL level and total cholesterol-HDL ratio, but no changes were observed in total cholesterol or triglyceride levels. Ostergaard et al. (2012) reported in their randomized controlled trial in children that cycling to school for 8 weeks improved clustered metabolic score compared to the control group. De Geus et al. (2008) studied the effects of a 1-year intervention of cycling to work on CVD risk factors in previously untrained healthy adults. They found beneficial effects of cycling to work on total cholesterol, LDL, HDL and diastolic blood pressure. However, the control group also showed improvements in total cholesterol and LDL.

Collectively, there is a tendency for beneficial associations between commuting physical activity and mortality as well as cardiovascular risk factors based on observational studies. Nevertheless, controversial findings do also exist. There is very limited information based on objective measurement of CPA in the existing literature, which may in part increase the risk for measurement error. Of note is the fact that there are very few RCT studies that have directly

assessed CPA and health outcomes. These few studies indicate, however, a positive effect of CPA on cardiovascular risk factors. The small number of RCT studies limits the reliability of the conclusions drawn herein.

#### 2.4.3 Occupational physical activity

The first epidemiological studies about the relationships between physical activity and health outcomes were related specifically to OPA (Morris et al. 1953, Morris et al. 1966). These very first studies revealed that OPA was inversely associated with mortality and CVD. Paffenbarger and Hale (1975) showed in their prospective study that CVD mortality was lower in the high OPA group compared to the low OPA group. In a review by Powell et al. (1987) it was stated that 20 out of the 24 studies done before 1970 focused specifically on OPA only. This highlights the focus on OPA in the first decades of the modern era of physical activity research, which have since then shifted towards inclusion of other dimensions of physical activity. In the review by Powell et al. (1987), they concluded that an inverse association was observed between OPA and incidence of CHD in 62% of the reviewed studies and 64% of the studies concentrating on LTPA published before 1970. Moreover, 83% of the studies that combined OPA and LTPA revealed a similar inverse association.

Changes in work-related physical activity associated with the industrialization of the Western society has maintained the interest in studying OPA and health-related factors to the present day. Church et al. (2011) have estimated that OPA related energy expenditure has decreased by more than 100 kcal per day over the last five decades (Church et al. 2011). Salonen et al. (1988) reported, in a Finnish study sample, an inverse association between OPA and ischemic heart disease adjusted for age, health status, family history and BMI. In a prospective study by Barengo et al. (2004), moderate and high OPA was inversely associated with all-cause mortality and decreased mortality by 21-27%. A recent meta-analysis of prospective cohort studies (Samitz et al. 2011), consisting of over 1 300 000 subjects concluded that OPA was inversely associated with allcause mortality. In another meta-analysis of prospective studies, it was found that high OPA was inversely related to CVD in both sexes and moderate OPA also in men but not in women (Li & Siegrist 2012). Autenrieth et al. (2011) found an inverse association between OPA and CVD mortality but not all-cause and cancer mortality.

However, Holtermann et al. (2009, 2010) however reported a positive association between OPA and CVD mortality, whereas Besson et al. (2008) and Clays et al. (2014) reported no association between OPA and all-cause or CVD mortality. Some studies show that high OPA is adversely associated with cardiovascular health outcomes (Holtermann et al. 2009, 2010, 2012, Virkkunen et al. 2007, Krause et al. 2007), whereas some others show that either moderate (Li et al. 2012, Wennberg et al. 2006) or high (Li et al. 2012) OPA is inversely related to incidence of CVD in prospective studies. To date, there is no clear consensus abou the association of OPA with health outcomes. However, recent study results indicate that high OPA may expose an individual to adverse effect on

health outcomes, and seems to have a different relationship with health than that of LTPA (Holtermann et al. 2009, Holtermann et al. 2012, Virkkunen et al. 2007, Krause et al. 2007, Clays et al. 2014, Li et al. 2013, Kukkonen-Harjula 2007). In prospective studies, OPA has been reported to be inversely associated with blood pressure in men without a history of cardiovascular disorders (Holtermann et al. 2010, 2013) but not in those with the disorders (Holtermann et al. 2010). Furthermore, a recent meta-analysis of prospective studies concluded no association between OPA and blood pressure (Huai et al. 2013).

Additionally, previous cross sectional studies have shown no association between OPA and metabolic syndrome (Sisson et al. 2009, Mozumdar & Liguori 2011). One of the first Finnish studies by Lehtonen & Viikari (1978) showed high OPA to be associated with higher HDL and triglycerides compared to low OPA. However, these results were without any adjustments. Some of the recent studies have shown no associations with any of the single CVD risk factors (Oppert et al. 2006, Sisson et al. 2009, Mozumdar & Liguori 2011). Nevertheless, an inverse association between OPA and blood pressure (Barengo et al. 2006, Fransson et al. 2003) and a positive association with HDL-cholesterol (Lakka & Salonen 1992, Barengo et al. 2006, Fransson et al. 2003, Sofi et al. 2007, Salonen et al. 1988) and systolic blood pressure (Pols et al. 1997, Clays et al. 2012) have been observed. Clays et al. (2012) observed high self-reported OPA to be positively associated with ambulatory blood pressure, whereas a similar association was not found for objectively measured OPA. Furthermore, no association was observed between OPA and homeostasis model assessment of insulin resistance (HOMA-index) was observed in men, although a positive association was found in women (Larsson et al. 2012).

In a summary, there are somewhat controversial findings from observational studies concerning the association of OPA and health outcomes. During the first few decades when these studies were performed, it was concluded that OPA was inversely related to health outcomes. Some recent studies have also shown that high OPA is adversely associated with health outcomes. Similarly, low occupational physical activity (high sedentariness) is adversely related to health outcomes. Noteworthy, OPA is largely confounded by many factors such as socioeconomic status and education as examples. These confounding effects may be associated with the conflicting results observed and may underline the complexity of OPA as an exposure outcome.

#### 2.5 Physical fitness and health

#### 2.5.1 Cardiorespiratory fitness and cardiovascular risk factors

Cardiorespiratory fitness has been shown to be inversely associated with mortality, CVD incidence and CVD risk factors in cross-sectional and prospective studies (Lakka et al. 1994, Grundy et al. 2012, Kodama et al. 2009, Myers et al. 2002, Blair et al. 1995). One of the first cross sectional studies from the Cooper

Clinic revealed an inverse but weak association between cardiorespiratory fitness and some of the cardiovascular risk factors in men and women adjusted for age and body mass index (Cooper et al. 1976, Gibbons et al. 1983). However, Haskell et al. (1980) reported no association between CRF and HDL cholesterol in women or men. Furthermore, Hagan et al. (1983) found an inverse association between maximal aerobic capacity and HDL but not LDL or total cholesterol in male runners compared to matched sedentary counterparts. Suzuki et al. (1998) reported CRF to be inversely associated with CVD risk factors such as LDL, HDL and triglycerides in 20-64 years old adults. More recent cross-sectional studies have observed an inverse association between cardiorespiratory fitness and the clustered CVD risk factor as well as single risk factors independent of body fat (Delvaux et al. 2000, Ekblom-Bak et al. 2009, Racette et al. 2006, Sacheck et al. 2010, Laaksonen et al. 2002), independent of physical activity (Ekblom-Bak et al. 2010), and independent of muscular fitness (Wijndaele et al. 2007).

In a prospective study by Carnethon et al. (2003), low cardiorespiratory fitness was associated with higher risk for the incidence of hypertension, hypercholesterolemia, diabetes and metabolic syndrome after controlling for age, sex, race, smoking and familial hypertension, diabetes or premature myocardial infarction in young adults. Lamonte et al. (2000) found in an ACLS study that CRF was beneficially associated with conventional cardiovascular risk factors after adjusting for age, body fat, smoking and familial CVD history in middleaged subjects with and without CVD.

Cardiorespiratory fitness and blood pressure. Previous cross-sectional studies have shown an inverse association between CRF and blood pressure (Cooper et al. 1976, Gibbons et al. 1983, Jette et al. 1992). Kokkinos et al. (2006) reported in their cross-sectional study that cardiorespiratory fitness was inversely associated with ambulatory blood pressure in prehypertensive men and women adjusted for several confounders. Chen et al. (2010) observed in over 35 000 middleaged participants that those in the highest quartile of CRF exhibited 6 mmHg lower systolic blood pressure compared the least fit quartile. Nevertheless, BMI was more strongly associated with systolic blood pressure than CRF.

In prospective studies, cardiorespiratory fitness has been shown to be inversely associated with incidence of hypertension. Blair et al. (1984) found that the risk for incidence of hypertension was 52% higher in those belonging to the low CRF group compared to the high CRF group after adjustment for age, BMI, sex and baseline blood pressure during a median of four years of follow-up. Furthermore, Sawada et al. (1993) found in their five-year prospective study that the incidence of hypertension was lower in the highest compared to the lowest cardiorespiratory fitness group after adjustments for age, smoking, alcohol consumption, and familial history of hypertension in middle-aged Japanese men. Carnethon et al. (2003) observed that a 1-minute decrease in time to exhaustion in a maximal exercise test was related to a 19% higher risk of developing hypertension after 15 years of follow-up. In an ACLS study, Chase et al.

(2009) found a linear inverse association between CRF and incidence of hypertension in a follow-up lasting an average of 18 years after adjustments for smoking, alcohol intake, resting systolic pressure, BMI, baseline health status and family history of diseases.

CRF and triglycerides and lipoproteins. In addition to blood pressure, CRF has also been shown to be beneficially associated with triglycerides and lipoproteins in previous cross-sectional studies (Cooper et al. 1976, Gibbons et al. 1983, Lamonte et al. 2000, Lee et al. 2005, Farrel et al. 2012, Jette et al. 1999). In a study sample of over 80 000 20-90 years old men and women, Grundy et al. (2012) showed that CRF was inversely associated with triglycerides and non-HDL concentrations, and positively with HDL concentration. Nevertheless, differences between men and women have been observed in some studies (Jette et al. 1999, Grundy et al. 2003, Grundy et al. 2005). CRF was inversely associated with triglycerides and positively with HDL in women but not men in a young adult population of over 500 participants (Sacheck et al. 2009). Furthermore, the same study found no association between CRF and LDL in men or in women (Sacheck et al. 2009).

CRF and glucose homeostasis. In cross-sectional studies, Sacheck et al. (2009) found that CRF was inversely associated with fasting plasma glucose in men but not women, whereas Gatterer et al. (2011) reported no association between CRF and fasting plasma glucose in prediabetic men or women. Earnest et al. (2013) observed in nearly 40 000 subjects an inverse graded association between CRF and fasting glucose. Nevertheless, some studies have reported no association between physical fitness or activity and fasting glucose levels, but an inverse association with plasma glucose level in oral glucose tolerance test (Gatterer et al. 2011, Healy et al. 2006). Prospective studies have shown an inverse relationship between CRF and fasting glucose and incidence of type 2 diabetes (Wei et al. 1999, Lynch et al. 199, Hu et al. 2005). Wei et al. (1999) observed an increased risk of impaired glucose tolerance and incidence of type 2 diabetes in individuals with low CRF. Lynch et al. (1996) also found that a CRF level higher than 31 ml/kg/min decreased the risk of diabetes in middle-aged men.

To summarize, CRF has been consistently shown to be associated with different health outcomes, especially in prospective studies. Cross-sectional studies have shown slightly more controversial findings regarding cardiovascular risk factors, but they do indicate a beneficial association between CRF and the risk factors. It is noteworthy that in many studies these associations have been observed independent of body fat, physical activity or muscular fitness.

#### 2.5.2 Muscular fitness and cardiovascular risk factors

Whereas the evidence is strong for the beneficial effect of cardiorespiratory fitness on health outcomes from observational studies, muscular fitness is far less studied. The majority of studies investigating muscular fitness and mortality have been conducted by assessing grip strength as a measure of muscular fit-

ness. Those studies (e.g. Rantanen et al. 2000) have shown that maximal strength is inversely associated with mortality in elderly study population. Fitzgerald et al. (2004) found that moderate muscular fitness (combined measures of maximal strength of upper and lower body and sit-ups) was associated with a reduction in the risk of mortality by 36% in adults, after multiple adjustments including CRF. Nevertheless, high muscular fitness was not associated with a reduction of risk compared to low muscular fitness. Moreover, Katzmartzyk & Craig (2002) reported that sit-up performance was inversely related to mortality, whereas grip strength and push-up performance were not, after adjustment for aerobic fitness. Ruiz et al. (2008) found in their study of nearly 9000 adults that maximal strength was inversely associated with allcause and cancer mortality but not with CVD mortality after multiple adjustments including BMI and CRF. Furthermore, Artero et al. (2011) reported in hypertensive individuals that high maximal strength but not moderate maximal strength was inversely associated with risk reduction of all-cause mortality compared to low maximal strength. Ortega et al. (2012) observed in over one million participants that low maximal strength in adolescence was associated with higher risk of all-cause mortality and cardiovascular mortality after adjustments for BMI and diastolic blood pressure (follow-up of 24 years). The risk of all-cause mortality was of a similar magnitude as those of BMI and diastolic blood pressure. Nevertheless, the study did not control for CRF. Moreover, Timpka et al. (2014) showed that muscular strength in adolescence was inversely associated with CVD events and mortality later in middle-aged men independent of various confounders such as smoking, BMI and CRF.

