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THE ASSOCIATION OF CARDIORESPIRATORY FITNESS, PHYSICAL ACTIVITY AND ISCHEMIC ECG FINDINGS WITH CORONARY HEART DISEASE-RELATED DEATHS AMONG MEN

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Abstract

Despite advances in treatment of cardiovascular diseases, coronary heart disease (CHD) remains the most common cause of death in the Western countries; and its first manifestation is often sudden cardiac death (SCD). The development of CHD is a lifelong process, the pace of which is governed by the burden of several risk factors. The purpose of this study was to investigate the association of levels of cardiorespiratory fitness (CRF), exercise-induced myocardial ischemia and physical activity with the risk of CHD-related death, including SCD events among men with different risk factor profiles.

This study is based on the population of the Kuopio Ischaemic Heart Disease Risk Factor Study, which recruited a sample of 2682 men aged 42–60 years. Their CRF was assessed with a maximal exercise test using respiratory gas analysis. Exercise-induced ST segment depression was defined as a ≥1 mm ST segment depression on the electrocardiogram. Anthropometric measurements, blood sample analyzes and questionnaires regarding leisure-time physical activity (LTPA) and smoking were performed at baseline.

Men with both low CRF and exercise-induced ST segment depression were at higher risk of death from CHD and SCD than men with high CRF without ST segment depressions. Men with low CRF and low LTPA were at higher risk of SCD than men with low CRF and high LTPA. The amount of LTPA did not alter the incidence on SCD among men with high CRF. These findings were adjusted for age, type 2 diabetes and CHD, smoking, alcohol consumption, body mass index, systolic blood pressure, serum low density lipoprotein cholesterol, and serum C-reactive protein level.

These findings emphasize the importance of physical activity and treatment of other modifiable risk factors, especially among the men with low CRF.

Keywords: cardiorespiratory fitness, coronary heart disease, exercise stress test, leisure-time physical activity, myocardial ischemia, risk factors, sudden cardiac death

Hagnäs, Magnus, Aerobisen suorituskyvyn, fyysisen aktiivisuuden ja iskeemisten EKG-löydösten yhteys miesten sepelvaltimotautikuolemiin.
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Tiivistelmä

Sydän- ja verisuonisairauksien ennaltaehkäisystä ja hoidon edistysaskeleista huolimatta sepelvaltimotauti on edelleen kehittyneiden maiden yleisin kuolinsyy, sydänperäisen äkkikuoleman ollessa usein taudin ensimmäinen ilmentymä. Sepelvaltimotaudin syntyminen on pitkäaikainen prosessi, jossa riskitekijät määrittävät suurelta osin taudin etenemisen nopeuden. Tämän tutkimuksen tavoitteena oli selvittää kliinisessä rasituskokeessa todetun aerobisen suorituskyvyn, sydänlihasiskemian sekä fyysisen aktiivisuuden yhteyttä sepelvaltimotautikuolemiin ja sydänperäisiin äkkikuolemiin eri sydän- ja verisuonisairauksien riskitekijäyhdistelmien omaavien miesten keskuudessa.

Tämä tutkimus perustuu Kuopio Ischaemic Heart Disease Risk Factor Study- aineistoon, johon kuuluu 2682 42–60 vuotiasta miestä. Tutkittavien aerobista suorituskykyä arvioitiin kliinisessä rasituskokeessa mittaamalla hapenkulutus suoraan hengityskaasuista. Sydänlihasiskemian merkkinä pidettiin rasituksen provosoimaa ≥1 mm ST-välin laskua tutkittavien EKG:ssa. Tutkittavilta kartoitettiin alussa antropometriset mittaukset, verikokeet sekä kyselylomakkeilla selvitettiin mm. vapaa-ajan liikunnan määrää ja tupakointia.

Miehet, joilla todettiin huono suorituskyky sekä samanaikainen rasituksen aiheuttama sydänlihasiskemia olivat suuremmassa vaarassa menehtyä sepelvaltimotautiin ja sydänperäiseen äkkikuolemaan verrattuna miehiin, joilla todettiin hyvä suorituskyky eikä rasituksen aiheuttamaa sydänlihasiskemiaa. Miehet joilla todettiin huono suorituskyky, mutta harrastivat enemmän liikuntaa vapaa-ajalla, olivat pienemmässä vaarassa sydänperäiseen äkkikuolemaan kuin huonokuntoiset miehet, jotka harrastivat vähemmän liikuntaa vapaa-ajallaan. Vapaa-ajan liikunnan määrä ei muuttanut sydänperäisen äkkikuoleman esiintyvyyttä hyväkuntoisten miesten keskuudessa. Nämä tulokset vakioitiin iän, tyypin 2-diabeteksen, todetun sepelvaltimotaudin, tupakoinnin, alkoholin kulutuksen, painoindeksin, systolisen verenpaineen, seerumin LDL-kolesterolin ja C-reaktiivisen proteiinin suhteen.

Nämä löydökset korostavat liikunnan harrastamisen tärkeyttä muiden riskitekijöiden hoidon ohessa, erityisesti lähtötasoltaan huonokuntoisilla miehillä.

Asiasanat: aerobinen suorituskyky, kliininen rasituskoe, riskitekijät, sepelvaltimotauti, sydänlihasiskemia, sydänperäinen äkkikuolema, vapaa-ajan liikunta

To my mother

Acknowledgements

Abbreviations

CHD   Coronary heart disease
CI   Confidence Interval
CRF   Cardiorespiratory fitness
ECG   Electrocardiogram
HDL   High density lipoprotein
kcal   Kilocalories
KIHD   Kuopio Ischaemic Heart Disease Risk Factor Study
LDL   Low density lipoprotein
LTPA   Leisure-time physical activity
MET   Metabolic equivalents
mmol   Millimole
SCD   Sudden cardiac death

List of original articles

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I   Hagnäs, M. J., Kurl, S., Rauramaa, R., Lakka, T. A., Mäkikallio, T. H., Savonen, K., & Laukkanen, J. A. (2015). The value of cardiorespiratory fitness and exercise-induced ST segment depression in predicting death from coronary heart disease. International Journal of Cardiology, 196, 31-33. doi:10.1016/j.ijcard.2015.05.134

II Hagnäs, M. J., Lakka, T. A., Kurl, S., Rauramaa, R., Mäkikallio, T. H., Savonen, K., & Laukkanen, J. A. (2017). Cardiorespiratory fitness and exercise-induced ST segment depression in assessing the risk of sudden cardiac death in men. Heart (British Cardiac Society), 103(5), 383-389. doi:10.1136/heartjnl-2015-309217

III Hagnäs, M. J., Lakka, T. A., Mäkikallio, T. H., Kurl, S., Savonen, K., Rauramaa, R., & Laukkanen, J. A. (2017). High leisure-time physical activity is associated with reduced risk of sudden cardiac death among men with low cardiorespiratory fitness. Manuscript.

Some previously unpublished results will also be presented.

