# Fitness, cognition and cardiovascular disease

## – Epidemiological studies

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Fitness, cognition and cardiovascular disease – Epidemiological studies

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*"My own heroes are the dreamers, those men and women who tried to make the world a better place than when they found it, whether in small ways or great ones. Some succeeded, some failed, most had mixed results... but it is the effort that's heroic, as I see it. Win or lose, I admire those who fight the good fight."*

George R.R. Martin

*To my family*

## ABSTRACT

Physical activity and fitness have well established health bringing benefits. Low socioeconomic status is a known risk factor for cardiovascular disease. This association is commonly attributed to individual factors such as educational attainment, supposedly bringing about health-related behaviours. However, individual factors do not fully account for the observed health disparities, demanding further investigation. The aims of this thesis were to investigate how physical activity and fitness varies according to neighbourhood socioeconomic status among middle-aged individuals in the Gothenburg region, using data collected for the SCAPIS-pilot study in 2012. Additional aims were to identify the role of factors related to fitness and cognitive function in the development of heart failure and cardiovascular disease in youth, with an extended follow up via population registries. For this purpose, we used data from the Swedish military service conscription registry, containing information of about 1.8 million Swedish men. We separately studied the association between cardiorespiratory fitness, muscle strength, resting heart rate, and cognitive capacity for future cardiovascular disease, recorded in the national inpatient- and cause of death registries.

Data from the SCAPIS-pilot showed that inhabitants of low-SES areas have a lower general activity level, lower rate of fulfilment of the national physical activity guidelines, and 12% lower levels of cardiorespiratory fitness, on average. These disparities translate into increased risk of cardiovascular disease, found in previous studies. Conscripts with lower levels of cardiorespiratory fitness and muscle strength, lower cognitive test scores, and higher resting heart rate showed increased risk of developing heart failure at an early age. High resting heart rate was not associated with increased risk for any other of the cardiovascular outcomes that were studied.

In summary, the results of this thesis provide new knowledge about how physical activity and cardiorespiratory fitness are potential mediators of social inequalities in cardiovascular disease. In addition, new information regarding factors in early life that influence cardiovascular health in middle age is provided.

**Keywords**: Epidemiology, Physical activity, Fitness, Heart rate, Cognition, Heart failure

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## LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I Lindgren M, Börjesson M, Ekblom Ö, Bergstrom G, Lappas G, Rosengren A. Physical activity pattern, cardiorespiratory fitness, and socioeconomic status in the SCAPIS pilot trial - A cross-sectional study.
*Preventive Medicine Reports 2016;4:44-9.*

II Lindgren M, Åberg M, Schaufelberger M, Åberg D, Schiöler L, Torén K, Rosengren A. Cardiorespiratory fitness and muscle strength in late adolescence and long-term risk of early heart failure in Swedish men.
*European Journal of Preventive Cardiology 2017;24:876-84*

III Lindgren M, Eriksson P, Rosengren A, Robertson J, Schiöler L, Schaufelberger M, Åberg ND, Torén K, Waern M, Åberg M. Cognitive performance in late adolescence and long-term risk of early heart failure in Swedish men.
*Submitted*

IV Lindgren M, Robertson J, Adiels M, Schaufelberger M, Åberg M, Torén K, Waern M, Åberg ND, Rosengren A. Resting heart rate in late adolescence and long-term risk of cardiovascular disease in Swedish men.
*Manuscript*

## CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| AF | Atrial fibrillation |
| BMI | Body mass index |
| CAD | Coronary artery disease |
| CHD | Coronary heart disease |
| CI | Confidence interval |
| CVD | Cardiovascular disease |
| CPM | Counts per minute |
| CRF | Cardiorespiratory fitness |
| HF | Heart failure |
| HR | Hazard ratio |
| ICD | International classification of disease |
| IPR | Inpatient registry |
| IQ | Intelligence quotient, cognitive capacity |
| IQR | Interquartile range |
| IS | Ischemic stroke |
| LIPA | Low intensity physical activity |
| LISA | Longitudinal integration database for health insurance and labour market studies |
| LVM | Left ventricular mass |
| MET | Metabolic equivalent |
| MI | Myocardial infarction |
| MPA | Moderate-intensity physical activity |
| MVPA | Moderate to vigorous physical activity |
| OPR | Outpatient registry |
| OR | Odds ratio |
| PA | Physical activity |
| RHR | Resting heart rate |
| SED | Sedentary |
| SES | Socioeconomic status |
| VO2max | Maximum oxygen consumption |
| VPA | Vigorous intensity physical activity |
| Wmax | Maximum work capactiy (Watts) |

# INTRODCUCTION

## A brief history

The notion that physical activity (PA) is an important determinant of health and longevity has a long history. Hippocrates (ca. 460-370 BC) famously advised that exercise, although not too much, was beneficial for health.[1] Galen (ca. 129-210 AD) further developed his ideas and emphasized the importance of vigorous movement, resulting in change in respiration. Like Hippocrates, he believed that excessive activity or athletics posed a health risk. His ideas greatly influenced the preventive medicine literature well into the 19th century.[2] The Italian physician Bernardini Ramazzini (1633-1714) is acknowledged as the father of occupational medicine. Comparing different tradesmen, he found that running messengers were spared from the health hazards of sitting professions such as tailors and cobblers, stating that their general ill health was an effect of their sedentary life and that they should be advised to increase their physical activity, at least on holidays.[3] In what may be the first recording of the effect of physical activity on angina pectoris, English physician William Heberden (1710-1801) described a patient who "set himself a task of sawing wood for half an hour each day, and was nearly cured".[4]

In the postwar period, professor Jeremy N Morris, of the London School of Hygiene and Tropical Medicine, applied modern quantitative methods to investigate the relationship between physical activity and coronary heart disease (CHD). In a classic study, Morris et al. showed that the conductors (active occupation) had a substantially lower risk of myocardial infarction (MI) as compared to drivers (sedentary occupation) of buses, trams and trolleys.[5] His colleague, Dr. Paffenbarger, later initiated two cohort studies, the San Francisco Longshoremen study and the College Alumni Health Study. Both have led to groundbreaking reports on physical activity and health.[6] In a report from the San Francisco Longshoremen, those with low caloric output jobs showed higher rates of coronary death compared to the medium- and high output groups.[7] Subsequently, increasing interest was aimed at the association between cardiorespiratory fitness (CRF) and health. A landmark study was published in 1989, when Blair et al. showed strong associations of physical fitness and all-cause mortality among men and women in the Aerobics Center Longitudinal Study.[8] Following this, he showed that improvements in fitness were associated with an almost 50% reduction in mortality risk.[9] Subsequently, efforts were made in order to further quantify the fitness-mortality relationship. In a meta-analysis of 33 longitudinal studies, Kodama et al. showed that a 1 metabolic equivalent (MET) increase of CRF was associated with a 15% and 13% risk reduction for all-cause mortality and CHD or cardiovascular disease (CVD) events and mortality, respectively.[10]

## Physical inactivity and cardiovascular disease

In a global perspective, although large regional differences are present, CVD mortality has trended downward during the last decades.[11] In spite of this, CVD persists as the main cause of death worldwide and may account for approximately 30% of all deaths,[12] the majority of which occur in middle- and low-income countries.[13] The vast majority of CVD is related to lifestyle and common modifiable risk factors. The

INTERHEART- study showed that 9 commonly known and modifiable risk factors (smoking, ApoB/ApoA, hypertension, diabetes, abdominal obesity, psychosocial factors, fresh fruit & vegetable intake, alcohol, physical inactivity) could account for 90% of the risk for myocardial infarction in men and 94 % in women, respectively.[14]

PA and CRF have widely documented health-promoting effects, including but not limited to the heart and vascular system. Regular PA and CRF prevents both the accumulation of cardiovascular risk factors[15] as well as manifestation of cardiovascular disease.[8, 10] It has been shown that the process of atherosclerosis begins already in childhood.[16] Beyond this, regular physical activity prevents age-related frailty,[17] has positive effects on memory,[18] cognition,[19] and can help treat psychiatric symptoms and disorders such as anxiety[20] and depression.[21] Regular PA may also contribute to the prevention of certain malignancies, particularly breast- and colon cancer.[22] Conversely, there is rising concern that sedentary behavior is a risk factor for disease and death from any cause, an effect that seems largely independent of the amount of PA or fitness level.[23]

### *Heart failure*

Heart failure is an important component in cardiovascular disease, representing an advanced stage of a variety of cardiovascular disorders, with coronary heart disease and hypertension predominant factors in Western populations, including Sweden, but may also be a result of acquired or congenital heart disease, arrhythmias or primary disease of the myocardium such as the cardiomyopathies. As such, heart failure is a clinical syndrome, signified by typical symptoms (including shortness of breath, ankle swelling and chronic fatigue) and signs (jugular vein stasis, pulmonary crackles and pitting edema) that can be attributed to cardiac malfunction.[24] HF is commonly classified in relation to the left ventricular (LV) ejection fraction (EF), which is a measurement of the proportion of volume ejected with each ventricular contraction (end-diastolic volume – end-systolic volume divided by the end-diastolic volume). Briefly, patients with reduced EF (<40%) are classified as HF with reduced EF (HFrEF) while those with EF within normal range (≥50) are classified as HF with preserved EF (HFpEF). EF 40-50% constitutes a grey area that is classified as mid-range, or HFmrEF.[24] These subtypes differ with respect to comorbid diseases, and it has been found that HFrEF is more commonly associated with CHD. HFpEF is more frequently associated with atrial fibrillation (AF) and hypertension and is more common among women.[25]

While HF is most frequent in the older part of the population, it is becoming increasingly common among the young in Sweden.[26] Increased rates of first time hospital admissions have also been found in the younger subset of the population.[27] These findings indicate that while HF is still rare in the younger population, the problem is increasing. Given the severity and poor prognosis of the condition[27] and that the divergent trends between the younger and older parts of the population is still largely unknown, this requires further investigation.