Furthermore, Maslow et al. (2010) found in their prospective study that maximal strength was inversely associated with the incidence of hypertension in prehypertensive but not in normotensive individuals after adjustment for smoking, alcohol, family history of hypertension and baseline blood pressure. Nevertheless, when further adjusted for either CRF or BMI, associations were no longer statistically significant.

Interestingly, one of the first cross-sectional studies by Kohl et al. (1992) found interestingly an adverse association between maximal strength and HDL cholesterol, as well as triglycerides after controlling for age, cardiorespiratory fitness and sum of skinfolds (Kohl et al. 1992). Nevertheless, more recent studies have shown an inverse association between cardiovascular risk factors and muscular fitness index (Artero et al. 2011, Garcia-Artero et al. 2007, Magnussen et al. 2012, Steene-Johannessen 2009, Lopez-Martinez et al. 2013) and maximal strength (Atlantis et al. 2009, Jurca et al. 2004, Jurca et al. 2005, Wijndaele et al. 2007). After adjustment for cardiorespiratory fitness, these associations have, however, attenuated and decreased to non-significant levels in some (Jurca et al. 2005, Wijndaele et al. 2007) but not all studies (Artero et al. 2011, Garcia-Artero et al. 2007, Kim et al. 2011, Magnussen et al. 2012, Steene-Johannessen 2009, Wijndaele et al. 2007).

Collectively, the evidence from observational studies indicates an inverse association between muscular fitness and different health outcomes. There are,

however, controversial findings regarding whether the associations are independent of CRF. Compared to CRF, far fewer studies have concentrated on muscular fitness and health outcomes.

#### 2.5.3 Cardiorespiratory fitness and inflammatory biomarkers

In addition to physical fitness, there is evidence from cross-sectional and prospective studies to show that physical activity is inversely related to low-grade inflammation (Ford et al. 2002, Hamer et al. 2012, Pischon et al. 2003, Elosua et al. 2005). These associations have remained statistically significant even after adjustment for BMI in some (Elosua et al. 2005, Ford et al. 2002, Hamer et al. 2012,) but not all studies (Pischon et al. 2003). The anti-inflammatory effect of physical activity has been suggested to be induced by contractions of skeletal muscles. It has been shown that during exercise muscle fibers produce IL-6, which stimulates and inhibits the cascade of other inflammatory biomarkers to produce anti-inflammatory actions. (Pedersen 2006) Reviews and meta-analyses from observational studies show consistently an inverse association between physical activity and inflammatory factors (Beavers et al. 2010, Hamer 2007, Kasapis & Thompson 2005, Lavie et al. 2011, Plaisance & Grandjean 2006). However, the evidence from randomized controlled trials is somewhat limited and inconclusive (Beavers et al. 2010, Hamer 2007). A meta-analysis of five randomized controlled trials did not observe a significant change in CRP after aerobic physical activity interventions (Kelley & Kelley 2006).

Many cross-sectional studies have observed an inverse association between CRF and CRP (Church et al. 2002, Lamonte et al. 2002, Lin et al. 2010, Kuo et al. 2007, Aronson et al. 2004, Hammet et al. 2006, Lakka et al. 2005, Williams et al. 2005). After multiple adjustments, including BMI, most (Church et al. 2002, Lamonte et al. 2002, Aronson et al. 2004, Williams et al. 2005) but not all studies (Hammet et al. 2006) report significant independent associations. Furthermore, in a review by Hamer (2007) it was concluded that there is evidence for a consistent inverse association between CRF and CRP concentrations from observational studies in individuals with metabolic syndrome or type 2 diabets and in elderly subjects. Nevertheless, a cross-sectional study by Arsenault et al. (2009) showed an inverse association between CRP and CRF in women but not in men. Moreover, Hamer & Steptoe (2008) found in their prospective study that changes in CRP a three year follow-up were associated with adiposity but not with CRF. In adolescents, an inverse association between CRF and CRP concentrations has been observed in some (Christodoulos et al. 2012, Steene-Johannessen et al. 2013, Parret et al. 2010) but not all cross-sectional studies (Ruiz et al. 2008).

There are fewer cross-sectional and prospective studies about the association between CRF and IL-6 and TNF-alpha. In a cross-sectional study by Taaffe & Tamara (2000), elderly individuals in the highest two quartiles for walking speed had lower IL-6 concentrations compared to the lowest quartile after multiple adjustments including BMI. Nevertheless, no associations between CRF and IL-6 have been observed in healthy adults (Arsenault et al. 2009) and ado-

lescents (Martinez-Gomez et al. 2010, Steene-Johannessen et al. 2013). Halle et al. (2004) observed an inverse association between CRF and TNF-alpha in adolescents, whereas no association has also been reported in adolescents (Steene-Johannessen et al. 2013) and middle-aged adults (Arsenault et al. 2009).

Hamer (2007) reported in his review that although the majority of the observational studies show an inverse association between CRF and inflammatory factors, the evidence from RCTs are inconclusive. Arikawa et al. (2011) reported a decrease in CRP after a 16-week aerobic exercise intervention in young female adults. The decrease in CRP was more prominent among obese individuals. Lakka et al. (2005) found in their 20-week aerobic training intervention with over 600 hundred adults that CRP concentration decreased in those individuals with high CRP baseline levels. Friedenreich et al. (2012) found a decrease in CRP but not in IL-6 or TNF-alpha among postmenopausal women after a one-year aerobic exercise intervention. However, the decrease in fat content largely explained the decrease in CRP. Church et al. (2010) found in 162 middle-aged adults that an exercise intervention did not decrease CRP, and thus they concluded that exercise training not associated with weight does not decrease CRP. A more recent review also found mixed results regarding the effects of aerobic exercise on inflammatory biomarkers (You et al. 2013).

In conclusion, observational studies suggest an inverse association between CRF and inflammatory factors. Nevertheless, the results from RCT studies remain inconclusive. Some study results indicate that body fat content might be more strongly related to inflammatory factors than CRF.

#### 2.5.4 Muscular fitness and inflammatory biomarkers

Most previous studies have concentrated on associations between aerobic physical activity or aerobic fitness and inflammatory factors, whereas the relationship between measures of muscular fitness and markers of inflammation is less studied (Artero et al. 2012). Previous studies have shown in adolescents that muscular fitness index as a combination of measures of maximal strength and muscular endurance (grip strength, standing broad jump, sit-ups and trunk extensor endurance tests) is inversely associated with CRP independent of cardiorespiratory fitness (Artero et al. 2013, Ruiz et al. 2008, Steene-Johannessen et al. 2013). After adjustment for adiposity, a significant association was also found in the entire study population (Steene-Johannessen et al. 2013) or in an overweight subgroup only (Ruiz et al. 2008), whereas in one study the association became non-significant (Artero et al. 2013). No associations have been found between muscular fitness and IL-6 or TNF-alpha concentrations in adolescents (Steene-Johannessen et al. 2013). In addition, a previous cross-sectional study reported an inverse association between maximal strength and IL-6, independent of adiposity in an elderly study sample (Visser et al. 2002).

Previous reviews have concluded, albeit based on a limited number of studies, that resistance training may induce a beneficial effect on CRP (de Salles et al. 2010, Strasser et al. 2012). Interventions have shown that resistance training alone can decrease CRP levels in sedentary adults (Donges et al. 2010),

overweight women (Olson et al. 2007), obese postmenopausal women (Phillips et al. 2012) and older adults with (Brooks et al. 2006) or without type 2 diabetes (Martins et al. 2010). However, contradictory findings also exist in sedentary adults (Brooks et al. 2006) overweight and obese postmenopausal women (Brochu et al. 2006) and older adults with (Swift et al. 2012) or without type 2 diabetes (Levinger et al. 2009). In a previous study, concurrent strength and aerobic training has been shown to reduce CRP concentration (Jorge et al. 2011) in type 2 diabetic patients. Furthermore, concurrent strength and aerobic training has been demonstrated to be even more effective in modifying inflammatory profile than aerobic exercise alone in older adults with type 2 diabetes (Balducci et al. 2010).

A recent review by Strasser et al. 2012 concluded, albeit based on only 5 studies, that resistance training did not decrease IL-6 concentration. A previous cross-sectional study in children reported similar findings (Steene-Johannessen et al. 2013). Moreover, intervention studies in sedentary adults (Donges et al. 2010), middle-aged obese men (Klimcakova et al. 2006) and obese postmenopausal women (Phillips et al. 2012) have also shown no significant changes in IL-6 concentration. The majority of resistance training studies report no changes in TNF-alpha concentration (Calle et al. 2010, de Salles et al. 2010, Levinger et al. 2009, Strasser et al. 2012). However, some studies have found resistance training to decrease TNF-alpha concentration in obese postmenopausal (Phillips et al. 2012) and elderly women (Phillips et al. 2010).

There is some indication from observational and RCT studies to suggest that muscular fitness is associated with inflammatory biomarkers. However, there are controversial findings between different study groups suggesting that possibly elderly, overweight and sedentary individuals as well as different patient groups, such as type 2 diabetics may gain advantage of having high muscular fitness on inflammatory biomarkers. The meta-analysis from RCT studies are yet low in number, which decrease the reliable conclusions to be drawn. Nevertheless, in spite of the controversial study results, it seems that among the inflammatory biomarkers, muscular fitness is most strongly related to CRP.

#### 3 AIMS OF THE STUDY

The beneficial effects of physical activity and fitness on cardiovascular health have been well documented previously (e.g. Morris et al. 1953, Paffenbarger et al. 1978, Blair et al. 1995). However, the relationships between different domains of physical activity and cardiovascular health are not well defined. In particular, only a few studies have assessed different dimensions of physical activity simultaneously. Although a large body of evidence shows that physical activity and cardiorespiratory fitness are associated with various health outcomes, less information is available about muscular fitness. This is particularly true when considering the association between different dimensions of muscular fitness and cardiovascular outcomes (Artero et al. 2012). There is particular lack of information about whether the dimensions of muscular fitness are associated with cardiovascular and inflammatory outcomes independent of cardiorespiratory fitness.

Therefore, the specific aims of the present study were:

- To examine the relationships between leisure time, commuting and occupational physical activity with cardiovascular risk factors and physical fitness.
- To study the associations of maximal strength and muscular endurance with cardiovascular risk factors independent of cardiorespiratory fitness.
- To investigate the associations of maximal strength and muscular endurance test scores with cardiorespiratory fitness and body composition.

#### 4 METHODS

### 4.1 Subjects

In the present study, one 1155 Finnish men were called up to military refresher training organized by the Finnish Defence Forces. They were offered a chance to participate in the study. The call up to military refresher training and information about the study plan for participants were sent five months before the measurements, which were carried out in eight different sessions during 2008 (March–November).

In Finland, military service is compulsory for adult men. The military service can last 6-12 months depending on whether an individual is deployed as a rank and file or non-commissioned officer. Annually almost 75-80% of the adult Finnish males perform their military service. Therefore, the population represents quite well the average young adult Finnish male. After finishing the military service they return to their "normal" life as reservists. As reservists, they can be called up to the military refresher training lasting typically around 3-7 days. Among the men who were called up in 2008 (n=1155), 80% participated in the military refresher training (n=920). The most typical reasons for nonparticipation were work-, study-, or health-related issues. Out of the 920 men, 846 (92%) (age  $25.5 \pm 4.6$  years) volunteered to take part in the study. Not all the participants took part in each of the measured variables, so the final study sample consisted of 686-846 (75-92%) young Finnish men (Table 1). Those participants who reported using medication for diabetes, high cholesterol or hypertension (n=8) were excluded in the publications 1-3. The description of the study sample in the publications 1-4 is presented in the table 1.