Contents

1   Introduction

Despite advances in the treatment of coronary heart disease (CHD), it is still the most common cause of death in the world. In 20–30% of CHD cases, the first symptom is sudden cardiac death (SCD) (Huikuri, Castellanos, & Myerburg, 2001; World Health Organisation, 2014). The development of CHD is a lifelong process, the pace of which is governed by the burden of several risk factors. Early identification of subjects at an increased risk of CHD provides the opportunity to treat the risk factors and thereby potentially change the course of the disease.

Although low cardiorespiratory fitness (CRF) seems to be one of the strongest predictor for death from CHD (Kodama *et al.*, 2009; Ross *et al.*, 2016), its importance is underrated in the clinical setting (Mark & Lauer, 2003). Low leisure-time physical activity (LTPA) has also been associated with an increased risk of death from CHD and SCD (Talbot, Morrell, Metter, & Fleg, 2002). It has even been postulated that lack of physical activity is one essential cause of most chronic disease and premature death (I. M. Lee *et al.*, 2012). Exercise-induced myocardial ischemia, as defined by the appearance of ST segment depression in an electrocardiogram (ECG), is an established risk factor for death from either CHD or SCD (Detrano *et al.*, 1989). However, the value of combining CRF with LTPA and exercise-induced ST segment depression in the prediction of CHD outcomes in the clinical practice is still unknown.

The purpose of this study was to investigate how effectively the risk of death from CHD and SCD in middle-aged men can be predicted by examining a combination of CRF, LTPA and exercise-induced ST segment depression.

2 Review of the literature

2.1 Coronary heart disease

CHD is a disease in which a waxy substance called plaque builds up inside the coronary arteries (Figure 1) (Montalescot *et al.*, 2013). The coronary arteries supply the heart with oxygen-rich blood. Although the first symptoms of CHD can appear suddenly, the clinical manifestation reflects a disease process that has begun decades before the first symptoms become apparent (Figure 2). The symptoms of CHD generally appear once the plaque growth is sufficient to narrow one or more arteries. The typical symptom of CHD is chest pain/discomfort, experienced during physical activity, or, as disease progresses, even during normal daily activities (Montalescot *et al.*, 2013).

Despite the progressive nature of CHD, a myocardial infarction usually presents suddenly when the plaque destabilizes and ruptures, resulting in thrombus formation and thereby a blockage of blood flow (Lloyd-Jones, Larson, Beiser, & Levy, 1999; Montalescot *et al.*, 2013). This results in ischemia in areas of the myocardium, which in turn can lead to necrosis and apoptosis of myocardial tissue or even electrical rhythm disturbances followed by SCD. The sudden appearance of myocardial infarction usually leaves little or no time for prevention, and it is therefore important to identify subjects at risk of myocardial infarction and SCD at an early stage to allow prevention.

Autopsy studies have indicated that most elderly people have some plaque formations in the coronary arteries even in absence of symptomatic disease. However, how best to predict which individuals are at risk of obstructive CHD and SCD has been the subject of decades of ongoing research (Dawber, Meadors, & Moore, 1951). In general, these outcomes can be predicted by the examination of risk factors for CHD – more precisely, by the assessment of combinations of risk factors (Cahalin *et al.*, 2014; Lloyd-Jones *et al.*, 1999; Montalescot *et al.*, 2013). Therefore, CHD risk factor calculators (e.g. ASCVD, SCORE, Framingham, FINRISK and Reynolds Risk Score) have been developed to help physicians identify subjects at risk (American College of Cardiology and American Heart Association, 2017; Conroy *et al.*, 2003; Donald W Reynolds Foundation and the National Heart Lung and Blood Institute, 2017; Framingham Heart Study, 2017; Goff *et al.*, 2013; The National Institute for Health and Welfare (THL), Finland,

2017). However, none of these calculators considers all risk factors, and most even leave out CRF.

Low CRF appears to be one of the most important risk factor for CHD-related deaths (Kodama *et al.*, 2009; J. A. Laukkanen *et al.*, 2001; Mark & Lauer, 2003; Morris, Ueshima, Kawaguchi, Hideg, & Froelicher, 1991). Recent studies have recommended adding a subject's CRF to the overall risk score for a more accurate CHD risk assessment (Conroy *et al.*, 2003; Goff *et al.*, 2013; Mark & Lauer, 2003; Morris *et al.*, 1991).

Fatty Deposits
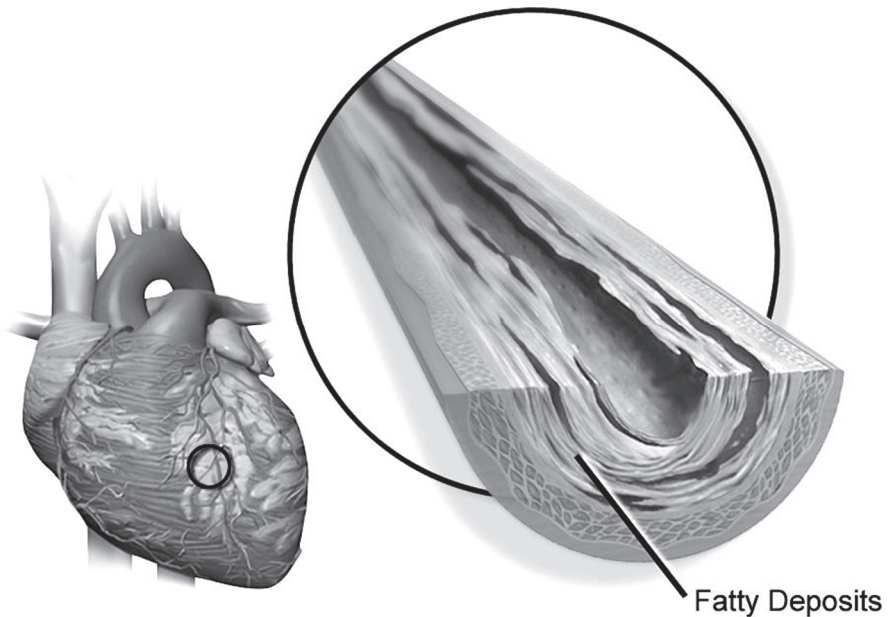
Fig. 1. Coronary Heart Disease. (Published by permission of Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436.)
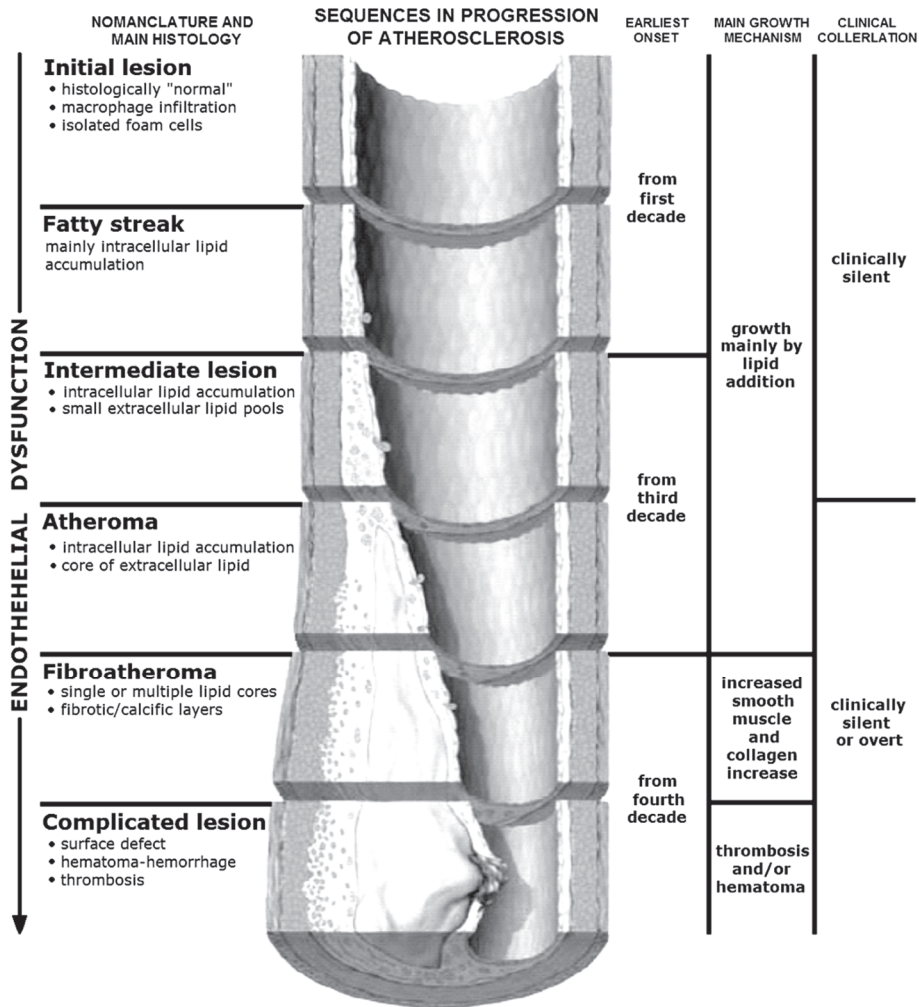
Fig. 2. The narrowing of arteries over decades. (Published by permission of en.wikipedia to Commons., CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=2816579)