The obesity epidemic[28] may be an important contributing factor. High BMI has been found a strong predictor of HF in young Swedish men, increased risk found already within the normal range of BMI.[29] It has become evident that physical inactivity is

also an increasing threat to global public health. It is estimated that 31% of the adult population do not adhere to current PA recommendations.[30] Furthermore, it has been estimated that 6-10% of deaths from all non-communicable diseases and up to 30% of deaths from coronary artery disease can be attributable to physical inactivity.[31] While regular PA and CRF has been frequently associated with lower risk of HF in middle-aged and older populations,[32, 33] few studies have considered CRF in young adulthood with respect to long-term HF-risk, and have not considered the multiple origins of HF.[34]

## Definitions

### *Physical activity and physical fitness*

Physical activity (PA) is commonly defined as bodily movement via skeletal muscles, resulting in energy expenditure above the base metabolic rate that can be expressed in kilocalories,[35] the amount of which is determined by its different aspects or components, i.e. intensity, frequency and duration. It can be categorized in different ways, one being through different segments of daily life such as occupation, leisure-time and sleep. Exercise can be described as a subcategory of PA that is planned, structured and repetitive, with the goal of improving or maintaining physical fitness. As opposed to physical activity, which is a behavior, physical fitness is a set of attributes that are either health- or skill-related. Health related fitness has been described as a composition of several traits including CRF but also muscular strength and –endurance, body composition and flexibility.[35]

Interest in studying the effects of different intensities of physical activity has led to the establishment of definitions for different ranges. Commonly the intensity of activity can be classified as sedentary, light- moderate- and vigorous, typically expressed as a quotient with the basal metabolic rate or Metabolic equivalent (MET) as denominator. 1 MET corresponds to ca. 3.5 milliliters of oxygen consumption per kilogram bodyweight and minute (ml $O_2$ * $kg^{-1}$ * $min^{-1}$). Sedentary behavior is commonly defined as <1.5 METs, light intensity physical activity (LIPA) as 1.5≤ and <3 METs, moderate-intensity (MPA) as 3≤ and <6 METs, and vigorous-intensity (VPA) as ≥6 METs.[36] For reference, Table 1 adopted from Ainsworth et al.[37-39] contains examples of MET-values for common daily life activities and exercises. The total amount of energy expenditure may be expressed as a product of the total duration at a certain activity level expressed as MET-minutes.

It is important to consider the difference between relative and absolute intensities of PA, as certain MET levels will cause different levels of exertion depending on individual attributes such as age, sex and body mass index (BMI). While absolute intensity is commonly expressed as METs, the relative intensity is harder to measure. This can be done in different ways, such as relating the absolute intensity perceived exertion level such as the Borg scale[40] or cardiorespiratory fitness level.[36,41]

*Measuring Physical Activity*

Methods for measuring physical activity can be crudely divided into subjective and objective measurements. Subjective methods typically rely on self-recollection or -re-

**Table 1.** Intensities of common exercises and daily life activities expressed as metabolic equivalents (METs).

| Physical activity | METs |
|---|---|
| Low intensity | |
| Desk work, sitting | 1.5 |
| Walking slow on level surface (<2mph or 3.2 km/h) | 2.0 |
| Medium intensity | |
| Walking, brisk pace on level surface (3 mph or 4.8 km/h) | 4.0 |
| Garden work (mowing lawn, weeding, cultivating) | 4.5 |
| Bicycling, leisure (<10mph or 16km/h) | 4.0 |
| Bicycling, stationary, 100W, light effort | 5.5 |
| Vigorous intensity | |
| Heavy gardening (e.g. continuous shoveling) | 6.0 |
| Jogging (general) | 7.0 |
| Calisthenics (e.g. pushups, pullups, situps) vigorous effort | 8.0 |
| Rope Jumping (general) | 10.0 |

cording of activities, whereas objective methods include direct measurement of energy expenditure (eg. doubly labelled water, direct and indirect calorimetry[42]) and different wearable devices such as accelerometers, pedometers and heart-rate monitors. While direct measurement methods have benefits in terms of accuracy, they are often cost- and time-intensive, making them less practical for large-scale epidemiological studies. Traditionally, epidemiological studies have therefore employed different tools for self-reporting level of PA, usually via questionnaires. This method has obvious benefits in terms of cost-efficiency, allowing for the collection of large data samples, has low participant burden and is widely accepted and used.[43] It is, however, limited in terms of validity and reliability[44] and inaccurate recall[45] and social desirability[46] may constitute sources for bias. Even so, questionnaires have been found useful for ranking individuals for activity level, allowing for studying risk ratios across activity levels, and for tracking changes in activity on a population level.[44, 47]

Objective methods such as accelerometry allow for more detailed assessment of the physical activity pattern. Conceptually, the accelerometer is based on a small mass inside a confined chamber, connected to a spring. When the device experiences an acceleration, the spring is able to accelerate the mass at the same rate, which can then be measured. The accelerometer itself is a small device that continuously measures linear acceleration in one or several planes at a fixed sampling rate, usually between 30-100 Hz. Commonly, the device records data as a unitless metric called "counts", a product of the amplitude and frequency of activity. The raw data is compressed into lower resolution or "epochs", the usual length of which is one minute (counts/minute, CPM). Modern devices allow for customization of the sampling rate as well as epoch lengths to suit the research question undertaken. Grading of activity into intensity specific categories is made according to specified cut-off thresholds (sedentary, low, moderate, and vigorous intensities).

Importantly, because of the complex nature of PA, no golden standard exists that may capture all of its aspects or dimensions. It is therefore important to choose measurement method according to the research question at hand, as well as limitations such as study setting and budget.[43]

### *Cardiorespiratory fitness*

Cardiorespiratory fitness (CRF) can be measured directly via maximum performance testing and subsequent measurement of maximum oxygen uptake ($VO_2^{max}$). However, direct testing requires resources in terms of lab equipment for measuring respiratory gas exchange, and maximal testing may pose a health risk for individuals with pre-existing CVD. Because of this, submaximal exercise tests have been developed as an available, easily used alternative of estimating $VO_2^{max}$, more suitable for large scale epidemiological studies. The most commonly used method is the Åstrand method[48], based on the linear relationship between heart rate and oxygen consumption that is usually conducted at 60-70% of maximal work-rate. The different tests used for this thesis are further described in the methods section.

### *Muscle strength*

While cardiorespiratory fitness is well known to be a strong predictor for health and longevity, physical fitness has several different components, as described above.[35] Muscular strength has received increasing recognition as a factor associated with cardiovascular risk factors[49] and all-cause mortality.[50] Resistance training has been shown to have positive effects on musculoskeletal health, cardiovascular risk factors (insulin sensitivity, blood pressure, blood lipids, and body composition)[51] as well as psychiatric disorders such as anxiety and depression.[52, 53] Muscular strength has been associated with lower mortality in risk populations[54] and populations with pre-existing cardiovascular disease.[55] However, in the few studies performed on the association of muscle strength and CVD mortality in healthy populations, most have not made adjustments for CRF[50, 56, 57] or have been unable to prove an independent association from CRF level.[58]

### *Physical activity recommendations*

Current PA guidelines typically recommend at least 150 minutes of medium- to vigorous PA (MVPA) per week, spent in prolonged bouts of at least 10 minutes, preferably on most days of the week,[59-62] while some have used the alternative of at least 75 minutes of vigorous PA (VPA) per week.[62] Some also make recommendations for muscle strengthening activities of predominantly compound exercises, engaging large muscle groups, at least 2 times per week. The suggested workload has been 60-80% of the 1 repetition maximum or 1 RM (the maximum load that can be lifted for 1 repetition) with 2-3 sets of 8-12 repetitions.[61] Older individuals are typically recommended the same amount of physical activity although there are also additional recommendations on neuromotor activity (balance, coordination, gait) which helps preventing falls among individuals at risk. For older individuals with poor mobility, it is generally recommended to be as active as their condition allows. Some guidelines have addressed the issue of sedentary time, and have made recommendations aimed at reducing prolonged sitting, including for example short breaks from desk work or re-

ducing screen-time,[60] preferably with muscle engaging activities.[61] However, there is still a lack of evidence with respect to more detailed recommendations on maximum sedentary or sitting time and what activities to substitute with. Recommendations differ between children and adults and children are recommended at least 60 minutes of MVPA daily. While most daily activity should be of aerobic character, regular VPA including muscle- and bone-strengthening activities are recommended at least 3 times per week.[62]

### *Resting heart rate*

Higher levels of CRF are associated with lower resting heart rate (RHR), and aerobic conditioning decreases RHR.[63] This effect is commonly attributed to an increased activity of the parasympathetic nervous system via the vagus nerve, although it has recently been suggested that the effect may be partly mediated via modulation of the intrinsic pacemaker activity of the sinus node.[64] While CRF is well known to predict health outcomes, resting heart rate (RHR) has also been found to predict risk of death from all causes and CVD, an effect that has been found to be partly independent that of CRF.[65, 66] High resting heart rate is a predictor of death in HF[67] and coronary artery disease.[68]A high resting heart rate has also been found to be associated with increased risk of the development of CVD risk factors such as diabetes,[69] hypertension,[70] and the metabolic syndrome.[71] Furthermore, a high resting heart rate has been found to predict CVD among previously healthy middle-aged individuals in several studies. A limitation of these studies is that they have not taken into account the concurrent levels of CRF[72-75] and PA[74] that independently predict cardiovascular risk.[76, 77] There are no large scale studies investigating the association of RHR with CVD while considering CRF-level. In middle-aged populations, reverse causality poses a risk as high resting heart rate may be attributable to undiagnosed or subclinical CVD. Whether a high RHR in young adulthood is associated with risk of CVD has not been established.

### *Cognitive epidemiology and cardiovascular disease*

As described above, cardiovascular disease is largely attributable to a number of well-known and modifiable risk factors.[14] Reduction of risk factor burden is therefore dependent on behavioural changes, such as improvements in diet, smoking cessation and increased physical activity. Such interventions put high demand on individual abilities in terms of motivation, comprehension and adherence. It has been repeatedly shown that intelligence, measured via test scores for cognitive ability, is a factor strongly associated with health and longevity. Conversely, a low cognitive test score has been found to be a strong risk factor for all-cause mortality.[78] Further, cognitive capacity is associated with increased levels of cardiovascular risk factors,[79, 80] as well as cardiovascular disease and death[81, 82]. Cognitive ability tests have been found to have high validity,[83] and test scores have shown stable estimates from adolescence up to higher ages.[84] Because of this, cognitive ability might be added to important predictors of cardiovascular disease.