TABLE 1. Characteristics of the study sample for body composition, physical fitness and cardiovascular risk factors (mean + standard deviation)

	Mean (SD)
	2F 0 (F 0)
Age (yrs.)	25.0 (5.0)
Smoking (%)	38.3
Anthropometric and body composition	
variables	
Height (cm)	180.0 (6.3)
Body mass (kg)	80.6 (13.4)
Waist Circumference (cm)	86.3 (10.4)
Body mass index	24.8 (3.8)
Fat mass (kg)	15.1 (8.6)
%Body fat	17.9 (7.2)
Fat free mass (kg)	65.4 (7.4)
Physical fitness	
Repeated squats (reps/min)	44(9)
Sit-ups (reps/min)	38 (10)
Push-ups (reps/min)	29 (13)
Leg extension force (N)	2939 (871)
Bench press force (N)	900 (199)
Grip strength (kg)	53.1 (8.9)
VO <sub>2</sub> max (mL min <sup>-1</sup> ·kg <sup>-1</sup> )	41.6 (8.1)
Maximal heart rate (beats/min)	192 (8)
Maximal load (W)	244 (46)
Cardiovascular risk factors	
Total cholesterol (mmol/L)	4.5 (0.9)
HDL (mmol/L)	1.5 (0.4)
LDL (mmol/L)	2.4 (0.6)
Triglycerides (mmol/L)	1.0 (0.5)
Glucose (mmol/L)	5.4 (0.4)
Systolic pressure (mmHg)	123 (12)
Diastolic pressure (mmHg)	77 (9)
C-reactive protein (pg/mL)	1.7 (4.6)
Interleukin-6 (pg/mL)	1.1 (1.3)
Tumor necrosis alpha (pg/mL)	2.0 (1.4)

The study sample was compared with corresponding cohorts of 20 to 30 yearold Finnish men in the national register data (Statistics Finland) from 2007 to 2008 for the following variables: age, education, and place of residence. Based on these comparisons, it can be concluded that the study sample was representative with the exceptions that the Northern part of Finland was underrepresented and individuals with 13 to 15 years of education were overrepresented in the study sample.

The subjects were carefully informed about the design of the study, and they signed an informed consent before voluntary participation in the study. This study was approved by the Ethical Committee of the Central Finland Health Care District.

#### 4.2 Experimental design

The participants arrived at the garrisons latest by 14:00 o'clock. A standardized dinner (1100 kcal consisting of 60% of carbohydrates, 15% of protein and 25% of fat) was served to each participant. They also filled in a questionnaire with questions on background information (e.g. age, smoking), health behaviour (e.g. physical activity) and questions to screen for possible health contraindications for physical fitness tests. The participants were divided into groups of 10 persons for measurements, which started the next morning at 5:50 after a night of sleep with an overnight fast with only water consumed ad libitum. At first, body composition and blood pressure were measured, and then blood samples were drawn from the antecubital vein using Terumon Venosafe (Terumo Europe, Leuven, Belgium). Thereafter, participants ate a light breakfast and drank a maximum of 1 cup of coffee or tea. After breakfast, grip strength and bilateral maximal isometric leg extension and bench press were measured. Finally, an indirect graded cycle ergometer test and tests of muscular endurance (push-ups, sit-ups, repeated squats) were performed (Figure 1).

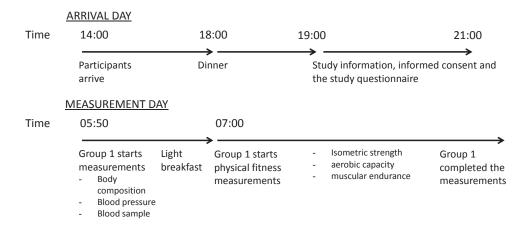


FIGURE 1 The research protocol of the study.

#### 4.3 Data collection

#### 4.3.1 Assessment of physical activity

The frequency and intensity of weekly leisure time physical activity (LTPA) was determined with the following question: "Which of the following definitions best describe your leisure time physical activity habits? - ("Think of the last three months and consider all leisure time physical activity that lasted at least 20 minutes per session)". Response categories were: (1) less than once a week, (2) no vigorous activities, but light or moderate physical activity at least once a week, (if more often than once, please define the numbers per week), (3) vigorous activity once a week, (4) vigorous activity twice a week, (5) vigorous activity three times a week, and (6) vigorous activity at least four times a week. LTPA was classified as low (responses 1-2), moderate (responses 3-4) and high activity (responses 5-6) (Fogelholm et al. 2006). The LTPA question used in the present study has been validated against fitness, observing that vigorous physical activity showed a consistent dose-response relationship with cardiorespiratory and muscular fitness (Fogelholm et al. 2006). There is no specific study available concerning validation against objective physical activity measurement and the LTPA question used herein. In general, acceptable to good reliability but poor to moderate validity has been reported for physical activity questionnaires (Helmerhorst et al. 2012).

The engagement and duration of commuting physical activity (CPA) was determined with the following question: "How many minutes do you walk or cycle during your way to and from work, and when running errands per day?". Response categories were: (1) no walking or cycling to work, (2) less than 15 minutes a day, (3) 15-29 minutes a day, (4) 30-59 minutes a day and (5) 60 minutes or more a day. CPA was classified as low (responses 1-2), moderate (response 3) and high (responses 4-5) activity (Hu et al. 2002). Moderate test-retest reliability has been shown in a previous study using similar questions (min/week) about CPA (ICC=0.53, 95% CI: 0.37-0.65) (Evenson & McGinn 2005). To the best of our knowledge, the present questionnaire has not been validated previously, although it has been widely used in earlier population-based studies (e.g. Barengo et al. 2006).

Occupational physical activity (OPA) was assessed with the following question: "How physically demanding is your work? (if you are not working at present, please answer concerning your previous work)". Response categories were: (1) mostly sedentary work without much walking, (2) walking quite a lot at work without lifting or carrying heavy objects, (3) lots of walking and lifting at work or taking the stairs or walking uphill, and (4) physically very demanding work including lots of lifting or bearing heavy objects, digging or shovelling at work. OPA was further classified as low (response 1), moderate (responses 2-3) and high (response 4) activity (Li et al. 2012). Good repeatability of single-item OPA questions similar to the one used in the present study has been

shown in previous studies ( $K_w$ =0.80: Kurtze et al. 2007), (ICC=0.82: Evenson & McGinn 2005). In addition, moderate subjective criterion validity against physical activity records (ICC=0.57-0.82) has been reported for the individual answer options (hours per week) (Ainsworth et al. 1993). Moreover, moderate construct validity has been reported between single-item OPA questions and accelerometers (r=-0.45-0.48: Kurtze et al. 2007).

#### 4.3.2 Maximal strength and muscular endurance

Bilateral maximal isometric leg extension and arm extension forces were measured using dynamometers for leg press and bench press, respectively (figures 2-3). Knee angle was set to 107° with a goniometer, and hands were placed on handle grips for the leg extension test (Häkkinen & Häkkinen 1995). During the maximal bench press protocol, participants were in a supine position with their back flat on a bench and feet flat on the floor, with elbows and shoulders positioned at an angle of 90°. Warm-up included at least two submaximal trials prior to maximal trials. Three maximal trials were performed with 30 seconds recovery between trials. The best performance was included for further analysis. The participants were instructed on the testing protocol and saw a demonstration of correct technique for each test prior to testing. They were also instructed to produce maximal strength as fast as possible and to maintain it for three seconds. Furthermore, the testing personnel encouraged them during the maximal efforts. Maximal force was collected with an AD-converter (CED power 1401, Cambridge Electronic Design, ltd, England) at a frequency of 1-Khz on a computer. Data was analyzed with Signal (2.16) software. The repeatability has been reported to be high in maximal isometric strength tests (r=0.98, C.V=4.1%; Viitasalo et al. 1980).



FIGURE 2 Bilateral maximal isometric leg extension measurement



FIGURE 3 Bilateral maximal isometric bench press measurement

Maximal isometric grip strength was measured in a sitting position (Saehan Corporation, Masan, South Korea) (figure 4). Grip width was adjusted individually by two handle options. Elbow angle was held at 90° during the performance. The test was executed twice for each hand, alternating hands between trials. For the analysis, the best result of each hand was averaged for the determination of overall grip strength. The test-retest reliability of the measurement has been reported to be high in young adults (ICC=0.94) (Tsigilis et al. 2002).



FIGURE 4 Assessment of maximal grip strength measurement

A maximal strength index (MSI) was calculated by transforming the results of the three maximal isometric strength test scores to z-scores in publication 4. Bilateral maximal isometric leg extension and arm extension forces were used to calculate maximal strength index (MSI) in the z-score in publications 2-3. Thereafter, the z-scores of maximal strength tests were averaged to form MSI.

Tests for muscular endurance consisted of push-ups, sit-ups and repeated squat tests (figures 5-7). The push-up test measures performance of arm and shoulder extensor muscles, as well as trunk muscles to stabilize the trunk during the performance (Esco et al. 2010, Fogelholm et al. 2006, Freeman et al. 2006). The sit-up test is a measure of the abdominal and hip flexor muscles (Tsigilis et al. 2002, Viitasalo et al. 1980, McGuigan et al. 2010), while repeated squats measures the performance of the knee flexor and extensor muscles (Häkkinen &

Häkkinen 1995). The participants were instructed to perform as many repetitions as they were able to during 60 seconds. Between each test, a recovery period of 5 minutes was allotted. Only repetitions completed with correct technique were counted. During the test performances, test personnel observed participants' technique. The test-retest reliability of push-up, sit-up and repeated squat tests has been reported to be high among young adults and middle-aged adults (ICC=0.93-0.95, ICC=0.83-0.93, r=0.95, respectively; Augustsson et al. 2009, Alaranta et al. 1994). A muscular endurance index (MEI) was calculated by transforming the results of the three muscular endurance test scores to z-scores. Thereafter, the z-scores of muscular endurance tests were averaged to form MEI.



FIGURE 5 Assessment of push-up tests.



FIGURE 6 Assessment of sit-up tests.



FIGURE 7 Assessment repeated squat tests.

#### 4.3.3 Cardiorespiratory fitness

Cardiorespiratory fitness (VO<sub>2</sub>max) was determined using an indirect graded cycle ergometer test (Ergoline 800S, Ergoselect 100K, Ergoselect 200K, Bitz, Germany) (Figure 8). A progressive protocol was used, which initially started at a power output of 50 W and was increased 25 W every 2 minutes until exhaustion (volitional will to finish or a decrease of pedalling cadence to below 60 rpm/min). Heart rate (HR) was recorded continuously during the test using heart rate monitors (Polar Vantage NV or S610, S710 or S810, Kempele, Finland). Predicted VO<sub>2</sub>max was determined from HR and maximal power (Watts, W) (Fitware, Mikkeli, Finland) with the following equation: VO<sub>2</sub>max (ml·kg<sup>-1</sup>·min<sup>-1</sup>) = 12.35\*Pmax/kg + 3.5, where Pmax is maximal power and kg is body mass in kilograms. The intra class correlation has been reported to be high with this method (ICC r = 0.82-0.94) for men (Santtila et al. 2013).



FIGURE 8 Assessment of cardiorespiratory fitness

#### 4.3.4 Cardiovascular risk factors

Cardiovascular risk factors consisted of blood pressure, serum lipids and plasma glucose. Blood pressure was recorded twice at 1-2 min intervals in a seated position using an automatic blood pressure device (Omron M6 Comfort, Netherlands). In the analysis, the mean of the two values was used. Blood samples were drawn from the ulnar vein using Terumon Venosafe (Terumo Europe, Leuven, Belgium) and were centrifuged at a speed of 3500 rpm. Glucose, serum high-density lipoprotein cholesterol (HDL) and triglycerides (TG) were analyzed with the Konelab 20 XTi -device (Thermo Electron Co, Vantaa, Finland) and the isolated low density lipoprotein cholesterol (LDL) fraction was used for direct measurement of LDL-cholesterol (CHOD-PAP method). The ranges for triglycerides, HDL cholesterol and LDL cholesterol assays were 0.1-15; 0.09-11; 0.04-2.84 and 0.3-8.9 mmol·l¹, respectively. Intra- and inter-assay coefficients of variance were 1.0% and 3.8% for TG, 3.4 and 3.9% for s-LDL, and 0.5% and 7.6% for s-HDL, respectively. Sensitivity for glucose was 0.1 mmol/l, and intra- and inter-assay coefficients of variance were 1.0 and 2.0%, respectively.