2.1.1 Risk factors

Risk factors for CHD-related deaths can be divided into two categories: modifiable and unmodifiable. The most common unmodifiable risk factors are age, gender and family history of CHD. Modifiable risk factors include hypertension,

hypercholesterolemia, unhealthy diet, overweight, diabetes, obstructive sleep apnea, smoking, inflammation, excessive/heavy alcohol consumption, socioeconomic class, CRF and physical inactivity (Conroy *et al.*, 2003; Ekelund, Franks, Sharp, Brage, & Wareham, 2007; Goff *et al.*, 2013; Kodama *et al.*, 2009; T. A. Lakka *et al.*, 1994; Mark & Lauer, 2003). Many risk factors are interconnected – for example, diet affects obesity, hypertension and hypercholesterolemia. The World Health Organization has estimated that 8 risk factors (heavy alcohol consumption, smoking, hypertension, overweight, diabetes, diet and physical inactivity) account for 61% of all cardiovascular deaths (World Health Organization, 2009). Although an individual cannot change their family history, age or gender, they can greatly decrease the risk of CHD by modifying other factors, especially if the risk factors are treated from an early age.

Age

As it is the strongest non-modifiable risk factor, all CHD risk calculators consider age (Goff *et al.*, 2013). The development of CHD begins in youth and its rate of progression is largely dependent on other risk factors (Figure 2). In some cases, a plaque destabilization might result in myocardial infarction or SCD in young adulthood. However, clinical CHD does not generally appear before the age of 40 (Lloyd-Jones *et al.*, 1999). In 2010 the prevalence of CHD in the United States 2010 at the age of 18–44 was 1.2% in persons aged 18–44 years, 7.1% in those aged 45–64 years and 19.8% in those aged 65 years and over (Center for Disease Control and Prevention, 2011).

Gender

It is estimated that CHD develops 5–10 years later in women than in men (Montalescot *et al.*, 2013). The prevalence of CHD among men in the United States 2010 was 7.8% and among women 4.6% (Center for Disease Control and Prevention, 2011). This has been attributed to unhealthy behaviour among men (Barrett-Connor, 1997). However, as well as having a lower burden of risk in several factors, women also have an independently smaller risk for CHD (Isles, Hole, Hawthorne, & Lever, 1992). In women, the risk of CHD increases after the menopause, but still does not reach the risk level exhibited by men (Barrett-Connor, 1997; Collins *et al.*, 1995).

Family history of coronary heart disease

Family history of CHD is an independent contributor to CHD risk, and can be used for risk assessment alongside other factors (Kashani, Eliasson, Vernalis, Costa, & Terhaar, 2013). Family history is a particularly important factor in younger subjects (Otaki *et al.*, 2013). A positive family history of CHD is usually defined as a first-degree male relative (father or brother) who had a myocardial infarction before the age of 55, or a first-degree female relative who had one before the age of 65. If both parents developed CHD before the age of 55, the risk of developing CHD can rise 50% higher compared to the general population (Montalescot *et al.*, 2013; World Heart Federation, 2017).

Arterial Hypertension

Hypertension is a condition in which the blood pressure in the arteries is elevated. High blood pressure does not usually cause symptoms, but long-term hypertension is a major risk factor for CHD, stroke, heart failure and kidney disease (Lackland & Weber, 2015; Lewington *et al.*, 2002). Blood pressure above 140/90 millimetre of mercury (mmHg) is considered elevated (Mancia *et al.*, 2013). Hypertension is to some extent linked to unhealthy lifestyle and thus can be treated by lifestyle modifications, including weight loss, decreased salt intake, exercise and healthy diet. Blood pressure medication is often needed as a part of the treatment. The prevalence of hypertension is around 30–45% of the general population, and is considered to be one of the main treatable risk factors for CHD (Lackland & Weber, 2015; Mancia *et al.*, 2013; Redon *et al.*, 2016). The World Health Organization has estimated that hypertension is the leading risk factor for global mortality (13% of deaths globally) (World Health Organization, 2009).