Several causes have been suggested underlying the observations of cognition and health:

1. Cognitive ability may serve as an indicator of exposures predating the measurement, for example during childhood or even prenatally. Examples of such exposures are low birthweight[85] and childhood socioeconomic status.[86] Even so, attempts to correct for early life socioeconomic factors have not been able to explain the cognition-mortality association.[78, 87, 88] Regarding cardiovascular outcomes, in a recent meta-analysis by Dobson et al, adjustment for early life factors (birth weight, social class, deprivation category) only slightly attenuated the associations between early life IQ with CVD and CHD, respectively.[89]

2. Later life socioeconomic factors such as educational attainment and occupation may serve as mediators to the observed associations, as higher intelligence may provide the possibility of educational attainment and entry to safer job environments. Socioeconomic factors in adulthood are well known to be associated with future cardiovascular outcomes.[90, 91] In a meta-analysis of longitudinal studies investigating the relationship between early life IQ and all-cause mortality, Calvin et al. showed a 33% reduction of risk when adjusting for indices of adult socioeconomic status, supporting this idea.[78]

3. It is possible that early life intelligence affects cardiovascular risk via healthy behaviours and adherence to lifestyle interventions as well as medical treatment.[92] For example, adolescent intelligence has been linked to cardiorespiratory fitness,[80] smoking cessation,[93] as well as adherence to statin treatment after myocardial infarction.[94] It is well known that cardiovascular risk factors start accumulating in early life and often track over into adulthood. [95] Health literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions".[96] Indices of health literacy has been found to predict self-management skills and outcomes among patients with hypertension, diabetes[97, 98] and HF.[99]

4. Another possible explanation is that cognitive function is a marker for system integrity, a general trait of a well-functioning body that provides resilience towards external or environmental insults.[100] Recent findings of a genetic origin of the health-cognition relationship may give support to this hypothesis but requires further investigation.[101]

## AIMS

The aim of this thesis was to study different aspects of physical activity and fitness and their social and individual determinants, in relation to cardiovascular disease, with special attention to heart failure. The aims of the individual studies are listed below:

*I* To investigate the association of residential area socioeconomic status, physical activity pattern and cardiorespiratory fitness in a middle aged population in Gothenburg, Sweden

*II* Analysing the longitudinal relationship between cardiorespiratory fitness, measured at compulsory military service conscription, with future risk of heart failure in young Swedish men

*III* To analyse the longitudinal relationship between cognitive capacity (intelligence quotient, IQ) with the future risk of heart failure among Swedish male conscripts

*IV* To analyse the longitudinal relationship between resting heart rate, measured at military conscription, with the future risk of cardiovascular disease and death

# METHODS

## Study populations

This thesis includes studies on two populations; the SCAPIS pilot study and the Swedish military conscription registry. The regional ethics board in Gothenburg approved all studies.

### *SCAPIS*

The population for study I originated from the Swedish CArdioPulmonary bioImage Study (SCAPIS) pilot study, conducted in Gothenburg, Sweden, 2012. SCAPIS is a nationwide observational cohort study and a joint effort of 6 universities and university hospitals (Gothenburg, Linköping, Malmö/Lund, Stockholm, Umeå and Uppsala). The study aims at improving knowledge of the epidemiology and mechanisms of CVD, chronic obstructive pulmonary disease (COPD) and metabolic disorders using novel imaging- and biomolecular methods, and to improve the diagnosis, risk prediction and treatments of disease.[102] The first step of the study, aimed at recruiting and characterizing a cohort of 30,000 middle-aged men and women (age 50-64), is estimated to be finished in 2018. The extensive study-protocol takes place during two or three days and is depicted in Figure 1.

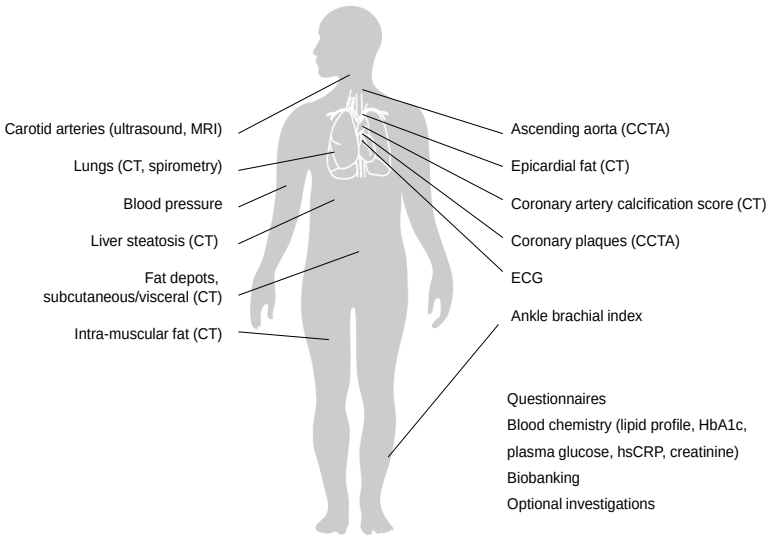



**Figure 1**. Information collected from the subjects in SCAPIS. MRI: magnetic resonance imaging; CT: computed tomography; CCTA: coronary computed tomography angiography; ECG: electrogradiogram; HbA1C: glycated hemoglobin; hsCRP: high-sensitivty C-reactive protein. Reprinted with permission.[102] Original work by Bergström, G et al. "The Swedish CArdioPulmonary BioImage Study: objectives and design", J Intern Med, 2015

The pilot was aimed specifically at investigating differences in risk factor distribution with respect to socioeconomic differences. The city of Gothenburg is socially segregated, with marked differences between geographical areas within the city. Official reports confirm that residents of low socioeconomic (SES) areas in Gothenburg have significantly shorter life expectancy and levels of perceived health.[103] In order to ensure equal recruitment, more invitations were sent out in low-SES areas (12-13% of the target population compared to 6-7% in high-SES areas). The geographical areas studied (according to the previous borough plan) were from the north-east parts of Göteborg; Bergsjön, Gunnared, Biskopsgården (low SES) and Askim, Älvsborg. Torslanda (high SES), see Figure 2. The final participation rate was 50% (1111 out of 2243) overall and was substantially lower among low-SES residents, 39% compared to 68% among the high SES residents.[104] All participants provided written informed consent.

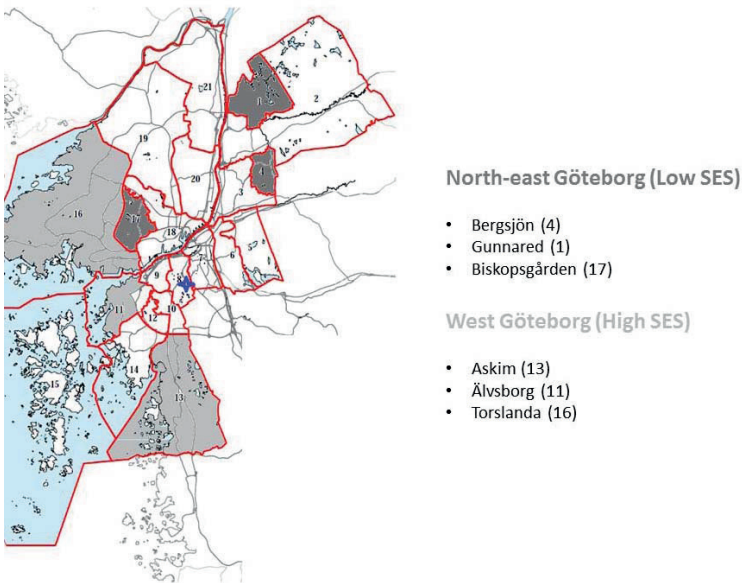



**Figure 2.** Borough plan of Göteborg highlighting the studied geographical areas of study I (SES=socioeconomic status).

### *The SCAPIS shadow cohort*

In order to assess the validity of the pilot study, an anonymous record of the background population was created using data from register authorities (Statistics Sweden and the National Board of Health and Welfare) which included sociodemographics, health records, as well as participation status for SCAPIS. While sociodemographic variables varied considerably between residential areas, their association with participation rates proved equal across the studied SES areas. The authors found that most diseases were associated with sociodemographic conditions.[104] Unpublished data from the same source have also shown large differences in the geographical distribution of CVD and risk factors, disfavouring the low-SES areas. The lowest participation rates were found among individuals born outside Europe, living single in a low SES area, having low education, being outside the labour market and having low income.

## Other data sources

### *The Swedish Military Service Conscription Registry*

Until the abolishment of the compulsory military service conscription, all Swedish men were obliged to enlist into military service, the only exemptions being serious mental or physical illnesses, disabilities, or previous incarceration, usually limited to about 2-3% yearly. The enlistment protocol took place during a 2-day period and consisted of a physical examination, including anthropometrics and blood pressure measurements, followed by psychological evaluation and different aptitude tests, including cognitive ability assessment, estimation of CRF and muscle strength. Figure 3 shows an overview of the exclusion criterion used for the different studies and the final number of participants for each study.

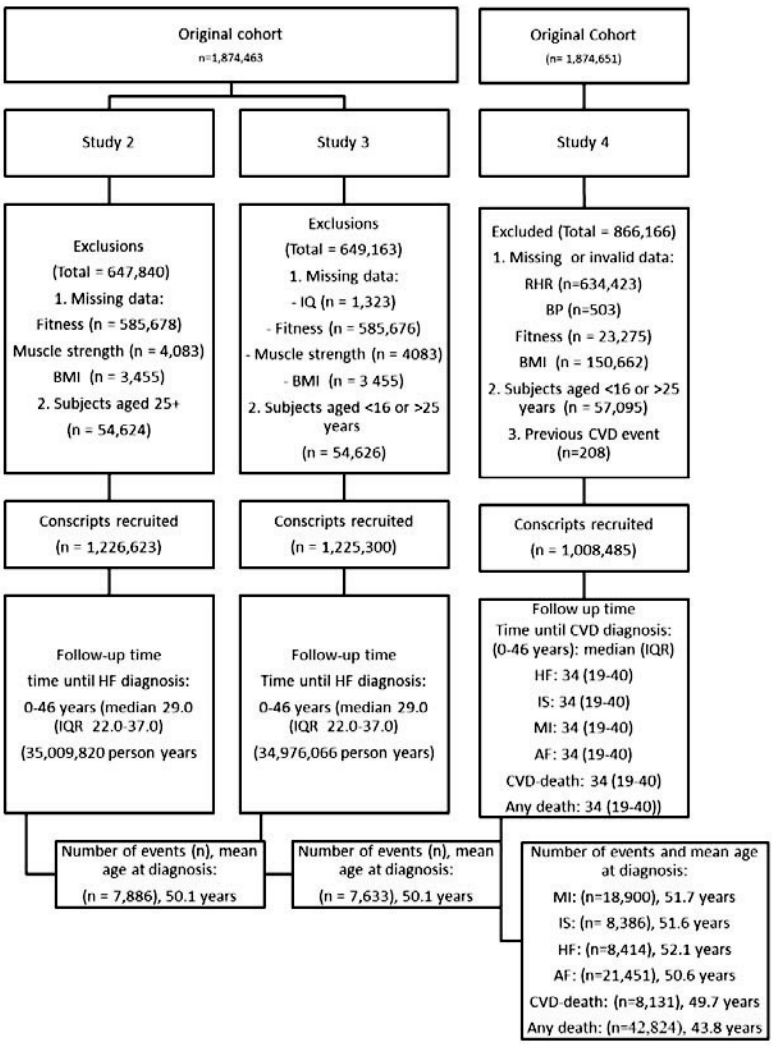



**Figure 3.** Overview of included and excluded participants of studies II-IV, showing median years of observation (follow-up time) and number of cases.