A continuous cardiovascular risk factor score was used in the present study (publications 1 and 2) similar to earlier studies (Steene-Johannessen et al. 2009, Wijndaele et al. 2007). Firstly, the values of each cardiovascular risk factor (plasma glucose, serum triglycerides, serum high-density lipoprotein cholesterol, serum low-density lipoprotein cholesterol, systolic and diastolic blood pressure) were transformed to z-scores. HDL cholesterol was inverted before including it in the risk score. The continuous clustered cardiovascular risk factor score was calculated from the mean of z-score values of all cardiovascular risk factors.

#### 4.3.5 Inflammatory biomarkers

Blood samples were drawn from the antecubital vein using Terumon Venosafe (Terumo Europe, Leuven, Belgium) after an overnight fast, and were centrifuged at a speed of 3 500 rpm. Serum concentrations of CRP, TNF-alpha 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 0.10 mg/L for CRP sensitivity, 0.11 pg/mL for IL-6, and 0.19 pg/mL for TNF-alpha. The maximum intra- and interassay CV% were 4.8 and 6.1% for CRP, 5.9% and 9.8% for IL-6, and 6.1% and 7.7% for TNF-alpha, respectively.

#### 4.3.6 Body composition and waist circumference

Body composition was determined using bioelectrical impedance analysis (BIA) (Inbody 720, Seoul, South Korea) to determine body weight, fat mass (FM), body fat percentage (BF%) and fat free mass (FFM) (figure 9). BIA estimates of body composition have been shown to highly correlate with the DXA-method (r=0.82-0.95) (Boneva-Asiova & Boyanov 2008). Body mass and height were

measured to the closest 0.1 kg and 0.1 cm, respectively on a commercial scale. Body mass index (BMI) was calculated and waist circumference (WC) was measured twice using a cloth tape measure at the level of iliac crest after exhaling.



FIGURE 9 Assessment of body composition with the bio-impedance method.

#### 4.4 Statistical analyses

Data was analyzed with R program for statistical computing and PASW-software (PASW for Windows 18.0.1). Those participants who reported using medication for diabetes, high cholesterol or hypertension (n=8) were excluded of the statistical analysis in publications 1-3. The final study samples ranged from 686 to 846 depending on the measured variables available for a given individual.

In each publication, means and standard deviations (SD) were calculated and in article IV minimum and maximum values were also reported. In article I, analysis of covariance with Bonferroni post hoc was used to compare physical fitness, body composition and CVD risk factors between the low, moderate and high PA categories in each physical activity domain. Covariates included age, smoking, the other two physical activity domains and waist circumference. Multinomial logistic regression was used to estimate the odds ratios and 95% CI for the continuous CVD risk factor score using the highest category as the reference group in each of the physical activity domain. To calculate the odds ratio, cardiovascular risk was dichotomized at the cutpoint value of above 1 SD, similar to earlier studies (Steene-Johannessen et al. 2009, Wijndaele et al. 2007).

In article II, Multinomial logistic regression was used to study the associations of cardiorespiratory and muscular fitness with single and clustered cardiovascular risk factors using models with different combinations of covariates (smoking, age, fitness variables, waist circumference and self-reported leisure time physical activity).

In article III, differences between the groups of those with and without abdominal obesity were analyzed with independent t-test and z-test for comparing column proportions. The associations of maximal strength index, muscular endurance index, cardiorespiratory fitness and waist circumference with inflammatory biomarkers were examined with Pearson correlation coefficients. Because the inflammatory factors were not normally distributed they were transformed to logarithmic transformations. Logistic regressions were used to study the associations of muscular endurance and maximal strength with inflammatory factors using smoking and cardiorespiratory fitness as covariates for waist circumference groups.

In article IV, after verifying the normality, the associations between physical fitness and body composition variables were examined with Pearson correlation coefficients and simple regression analyses. FFM and WC were chosen as body composition variables describing muscle and fat mass, respectively, in all of the regression models. In addition to body composition variables, push-ups, maximal isometric strength of the upper extremities and grip strength were chosen as independent variables when predicting the scores of upper body tests. Similarly, repeated squats and isometric maximal strength of the lower extremities were chosen as independent variables when predicting the scores of lower body tests. Moreover, VO<sub>2</sub>max and the sit-up test were included in each of the models. Further, because of the intercorrelated structure of muscular endurance and of maximal strength tests multiple multivariate regressions were performed to calculate the standardized β-coefficients. First, muscular endurance tests were explained by maximal strength tests and body composition. Secondly, strength tests were explained by endurance tests and body composition. The level of significance was set at p<0.05.

#### 5 RESULTS

### 5.1 Physical activity, physical fitness and body composition

The distribution of low, moderate and high LTPA was 30%, 40% and 30% and, for CPA corresponding values were 28%, 38% and 35%, and for OPA 27%, 19% and 54%, respectively. Positive trends were found for all fitness parameters and waist circumference across the LTPA groups, whereas a positive trend was found for cardiorespiratory fitness, sit-ups, repeated squats and waist circumference across the CPA groups. OPA was not associated with any variable other than grip strength (Table 3). All of these analyses were adjusted for age, smoking and the other two types of physical activity

The high LTPA group had a lower concentration of glucose and higher systolic blood pressure compared to the moderate group, as well as higher HDL -cholesterol compared to the low group after adjustment for age, smoking and the other two types of physical activity (Table 3). After these adjustments, the high CPA group had significantly lower systolic and diastolic blood pressure compared to the low CPA group (Table 3). After further adjustment for waist circumference, statistically significant differences between the activity groups remained for systolic blood pressure across the LTPA groups only and for plasma glucose between the OPA groups (Table 4).

Group comparisons of physical fitness and waist circumference (mean + SD) between the activity groups in LTPA, CPA and OPA adjusted for age, smoking and the other two types of physical activity. TABLE 3

									Grip				Leg		Waist	
	<b>V</b> 0 <sup>2</sup>		Push-		Repeated		Sit-		streng	ш	Bench		extesi-		circum-	
	max		sdn		squats		sdn		ŧ	2	ress		ou		ference	
	(mL·min		(reps/				(reps/			'						
LTPA	( -6X-		min)		(reps/min)		min)		(kg)	_	<del>2</del>		Ĉ		(cm)	
Low	37.6 ±		24±11		40 <del>±</del> 9		33±9		52.7 ±	ω	129 ±		2739 ±		87.5 ±	
	6.9								8.9	_	. 67		826		11.7	
Moderate	41.6±	∢	27±11	ø	44±8	4	38∓8	4	52.6 ±	ω	372 ±	B	2939 ±		86.5 ±	
	7.3								8.5	_	.62		830		10.6	
High	45.7 ±	A, B	37±13	A, B	48±7	Ą, B	44±10	Ą B	54.3 ±	b 1	Ŧ 600	A, B	3162 ±	A, b	84.8 ±	Ø
	8.1								9.4	N	:27		924		8.3	
CPA																
Low	39.4 ±		27±12		42±9		36±10		53.6 ±	ω	388 ±		2894 ±		87.5 ±	
	7.6								9.5	_	96		873		11.7	
Moderate	41.6±	æ	28±13		44±7		39±10		53.2 ±	ဟ	∓ 90(		2894 ±		86.5 ±	
	8.1								9.2	1.1	:01		962		10.6	
High	43.4 ±	A, b	31±13		45±9		39±10	æ	52.7 ±	ဟ	03 ∓		3032 ±		84.8 ±	В
	8.1								8.4	_	199		943		8.3	
OPA																
Low	40.9 ±		28±13		44±9		39±11		52.3 ±	ω	∓ 668		2960 ±		₹6.9	
	8.0								9.7	1.1	:22		864		10.8	
Moderate	42.4 ±		27±13		44±8		39±11		52.6 ±	ω	384		2920 ±		86.2 ±	
	8.3								8.6	+1	:186		885		9.1	
High	41.8 ±		30±13		44∓9		38±10		53.9 ∓	<b>a</b>	∓ 60€		2955±8		82.8 ∓	
	7.9								8.7	_	91		26		10.5	

A p<0.001 compared to low group, **a** p<0.05 compared to low group, **B** p<0.001 compared to moderate group, **b** p<0.05 compared to moderate group

Group comparisons of selected cardiovascular risk factors (mean + SD) between the activity groups in leisure time (LTPA), commuting (CPA) and occupational physical activity (OPA). TABLE 4

	Diastolic		Serum							
blood pres- sure	-S		HDL- cholesterol		Serum LDL- cholesterol	_ •	Plasma glucose		Serum trigly- cerides	
M		M		M		M		M	M (mmol/L)	M
1 2 (mm/Hg)		1	(mmol/L)	1	(mmol/L)	1 2 (m	(mmol/L)	1		1
					1					
8 ± 8/			1.44 ± 0.34		$2.47 \pm 0.05$	5.3	5.39 ± 0.44		$1.11 \pm 0.60$	
20 ± 8		a	$1.49 \pm 0.38$		$2.45 \pm 0.64$	5.4	$5.43 \pm 0.39$		$1.01 \pm 0.48$	
b a 77±8			$1.55 \pm 0.35$	Ø	$2.35 \pm 0.58$	5.3	$5.36 \pm 0.41$	q	$0.96 \pm 0.49$	
78 ± 8			$1.47 \pm 0.37$		$2.48 \pm 0.71$	5.3	$5.38 \pm 0.41$		$1.07 \pm 0.59$	
77 ± 9			$1.49 \pm 0.36$		$2.40 \pm 0.62$	5.3	$5.36 \pm 0.41$		$1.05 \pm 0.58$	
a 76±8		æ	$1.51 \pm 0.35$		$2.41 \pm 0.55$	5.4	$5.43 \pm 0.41$		$0.96 \pm 0.39$	
77 ± 8			$1.47 \pm 0.37$		$2.45 \pm 0.65$	5.3	$5.35 \pm 0.39$		$1.05 \pm 0.58$	
76 ± 8			$1.48 \pm 0.36$		$2.45 \pm 0.60$	5.3	$5.38 \pm 0.43$		$1.02 \pm 0.55$	
77 ± 8			$1.50 \pm 0.36$		$2.40 \pm 0.63$	5.4	$5.42 \pm 0.41$	a	1.01 ± 0.48	

M1 (Model 1) adjusted for age, smoking and the other two types of physical activity; M2 (Model 2) adjusted for age, smoking, the other two types of physical activity and waist circumference

Furthermore, the likelihood of having a continuous CVD risk factor score was significantly higher (16-21%) in the moderate and low CPA groups compared to the high CPA group after adjustment for age smoking and the other two types of physical activity. Additional adjustment for waist circumference attenuated these likelihoods. However, the moderate CPA group had a higher likelihood (17%) compared to the high CPA group. Moreover, the likelihood was not significantly higher in the low or moderate LTPA or OPA groups when compared to their high physical activity reference groups in either regression model (Table 5).

TABLE 5 Odds ratios for having the clustered CVD risk factor score in the leisure time (LTPA), commuting (CPA) and occupational physical activity (OPA) groups.

	Model 1	Model 2
LTPA		
Low	1.39 (0.82-2.35)	0.96 (0.54-1.69)
Moderate	0.98 (0.59-1.63)	0.70 (0.41-1-21)
High	1	1
CPA		
Low	1.87 (1.16-3.02)	1.54 (0.91-2.59)
Moderate	1.99 (1.21-3.28)	2.00 (1.17-3.41)
High	1	1
OPA		
Low	1.04 (0.65-1.64)	0.96 (0.58-1.58)
Moderate	0.72 (0.41-1.26)	0.75 (0.42-1.37)
High	1	1

Model 1 Adjusted for age, smoking and the other two types of physical activity Model 2 Adjusted for age, smoking, the other two types of physical activity and waist circumference

# 5.2 Associations of physical fitness with cardiovascular risk factors and inflammatory biomarkers

Maximal strength was inversely associated with triglycerides, LDL-cholesterol, systolic and diastolic blood pressure controlling for age and smoking. However, after adjustment for CRF, only a weak positive association was found between maximal strength and diastolic blood pressure. Muscular endurance was associated with all of the cardiovascular risk factors and the further adjustment for cardiorespiratory fitness attenuated these associations, although they all remain statistically significant (table 6). Cardiorespiratory fitness was inversely associated with all of the cardiovascular risk factors, except HDL-cholesterol after adjustment for age and smoking. Further adjustment for maximal strength and muscular fitness attenuated the associations, leaving statistically significant associations with LDL-cholesterol, HDL-cholesterol and triglycerides (table 6).

The associations of maximal strength, muscular endurance and cardiorespiratory fitness with single cardiovascular risk factors (the standardized  $\beta$ -coefficients from multivariate regression models).