Hypercholesterolemia

Cholesterol is a type of lipid molecule that is a structural component in human cell membranes and is a precursor for many hormones (National Heart, Lung, and Blood Institute, 2013). Cholesterol is often divided into 'good cholesterol' which is high density lipoprotein (HDL) and 'bad cholesterol', low density lipoprotein (LDL). LDL cholesterol is essential in the development of CHD (Steinberg, Parthasarathy, Carew, Khoo, & Witztum, 1989). The lower the LDL cholesterol level, the lower the risk of developing CHD (Chen *et al.*, 1991; Steinberg *et al.*,

1989). Some LDL cholesterol is produced in the liver and the rest comes from diet, mainly saturated fats (dairy fats and meat fats) (Turpeinen, 1979). The Finnish Mental Hospital Study showed that cholesterol levels and the occurrence of CHD related deaths can be lowered by decreasing the amount of dietary dairy fat (Turpeinen *et al.*, 1979). The Framingham study demonstrated that both low HDL and high LDL are associated with an elevated risk of CHD-related death (Castelli *et al.*, 1986). The data showing a strong correlation between lower LDL cholesterol levels and lower incidence of CHD related deaths resulted in development of many cholesterol-lowering drugs, which are now the cornerstone of CHD treatment.

Unhealthy diet

A healthy diet is a cornerstone of CHD risk reduction (Montalescot *et al.*, 2013). Weight gain should be avoided by ensuring that energy intake is proportionate to energy consumption. Polyunsaturated fats, such as fish oils and olive oil are preferable to saturated fats such as dairy and meat products (Estruch *et al.*, 2013; Perk *et al.*, 2012). Trans unsaturated fats should be avoided. High intake of carbohydrate intake has been associated with higher risk of total mortality (Dehghan *et al.*, 2017). No dietary supplements are recommended. Salt consumption should be less than 5 g per day. Daily consumption of fruit and vegetables should be 200 g each (Montalescot *et al.*, 2013). The so called Mediterranean diet (characterized by a high intake of olive oil, fruit, nuts, vegetables and cereals, with a moderate intake of fish and poultry and a low intake of dairy products, red meat, processed meats and sweets, and a moderate intake of wine with meals) has been associated with a reduced risk of CHD (Estruch *et al.*, 2013; Mente, de Koning, Shannon, & Anand, 2009).

Overweight

Obesity relates to other CHD risk factors like diabetes, cholesterol and lack of exercise. It is a leading preventable cause of death worldwide. An estimated 39% of all adults were overweight in 2014 (World Health Organisation, 2014). One measure of overweight is the body mass index (BMI), which is calculated as the weight in kilogram (kg) divided by the square of the height in metres (m). A BMI over 25 kg/m^2 is considered overweight and over 30 kg/m^2 is considered obese (Montalescot *et al.*, 2013). BMI doesn't distinguish fat mass from lean mass nor for the location of the fat-tissue. Abdominal fat expands the risk of CHD and

diabetes more than fat elsewhere. Other measures of overweight include waist circumference, waist to hip ratio and different analyses of body fat. Obesity is a result of an excess of energy intake over energy consumption. Environmental and hereditary factors play a crucial role in determining an individual's predisposition to weight gain (Locke *et al.*, 2015; R. K. Singh, Kumar, & Mahalingam, 2017).

Diabetes

Diabetes is a metabolic disease in which blood sugar levels are elevated over a prolonged period. Both type 1 (insulin dependent, usually presenting in youth) and type 2 (insulin resistance, usually related to obesity) diabetes are strong risk factors for CHD. Diabetes increases the risk for and the progression of CHD (Montalescot *et al.*, 2013). Complications of diabetes affect all blood vessels including the coronary arteries. Diabetes increases the risk of CHD twofold (The Emerging Risk Factors Collaboration, 2010). It has been approximated that 8.3% of the adult population has diabetes (Shi & Hu, 2014). The costs of diabetes care are substantial: it has been approximated that diabetes accounts for 25% of all health care costs in the United States ("Economic Costs of Diabetes in the U.S. in 2012," 2013). Diabetes also increases the costs of treating myocardial infarctions (Johnston *et al.*, 2015). The coronaries of subjects with diabetes are usually more complex e.g. multivessel disease, involving more calcified and more obstructive lesions (Uddin *et al.*, 2005). Therefore, it is an important risk factor to treat at an early stage from both a healthcare and economic perspective.

Obstructive sleep apnea

Obstructive sleep apnoea is a disorder characterized by snoring and pauses of breathing during sleep. Sleep apnea is a treatable risk factor for CHD which is linked to obesity and physical inactivity (Iftikhar, Kline, & Youngstedt, 2014). Subjects with obstructive sleep apnea have a risk for CHD an estimated 37% greater than the general population (Dong, Zhang, & Qin, 2013).

Smoking

Tobacco smoking, including as an environmental exposure i.e passive smoking, is a strong independent risk factor for CHD (Meyers, Neuberger, & He, 2009). Smoking damages the lining of the arteries, leading to a build-up of plaque in the

arteries and increases blood clotting leading to an increased risk of myocardial infarction (Critchley & Capewell, 2004). Smoking cessation has been shown to be beneficial for all subjects at any time, not only those with CHD (Critchley & Capewell, 2004; Peto *et al.*, 2000). Smoking is one of the leading causes of preventable death globally. The risk of premature mortality can be greatly reduced by cessation of smoking, up to 36% after myocardial infarction. Therefore, smoking should be systematically assessed and addressed when treating subjects at risk for, or with extant, CHD (Montalescot *et al.*, 2013).

Inflammation

Inflammation is a biological response by which cells of the immune system and the substances they produce – cytokines – protect the body from infection with foreign organisms, such as bacteria and viruses. It has been postulated that the development of CHD is partly a process of inflammation, as patients with CHD have a slight but noticeable elevation in high-sensitivity C-reactive protein (hs-CRP), a marker for inflammation (Emerging Risk Factors Collaboration *et al.*, 2010). An increased level of hs-CRP (without infection) has been associated with long-term CHD outcomes (Emerging Risk Factors Collaboration *et al.*, 2010). One trial has showed a reduced incidence of cardiovascular events among patients receiving regular antiinflammatory therapy (canakinumab) (Ridker *et al.*, 2017). However, the use of hs-CRP in the risk assessment of CHD is uncertain and not widely used in clinical practice (Danesh *et al.*, 2004; Goff *et al.*, 2013).

Alcohol consumption

Excessive alcohol consumption is a major global risk factor for mortality and morbidity. It has many long-term adverse effects including cancer, impaired brain function, pancreatitis, liver failure, cardiomyopathies, injuries and death (Bagnardi *et al.*, 2015; Rehm & Monteiro, 2005; Rehm, Samokhvalov, & Shield, 2013; Shield, Gmel, Patra, & Rehm, 2012). However, alcohol's effect on CHD is not entirely clear. Some studies show that alcohol is beneficial for CHD (Renaud & Lorgeril, 1992; Rimm *et al.*, 1991), while others report the opposite (Roerecke *et al.*, 2011). It seems that low alcohol consumption without heavy drinking episodes has a beneficial effect on CHD (Roerecke & Rehm, 2014). However, alcohol consumption has also been linked to other unhealthy behaviors and therefore should be limited (Roerecke *et al.*, 2011; Shield *et al.*, 2012). Guidelines

recommend limiting the consumption of alcoholic beverages to 10 g/day (1 glass of wine) for women and 20 g/day for men (Montalescot *et al.*, 2013).