### *The Swedish National Inpatient Registry*

Sweden has a universal health care system, providing low-cost, universal health care to all citizens. At discharge, patients receive diagnostic codes according to the international classification of disease (ICD), which are mandatorily reported to the Swedish National Inpatient Registry (IPR). There was a gradual increase in coverage between the years 1968 and 1986, as more county councils and hospitals were added, and it is considered complete from 1987. Starting in 2001, diagnoses from hospital outpatient care are also recorded.

### *The LISA registry*

The longitudinal integration database for health insurance and labour market studies (LISA) integrates existing data from the labour market, and from the educational and social sectors and is administered by Statistics Sweden. The individual is the primary object in LISA, but data on connections to family, companies and places of employment are also available. The database holds annual registers since 1990 and includes all individuals 16 years of age and older that were registered in Sweden as of December 31 for each year. For the present thesis, information on parental education was collected as a marker of socioeconomic position. The classification has seven categories: <9 years, pre-high school education of 9 years, high school education, university (<2 years), university (≥2 years), postgraduate education, and postgraduate research training. The highest level achieved of either parent was used. The register covers 80% of the population.

### *The Cause of Death Registry*

The Cause of Death Registry (CRD), held by the national board of Health and Welfare, contains the cause of death classified according to the international classification for disease (ICD). It is updated yearly since 1961, there is also a historical register dating back through the years 1952-1960. Until 2011, the register keeps records of the cause of death for all Swedish residents, deaths occurring outside the country included. From 2012, the register also contains records of deaths of all deaths occurring in Sweden, including non-residents.

## Measurements

### *Physical activity*

In study I, the daily movement pattern was measured using using the ActiGraph model GT3X/GT3X+accelerometer (Actigraph LCC, Pensacola, FL, USA). Strong agreement has previously been found between the two accelerometer models, allowing for interchangeable use within the study.[105] The Actigraph accelerometer is a small (3.8 x 3.7 x 1.8 cm) and light (27g) device. It has previously been validated in laboratory[106], and in free-living conditions[107], against other devices[108] and is currently the monitor most commonly used in accelerometer studies.[109] The device has a wide force range (magnitude range of +/- 6 g's [g= standard gravity unit, 9.80665 m/s$^2$]) and bandwidth (the amount of times per second the device can make a reliable reading of acceleration), allowing for recording of PA from very low frequencies up to the kHz-range. The Actigraph samples raw data through a 12-bit Analog to digital converter (rang-

ing from 30 to 100 Hz) and stores it in a flash memory card for future analysis. Data were extracted and analysed using Actilife software (v.6.10.1). The filtering process is aimed at limiting the readings within the range of human movement (between 0.25 and 2.5 Hz). Following this, each sample is summarized into a pre-specified time interval (epoch) and a unitless metric of movement (counts). For the present study, raw data sampling frequency was set to 30 Hz. and extracted as 60-second epochs with low frequency extension filter that extends the lower range of signals passing. Uniaxial (vertical axis) analyses were performed in order to facilitate comparisons with previous research. Modern devices allow for measurement of three individual planes (vertical, anteroposterior (AP), and medio-lateral (ML)) that can be summarized to a composite vector magnitude (VM). While this has been suggested to improve measurement accuracy, triaxial measurement requires new calibration algorithms. This is an ongoing development and there is currently no definitive consensus for which approach to use.[110]

Participants of SCAPIS were instructed to carry the accelerometer in an elastic band on the right hip for 7 consecutive days after the first study visit, except during water based activities. Following completion, the accelerometer was returned to the lab via prepaid mail for analysis.

### *Cut-offs and intensity category definitions*

A wear-time of at least 600 minutes during at least four of the study days were required for inclusion.[111] Wear time was defined as the non-wear time subtracted from 24 hours. Non-wear time was defined as an interval of zero counts of activity for at least 60 consecutive minutes, allowing for 1-2 minutes of activity between 0-100 counts.[112] Regarding intensity specific PA-categories, sedentary time (SED) was defined as time spent at less than 100 cpm.[113] The count thresholds for medium (MPA) and vigorous activity (VPA) have previously been derived from studies that have calibrated the accelerometer output against energy expenditure. Accordingly, in this study, MVPA was defined as >2020 cpm (corresponding to ≥3 METs, with no further distinction between MPA and VPA) and light intensity (LIPA) as cpm between 100 and 2019 (corresponding to 1.5-3 METs).[112] The mean counts per minutes (mean cpm) is a measure of mean daily activity and was calculated by dividing the total number of counts by total wear time. As a prerequisite for the analysis of fulfilment of PA-recommendations, MVPA was analysed as total minutes as well as the amount spent in continuous bouts of 10 minutes or more. In order to capture the rate of fulfilment of PA-recommendations, we created different categories using varying strictness of interpretation as follows: (1) accumulating at least 150 min/week; (2) accumulating at least 150 min/week from prolonged bouts of 10 min or more; (3) accumulating at least 30 min/day on at least 5 days of the week; and (4) accumulating at least 30 min/day on at least 5 days of the week, all from bouts of 10 min or more.[76]

### *Physical fitness tests*

For all studies, participants underwent cardiorespiratory fitness tests by cycle ergometry. Participants of study I underwent a submaximal test according to the Åstrand-Rhyming method,[48] that has previously been validated against peak oxygen consumption ($VO_2^{max}$).[114] As part of the enlistment protocol, conscripts underwent a maximal

cardiorespiratory fitness test. The protocol started with a resting ECG, following 5 minutes of submaximal performance at between 75 and 175W, depending on body height. The work resistance was incrementally increased by 25W/min, while subjects were simultaneously instructed to maintain a continuous tempo of 60-70 RPMs. The final work rate in Watts ($W_{max}$) was recorded and divided by body weight because of the higher correlation with peak oxygen consumption ($VO_2^{max}$) than the predicted $VO_2^{max}$ (correlation coefficient of 0.6–0.7).[114, 115] The Wmax/kg was transformed into a standard nine (STANINE) scale (a normal distributed scale from 1-9 with a mean of 5 and a standard deviation of 2), that was used as the exposure variable for later analyses. Isometric muscle strength was measured by a combination of three exercises: knee extension (weighted 1.3×), elbow flexion (weighted 0.8×), and hand grip (tested with a tensiometer; weighted 1.7×).[116] Weighted values were integrated into one estimate in kiloponds (1kp=1kg*g) (before 1979) or Newtons (after 1979) and transformed into stanine score (1-9).

### *Cognitive capacity testing*

The cognitive test battery, including concepts, design and validity, has been thoroughly described in a doctoral thesis by Berit Carlstedt.[83] Cognitive capacity was measured using a composite of four different cognitive tests, each designed to evaluate different aspects of intelligence. 1) In the 1960s, the logical test contained 25 questions and was designed to measure the ability to apply a set of written instructions to a problem solving task; 2) a verbal test of "concept discrimination" (removal of the right word from a set); 3) a visuospatial test, containing questions on 2D-puzzles; and 4) a test of technical comprehension, containing 52 problem-solving questions requiring basic mathematics and physics.

In the 1980:s, the tests were revised to contain 40 questions each. The verbal and visuospatial tests where amended in order to increase mainly test reliability. The verbal test was exchanged for a synonyms test (testing the capability to select the correct synonym or antonym from a given set of words). The visuospatial test was exchanged for the metal folding-test, evaluating the ability to extrapolate the correct 3D-image from a series of 2D-drawings. The results of the four sub-tests were weighted equally and summed to give a measure of general cognitive performance. To achieve long-term stability between data-sets, results were standardized against previous years into stanine score (1-9), referred to as IQ-category or IQ-stanine. The same procedure was used for the different subtests. Because raw data were not recorded before 1996, only stanine scores were used in the present analyses.

### *Ascertainment of outcomes and comorbidities*

The Swedish personal identification number, unique to every Swedish citizen, allows for the linkage between different registries.[118] For studies 2-4, linkage to the IPR was made for follow-up of the studied outcomes, until the end of follow-up at 31 December 2014. The ICD-8 was used for the years 1968-1986, the ICD-9 for the years 1987-1996 and ICD-10 thereafter. Table 2 gives an overview of the studied outcomes, comorbidities included in analyses and the corresponding ICD-codes used. Because of the great variation of primary diagnoses, a first diagnosis of HF was accepted regard-

less of diagnostic position. A hierarchal classification previously used by our group[27] was used in order to distinguish heart failure of different etiological origins (study II and III).