					Systolic		
	TDT	HDL	Serum-	Plasma	plood	Diastolic blood	boold
	cholesterol	cholesterol	triglycerides	glucose	pressure	pressure	
Maximal strength							
index (MSI)							
Model A	- 0.12 ***	0.07	- 0.12 ***	- 0.04	- 0.07 *	- 0.14 ***	
Model B‡	- 0.05	0.003	- 0.02	0.0001	- 0.04	* 80.0	
Muscular endurance							
index (MEI)							
Model A	- 0.23 ***	0.24 ***	- 0.25 ***	- 0.16 ***	- 0.22 ***	- 0.21 ***	
Model B‡	- 0.15 **	0.17 ***	* 60.0 -	- 0.14 **	- 0.23 ***	- 0.17 ***	
Cardioresniratory							
fitness (CRF)							
Model A	- 0.22 ***	0.21 ***	- 0.30 ***	- 0.13 ***	- 0.11 **	- 0.17 ***	
Model B †	- 0.14 **	0.11 *	- 0.24 ***	- 0.02	0.03	- 0.08	
	,						

Model A adjusted for age and smoking Model B  $\ddagger$  adjusted for age, smoking and CRF Model C  $\dagger$  adjusted for age, smoking, MSI and MEI. \*\*\* p<0.001, \*\* p<0.005, \*p<0.05

Maximal strength, muscular endurance and cardiorespiratory fitness were all inversely associated with the continuous clustered cardiovascular risk factor score after adjustment for age and smoking. In addition, muscular endurance was inversely associated with the clustered risk factor independent of cardiorespiratory fitness, whereas maximal strength was not independently associated. Cardiorespiratory fitness was inversely associated with the clustered risk factor independent of maximal strength and muscular endurance (table 7). Furthermore, when waist circumference was further adjusted in the regression models, the associations of cardiorespiratory fitness and muscular endurance with single and clustered CVD risk factors became non-significant. Moreover, in a model including waist circumference and all fitness parameters the strongest relationship was observed between waist circumference and the clustered CVD risk factor score ( $\beta$ =0.41, p<0.001), and values for all fitness parameters were non-significant.

TABLE 7 Associations of maximal strength, muscular endurance and cardiorespiratory fitness with continuous clustered cardiovascular risk factor score (the standardized β-coefficients from multivariate regression models).

	Maximal strength	Muscular endurance	Cardiorespiratory fitness
Model A	- 0.16 ***	- 0.37 ***	- 0.32 ***
Model B	0.06 ‡	- 0.26 * ‡	- 0.16 *** <b>†</b>
Model C	0.04 ‡	- 0.05 ‡	- 0.08 †

Model A adjusted for age and smoking, ‡ Model B adjusted for age, smoking and CRF, † Model B adjusted for age, smoking, MSI and MEI, ‡ Model C adjusted for age, smoking, waist circumference and CRF, † Model C adjusted for age, smoking, waist circumference, MSI and MEI. \*\*\* p<0.001, \*\* p<0.005, \*p<0.05

All physical fitness variables were inversely and weakly to moderately correlated with CRP and IL-6 concentrations in abdominally obese and non-obese groups, except that no association was found between maximal strength and CRP in the obese group (Table 8). Moreover, maximal strength was weakly and inversely associated with TNF-alpha concentration in those without abdominal obesity, but not in abdominally obese individuals. Waist circumference was from weakly to moderately and positively associated with all inflammatory factors in those without abdominal obesity and with CRP in those with abdominal obesity.

TABLE 8 Pearson correlation coefficients for physical fitness variables, waist circumference and inflammatory factors in the entire study population and stratified by waist circumference

	Maximal Strength	Muscular Endurance	Cardiorespira- tory Fitness	Waist Cir-
	(MSI)	(MEI)	(CRF)	cumference
The entire study				
population (n=686)				
CRP	- 0.28 ***	- 0.46 ***	- 0.46 ***	0.47 ***
IL-6	- 0.20 ***	- 0.26 ***	- 0.29 ***	0.26 ***
TNF-alpha	- 0.07 *	- 0.05	- 0.03	0.10 **
Waist (<102 cm)				
(n=635)				
CRP	- 0.24 ***	- 0.41 ***	- 0.42 ***	0.42 ***
IL-6	- 0.16 ***	- 0.24 ***	- 0.25 ***	0.19 ***
TNF-alpha	- 0.08 *	- 0.04	- 0.02	0.10 *
Waist (>102 cm)				
(n=51)				
CRP	- 0.24	- 0.42 **	- 0.41 **	0.32 *
IL-6	- 0.46 ***	- 0.44 ***	- 0.30 ***	0.27
TNF-alpha	0.10	0.13	0.13	- 0.03

\*\*\* p<0.001, \*\* p<0.005, \*p<0.05

After adjustment for age, smoking and cardiorespiratory fitness, maximal strength and muscular endurance were inversely and weakly associated with CRP and IL-6 concentrations in those without abdominal obesity and moderately with IL-6 in those with abdominal obesity. Moreover, after adjustment for smoking and muscular fitness, cardiorespiratory fitness was inversely and weakly to moderately associated with CRP in both abdominally obese and non-obese, and weakly associated with IL-6 in those without abdominal obesity. TNF-alpha was not associated with any of the physical fitness variables (Table 9).

TABLE 9 The associations of maximal strength, muscular endurance and cardiorespiratory fitness with inflammatory factors (the standardized beta-coefficients from the regression models) stratified for waist circumference.

	Maximal Strength (MSI) †	Muscular Endurance (MEI) †	Cardiorespira- tory Fitness (CRF) ‡
Waist (<102 cm)			
(n=635)			
CRP	- 0.11 **	- 0.26 ***	- 0.26 ***
IL-6	- 0.08 *	- 0.14 **	- 0.13 *
TNF-alpha	- 0.08	- 0.04	0.02
Waist (>102 cm)			
(n=51)			
CRP	- 0.09	- 0.28	- 0.36 *
IL-6	- 0.49 ***	- 0.39 *	- 0.08
TNF-alpha	0.08	0.07	0.07

Adjusted for smoking and † CRF or ‡ MSI and MEI. \*\*\* p<0.001, \*p<0.05

# 5.3 Associations of muscular fitness test scores with cardiorespiratory fitness and body composition

The number of push-ups was moderately correlated with maximal force in bench press and  $VO_2$ max (p<0.001), whereas repeated squats correlated weakly with maximal leg extension force and moderately with  $VO_2$ max (p<0.001) (Figure 10). In addition, maximal force in bench press was also correlated with the number of sit-ups (r=0.37, p<0.001) and maximal grip strength (r=0.34, p<0.001). The number of push-ups correlated with repeated squats (r=0.55, p<0.001) and sit-ups (r=0.65, p<0.001). In addition, sit-ups and MEI correlated with  $VO_2$ max (r=0.48-0.58, p<0.001, respectively) (Table 10).

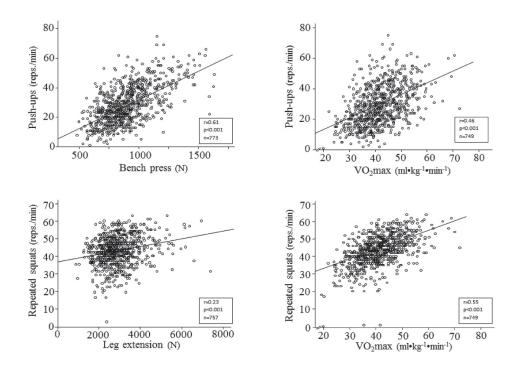


FIGURE 10 Correlation coefficients for push-ups and bench press, push-ups and VO<sub>2</sub>max, repeated squats and leg extension, and repeated squats and VO<sub>2</sub>max (B).

TABLE 10 Pearson correlation coefficient for muscular endurance, muscular strength and cardiorespiratory fitness.

	Bench press (N)	Leg extension (N)	Grip strength (kg)	VO₂max (mL•kg <sup>-1</sup> •min <sup>-1</sup> )
Repeated squats (reps/min)	r 0.28 ***	r 0.23 ***	r - 0.02	r 0.55 ***
Sit-ups (reps/min)	0.37 ***	0.14 ***	- 0.04	0.48 ***
Push-ups (reps/min)	0.61 ***	0.22 ***	0.13 ***	0.46 ***
Muscular endurance index	0.49 ***	0.22 ***	0.02	0.58 ***
Maximal strength index	0.80 ***	0.77 ***	0.71 ***	0.03
Grip strength (kg)  *** p<0.001	0.34 ***	0.27 ***	1.0	- 0.03

Among the body composition variables, FFM was the most strongly associated with maximal strength tests, reaching a moderate association, whereas muscular endurance tests were either weakly or non-significantly associated with FFM. Muscular endurance tests were more strongly associated with waist circumference, albeit only reaching weak to moderate associations. (tables 11-12). In addition, the multiple multivariate regressions revealed a moderate association between push-ups and bench press ( $\beta$ =0.67, p<0.001) and weak association with VO<sub>2</sub>max ( $\beta$ =0.24, p<0.001). A weak to moderate association was observed between repeated squats and leg extension ( $\beta$ =0.19, <0.001) as well as with VO<sub>2</sub>max ( $\beta$ =0.43, p<0.001) (Table 12-13).

TABLE 11 Pearson correlation coefficients between maximal strength and muscular endurance and body composition variables

	Body mass	Waist circumfe-	Body mass	Fat mass	% Body	Fat free mass
	(kg)	rence (cm)	index	(kg)	fat	(kg)
Leg extension (N)	0.28 ***	0.21 ***	0.28 ***	0.12 ***	0.06 ***	0.36 ***
Bench press (N)	0.21 ***	0.08 *	0.24 ***	- 0.01	- 0.09 *	0.39 ***
Grip strength (kg)	0.27 ***	0.17 ***	0.18 ***	0.03	- 0.06	0.44 ***
Repeated squats	- 0.35 ***	- 0.40 ***	- 0.29 ***	- 0.44 ***	- 0.43 ***	- 0.13 ***
(reps/min)						
Sit-ups (reps/min)	- 0.32 ***	- 0.41 ***	- 0.32 ***	- 0.45 ***	- 0.45 ***	- 0.06
Push-ups (reps/min)	- 0.32 ***	- 0.39 ***	- 0.25 ***	- 0.44 ***	- 0.47 ***	- 0.07
Maximal strength	0.33 ***	0.21 ***	0.31 ***	0.06 ***	- 0.04	0.52 ***
index						
Muscular endurance	- 0.38 ***	- 0.47 ***	- 0.33 ***	- 0.51 ***	- 0.52 ***	- 0.11 *
index						

<sup>\*</sup> p<0.05, \*\*\* p<0.001

TABLE 12 Standardized beta-coefficients from a multiple multivariate regression model between body composition, muscular endurance and cardiorespiratory fitness test scores.

	Independent varia-	Standardized
Dependent variable	bles of the model	β-coefficient
Repeated squats	$VO_2$ max	0.43 ***
	Bench press	0.24 ***
	Leg extension	0.19 ***
	WC	- 0.12 *
	FFM	- 0.11 *
	Grip strength	- 0.05
Sit-ups	Bench press	0.39 ***
	WC	- 0.33 ***
	VO <sub>2</sub> max	0.25 ***
	Grip strength	- 0.13 ***
	FFM	0.08
	Leg extension	0.02
Push-ups	Bench press	0.67 ***
	VO <sub>2</sub> max	0.24 ***
	WC	- 0.24 ***
	FFM	- 0.16 ***
	Leg extension	- 0.01
	Grip strength	0.04

TABLE 13 Standardized beta-coefficients from a multiple multivariate regression model between body composition, maximal strength and cardiorespiratory fitness test scores.

	Independent varia-	Standardized β-
Dependent variable	bles of the model	coefficient
Grip strength	FFM	0.53 ***
	Push-ups	0.28 ***
	Sit-ups	- 0.21 ***
	WC	- 0.13 *
	Repeated squats	- 0.01
	VO <sub>2</sub> max	- 0.05
Bench press	Push-ups	0.70 ***
	FFM	0.36 ***
	VO <sub>2</sub> max	- 0.14 ***
	WC	0.12 *
	Repeated squats	0.05
	Sit-ups	0.23
Leg extension	FFM	0.31 ***
· ·	Repeated squats	0.27 ***
	Push-ups	0.19 ***
	WC	0.14 *
	VO <sub>2</sub> max	- 0.08

#### 6 DISCUSSION

The main findings of the present study were that high commuting physical activity was associated with reduced likelihood for the clustered CVD risk factor, whereas a similar association was not evident in leisure-time or occupational physical activity. Secondly, muscular endurance was inversely associated with the clustered CVD risk factor independent of cardiorespiratory fitness, whereas cardiorespiratory fitness was similarly associated independent of the dimensions of muscular fitness. Maximal strength was not, however, associated with the CVD risk factor score independent of cardiorespiratory fitness. Thirdly, maximal strength and muscular endurance were inversely associated with some of the inflammatory biomarkers independent of cardiorespiratory fitness. In addition, cardiorespiratory fitness was inversely associated with some of the inflammatory biomarkers of muscular fitness. Although cross-sectional, the present findings may suggest that high levels of aerobic and muscular fitness are beneficially related to some of the cardiovascular risk factors and inflammatory biomarker concentrations in young healthy men. Therefore, it is suggested that different modalities of exercise training may induce cardioprotective and anti-inflammatory effects and thereby improve cardiovascular health.