Socioeconomic status

Socioeconomic status is an individual's or family's economic and social position, based on income, education and occupation. Low socioeconomic status has been associated with increased risk of CHD outcomes (Foraker *et al.*, 2011; Kivimäki *et al.*, 2007; Rosamond *et al.*, 1998). However, other risk factors like smoking, alcohol consumption and obesity should also be considered, while considering socioeconomic status as an independent risk factor for CHD (Lawlor, Smith, & Ebrahim, 2004; M. Lee, Khan, & Wright, 2017). Therefore, it is rarely used in the clinical setting.

Cardiorespiratory fitness

CRF can be defined as the ability of the circulatory and respiratory system to supply oxygen to skeletal muscles during physical activity. Thus, higher CRF results in the ability to exercise longer and faster. The level of CRF is often expressed in metabolic equivalents (MET), normally calculated indirectly from the subject's weight and maximal workload during an exercise stress test. The most accurate measurement of CRF is considered to be cardiopulmonary exercise test, in which oxygen consumption is measured directly from the inhaled and exhaled gases. However, this measure is rarely used in clinical practice (G. J. Balady *et al.*, 2004; Gary J. Balady *et al.*, 2010). One MET corresponds to an oxygen uptake of 3.5 mL/kg per minute or an energy consumption of 1 kcal (kilocalories)/kg/hour, Table 1 (Ainsworth *et al.*, 1993). A CRF <5 MET is considered low and middle-aged subjects should reach a CRF of at least 8 MET (Kodama *et al.*, 2009; Montalescot *et al.*, 2013). Age predicted MET can be used for a more accurate classification of an individual's level of CRF (Kokkinos *et al.*, 2017; Morise & Diamond, 1995).

The level of CRF is determined by several factors such as age, gender, life-style, overweight, diseases affecting the cardiorespiratory system and heredity (Blair, Cheng, & Holder, 2001; Bouchard *et al.*, 2011; Bruce, Kusumi, & Hosmer, 1973; Jackson *et al.*, 1995; A. S. Leon, Jacobs, DeBacker, & Taylor, 1981; Sandvik, Erikssen, & Thaulow, 1995; Wolfarth *et al.*, 2014). Estimates of heritability for CRF vary between 22 and 57% (Perusse *et al.*, 2001; Zadro *et al.*, 2017). Although exercise increases CRF, the response to exercise varies considerably between

individuals (Bouchard *et al.*, 2011; Wolfarth *et al.*, 2014; Zadro *et al.*, 2017). An individual's CRF generally decreases by 5%–15% over each year of adult life, however exercise can considerably reduce this annual decrease (Blaha *et al.*, 2016; E & Rc, 1990; Hagberg *et al.*, 1985; Jackson *et al.*, 1995).

As CRF is a measure of the circulatory and respiratory system's function, a low CRF is considered to be one of the strongest predictor of all-cause mortality and death from CHD (Kodama *et al.*, 2009; J. A. Laukkanen *et al.*, 2001; D. Lee, Artero, Sui, & Blair, 2010; Morris *et al.*, 1991; Ross *et al.*, 2016). One MET higher CRF has been associated with a 13–17% decreased risk of death from CHD (Al Rifai *et al.*, 2017; Gulati *et al.*, 2003; Kodama *et al.*, 2009). A high CRF appears to mitigate the increased risk of CHD caused by other risk factors such as age, diabetes, family history of CHD, overweight, age and hypertension (Al Rifai *et al.*, 2017; Ekelund *et al.*, 2007; Kokkinos *et al.*, 2017; Montalescot *et al.*, 2013; Perusse *et al.*, 2001; Schwingshackl, Missbach, Dias, König, & Hoffmann, 2014). Although many studies has shown that combining CRF with other risk factors is useful in predicting the risk of developing clinical CHD,(G. J. Balady *et al.*, 2004; Israel *et al.*, 2016; Mitchell *et al.*, 2006) the importance of CRF is undervalued in clinical practice (Kraus & Douglas, 2005; Mark & Lauer, 2003; Wilson *et al.*, 1998).

Table 1. The metabolic equivalents and amount of energy consumed during 30 minutes of different physical activities for a 70 kg individual (Ainsworth *et al.*, 1993).

MET	Kcal	Physical activity
0.9	31	Sleeping
1	35	Sitting quietly e.g. watching television
2	70	Eating, dressing, writing or playing piano
3	105	Light walking, cleaning, doing laundry, workload 50 watts
4	140	Baking, gardening, walking 5km/h, bicycling 15km/h
5.5	193	Light jogging, sexual activity, home-repairs, workload 100 watts
7	245	Jogging, jumping jacks, canoeing, workload 150 watts
8	280	Playing basketball, circuit training, manual forestry
10.5	368	Running 10km/h, swimming with vigorous effort, workload 200 watts
12.5	438	Bicycling 30km/h, running 2.4km in 12min, work as fire fighter, workload 250 watts

Physical inactivity

Physical activity is defined as a bodily movement produced by skeletal muscles that results in energy consumption. Exercise is defined as a planned physical

activity (Caspersen, Powell, & Christenson, 1985). An individual's level of physical activity is usually evaluated with questionnaires (Booth, Roberts, & Laye, 2012; Taylor *et al.*, 1978). The European guidelines recommend performing aerobic physical activity at moderate intensity for 30 minutes/day, 5 days/week, or preferably every day, to prevent cardiovascular disease (Perk *et al.*, 2012). However, even modest amounts of physical activity (5–10 minutes per day) have been associated with significant health benefits (Myers *et al.*, 2015). The importance of muscle strength should not be underestimated either. Although the health benefits of exercise have been widely studied and recognized (Blair *et al.*, 2001; Garcia-Palmieri, Costas, Cruz-Vidal, Sorlie, & Havlik, 1982; Pate *et al.*, 1995), up to 60% of adults in Europe perform no regular exercise (Ríos, Cubedo, & Ríos, 2013). Similar data have been reported in the United Sates (Centers for Disease Control and Prevention, 2007). A Canadian accelerometer study showed that only 15% of adults meet the national activity recommendations (Colley *et al.*, 2011).