**Table 2.** Overview of diagnostic codes of the studied outcomes and comorbidities according to version of the international classification of disease (ICD)

| Diagnosis | ICD-8 | ICD-9 | ICD-10 |
|---|---|---|---|
| Diabetes | 250 | 250 | E10-E14 |
| Hypertension | 401-405 | 401-405 | I10-I15 |
| Acute myocardial infarction | 410 | 410 | I21 |
| Heart Failure | 427.00, 427.10 | 428 | I50 |
| Any CHD diagnosis | 410-414 | 410-414 | I20-I25 |
| Congenital heart disease | 746-747 | 745-747 | Q20-Q28, Q87, Q89 |
| Valvular disease | 394, 395, 396, 398, 424 | 394-398, 424 | I05-I09, I33-I39 |
| Cardiomyopathy | 425 | 425 | I42, I43 |
| Atrial fibrillation | 427,92 | 427D | I48 |
| Stroke | 431, 433, 434, 436 | 431, 434, 436, 432X | I61, I63, I64, I62.9 |
| Ischemic stroke | 433, 434, 436 | 434, 436 | I63, I64 |
| Alcohol abuse | 291, 303 | 291, 303, 305.0 | F10 |
| Substance abuse | 294.3, 304 | 292, 304, 305.1-8 | F11-F19 |

### *Other measurements*

For study I, the protocol included measurement of anthropometric data including height, weight, waist- and hip circumference at first study visit, as well as measurement of brachial blood pressure (measured twice in each arm using Omron M10-IT, Omron Health care Co, Kyoto, Japan) and collection of samples for blood chemistry. Body mass index (BMI) was calculated as body weight (kg) divided by the body height (meters) squared and stratified into groups: 1. underweight (defined as BMI<20); 2. normal weight (BMI ≥20 and <25); 3. overweight (BMI ≥25 and <30); and 4. obese (BMI ≥30). Waist-to-hip-ratio (WHR) was calculated and classified as high or low according to current WHO guidelines, with >0.90 for men and >0.85 for women classified as high.[119] A detailed questionnaire was designed, containing 140 questions relating to self-reported health, family history, medication, occupational and environmental exposure, lifestyle, tobacco use, psychosocial well-being, socioeconomic status and other social determinants. For the present study, self-reported smoking, diabetes mellitus and chronic obstructive pulmonary disease or asthma diagnoses were dichotomized (yes/no).

For study II-IV, as part of the military service conscription, participants underwent physical examinations including measurement of height and weight, with light clothing and without shoes. Heart rate and blood pressure were measured according to a written protocol, where blood pressure was measured after 5 to 10 minutes of rest in supine position with an appropriately sized cuff at heart level. A single measurement was made if systolic blood pressure was below 145 and diastolic- between 50 and 80 mm Hg. Outside these values, a second measurement was performed and then

registered.[120] We excluded extreme values of RHR (>145 or <35 beats per minute (bpm)),[121] systolic and diastolic- blood pressure (>(75th centile+3 × interquartile range) and <(25th centile−3 × interquartile range))[120] that could be considered as outliers or due to errors in measurement and registration (study IV).

## Statistical analyses

The study designs used in this thesis are all observational and include both cross-sectional (study I) and longitudinal (studies II-IV) study designs.

For descriptive statistics, continuous variables were presented as means and standard deviations or medians and inter-quartile range, depending on the variable distribution, while categorical variables were expressed as percentages and n:s across categories of the studied exposure variable.

For study I, the relationship between area-level SES with continuous values of minutes of SED, LIPA, MVPA and CRF were analysed using linear-, and Poisson regression analyses. Odds ratios for the fulfilment of PA-recommendations across SES-areas were calculated using multiple logistic regression. Skewed variables were log transformed to approximate normality.

For studies 2-4, we used Poisson regression to calculate incidence rates, expressed as events per 100.000 person-years, and their corresponding confidence intervals (CIs). Cox proportional hazards regression analysis was used to estimate the longitudinal associations between CRF and muscle strength (study II), IQ (study III) and resting heart rate (study IV) with future risk of HF (study II and III) and CVD-outcomes (study IV) during follow-up, while adjusting for potential confounders. The follow-up period started at the date of conscription and participants were followed until either: (a) a first hospitalization for or death from a CVD event; (b) death from other causes; (c) emigration from Sweden; or (d) the end of the follow-up period on 31 December 2014. For each study, three regression models were created using varying sets of covariate adjustments. No adjustments were made for comorbidities occurring during the follow-up period as they may act as mediators in the pathway to CVD rather than confounders. Table 3 provides an overview of the statistical methods and covariates included for each study of this thesis. The proportional hazards assumptions were tested using plots based on weighted residuals. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, NC, USA) and R, version 3.3.2.

**Table 3**. Study designs and statistical methods

| | **Study I** | **Study II** | **Study III** | **Study IV** |
|---|---|---|---|---|
| Study design | Cross-sectional | Prospective | Prospective | Prospective |
| Statistical methods | Linear-, Poisson, Logistic regression | Cox proportional Hazard | Cox proportional Hazard | Cox proportional Hazard |
| Main exposure | SES-area | CRF stanine | IQ stanine | Resting heart rate (quintiles) |
| Covariates | Sex, Age, Accelerometer wear time, Smoking, educational level | Age at conscription, year of conscription, conscription test centre, body mass index, diabetes mellitus, hypertension, congenital heart disease, documented alcohol and substance abuse. parental education, and systolic and diastolic blood pressure. IQ and muscle strength | Age at conscription, year of conscription, conscription test center, body mass index. diabetes mellitus, hypertension, congenital heart disease, documented alcohol- and substance abuse. body height, systolic and diastolic blood pressure, parental education, cardiorespiratory fitness and muscle strength | Age at conscription, year of conscription, conscription test center, , comorbidities at baseline (diabetes, hypertension, congenital heart disease), documented alcohol- and substance abuse). Body mass index, systolic and diastolic blood pressure and cardiorespiratory fitness |

## RESULTS

### Physical activity pattern, cardiorespiratory fitness, and socioeconomic status in the SCAPIS pilot trial — A cross-sectional study (Study I)

The aim of the study was to investigate the relationship between area-level SES, PA-pattern and CRF in a middle aged population in Göteborg, Sweden.

Participants from low-SES areas were slightly older, had higher mean BMI and waist circumference and lower educational level. Large differences were observed with respect to the prevalence of smoking, hypertension and diabetes, disfavouring the low-SES areas.

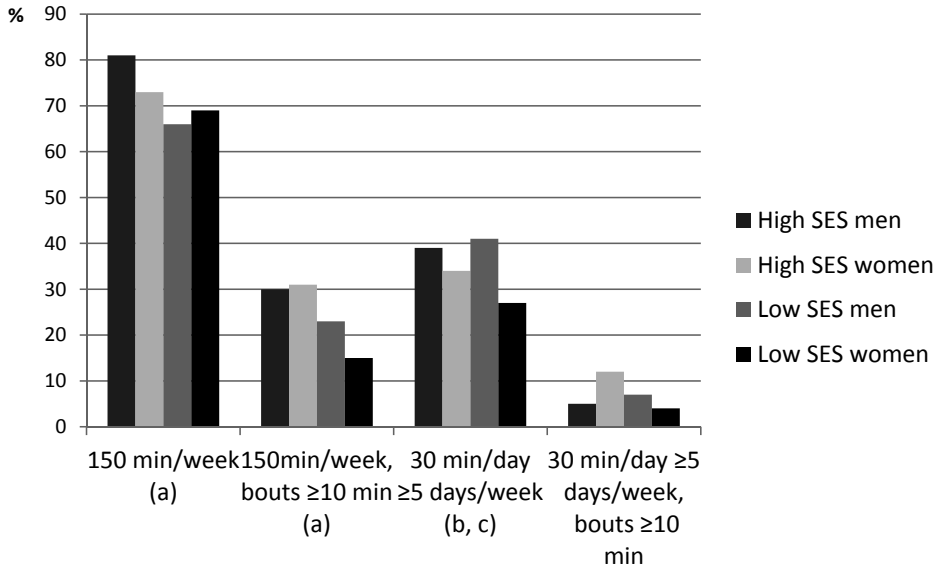
Regarding physical activity pattern, participants from low-SES areas showed lower average activity levels (estimated as mean cpm) as well as fewer average minutes spent in MVPA per day, when adjusting for age, sex and accelerometer wear-time. CRF levels were significantly lower among low-SES participants (Table 4).

**Table 4.** Physical activity patterns and cardiorespiratory fitness in relation to SES area. Data are shown as the median (Q1–Q3) (Gothenburg, Sweden, 2012)

| | SES | | All |
|---|---|---|---|
| **Accelerometry** | **High (n=492)** | **Low (n=455)** | **(n=947)** |
| Average wear time/day (min) | 861 (820-903)[a] | 847 (787-904)[a] | 855 (803-903) |
| Mean counts per minute (n) | 348[a,c] | 320[a,c] | 336 |
| Average MVPA/day (min) | 35.5 (22.9-49.3)[a,b,c] | 29.9 (18.7-45.2)[a,b,c] | 32.8 (19.9-48.3) |
| Average SED per day (min) | 519 (468-573)[b,c,d] | 507 (437-580)[b,c,d] | 515 (457-575) |
| Average LIPA per day (min) | 305 (256-350)[b,d] | 302 (249-357)[b,d] | 303 (253-352) |
| Cardiorespiratory fitness | (n=338) | (n=254) | (n=592) |
| (mL x min-1 x kg-1) | 28.5 (24.1-32.7)[a,c] | 25.1 (21.9-29.3)[a,c] | 26.8 (23.0-31.3) |

[a]Significant SES difference ($p<0.05$). [b]Significant sex difference ($p<0.05$). [c]Significant age difference ($p<0.05$). [d]Significant wear time difference ($p<0.05$)

Analyses of the fulfilment of national PA-recommendations showed that while the adherence rate was generally low (7 % for the strictest interpretation among the total population), participants from low-SES areas showed lower rates of adherence compared to high SES participants. While the rate of fulfilment varied with sex, we found no interaction effect across SES*sex (Figure 4).




[a]Significant SES difference (p<0.05). [b]Significant sex difference (p<0.05). [c]Significant wear time difference (p<0.05)

**Figure 4.** Fulfillment of different interpretations of MVPA guidelines between study groups by sex.

## Cardiorespiratory fitness and muscle strength in late adolescence and long-term risk of early heart failure in Swedish men (Study II)

During a maximal follow-up period of 46 (median=29, interquartile range [IQR=22-37]) years, among the 1,226,623 participants there was a total of 7,656 cases of HF recorded, 3,557 of which were in a primary diagnostic position. Participants with low fitness and muscle strength showed higher incidence rates across all categories of associated conditions and for both a primary and secondary diagnostic position of HF. For HF in any diagnostic position, the incidence rates were 9.13 and 8.98 cases per 100,000 person-years among participants in the high CRF and muscle strength categories, compared with 16.87 and 12.76 per 100,000 person-years among those with low CRF or muscle strength, respectively.