# 6.1 Associations of physical activity with cardiovascular risk factors and physical fitness

The prevalence of physical activity in the present study was different compared to other adult Finnish study samples. Wennmann et al. (2014) reported in over 6000 Finnish adults (25-74 yrs.) that the prevalence of low, moderate and high LTPA was 60%, 49% and 32%, CPA 63%, 26% and 11%, and, OPA 61%, 21% and 19%, respectively. Helakorpi et al. (2010) reported that among nearly 3000 15-64 years old participants the prevalence of low, moderate and high volumes of light-intensity aerobic type of LTPA was 52%, 11% and 35% and for vigorous aerobic type of LTPA 47%, 29% and 30%, respectively. In the present study,

LTPA and CPA were more evenly distributed between the activity groups and the proportion of those involved in high OPA (54%) was much higher compared to these recent studies. In addition, the proportion of participants with no self-reported physical activity (LTPA: 13 % and CPA: 11 %) was markedly lower in the present study.

An increased likelihood of the clustered CVD risk factor was found in the low and moderate CPA groups compared to the high group, whereas no association was observed between the LTPA groups. Similar to the present study, Kwasniewska et al. (2010) reported an inverse association between CPA and metabolic syndrome. Most recent cross-sectional studies have reported that high LTPA is associated with reduced likelihood of the clustered CVD risk factor (Ekblom-Bak et al. 2010, Churilla et al. 2012, DuBose et al. 2005), whereas a lack of association has also been observed (Ford et al. 2005). In the present study, the associations were attenuated after adjustment for waist circumference. This may suggest that the effect of CPA on CVD risk factors is partly mediated through waist circumference.

Furthermore, in the present study, there was no consistent pattern of differences in single CVD risk factors within the CPA or LTPA groups. The high CPA group had lower systolic and diastolic blood pressure compared to the low CPA group, and the high LTPA group had a lower concentration of plasma glucose and a higher concentration of HDL-cholesterol compared to the low activity group. However, these differences were small indicating little clinical significance. Furthermore, adjustment for waist circumference attenuated some of the associations to non-significant levels. Previous cross-sectional studies have shown, similar to the present study, an inverse association between CPA and blood pressure (von Huth et al. 2007, Gordon-Larsen et al. 2010, and between LTPA and blood pressure (Barengo et al. 2006, Jakes et al. 2003). Nevertheless, contradictory findings exist as well (Hu et al. 2002, Barengo et al. 2006, von Huth et al. 2007, Gordon-Larsen et al. 2010, Kronenberg et al. 2000, O'Donovan et al. 2005, DuBose et al. 2005). The contradictory findings observed may be explained, for example, by the different models for confounding factors, measurement error in PA assessments and different age and fitness levels of the study populations.

In the current study, no associations were observed between CPA and lipids or plasma glucose. This is in line with some of the recent cross-sectional studies (von Huth et al. 2007, Gordon-Larsen et al. 2010) and contradictory to other studies (Huth et al. 2007, Gordon-Larsen et al. 2010, Barengo et al. 2006). LTPA has been shown to be inversely associated with lipids in several previous cross-sectional studies (Jakes et al. 2003, Kronenberg et al. 2000, O'Donovan et al. 2005, von Huth et al. 2007), however, no associations have also been observed (Panagiotakos et al. 2003, von Huth et al. 2007, Fung et al. 2000, O'Donovan et al. 2005, DuBose et al. 2005). The most consistent positive associations in cross-sectional studies have been reported between HDL-cholesterol and LTPA (Barengo et al. 2006, Jakes et al. 2003, Kronenberg et al. 2000, Panagiotakos et al. 2003, von Huth et al. 2007, Fung et al. 2000).

The evidence from randomized controlled trials introduced by several meta-analyses supports the beneficial effects of physical activity on blood pressure (Cornelissen & Fagard 2005, Whelton et al. 2002, Cornelissen et al. 2013) and lipids (Durstine et al. 2001, Halbert et al. 1999, Kelley et al. 2004, Kelley et al. 2005, Leon & Sanchez 2001, Lokey & Tran 1989, Kodama et al. 2007, Leon et al. 2001, Tambalis et al. 2009). Nevertheless, opposing results have also been reported regarding lipids (Kelley et al. 2005, Lokey et al. 1989, Tambalis et al. 2009, Durstine et al. 2001).

The high LTPA group had significantly better results in all physical fitness parameters and waist circumference, whereas the high CPA group showed better results in cardiorespiratory fitness, some of the muscular endurance tests and waist circumference compared to other CPA groups. The results seem plausible, because LTPA can include a wide variance of physical activity from endurance to power and strength as well as motor coordination and flexibility exercises. Additionally, previous cross-sectional studies have shown, similar to the present study findings, that cardiorespiratory fitness is better in those who actively commute to work or school (Cooper et al. 2006, Andersen et al. 2009, Larouche et al. 2014, Ostergaard et al. 2013)

A significant association was observed between the clustered CVD risk factor and CPA but not LTPA in the current study. The contradictory findings may derive from few factors such as measurement error between different PA questionnaires, the age and health status of the participants and the crosssectional study design. Firstly, questionnaires always involve some uncertainty with validity, which may be affected, for example, by social desirability bias, whereby physical activity in over reported. If over reporting took place in the present study it may have been more common in the LTPA than the CPA question. This reasoning is based on the fact that CPA is a more routinely engaged activity that includes steady duration and possibly intensity as well, whereas engagement in LTPA can vary more over time including variations in volume and intensity. This would result in greater validity of the CPA question. In support of this speculation, Marshall et al. (2010) reported that routine activities such as active travel to work were more accurately remembered compared to the less structured activities such as LTPA. Similarly, Borrestad et al. (2013) observed an association between self-reported cycling to school and objectively measured cycling (r=0.60). Secondly, the study sample herein consisted of young and rather healthy participants, and compared to some populationbased studies (Wennman et al. 2014, Helakorpi et al. 2010), the variance in activity was smaller. This may have resulted in weaker associations between physical activity and CVD risk factors. Thirdly, as confounding factors are present in each observational study, they may interfere with the associations. Despite the attempt to control some of these factors, tother confounders may exist that modify the relationships.

Furthermore, no associations were observed in the current study for clustered CVD risk or single risk factors between the OPA groups. This is in line with the results of Sisson et al. (2009) and Mozumdar & Liguori (2011). In addi-

tion, some previous studies have shown no associations between OPA and single CVD risk factors (Oppert et al. 2006, Sisson et al. 2009, Mozumdar et al. 2011). Nevertheless, an inverse association between OPA and blood pressure (Barengo et al. 2006, Fransson et al. 2003), and a positive association with HDLcholesterol (Barengo et al. 2006, Fransson et al. 2003, Sofi et al. 2007, Salonen et al. 1988, Lakka & Salonen 1992) and systolic blood pressure (Pols et al. 1997, Clays et al. 2012) have been observed. Considering the young and rather healthy study sample in the present study, it seems plausible that no association was found. It can be speculated that work including either high or low physical activity may not have had a sufficient time to interact with the CVD risk factors, because the participants were young and at the beginning of their working careers. In addition, for an individual, it may be difficult to evaluate the mean physical demands of the work, especially in younger adults who are more likely to have short term or temporary jobs. Furthermore, it may appear that even the high physical occupational activity does not represent a sufficient stimulus to the cardiovascular and metabolic systems in young and healthy adults. This is indirectedly supported by the results in physical fitness, where no other differences between the OPA groups were observed other than grip strength. No differences in physical fitness or CVD risk factor parameters may thus be explained by the insufficient stimulus caused by OPA.

High OPA has been linked with better cardiorespiratory fitness and maximal isometric grip strength in some studies (Tammelin et al. 2001, Tammelin et al. 2002, Era et al. 1992, Torgen et al. 1999). However, similar to the present study, previous studies have also shown no association between OPA and cardiorespiratory fitness, as well as maximal isometric grip strength (Holtermann et al. 2012, Tuxworth et al. 1986, Ilmarinen et al. 1991). Engagement in either LTPA or CPA may, therefore, be recommended for those individuals with high occupational activity, in order to improve physical fitness and CVD risk factors.

### 6.2 Associations of physical fitness with cardiovascular risk factors

In the present study, muscular endurance was inversely associated with the clustered cardiovascular risk factor score and with each of the single CVD risk factors independent of cardiorespiratory fitness. Furthermore, cardiorespiratory fitness was associated with the clustered CVD risk factor and with some of the single CVD risk factors independent of muscular fitness. On the other hand, maximal strength was not associated with any of the single or the clustered cardiovascular risk factor independent of cardiorespiratory fitness.

Earlier cross-sectional studies have shown an inverse association between cardiovascular risk factors and muscular fitness index (Artero et al. 2011, Garcia-Artero et al. 2007, Kim et al. 2011, Steene-Johannessen et al. 2009) and maximal strength (Atlantis et al. 2009, Benson et al. 2006, Jurca et al. 2004, Jurca et al.

2005, Senechal et al. 2014, Wijndaele et al. 2007). After adjustment for cardiorespiratory fitness, these associations have attenuated and decreased to non-significant levels in some (Jurca et al. 2005, Wijndaele et al. 2007) but not all studies (Artero et al. 2011, Benson et al. 2006, Garcia-Artero et al. 2007, Kim et al. 2011, Senechal et al. 2014, Steene-Johannessen et al. 2009, Wijndaele et al. 2007). Cardiorespiratory fitness was associated with the clustered CVD risk factor independent of muscular fitness in the present study. Recently, previous studies have also shown CRF to be associated with CVD risk factors (Delvaux et al. 2011, Ekblom-Bak et al. 2009, Racette et al. 2006, Sacheck et al. 2010, Wijndaele et al. 2007).

Previous cross-sectional studies have measured either maximal strength only or a combination of muscular endurance and maximal strength to form a muscular fitness index. Therefore, comparison between the present and earlier findings is rather difficult. It has been suggested that combining measures of both upper and lower body strength would be a better predictor of health outcomes than grip strength only (Lee et al. 2012). Comparison with previous studies is also challenged by the fact that correction for body composition differs between the studies. In some studies, no corrections for muscular fitness scores have been used (Kim et al. 2011, Kohl et al. 1992, Steene-Johannessen et al. 2009), whereas in others the muscular fitness score has been divided by body mass (Artero et al. 2007, Jurca et al. 2004, Jurca et al. 2005, Steene-Johannessen et al. 2009) or fat free mass (Atlantis et al. 2009, Wijndaele et al. 2007). The findings from the present study suggest that future studies are also warranted to distinguish between muscular endurance and maximal strength due to their different associations with cardiovascular risk factors, body composition and other fitness parameters.

Some prospective studies have shown an independent relationship between muscular fitness and health outcomes independent of CRF (e.g. Artero et al. 2011, Grontved et al. 2013, Steene-Johannessen et al. 2009). This may imply that resistance training could be beneficially associated with health outcomes beyond those of CRF. Many of the previous studies report and conclude superior benefits of aerobic training for health outcomes compared to resistance training (Slentz et al. 2011, Bateman et al. 2011, Williams et al. 2007). This has been speculated to result from e.g. generally lower energy expenditure in resistance training compared to aerobic training (Slentz et al. 2011). However, some studies have shown resistance training to improve glycemic control and insulin sensitivity, but not lipid or lipoprotein concentrations, to a similar extent or even more than aerobic training (Sigal et al. 2007, Strasser et al. 2013, Strasser et al. 2010, Moe et al. 2011). These observations are, however, mainly limited to obese and/or type 2 diabetic subjects (Strasser et al. 2010, Church et al. 2010, Moe et al. 2011). A recent meta-analysis observed that in type 2 diabetic patients, the combined training elicited superior effects on glycemic control and blood lipids compared to aerobic or resistance training alone (Schwingschackl et al. 2014). Furthermore, in overweight and obese individuals combined training was the most effective at improving body composition characteristics (Schwingschackl

et al. 2013). Church et al. (2010) observed in their randomized controlled trial in type 2 diabetics that combined training had a greater effect on HbA1c-levels than either exercise type alone. Importantly, energy expenditure was matched equal in the different training groups in the study. Furthermore, combined self-reported resistance and aerobic training was inversely associated with lipids and lipoproteins independent of PA volume in a previous cross-sectional study (Pitsavos et al. 2009). These results may indicate that combining aerobic and resistance training yeilds more health benefit than either one alone. Therefore, combined training it is recommended in the PA guidelines (Haskell et al. 2007).