It is perhaps unsurprising that many studies have shown that sedentary lifestyle is the primary cause of many diseases including CHD (Booth *et al.*, 2012; I. M. Lee *et al.*, 2012; Thijssen *et al.*, 2010). The World Health Organization has estimated that physical inactivity is the fourth leading risk factor for global mortality (6% of deaths globally) (World Health Organization, 2009). Table 2 shows the effects of physical activity on various risk factors for CHD. Physical activity not only improves CRF but also glycemic control, lipids, body weight, endothelial function, hemostasis, blood pressure, depression and even reduces the risk of some types of cancer (Booth *et al.*, 2012; Glazer *et al.*, 2013; Arthur S. Leon & Sanchez, 2001; Schwingshackl *et al.*, 2014). Physical activity also increases the growth of coronary collaterals (Heaps & Parker, 2011). These so called "natural bypasses" are anastomotic connections between coronary arteries, which supply blood when the original vessel is obstructed by plaques (Koerselman, Graaf, Jaegere, & Grobbee, 2003). Improvement in coronary collateral circulation reduces symptoms of CHD, areas of myocardial infarction and the risk of SCD (Akin *et al.*, 2013; Meier *et al.*, 2010, 2012). Ischemic preconditioning is another positive effect of physical activity in subjects with obstructive CHD is. It occurs when the myocardium is subjected to repeated short ischemia without infarction, which leads to a protective reaction of the myocardium, the mechanism of ischemic preconditioning is not yet entirely clear (Frasier, Moore, & Brown, 2011; Incognito, Burr, & Millar, 2016; Yellon, Baxter, Garcia-Dorado, Heusch, & Sumeray, 1998).

Despite the clear association between physical activity and CRF, these appear to be discrete risk factors for CHD (DeFina *et al.*, 2015; Singhal & Siddhu, 2014;

Tager, Hollenberg, & Satariano, 1998; Talbot *et al.*, 2002; Williams, 2001). Vigorous physical activity has been suggested to momentarily increase the risk of SCD, however this risk is relative low, especially among active subjects, and the consensus is that physical activity decreases the risk of long-term CHD events (M. A. Mittleman *et al.*, 1993; Murray A. Mittleman & Mostofsky, 2011; Rognmo *et al.*, 2012).

Table 2. The responses to physical activity of various risk factors for coronary heart disease

Variable	Response	Reference
Cardiorespiratory fitness	Increases	(Lin *et al.*, 2015)
HDL Cholesterol	Increases	(A. S. Leon *et al.*, 2000; Arthur S. Leon & Sanchez, 2001)
LDL Cholesterol	Decreases	
Triglycerides	Decreases	
Hypertension	Reduces	(Fagard, 2001)
Type 2 Diabetes	Improves glycemic control	(Schwingshackl *et al.*, 2014; Thompson *et al.*, 2001)
Obesity	Weight loss	(Arthur S. Leon & Sanchez, 2001; Wing & Hill, 2001)
Smoking	Increased cessation rate	(Marcus *et al.*, 1999)
Coronary arteries	Growth of collaterals	(Heaps & Parker, 2011; Meier *et al.*, 2012)
Depression	Reduce mortality	(Win *et al.*, 2011)
Some cancers	Reduces occurrence	(Kruk & Czerniak, 2013)
Endothelial dysfunction	Improves	(Gielen, Erbs, Schuler, & Hambrecht, 2002)
Sleep apnea	Reduces	(Iftikhar *et al.*, 2014)

2.1.2 Symptoms

A history of chest pain remains the cornerstone of CHD diagnosis (Montalescot *et al.*, 2013). The clinical classification of chest pain caused by CHD includes: substernal chest discomfort; pain provoked by exertion or emotional stress; pain that is relieved within minutes by rest or nitrates (Montalescot *et al.*, 2013). When all three of these characteristics are present, typical angina is diagnosed. When two of the characteristics are present, the diagnosis is atypical angina or non-anginal chest pain (Montalescot *et al.*, 2013). However, CHD may manifest only by shortness of breath, and can even be asymptomatic. The severity of angina is usually classified using the Canadian Cardiovascular Society's system, which grades angina as Class 0–IV according to the threshold level of physical activity at which symptoms occur: 0 Asymptomatic, I Angina only with strenuous exertion,

II Angina with moderate exertion, III Angina with mild exertion, IV Angina at rest (Campeau, 1976). A higher grade of angina has been associated with an elevated long-term mortality risk, even after adjusting for baseline characteristics (H *et al.*, 2004; Kaul *et al.*, 2009).

2.1.3 Diagnosis

A subject with suspected CHD should first have a physical examination, including ECG, blood tests and in some cases chest X-ray (Montalescot *et al.*, 2013). The need for further examinations and tests is then determined by the subject's pre-test probability of CHD. In most cases the next step is an exercise stress test (in subjects with a pre-test probability of CHD 15–85%). However, if a subject's pre-test probability for CHD is high (>85%) a negative exercise stress test would not rule out CHD so they can be referred directly for invasive coronary angiography. Sometimes exercise stress test can be used to determine the urgency and treatment of subjects with high pre-test CHD probability. Not all subjects with diagnosed stable CHD need invasive coronary angiography, as the treatment of risk factors is central in preventing future CHD outcomes.(Montalescot *et al.*, 2013)

Exercise stress test

Exercise stress test has been used for over 60 years in the diagnosis of CHD.(Luong, Ignaszewski, & Taylor, 2016) It can also be used to evaluate the level of CRF, chronotropic incompetence, valvular heart disease, arrhythmias and to the risk of outcomes. It's widely available in health centres and hospitals and is relatively low-cost. The test is usually performed on a treadmill or a cycle ergometer, with an increasing exercise workload while 12-lead ECG, blood pressure and symptoms are monitored. The exercise protocol should be selected according to patient so that the exercise takes 6–12 minutes. A horizontal or down-sloping ST segment depression of at least 1 mm (0.1 millivolt) 60–80 ms after the J-point is considered a positive sign of CHD in most cases (Montalescot *et al.*, 2013; Sharma, Kohli, & Gulati, 2012). The sensitivity of an exercise stress test for the detection of obstructive CHD is reported to be between 23 and 100% (mean 68%) and the specificity between 17 and 100% (mean 77%), with the variation largely depending on the pre-test probability of, and definition of, CHD (Froelicher *et al.*, 1999; Members *et al.*, 2003; Morise & Diamond, 1995). Exercise stress tests are less sensitive and specific in women than in men (Morise & Diamond, 1995).

For more accurate CHD diagnosis and prediction of CHD-outcome, several exercise stress test findings should be considered: severity of ST segment depression, extrasystolia, other ECG changes, blood pressure reaction (e.g. inadequate rise or drop), heart rate, maximal workload, symptoms and cause of cessation (Banerjee, Newman, Bruel, & Heneghan, 2012; Froelicher *et al.*, 1999; Luong *et al.*, 2016; Sharma *et al.*, 2012). Exercise stress test findings should also be combined with the subject's CHD risk factor burden to evaluate the total risk of CHD and to predict the risk of CHD-events (Aktas, Ozduran, Pothier, Lang, & Lauer, 2004; Goff *et al.*, 2013; Israel *et al.*, 2016; Morris *et al.*, 1991). Subjects with normal exercise stress test and low clinical risk for CHD have an excellent prognosis (Miller, Roger, Hodge, & Gibbons, 2005).

When subjects are unable to exercise, there is interpretable ECG changes (e.g. ventricular paced rhythm or left bundle branch block), other contra indications or the results are inconclusive, other non-invasive test might be more appropriate than invasive coronary angiography.