Survival analysis using cox-proportional hazard regression showed an increased risk for all categories of HF, in a dose-response fashion. The hazard ratios (HR, 95% CI) for HF in any diagnostic position was 1.60 (1.44-1.77) for the lowest CRF category, in the fully adjusted model. Similar associations were found for muscle strength, even after adjustment for CRF (HR=1.45; CI [1.32-1.58]). The association proved strongest among cases associated with CHD, diabetes or hypertension (HR=1.88; CI

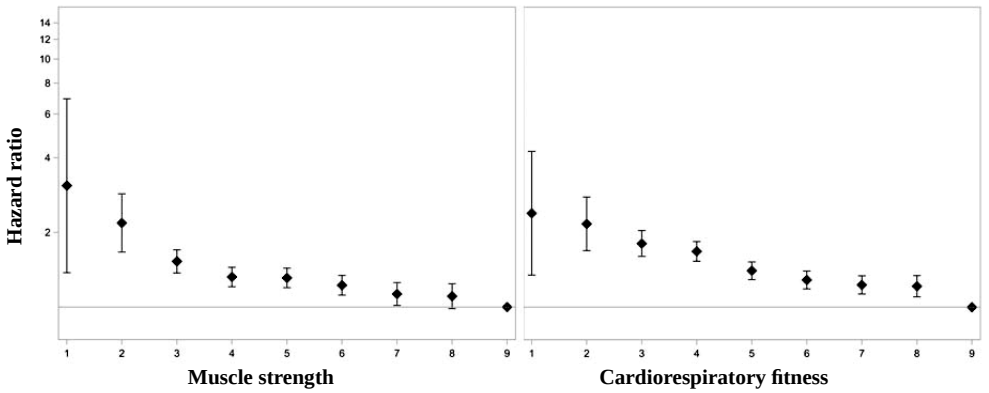



**Figure 5.** Association between stanines of CRF and muscle strength at conscription and risk of hospitalization with a primary or constributory discharge diagnosis of heart failure. The data is adjusted for age at conscription, year of conscription, test centre, body mass index, baseline comorbidities, documented alcohol or substance abuse, parenteral education, systolic and diastolic blood pressure, IQ, and cardiorespiratory fitness/muscle strength.

[1.64–2.16] and 1.61; CI [1.43–1.82] in the low CRF and muscle strength groups). Figure 5 shows the risk of HF in any diagnostic position across continuous stanines of CRF and muscle strength, respectively.

## Cognitive performance in late adolescence and long-term risk of early heart failure in Swedish men (Study III)

The aim of study III was to investigate the association between cognitive capacity (intelligence quotient, IQ) with future risk of HF at long-term follow up among male, Swedish conscripts recruited from the Swedish military service conscription registry. A total of 1,225,300 conscripts were included and followed up via the IPR and cause of death registries for diagnoses of HF and comorbidities. During a mean follow up of 29 years (0-46) and 34,976,066 person-years of follow-up, 7,633 cases of HF were documented, 3,542 of which in a main diagnostic position. Lower incidence rates were observed among conscripts with a higher IQ (12.58 cases/100,000 person-years in the highest IQ category compared to 52.29 cases/100,000 person-years in the lowest). Survival analysis showed a significant association between individual IQ-stanine and future risk of HF that persisted when adjusting for potential confounders. The HR for HF in any diagnostic position was 3.11 (CI [2.60-3.71]) in the lowest IQ category, corresponding to a HR of 1.32 (1.28-1.35) per standard deviation decrease of IQ (Table 5). Similar results were found for the different etiological categories, although the highest estimates were found among the large category with no associated condition (HR= 5.08 [CI=3.11-8.32]).

Interaction analyses showed that the association between IQ and risk of HF was stronger among normal-weight participants compared to overweight, and was not present among the obese.

**Table 5.** Hazard ratios (HRs) with 95% confidence intervals (CI) for HF hospitalization in any diagnostic position, across IQ stanines and per standard deviation (SD) decrease of IQ

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Heart failure in any diagnostic position (events/population) | 7633/1,225,300 | 7633/1,225,300 | 7041/1,175,613 |
| 9 (reference) | 1 | 1 | 1 |
| 8 | 1.20 (1.01–1.42) | 1.20 (1.01–1.42) | 1.16 (0.97–1.39) |
| 7 | 1.25 (1.06–1.46) | 1.24 (1.06–1.46) | 1.17 (1.00–1.39) |
| 6 | 1.50 (1.28–1.74) | 1.49 (1.28–1.74) | 1.38 (1.17–1.62) |
| 5 | 1.66 (1.42–1.92) | 1.65 (1.42–1.92) | 1.48 (1.26–1.73) |
| 4 | 2.09 (1.80–2.43) | 2.09 (1.80–2.43) | 1.84 (1.57–2.16) |
| 3 | 2.36 (2.02–2.75) | 2.36 (2.02–2.75) | 1.99 (1.69–2.35) |
| 2 | 2.97 (2.54–3.48) | 2.97 (2.54–3.47) | 2.38 (2.01–2.81) |
| 1 | 4.08 (3.45–4.81) | 4.06 (3.44–4.80) | 3.11 (2.60–3.71) |
| Per SD decrease | 1.40 (1.37-1.44) | 1.40 (1.37-1.44) | 1.32 (1.28-1.35) |

Model 1: adjusted for age at conscription, year of conscription, conscription test centre, body mass index. Model 2: additionally adjusted for comorbidities at baseline (diabetes mellitus, hypertension, congenital heart disease), documented alcohol and substance abuse). Model 3: additionally adjusted for body height, systolic and diastolic blood pressure, parental education, cardiorespiratory fitness, and muscle strength.

## Resting heart rate in late adolescence and long term risk of cardiovascular disease in Swedish men (Study IV)

During a follow up of maximum 46 years, we observed 8,414 cases of HF, 8,386 cases of ischemic stroke, 18,900 cases of acute myocardial infarction, 21,451 cases of atrial fibrillation, 8,131 cases of CVD-death and 42,824 deaths from all causes. High resting heart rate was associated with higher systolic- and diastolic blood pressure, and lower levels of CRF. Participants within the highest quintile of RHR showed the highest incidence rates across all the study outcomes. For HF in any diagnostic position, the incidence rate was 20.3 cases/100,000 person-years in the lowest quintile of RHR compared to 35.6 cases/100,000 person-years among those in the highest. Figure 6 shows results from the survival analysis. There was an increased risk of HF for the highest quintile of RHR compared to the lowest (HR=1.45[CI=1.35-1.56]) for HF in any diagnostic position) that remained significant in the fully adjusted model (HR=1.26[CI=1.17-1.35]). There was also a positive association between high RHR and all-cause death (HR=1.09[CI=1.05-1.12]) in the fully adjusted model. There was a weak association between high RHR with future risk of MI (HR=1.14 [CI=1.09-1.20]), that was attenuated after adjustment for systolic and diastolic blood pressure. No association was found for RHR and IS, while the association with AF was found to be weakly negative. There was a weakly positive association with all cause- and CVD mortality after adjustment for blood pressure (Figure 6). When further adjusting for CRF, a factor known to correlate strongly with RHR, associations became weaker

(HF, CVD- and all cause death). For MI and AF, the associations became weakly inverse, likely reflecting the strong inter collinearity between RHR and CRF. Significant collinearity was confirmed via estimation of the variation inflation factor (VIF, Figure 6).[122]

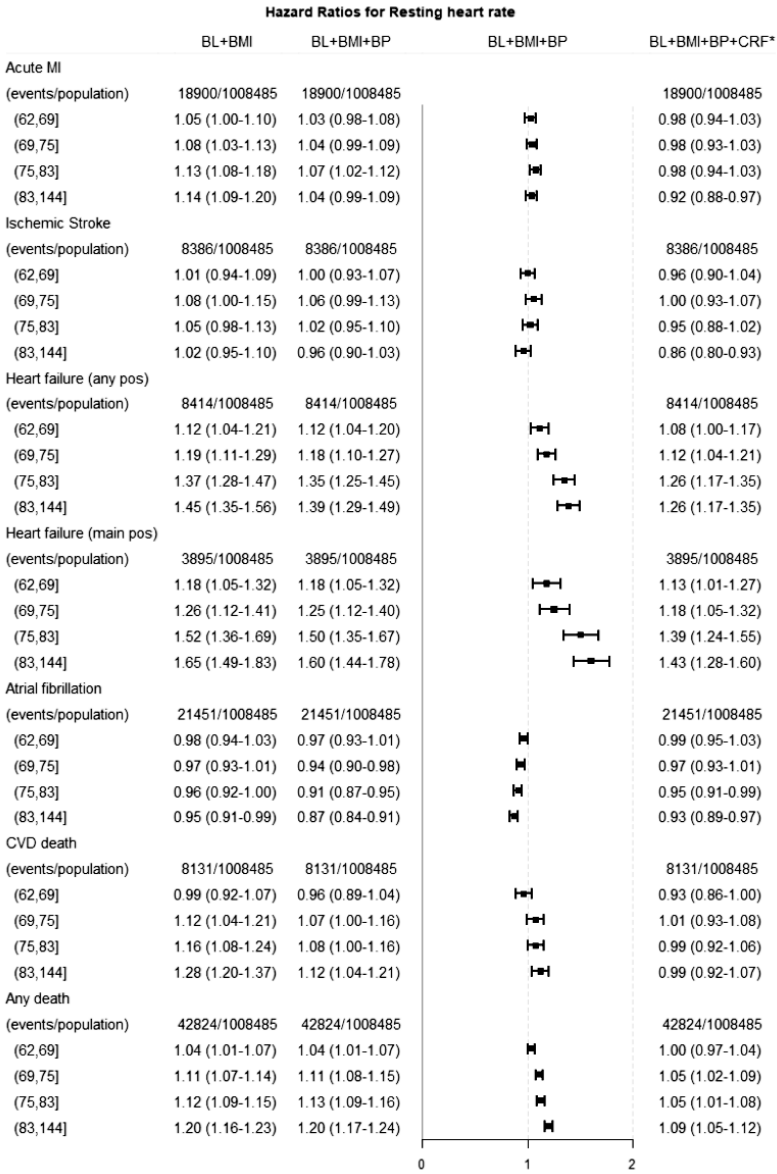



**Figure 6.** Hazard ratios (HR) with corresponding 95% confidence intervals for study outcomes by quintiles of resting heart rate (RHR). Baseline (BL): adjusted for age at conscription, year of conscription, conscription test center, comorbidities at baseline (diabetes, hypertension, congenital heart disease), documented alcohol- and substance abuse). BMI=Body mass index. BP = systolic and diastolic blood pressure. CRF=cardiorespiratory fitness. *Test for collinearity positive (variation inflation factor, VIF=4.5 [CRF Low]; VIF=6.8 [CRF medium]; VIF=4.8 [CRF high]).