The physiological mechanisms behind the potential cardioprotective effect of cardiorespiratory and muscular fitness were not addressed in the present study. Nevertheless, it may be speculated that the mechanisms are mostly similar in most part for both fitness dimensions but may differ in magnitude. However, the clear difference is that through resistance training there is more potential to increase muscle mass, whereas through aerobic training there is more potential to increase aerobic capacity and peripheral adaptations, e.g. skeletal muscle capillary density. The physiological mechanisms of the beneficial cardioprotective effects include improvements in glycemic control, glucose tolerance and insulin sensitivity (Roberts et al. 2013). These effects may be mediated by changes in increased protein content of GLUT4, insulin receptors, protein kinase b-alpha/beta, glycogen synthase and its total activity synthase as well as increased muscle glycogen stores (Holten et al. 2004, Castaneda et al. 2002). The reduced lipid and lipoprotein concentrations and their subclass distribution may result from increased lipoprotein lipase activity in skeletal muscle (Hamilton et al. 2004) and decreased hepatic triglyceride lipase activity (Pronk 1994). These lead to increased cleareance rate of plasma triglycerides, increased transport of lipids and lipoproteins from the peripheral circulation and tissues to the liver (Carnethon et al. 2003) and increased fatty acid oxidation (Strasser & Pesta 2013). In addition, exercise may improve autonomic nervous system and endothelial function (Carnethon et al. 2003).

A stronger association between waist circumference and the clustered cardiovascular risk factor was observed compared to cardiorespiratory fitness and muscular endurance in the current study. Most previous cross-sectional studies have shown that body fat outcomes were more strongly associated with CVD risk factors than cardiorespiratory fitness (Christou et al. 2005, Jago et al. 2010, Ondrak et al. 2007, Racette et al. 2006). Nevertheless, a rather similar magnitude of cardiorespiratory fitness and waist circumference as predictors of CVD risk factors has also been observed (Ekblom-Bak et al. 2009). Some studies have aimed to address how fitness, namely cardiorespiratory fitness, and fatness are related to health outcomes, and more specifically, to what extent they counteract each other for health outcomes. These studies are, however, limited only to cardiorespiratory fitness. Fogelholm (2010) reported that the risk of all-cause and CV mortality was higher in individuals with normal BMI and poor CRF compared to high BMI and good CRF. This finding indicates the ability of CRF to counteract the negative effects of obesity. However, high self-reported physi-

cal activity did not fully counteract obesity, resulting in a higher risk of type 2 diabetes and CVD risk factors for those with high BMI and physical activity compared to normal BMI and low physical activity (Fogelholm 2010). Blair & Brodney (1999) concluded in their review that physical activity and cardiorespiratory fitness were not only diminished the health risks of obesity. Moreover, they observed that regarding mortality and morbidity, active obese individuals had a lower risk compared to normal weight and inactive individuals. The beneficial effects of either resistance or aerobic training may thus, at least in part, be mediated by changes in body composition, namely reduction in body fat content, and perhaps more importantly in visceral adipose tissue.

It has also been debated whether physical activity or fitness is more strongly related with health outcomes. Although not directly assessed in the present study, these results may indicate that especially muscular endurance and cardiorespiratory fitness are more strongly related with CVD risk factors than dimensions of physical activity. Previous studies have reported similar findings regarding CRF (Sassen et al. 2009, Blair et al. 2001). Cardiorespiratory fitness has been observed to be more strongly related to mortality (Lee et al. 2011) and CVD risk factors (Sassen et al. 2009, McMurray et al. 1998, Hurtig-Wennlöf et al. 2007). than physical activity. This might partly be due to the genetic background of fitness and also to more precise, objective methods of measuring fitness, whereas self-reported physical activity is more sensitive to measurement bias. However, Blair et al. (2001) concluded in their review that when comparing subjects with similar cardiorespiratory fitness levels, those who were active exhibited better health compared to inactive individuals. This would imply a positive effect of physical activity on health independent of CRF.

### 6.3 Associations of physical fitness with inflammatory biomarkers

Our results revealed inverse associations of maximal strength and muscular endurance with CRP and IL-6 in normal weight individuals. In addition, an inverse association of maximal strength and muscular endurance with IL-6 was observed in those with abdominal obesity. These associations were independent of cardiorespiratory fitness. Moreover, cardiorespiratory fitness was inversely associated with CRP in the entire study population independent of muscular fitness. These results suggest that both muscular and cardiorespiratory fitness may mediate low-grade inflammation independent of each other in young healthy adults. Moreover, the associations were stronger in abdominally obese individuals and no associations were observed between any of the measures of physical fitness and TNF-alpha.

Previous cross-sectional studies have reported an inverse association between muscular fitness and CRP independent of cardiorespiratory fitness in adolescents (Ruiz et al. 2008, Steene-Johannessen et al. 2013) and between max-

imal strength and IL-6 in elderly participants (Visser et al. 2002). Further adjustments for adiposity have attenuated the associations in some (Steene-Johannessen et al. 201, Ruiz et al. 2008) but not all studies (Visser et al. 2002). Recent reviews have concluded, albeit based on a limited number of studies, that resistance training may have a positive effect on CRP (de Salles et al. 2010, Strasser et al. 2012), but no significant effect on IL-6 according to a recent review of resistance training studies (Strasser et al. 2012). In addition, a review by Hamer (2007) showed that two thirds of observational studies reported an inverse association between inflammatory factors and cardiorespiratory fitness, whereas no consistent evidence was found RCTs.

Taken together, the present results suggest that different modalities of physical fitness may be differentially associated with inflammatory biomarkers (Balducci et al. 2010). In a previous study, concurrent strength and aerobic training has been shown to reduce CRP concentration (Jorge et al. 2011) in type 2 diabetic patients. Furthermore, concurrent strength and aerobic training has been demonstrated to be even more effective in modifying inflammatory profile than aerobic exercise alone in older adults with type 2 diabetes (Balducci et al. 2010). Interestingly, in the present study, the magnitudes of inverse associations of cardiorespiratory fitness and muscular endurance with CRP were rather similar in individuals without abdominal obesity, which raises the question of whether the associations are mediated, at least partly, by the same biological mechanisms. This is pertinent considering that cardiorespiratory fitness and muscular endurance are at least moderately related, as evidenced in the present study (article IV).

In addition, the present findings may indicate that the association between fitness outcomes and inflammatory biomarkers differentiate across the level of adiposity. Interestingly, the relationship between muscular fitness and IL-6 was stronger in abdominally obese individuals, and cardiorespiratory fitness was not associated with IL-6 in these individuals. The results may indicate that resistance training is particularly beneficial for abdominally obese individuals with higher baseline levels of IL-6. However, these observations were detected in a rather small study sample (n=51).

In the current study, no associations were found between maximal strength, muscular endurance or cardiorespiratory fitness with TNF-alpha, which is in agreement with a previous cross-sectional study in adolescents (Steene-Johannessen et al. 2013). Although resistance training has been reported to decrease TNF-alpha concentration in obese postmenopausal (Phillips et al. 2012) and elderly women (Phillips et al. 2010), the most resistance training studies report no changes (Calle & Fernandez 2010, de Salles et al. 2010, Levinger et al. 2009, Strasser et al. 2012).

The discrepancy between the present study and some of the earlier findings may partly relate to age or health status of the participants, the length of the training history or the study design. In the previous studies (de Salles et al. 2010, Selvin et al. 2007), most of the participants were either middle-aged, elder-

ly people or type 2 diabetic patients, whereas in the present study the participants were young and healthy adult men.

The biological mechanisms responsible for the effects of exercise training on inflammatory biomarkers are not well understood. It has been proposed that resistance training decreases CRP by reducing cytokine production in adipose tissue, muscle and mononuclear cells directly (Kasapis & Thompson 2005). Exercise induces alterations in mechanisms involved in cell surface toll-like receptors, which are a class of transmembrane proteins that recognise pathogen associated molecule patterns. Chronic exercise decreases the gene and protein expression of the toll-like receptors and, therefore, may result in lower production of pro-inflammatory cytokines from the monocytes (McFarlin et al. 2004, Stewart et al. 2005). Increased insulin sensitivity may also be a mediating factor due to its anti-inflammatory properties (Dandona et al. 2001). Moreover, the proinflammatory effects of IL-6 may increase the production of CRP by the liver (Arikawa et al. 2011, Balducci et al. 2010). Exercise affects IL-6 through an inhibitory effect on IL-6 production or a facilitatory effect on IL-6 clearance (Nicklas et al. 2008). Moreover, pro-inflammatory cytokine (such as IL-4, IL-10, IL-1 alpha) production from peripheral mononuclear cells may be decreased by exercise (Smith et al. 1999). This may relate to IL-6, since IL-6 stimulates the production of IL-10 (Steensberg et al. 2003). Furthermore, exercise may regulate the synthesis of IL-6 and other cytokines to produce an anti-inflammatory effect by increasing levels of IL-6, which may further suppress TNF-alpha.

### 6.4 Associations between physical fitness tests and body composition

The results of the present study revealed significant relationships between muscular endurance and maximal strength test scores in upper but not lower extremities. In addition, muscular endurance test scores were positively associated with maximal oxygen consumption and inversely with body fat content, while maximal strength was associated with fat free mass.

Maximal bench press was moderately associated with number of pushups, whereas maximal leg extension and number of repeated squats were only weakly associated. The results suggest that the performance of repeated squats is mainly dependent on aerobic and anaerobic capacity rather than maximal strength characteristics, whereas push-ups are also associated with maximal force of the upper extremity muscles. The differences between muscular endurance tests of the lower and upper extremities and maximal strength may partly be explained by a higher relative load (body weight) in the push-up performance than in the repeated squat performance. Moreover, the expected positive association between muscular endurance test scores and maximal aerobic capacity is in line with previous studies (Duvigneaud et al. 2008, Esco et al. 2010, Fogelholm et al. 2006, Ross & Katzmarzyk 2003, Wong et al. 2004). The results may indicate that the 1-min push-up test also provides a reasonably accurate to estimate of maximal strength of the upper extremities. This could be particularly useful when field-based testing is needed, and would allowseveral subjects to be tested simultaneously. Furthermore, based on the present findings, the repeated squat test primarily assesses local muscular endurance. A field-based or laboratory test with an additional load is therefore required to estimate maximal strength of the lower extremities.

The relationships between maximal strength and body mass or body fat content variables were weak. These relationships have been shown to be similar (Johnson et al. 1994, Markovic & Jaric 2004, Mayhew et al. 1993) or stronger (Markovic & Jaric 2004, Mayhew et al. 1993, Mayhew et al. 2007, Wijndaele et al. 2007) in previous studies compared to the present study. Moreover, fat free mass was positively associated with all maximal strength test scores in the present study supporting previous findings (Johnson et al. 1994, Mayhew et al. 1993, Viitasalo et al. 1980). In addition, previous studies have also reported higher maximal strength and power in obese subjects compared to their lean counterparts (Hulens et al. 2001, Hulens et al. 2002, Maffiuletti et al. 2007), and this has been speculated to be due to a greater amount of fat free mass in obese than lean subjects.

The inverse associations between muscular endurance performance and body fat content are in concordance with previous studies (Duvigneaud et al. 2008, Esco et al. 2010, Fogelholm et al. 2006, Markovic & Jaric 2004, Ross & Katzmarzyk 2003, Wong et al. 2004). This may partly refer to natural scaling laws, since muscular endurance tests require a person to move the body against the gravity, and therefore heavier individuals may perform worse in dynamic muscular fitness tests (Jaric 2002). A higher amount of fat mass (dead weight) may also increase the moment of inertia (Hulens et al. 2001, Fogelholm et al. 2006).

#### 6.5 Methodological considerations and limitations

A strength of the present study is a nationally representative study sample of young men with varying degrees of physical fitness. The extensive data set included cardiorespiratory fitness and the dimensions of muscular fitness. Detailed measurements of muscular fitness (muscular endurance, maximal strength) are rare in previous cross-sectional studies. To the best of our knowledge, this was the first study to assess both muscular endurance and maximal strength with cardiovascular and inflammatory biomarkers.