Other non-invasive tests

Exercise stress echocardiography can be used to detect wall motion abnormality during stress, thereby increasing the sensitivity and specificity for detecting CHD (Schinkel *et al.*, 2003). In some cases, myocardial perfusion imaging can also be used for CHD diagnosis. It is a test where a cardiac specific radiopharmaceutical is administered during stress (exercise or pharmacological) and its distribution is analysed with single-photon emission computed tomography, which detects possible regions of ischemia (Schinkel *et al.*, 2003).

Coronary computed tomography angiography is another non-invasive way of diagnosing CHD, best used the rule out CHD among subjects with low pre-test probability (Abbara *et al.*, 2016). The coronary arteries can be visualized by taking a computed tomography image of the heart following the injection of a contrast agent into a vein. Both myocardial perfusion imaging and coronary computed tomography angiography expose the subjects to radiation, which should be considered in the selection of tests. The best non-invasive approach for CHD diagnosis is a hybrid CTA and perfusion test such as cardiac positron emission tomography/computed tomography (Kajander *et al.*, 2010).

Invasive coronary angiography

Subjects with an intermediate or high risk of CHD events, or a high pre-test probability of CHD (>85%) or angina pectoris symptoms despite optimal medical therapy are candidates for coronary angiography (Montalescot *et al.*, 2013). Coronary angiography is an invasive test in which a contrast agent is injected via a catheter selectively into the coronary arteries through either the radial or femoral artery and images showing the coronaries are acquired with x-ray radiation. If a more accurate evaluation of the coronaries is needed, measurement of fractional flow reserve, optical coherence tomography or intravascular ultrasound can be performed during the procedure (Montalescot *et al.*, 2013). If a percutaneous coronary intervention (angioplasty) is needed it can also be performed in the same procedure. If performed correctly, a coronary angiography should detect all clinically relevant obstructive CHD. Being an invasive test, coronary angiography carries a higher risk for complications than non-invasive investigations, and even a risk of mortality (<0.5%) (M. Singh *et al.*, 2009).

2.1.4 Treatment of stable coronary heart disease

The treatment of stable CHD differs considerably from that of unstable CHD (e.g. myocardial infarction and unstable angina pectoris). With stable CHD it is important to treat modifiable risk factors with medical treatment and lifestyle changes (Members *et al.*, 2003; Weintraub *et al.*, 2008). The prevention of clinical CHD is more effective than treating it once it has developed. Therefore modifiable risk factors should be addressed at an early stage in subjects at risk of CHD (Piepoli *et al.*, 2016). However, treating risk factors after CHD diagnosis is of even greater importance.

The need for revascularization in symptomatic patients is evaluated with coronary angiography, taking into account the extent of ischemia, and the expected benefits of intervention on the prognosis and symptoms. In more complex cases the treatment strategy (percutaneous coronary intervention or coronary artery bypass grafting) should be evaluated by a 'heart team' consisting of cardiac surgeons and non-invasive and interventional cardiologists.(Windecker *et al.*, 2015) Revascularization is usually performed via a percutaneous coronary intervention such as balloon angioplasty of the narrowed lesion and stent placement (Figure 3). In patients with significant left main disease, three vessel disease, or two vessel disease including proximal left anterior descending with complex stenosis coronary

artery bypass surgery (a surgical procedure where the stenotic lesions are bypassed usually with the internal thoracic artery and veins) may be used, (Figure 4). In the United States in 2007/2008, 78% of all revascularizations was performed via percutaneous coronary intervention (Epstein, Polsky, Yang, Yang, & Groeneveld, 2011). In Finland between 1994 and 2013 rates of percutaneuous coronary interventions more than quadrupled while rates of coronary artery bypass surgery declined by two thirds (Kiviniemi *et al.*, 2016).
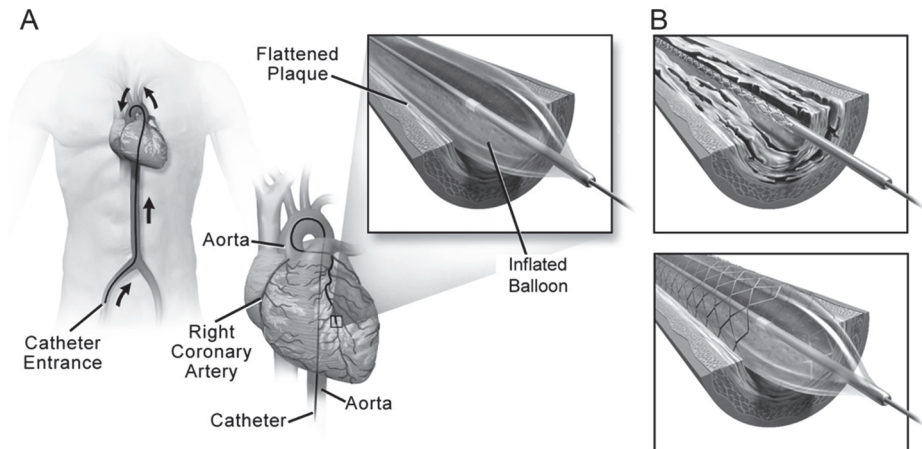
Fig. 3. Percutaneous coronary intervention A) Balloon angioplasty through the femoral artery. B) Stent placement. (Published by permission of BruceBlaus https://en.wikipedia.org/wiki/Angioplasty/)
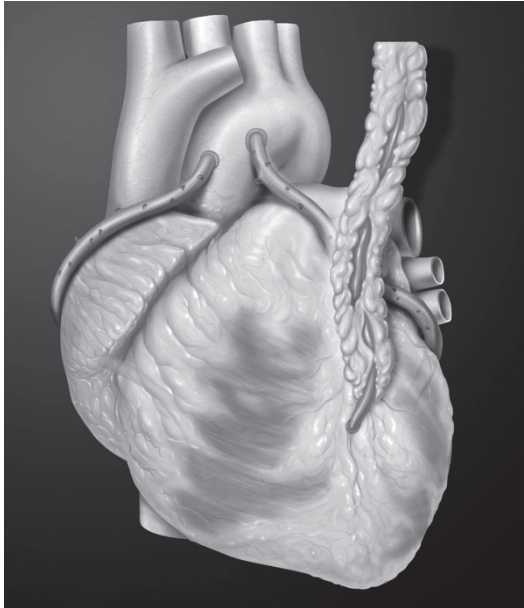
Fig. 4. Coronary artery bypass grafts; three grafts are depicted here, a left internal mammary artery (LIMA) to left anterior descending (LAD) and two saphenous vein grafts - one to the right coronary artery (RCA) system and one to the obtuse marginal (OM) system. The LIMA graft is surrounded by yellow fatty tissue in the forefront of the diagram, the RCA graft departs the left side of the aorta and wraps around the heart on the left side of the diagram, the OM graft departs the right side of the aorta and wraps around the heart on the right side of the diagram. (Published by permission of Patrick J. Lynch, medical illustrator - Patrick J. Lynch, medical illustrator)

Medical treatment

The two aims of medical treatment in stable CHD are to relieve symptoms and to prevent CHD events. For symptom relief, the most commonly used medications include nitrates, β-blockers and calcium channel blockers (Bangalore *et al.*, 2012; Henderson, O'Flynn, & Guideline Development Group, 2012; Montalescot *et al.*, 2013; Nissen *et al.*, 2004). For event prevention, antiplatelet agents (e.g. aspirin) are used to prevent coronary thrombus formation, lipid-lowering agents, such as statins, ezetimibe and proprotein convertase subtilisin/kexin type 9-inhibitors (PCSK9), reduce the risk of developing clinical CHD and stabilize plaques and angiotensin converting enzyme inhibitors (or angiotensin II receptor blockers) lower blood pressure and reduce the risk of CHD events (Antiplatelet Trialists'

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Collaboration, 1994; Montalescot *et al.*, 2013; Reiner *et al.*, 2011; Yusuf *et al.*, 2000).