## DISCUSSION

### Study I

In study I, we investigated the cross-sectional relationship between area-level socioeconomic status with CRF, PA-pattern, and rate of adherence with current physical activity (MVPA) guidelines. We found that living in a low SES residential area was associated with lower levels of CRF, less overall activity (as estimated by mean cpm) and fewer average minutes of MVPA. Low SES was associated with a lower rate of achievement of the recommended 150 minutes of MVPA per week which could be explained by differences in educational level.

Low SES is inarguably associated with elevated risk of CVD and has been associated with cardiovascular risk factors,[123] cardiovascular events[124] and mortality.[90] Disparities in risk factors,[125] health-related behaviors[126] and psychosocial factors[127] have previously been suggested as important mediators but could not explain the entirety of the observed relationship.[127, 128] However, SES is a complex construct and using different indicators may provide valuable insights needed for understanding the mechanisms linking SES to health outcomes. Studying residential area SES may also prove useful when considering health policies and services that are implemented and delivered by geographical places.[129] Residential SES has previously been associated with cardiovascular outcomes even after adjustments for individual indices.[130-133]

The present results are in line with previous studies investigating the relationship of SES with PA and fitness. In the present cohort, low individual SES (estimated by education) was associated with lower levels of MVPA estimated by accelerometry, and lower rates of achieving 150 minutes of MVPA per week, accumulated from prolonged bouts of 10 minutes, although there were no significant differences when adding the requirement of 30 minutes on most days of the week.[76] Scheers et al. found that high educational level was associated with achieving 75 minutes of VPA but not 150 minutes of MVPA, per week.[134] Studies employing self-reported PA have similarly indicated a socioeconomic gradient in PA.[135, 136] Regarding CRF, previous studies have found inverse associations between fitness and SES on both individual[137] and residential area level.[138] Our results indicate that there is an association of PA and fitness with area level SES that may only partly be explained by individual socioeconomic characteristics. Low-SES area inhabitants report less positive perceptions of their physical environment.[139] A potential explanation for the observed differences is that environmental characteristics of the neighborhood influence PA through its PA-promoting ability, so called walkability.[140]

### Study II

The main finding of this study was that, in a large cohort of young Swedish men, CRF and muscle strength measured at military service conscription was independently and inversely associated with risk of heart failure during follow-up.

Although CVD and HF typically present at higher ages, it is well known that cardiovascular risk factors accumulate over the life course, a process that may begin already in childhood.[95] Autopsy studies have revealed that formation of atherosclerotic plaques starts in early youth.[16] Our group previously found marked increase risk for HF among obese, as compared to normal weight adolescents,[29] raising concerns about the ongoing obesity epidemic. Previous studies have shown longitudinal associations with the development of HF for baseline CRF[141] and changes in CRF at follow up[33] in middle-aged subjects. CRF has been associated with indices of cardiac eccentric remodelling, left ventricular mass and diastolic function in healthy adults.[142, 143] CRF was also associated with left ventricular mass and –strain on echocardiography, two risk factors for development of HF,[144] at baseline and left ventricular strain and incident CVD at follow up among healthy adolescents in the CARDIA-study.[145] Our results showed an independent effect of muscle strength on subsequent HF risk that was comparable to that of having high CRF. Similar associations have previously been shown for CHD and stroke,[50] and for CVD (defined as CHD, stroke and HF)[34] in the present cohort. The associations were strongest for cases of HF associated with CHD, diabetes or hypertension. Taken together, these results indicate that the cardioprotective effects of CRF and muscle strength start in early life, and give support to the importance of promoting PA and CRF in the younger population.

### Study III

For this study, we aimed at investigating the longitudinal relationship between cognitive performance at military service conscription and future risk of HF. We found that conscripts with the lowest cognitive test scores had substantially elevated risk of HF regardless of concomitant associated conditions.

Previous studies have shown associations between early life IQ and CVD.[81, 146, 147] In a pooled meta-analysis of longitudinal studies, Dobson et al. showed that each SD decrease in childhood IQ was associated with 16% (relative risk, 1.16; 95% confidence interval, 1.07–1.26; P<0.001) increased risk of future CVD (defined as hospitalization for CVD, CHD, or stroke).[89] This can be compared to the present results showing an increased risk of 31% for HF associated with CHD, diabetes and hypertension for each SD decrease in IQ (HR=1.31 (CI=1.26-1.35)). However, the strength of the association was comparable across all etiological categories. While previous studies have suggested that the relationship between early-life IQ and CVD may be explained by lifestyle- and social factors in early life[82, 148] and socioeconomic factors in adulthood,[149] the present results were not affected by adjustments for markers of socioeconomic status and childhood social circumstances, although residual confounding may be present. As previously discussed, cognition in early life has been suggested to affect adult health via several pathways (Figure 7).

Previously, cognition has been linked to health-related behaviours, such as CRF,[80] smoking cessation[93] and adherence to secondary preventive statin treatment among patients after first MI.[94] Cognitive ability has previously been associated with health literacy,[92] which has been found to predict disease knowledge, self-management

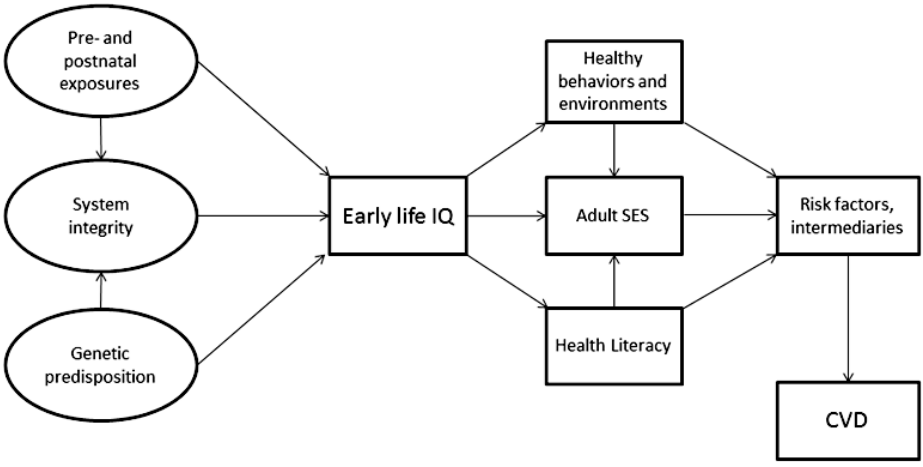



**Figure 7.** Overview of possible pathways between early life IQ and CVD.

skills[97] and outcomes in patients with hypertension, diabetes[98] and HF.[99] These results give support to evidence indicating the predictive effect of cognition in early life to cardiovascular health in adulthood. While causal relationships cannot be concluded from the present study, individuals with low cognitive capacity may gain from increased supporting functions in the health care system.

## Study IV

In the present study, high resting heart rate in adolescence was associated with increased risk of HF and all cause death, but not other cardiovascular outcomes, when simultaneously considering risk factors such as CRF, blood pressure and BMI.

Previous studies on middle-aged men and women have found associations between RHR and cardiovascular outcomes, including HF.[72, 74, 150-152] In a recent meta-analysis containing 21 longitudinal studies and 164,143 participants, Aune et al. showed positive associations between fatal and non-fatal CVD-outcomes, including a 18% risk increase of HF per 10 unit increase in RHR.[72] The only exception was AF, for which there was no significant association. The present negative findings may thus indicate that the relationship of RHR and CVD is largely dependent of the accumulation of other risk factors over the life-course, whereas the observed risk increase of HF may be mediated by other mechanisms. Several mechanisms linking elevated RHR to HF have been suggested. Elevated RHR has previously been associated with risk of diabetes,[69] hypertension,[70] metabolic syndrome[71] and CHD,[72] all of which are contributing factors in the development of HF. Even so, previous studies have failed to explain the association between RHR and HF by adjustment for pre-existing CHD.[150, 151, 153]

In the present study, RHR was associated with HF but not MI after adjustment for arterial blood pressure, supporting an association at least partly independent that of CHD. Although RHR has been associated with measures of cardiac remodelling such as left LVM and left-atrial dimension,[154, 155] these studies did not consider factors such as CRF or functional echocardiographic measurements including ejection fraction, global longitudinal strain and measures of diastolic function. Uncertainty remains as to whether these morphological changes represent physiological adaptations to conditioning, popularly known as "athletes' heart",[156] rather than pathological remodelling. Autonomic imbalance characterized by increased sympathetic and diminished parasympathetic activity is a known factor in HF, CHD and hypertension.[157] Among healthy adults, an impaired heart rate response during stress testing has been associated with sudden death from MI.[158] While aerobic conditioning has been found to increase cardiac parasympathetic-[63] but not sympathetic functioning[159] it has been suggested that, among healthy individuals, the protective effect of exercise on the autonomic nervous system is primarily mediated via increased parasympathetic functioning. Lastly, elevations in RHR during examination may be related to the physiological stress response, or "fight or flight" reaction, that has previously been suggested as an explanation to the association between psychological stress and CVD.[160] Chronic stress has previously been associated with HF[161] and CHD.[162] Acute stress is known to trigger cardiac events such as ischemia and arrhythmia,[163] and has recently been associated with a syndrome of reversible cardiac dysfunction, known as takotsubo- or stress cardiomyopathy.[164] Stress reactivity has been associated with LVM[165] and hypertension[166] in adolescents. Low resilience to stress has also been associated with hypertension,[167] diabetes,[168] CHD,[169] stroke[170] and HF[171] in the present or very similar cohort. Among the suggested mediators are health related behaviours, including physical activity. CRF is associated with HF risk,[172] and has been suggested to reduce the physiological stress response.[173] There have also been some conflicting findings, and trials on healthy adults have failed to show an effect of aerobic conditioning on cardiovascular sympathetic[174] and parasympathetic[175] responses to stressors.