However, there are some limitations to be considered. We used self-reported questionnaires to assess physical activity, which may have led to reporting bias as noted previously (Fogelholm et al. 2006). Self-administered questionnaires to assess physical activity may lead to under- or overestimation and may therefore be imprecise. Self-reported physical activity measures have also been shown to be prone to recall bias or influenced by social desirability

bias. Although acceptable to good reliability with self-report instruments of assessing physical activity have been shown, the validity may be poor to moderate (Helmerhorst et al. 2012). However, not even objectively measured physical activity as measured by accelerometers or pedometers can capture all physical activities, such as lifting weights, swimming or cycling (Strath et al. 2013). Although objectively measured PA has been shown to be slightly more reliable and valid compared to self-report assessments, this method is also prone to some of the same limitations as self-report assessments concerning for example generalisability, validity, simplicity, affordability and comprehensiveness (Pedijic & Bauman 2014). Therefore, as there is no gold standard for assessing physical activity, both self-report instruments and objective measurements and especially their combination, are needed in population based studies of physical activity (Haskell et al. 2012).

In the present study, predicted  $VO_2$ max was used instead of a direct measurement due to a large sample size. However, a protocol that continued until exhaustion was used, which is more accurate compared to sub maximal tests used in some studies. Moreover, this predicted model has been previously validated with high intra-class correlation (r=0.84-0.92), although only in normal-weight individuals with moderate physical fitness levels (Santtila et al. 2013). In addition, we were not able to examine the important roles that muscle cross-sectional area and maximal voluntary activation capacity play in maximal force production (Häkkinen et al. 1987).

The BIA method was chosen to assess body composition in the present study mainly because it is a time-efficient method for large study samples, and because the reliability of BIA has been shown to be moderate or even high for %body fat, fat mass and fat free mass when dual-energy x-ray absorptiometry has been used as a reference method (r>0.69–0.98) (Boneva-Asiova & Boyanov 2008, Pateyjohns et al. 2006). Nevertheless, the BIA method may underor overestimate body composition parameters (Pateyjohns et al. 2006, Sillanpää et al. 2014) and therefore the body composition results were only used in more detail in the publication 4.

Moreover, the results of observational studies are always influenced by confounding factors, and despite our attempts to control most of these (age, smoking, other domains of physical activity and waist circumference), there may be some factors that we could not account for (e.g. nutrition, stress, sedentary behaviour etc.). Finally, due to the cross-sectional study design, these results do not indicate causal relationships.

#### 7 MAIN FINDINGS AND CONCLUSIONS

The main findings of the present study were that moderate and high commuting physical activity was associated with reduced likelihood for the clustered CVD risk factor compared to low commuting physical activity. A similar association was not evident in leisure-time physical activity or occupational physical activity. Secondly, muscular endurance was inversely associated with the clustered CVD risk factor independent of cardiorespiratory fitness, whereas cardiorespiratory fitness was similarly associated independent of the dimensions of muscular fitness. Maximal strength was not associated with the clustered CVD risk factor independent of cardiorespiratory fitness. Thirdly, maximal strength and muscular endurance were inversely associated with some inflammatory biomarkers independent of cardiorespiratory fitness. Cardiorespiratory fitness was inversely associated with some inflammatory biomarkers independent of muscular fitness.

- 1. Commuting physical activity was associated with reduced likelihood for the clustered CVD risk factor score, whereas a similar association was not evident in leisure-time physical activity or occupational physical activity. This finding may indicate a beneficial role of aerobic type of exercise for cardiovascular risk factors.
- 2. Leisure-time physical activity was positively associated with variety of physical fitness dimensions, whereas commuting physical activity was associated with aerobic capacity and muscular endurance. Occupational physical activity was only associated with grip strength. These findings emphasize the advantage of leisure-time physical activity over commuting or occupational physical activity, on different physical fitness dimensions.
- 3. Muscular endurance was inversely associated with the CVD risk factor score independent of cardiorespiratory fitness, whereas cardiorespiratory fitness was similarly associated independent of the dimensions of muscular fitness. Maximal strength was not associated with the CVD risk factor score independent of cardiorespiratory fitness. These findings may indicate that

- both muscular endurance and cardiorespiratory fitness, but not maximal strength, induce additive cardiovascular health benefits beyond the independent benefits of each one.
- 4. Maximal strength and muscular endurance were inversely associated with IL-6, as well as with CRP in normal weight (waist < 102 cm) individuals independent of cardiorespiratory fitness. Cardiorespiratory fitness was inversely associated with CRP, as well as with IL-6 in normal weight individuals independent of muscular fitness. These findings may suggest that different modalities of exercise training induce anti-inflammatory effects and thereby decrease inflammation, which is one of the risk factors for the development of cardiovascular and metabolic diseases.
- 5. The relationships between physical fitness test results may indicate that the 1-min push-up test also gives a reasonably accurate to estimate of the maximal strength of the upper extremities, and may be especially useful when a field-based test is needed and/or a number of subjects are tested simultaneously. Moreover, the repeated squat test measures local muscular endurance, and therefore a field-based or laboratory test with an additional load is required to estimate maximal strength of the lower extremities.

#### YHTEENVETO (FINNISH SUMMARY)

Fyysisen aktiivisuuden ja fyysisen kunnon yhteydet verenkiertoelimistön sairauksien riskitekijöihin nuorilla aikuisilla miehillä.

Sydän ja verenkiertoelimistön sairauksien riskitekijöitä ovat mm. lihavuus, tupakointi ja riittämätön fyysinen aktiivisuus. Fyysinen aktiivisuus voi koostua työn ruumiillisesta rasituksesta, työmatkaliikunnasta tai vapaa-ajan liikunnasta. Koska nämä fyysisen aktiivisuuden osa-alueet ovat luonteeltaan erilaisia, voivat ne olla myös eri tavalla yhteydessä sairauksien riskitekijöihin ja fyysisen kuntoon. Yhtenä tämän väitöskirjatyön tavoitteena olikin selvittää, miten fyysisen aktiivisuuden eri osa-alueet ovat yhteydessä verenkiertoelimistön sairauksien riskitekijöihin ja fyysiseen kuntoon.

Fyysisen aktiivisuuden terveysvaikutuksia on tutkittu aina 1950-luvulta lähtien. Ensimmäisissä epidemiologisissa tutkimuksissa havaittiin työn ruumiillisen rasittavuuden olevan käänteisesti yhteydessä kuolleisuuteen ja sairauksien riskitekijöihin (Morris ym. 1953, Morris ym. 1966). Myöhemmissä tutkimuksissa on myös havaittu, että fyysisen aktiivisuuden lisäksi fyysinen kunto on yhteydessä terveyteen. Kestävyyskunnon on havaittu olevan voimakkaampi terveyttä selittävä tekijä kuin fyysinen aktiivisuus. Siinä missä aiemmat tutkimukset ovat osoittaneet kestävyyskunnon edut terveydelle, on tutkimustietoa huomattavasti vähemmän siitä, miten lihaskunto on yhteydessä terveyteen. Erityisen vähän tutkittua tietoa on siitä, miten lihaskunnon osa-alueet, lihaskestävyys ja maksimivoima, ovat yhteydessä terveyteen ja ovatko nämä yhteydet riippumattomia kestävyyskunnosta. Tämän väitöskirjatutkimuksen päätarkoituksena oli selvittää, miten lihaskestävyys ja maksimivoima ovat yhteydessä verenkiertoelimistön sairauksien riskitekijöihin itsenäisesti kestävyyskunnosta riippumatta. Tutkittavina riskitekijöinä olivat veren rasva-arvot (HDL, LDL, triglyseridit), verenpaine ja tulehdustekijät (IL-6, CRP, TNF-alpha).

Väitöskirjatutkimuksessa koehenkilöinä oli 846 nuorta suomalaista miestä  $(25.0 \pm 5.0 \text{ vuotta})$ , jotka osallistuivat tutkimukseen kertausharjoitusten yhteydessä. Koehenkilöiden fyysinen aktiivisuus määritettiin kyselyillä ja fyysinen kunto mitattiin objektiivisesti. Lihaskestävyyttä mitattiin minuutin mittaisilla istumaannousu-, etunojapunnerrus- ja toistokyykistystesteillä. Ylä- ja alaraajojen maksimivoimaa mitattiin bilateraalisilla isometrisillä voimadynamometreillä ja kestävyyskuntoa maksimaalisella polkupyöräergometritestillä. Verinäytteet otettiin yön yli jatkuneen paaston jälkeen aamulla. Lisäksi koehenkilöiltä mitattiin kehon koostumus bioimpedanssimenetelmällä sekä vyötärönympärys mittanauhalla.

Tämän väitöstutkimuksen tulokset osoittivat, että työmatka- ja asiointiliikunta olivat käänteisesti yhteydessä verenkiertoelimistön sairauksien klusteroituun riskitekijään. Sen sijaan vapaa-ajan liikunta-aktiivisuudella ja työn ruumiillisella rasittavuudella ei havaittu samanlaista yhteyttä. Vapaa-ajan liikunta oli yhteydessä parempaan fyysiseen kuntoon kestävyys- ja voimaominaisuuksissa. Työmatka- ja asiointiliikunnalla oli puolestaan positiivinen yhteys kestä-

vyyskuntoon ja lihaskestävyyteen, mutta työn ruumiillisella rasittavuudella ainoastaan puristusvoimaan. Tutkimuksen päätuloksina havaittiin, että lihaskestävyys oli käänteisesti yhteydessä sydän ja verenkiertoelimistön sairauksien riskitekijöihin ja tulehdustekijöihin itsenäisesti kestävyyskunnosta riippumatta. Sen sijaan maksimivoimalla ei havaittu samankaltaista yhteyttä itsenäisesti kestävyyskunnosta riippumatta. Lihaskestävyydellä ja maksimivoimalla oli kuitenkin käänteinen yhteys joihinkin tulehdustekijöihin kestävyyskunnosta riippumatta. Lisäksi havaittiin, että lihaskestävyyden ja maksimivoiman yhteys tulehdustekijöihin oli voimakkaampi ylipainoisilla kuin normaalipainoisilla koehenkilöillä.

Tämä väitöskirja antaa viitteitä siitä, että lihaskunto ja etenkin lihaskestävyys ovat edullisesti yhteydessä verenkiertoelimistön sairauksien riskitekijöihin. Lisäksi kestävyystyyppinen liikunta, kuten työmatka- tai asiointiliikunta, on käänteisesti yhteydessä verenkiertoelimistön sairauksien riskitekijöihin. Yhdessä nämä tulokset osoittavat, että kestävyystyyppisen liikunnan ja kunnon lisäksi myös lihaskunnon rooli voi olla merkittävä sydänterveydelle.

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#### **ORIGINAL PAPERS**

Ι

# ASSOCIATIONS OF LEISURE-TIME, COMMUTING AND OCCUPATIONAL PHYSICAL ACTIVITY WITH PHYSICAL FITNESS AND CARDIOVASCULAR RISK FACTORS IN YOUNG MEN

by

Jani Vaara, Heikki Kyröläinen, Mikael Fogelholm, Matti Santtila, Arja Häkkinen, Keijo Häkkinen & Tommi Vasankari 2015

Journal of Physical Activity and Health vol 11, 1482-91

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#### II

### ASSOCIATIONS OF MAXIMAL STRENGTH AND MUSCULAR ENDURANCE WITH CARDIOVASCULAR RISK FACTORS

by

Jani Vaara, Mikael Fogelholm, Tommi Vasankari, Matti Santtila, Heikki Kyröläinen 2014

International Journal of Sports Medicine 35, 356-60

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#### III

## MAXIMAL STRENGTH, MUSCULAR ENDURANCE AND INFLAMMATORY BIOMARKERS IN YOUNG ADULT MEN

by

Jani Vaara, Tommi Vasankari, Mikael Fogelholm, Matti Santtila, Keijo Häkkinen, Heikki Kyröläinen 2014

International Journal of Sports Medicine 35, 1229-34

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#### IV

## ASSOCIATIONS OF MAXIMAL STRENGTH AND MUSCULAR ENDURANCE TEST SCORES WITH CARDIORESPIRATORY FITNESS AND BODY COMPOSITION

by

Jani Vaara, Heikki Kyröläinen, Jaakko Niemi, Olli Ohrankämmen, Arja Häkkinen, Sheila Kocay, Keijo Häkkinen, 2012

Journal of Strength and Conditioning Research 26, 2078-86

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