## Strengths and limitations

The strengths of study I include the selection of a population from city areas with major contrasts with respect to socioeconomic status. The use of objective measurements allows for detailed assessment of the different aspects of the PA-pattern and CRF. There are, however, also some limitations to the methods employed. Firstly, the accelerometer measures movement in absolute numbers, not taking into consideration the relative intensity of PA undertaken, which may vary according to individual characteristics such as age, BMI and gender. Because it only measures linear accelerations, it does not take into consideration posture and cannot distinguish sitting from standing. Other factors that influence the level of exertion are also not registered, such as elevations or weight load. Because the accelerometer is hip-worn, it will not register upper-body movements. While the current definition of non-wear time might lead to exclusion of participants, it allows for comparisons with other studies, and non-wear time may represent mainly sedentary time.[176] Data was registered throughout the year, minimizing the risk of seasonal variability of PA confounding our results. In a Swedish study by Hagströmer et al., there was only a small seasonal difference for objec-

tively measured MVPA that affected only southern regions, while no difference was found across other accelerometer intensity categories or mean cpm.[177]

In the SCAPIS-pilot study (study I), participations rates varied between the studied geographical areas, constituting a potential source of selection bias. The lower response rate among low-SES area inhabitants may lead to underestimation of the observed disparities because non-participants may be even less active. Propensity score matching based on population registry data has been suggested as a way of counteracting these effects,[104] and should be considered for future investigations.

The Swedish military service conscription registry uniquely provides data on physical and cognitive performance for the majority of the adult male population and follow-up via the IPR has provided a large number of CVD-cases. Although diagnoses in the IPR have not been formally validated (as it is kept for administrative reasons and not for clinical research), the validity has been found generally high for diagnoses of CVD.[178] Study generalizability is limited on account of the population being comprised of mainly 18-year old, Caucasian men, and may not be representative of other ethnicities or of women (further discussed in the following section). Due to limitation of follow-up, observed cases are young (mean age=50-52 in study IV). Compared to the typical HF patient,[27] the observed cases may not be fully generalizable to the general HF population. Additionally, information regarding physical activity in later life and lifestyle variables (e.g. smoking, diet) was not recorded and is a potential source of residual confounding.

Regarding CRF testing, this thesis has employed measurement methods that have separate strengths and limitations making them suitable for different study settings. The Åstrand-Rhyming method was used for the participants of the SCAPIS pilot. The test extrapolates an estimation of VO2max from a submaximal heartrate, introducing the risk of measurement errors. However, the method has been extensively studied for validity and reliability of measurement.[114] Using a submaximal test is also more suitable in a population where preexisting conditions make maximal exertion potentially harmful. It is also less demanding in terms of staff and surveillance as compared to direct measurement of VO2max. The maximal CRF test used during military service conscription provides a value of maximum work capacity in Watts (Wmax). Although this value does not equate to direct measurement, when standardized by body weight, Wmax has been found to correlate well with direct measurement of VO2max.[115, 116]

### *What about women?*

Because the previously mandatory military service conscription did not apply to women, they are not represented in this material, raising the question whether the present results apply to the female population in Sweden. It must be acknowledged that CVD differs in its presentation with respect to sex. In western countries, CVD generally presents at lower ages among men. For CHD, after consideration of age and risk factors, men have been found to have about twice the risk of women, although the risk ratio narrows after middle age.[179] In a recent nationwide registry study in Sweden, the mean age at first MI has been found about 4 years higher in women as compared

to men.[180] Young women have been found to have higher short-term mortality risk in-hospital compared to men, which could be explained by higher burden of comorbidities.[180] For stroke, the incidence rates[181] and prevalence[182] have also been found higher in men across all age groups. While women have a slightly higher relative risk of HF after MI,[183] HF typically presents earlier in men.[27] Although recent data has shown decreasing age-adjusted prevalence of HF in both sexes in Sweden, the decline was more pronounced among women after 2003,[26] a finding that has been suggested to be attributable to differing mortality trends with respect to sex.[26, 184] There is evidence suggestive of differential characteristics of HF with respect to sex. It has been suggested that HF with preserved ejection-fraction (HFpEF) is more common among women, and that women are more prone to cardiac concentric remodeling, although the mechanisms are largely unknown.[185]

It is also possible that risk factors, including PA and CRF, affect men and women differently. Concerning CHD, it has been found that blood pressure may elicit a greater risk in women, whereas elevated cholesterol poses a greater risk among men.[186] A systematic review of 30 prospective studies from the United states, United Kingdom, Germany, Sweden, Norway, Finland, Canada and China, included 68 000 men and 347 000 women in gender-specific analyses of the association between PA and CVD. Comparing the most active participants with the least, the median relative risk reduction was 40% among women participants, as compared to 30% among men.[187] CRF has been found to comparably predict all cause death[8] and CVD,[10] including HF[188] among men and women.

Cognitive function in early life has been found to predict mortality from all causes among women and men.[78] Regarding CVD-outcomes, many studies on the association with early life IQ have not included women[81, 82, 147] or did not consider the possibility of an interaction with sex.[146] However, in a study of the Aberdeen Children of the 1950s Cohort, Lawlor et al. found that the increased risk for CHD and stroke associated with low IQ was higher in women, although the interaction disappeared after adjustment for educational attainment.[149] Similarly, in 65,765 men and women in the Scottish Mental Survey of 1947, Calvin et al. found that the association with childhood IQ and risk of CVD related death was stronger among women.[88] Other studies found no evidence of an interaction by sex.[189, 190]

In middle-aged or older adults, RHR has been found to predict CVD outcomes including fatal[191, 192] and non-fatal[74] CVD/CHD, AF[193], IS[74] and HF[190] in men and women, although there is also some evidence of a sex*RHR interaction with the risk of HF[151], AF,[192] IS,[192] and nonfatal CVD.[191]

In summary, while there is strong evidence supporting that the beneficial effects of PA and CRF apply to men and women, the evidence regarding the impact of early life cognition and heart rate on long-term cardiovascular health in women are scarcer. Future studies should investigate whether the results of this thesis is generalizable to the female population.

## CONCLUSION

This thesis provides evidence about PA and CRF as potential mediators to socio-economic differences with respect to CVD. Inhabitants of low-SES areas in the Gothenburg region showed lower levels of MVPA and fulfilment of national PA-recommendations, as well as 12% lower CRF compared to high-SES inhabitants. This association is partially dependent of the characteristics of the neighborhood, which should be considered when creating new policies aimed at increasing PA and CRF in the general population. Potentially, efforts aimed specifically at increasing activity levels in areas with low SES could have a large impact on public health at lower cost.

Longitudinal results from the Swedish military service conscription registry provide new insights on how factors in early life may affect cardiovascular health in middle age. Specifically, low CRF, muscle strength, cognitive capacity and high resting heart rate are independently associated with increased risk of HF in later life. As increased physical activity potentially improves all of these factors, the results of this thesis imply that interventions aimed at raising activity-levels in childhood and adolescence may affect health throughout the life-course. Evidence regarding the character and strength of the associations among women and other populations are still lacking and require further investigation.

## FUTURE PERSPECTIVE

This thesis has shown cross-sectional disparities in PA and CRF between living areas of contrasting socioeconomic status, disfavoring residential areas of low SES. To further strengthen this observation and possible implications for public health, future studies should further quantify the impact of socioeconomic differences in PA and CRF in relation to cardiovascular health using longitudinal designs and various measures of SES. Furthermore, using measures of public health impact such as population attributable fraction could potentially help determine to what extent social inequalities in health are determined by physical inactivity, providing information of critical value for policymaking shaping community health.

Results from the military service conscription registry has added new knowledge about how factors in early life may influence health across the life-course. Low CRF and muscle strength at conscription were independently associated with 50-60% increased risk for heart failure at a young age. It would be valuable to further assess the significance of how longitudinal trends may affect the associations observed, as changes of fitness[9] and heart rate[73] in mid-life has previously been found to predict cardiovascular outcomes. While resting heart rate is longitudinally associated with heart failure, it is uncertain whether this is represents a causal association or can be explained by residual confounding. Future studies should investigate whether the association with HF is stable across various etiological conditions, preferably while simultaneously considering measures of CRF and PA-pattern.

While measures of cognitive capacity have been found to be stable across adult life,[84] efforts should be made in order to determine the possible mediating factors, for which repeated measurements could prove valuable.[88] There is emerging evidence regarding genetic factors as an important cause for the association.[101] Whether the association is caused by pleiotropic effects (intelligence and health outcomes sharing a common genetic origin) or constitutes evidence of a causal pathway between genetic predisposition and disease is unknown. Mendelian randomization has been suggested as a tool for answering these questions, but has not been able to provide evidence of a causal association as of yet.[194]

## POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Regelbunden fysisk aktivitet och kondition har väldokumenterade positiva hälsoeffekter på den mänskliga fysiologin, inte minst vad gäller hjärt- och kärlsjukdom och dess riskfaktorer. Låg socioekonomisk status utgör en känd riskfaktor för hjärt-kärlsjukdom och förtida död. Dessa skillnader i hälsoutfall kan tillskrivas bland annat utbildningsnivå vilket predisponerar för möjlighet till aktiva val avseende livsstilsrelaterade faktorer. Kognitiv förmåga har även identifierats som en prediktor för hjärtkärlsjukdom, mekanismerna är omdiskuterade men det finns belägg för att effekten medieras av socioekonomiska- och livsstilsrelaterade faktorer.

Syftet med denna avhandling är att bidra med ny kunskap om sambanden mellan fysisk aktivitetsgrad, kondition och kognition, med risk för hjärt-kärlsjukdom, särskilt hjärtsvikt.

Denna avhandling hade två övergripande mål. Det första var att kartlägga skillnader i fysisk aktivitet och konditionsnivå med avseende på socioekonomisk status i en medelålders Göteborgsbefolkning. Detta arbete utfördes med data från SCAPIS-pilotstudie (Göteborg, 2012. För övriga arbeten har målsättningen varit att identifiera riskfaktorer för hjärtsvikt och hjärt-kärlsjukdom i ungdomen, med en lång uppföljningstid. För detta har nationella värnpliktsregistret använts, där kondition, kognitiv förmåga, och vilopuls i samband med mönstring har studerats med avseende på framtida insjuknande, dokumenterade i det nationella patientregistret.

Data från SCAPIS-pilotstudie visade på lägre generell aktivitetsnivå bland invånare i bostadsområden med låg socioekonomi samt 12 % lägre konditionsnivå, skillnader som kan översättas till betydande riskökning för att utveckla hjärt-kärlsjukdom. Rekryter med sämre kondition, lägre kognitiv förmåga och högre vilohjärtfrekvens uppvisade ökad risk för att utveckla hjärtsvikt.

Sammantaget bidrar arbetet med ny kunskap om sociala skillnader i fysisk aktivitet som möjlig delförklaring till observerade skillnader i hälsoutfall samt om faktorer i ungdomsåren som har betydelse för den kardiovaskulära hälsan senare i livet.

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