2.1.5 Myocardial infarction

Even if stable CHD is treated according to all guidelines the risk of myocardial infarction is eminent. A previously non-obstructive plaque might destabilize (e.g. rupture) and cause thrombus formation resulting in an occluded coronary. An occluded artery results in loss of blood flow to areas of the myocardium, leading to infarction and therefore should be revascularized. Symptoms of myocardial infarction usually include acute chest pain which may radiate to the left arm or lower jaw. However, sometimes manifests only as a shortness of breath or may even be asymptomatic. Myocardial infarction can be recognized via ECG, elevated biomarkers of myocardial necrosis and imaging or pathology tests (Thygesen *et al.*, 2012).

2.2   Coronary heart disease mortality

CHD is the most common cause of death in the world, especially in countries with a predominantly Western lifestyle (Cahalin *et al.*, 2014; World Health Organisation, 2017). A myocardial infarction might be the first symptom on CHD. In 20–30% of cases, SCD is the first symptom of CHD and 25–50% of all deaths from CHD occur suddenly (Huikuri *et al.*, 2003; R. J. Myerburg, Jr, Mitrani, Kessler, & Castellanos, 1997; Robert J. Myerburg & Junttila, 2012; Priori *et al.*, 2015).

2.2.1 Sudden cardiac death

SCD is defined as an unexpected death with cardiac cause within 1 or 24 hours after onset of symptoms (J. A. Laukkanen *et al.*, 2010; Zipes & Wellens, 1998). In North America and Europe the annual incidence of SCD ranges between 50 to 100 per 100 000 of the general population (Fishman *et al.*, 2010). It has been estimated that 80% of all SCDs are caused by CHD, 10–15% are due to cardiomyopathies and less than 5% are due to arrhythmias caused by channelopathies (Huikuri *et al.*, 2001; Robert J. Myerburg & Junttila, 2012). In younger subjects there is a predominance of channelopathies, cardiomyopathies and myocarditis (Priori *et al.*, 2015). The proportion of subjects with CHD who have an SCD outcome decreases with advanced age (Zipes & Wellens, 1998). The majority of SCDs are caused by

acute myocardial infarctions triggering lethal cardiac arrhythmias in subjects without known CHD (Davies, 1992). Lethal arrhythmias can also be triggered by myocardial scarring by a previous myocardial infarction (Huikuri *et al.*, 2001). Most cases of SCD occur in subjects with no clinically recognized heart disease, Figure 5 (Huikuri *et al.*, 2001).
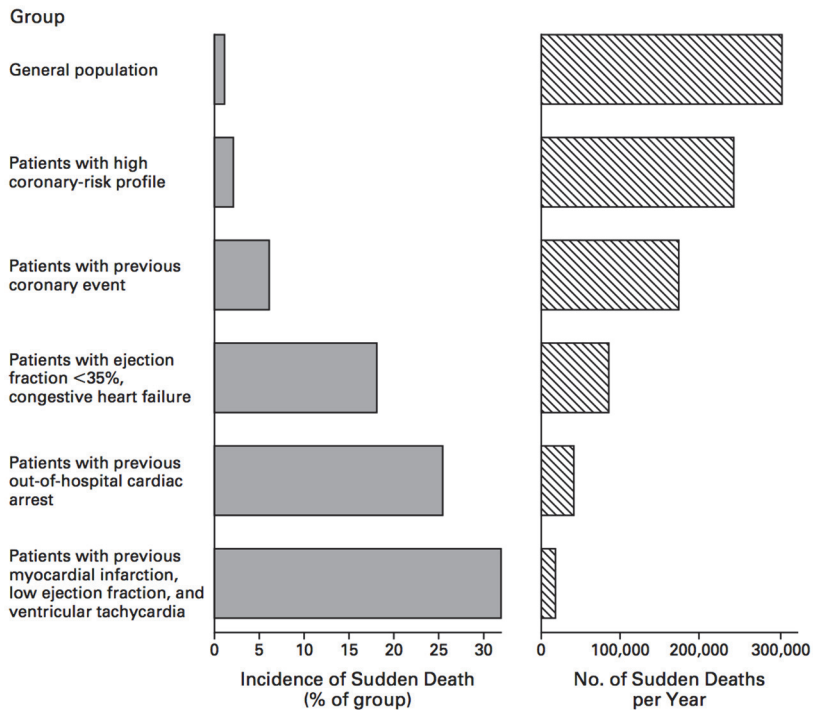
Fig. 5. The incidence of sudden death in specific populations and the annual numbers of sudden deaths in those populations. Most deaths occur in the larger, lower-risk subgroups. Reproduced with permission from Huikuri, H. V., Castellanos, A., & Myerburg, R. J. (2001). Sudden death due to cardiac arrhythmias. The New England Journal of Medicine, 345(20), 1473–1482, Copyright Massachusetts Medical Society.

Prevention of sudden cardiac death

Identifying subjects at high risk of SCD offers the opportunity to reduce the risk by treatment of the specific cause, and to start medication to address other risk factors. Most SCDs occur among subjects with CHD, the risk factors for which are well

known. Treating CHD is the most effective way to prevent SCD. It has been estimated that 40–50% of observed reductions in SCD result directly from the treatment of CHD and other cardiac conditions (Ford *et al.*, 2007; Piepoli *et al.*, 2016; Priori *et al.*, 2015). A family history of CHD-related SCD might place an individual at elevated risk of SCD (Priori *et al.*, 2015). Efforts to identify specific risk factors for SCD related to underlying CHD have generally yielded poor results. Deo and colleagues recently developed a predictive model of SCD for the general population, which combines 12 independent risk factors (age, male sex, black race, current smoking, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum potassium, serum albumin, high-density lipoprotein, estimated glomerular filtration rate and QTc interval), however this model has not yet been validated in other cohorts (Deo *et al.*, 2016).

A markedly reduced left ventricular function caused by CHD or cardiomyopathies has been shown to predict SCD, and in some cases a cardioverter defibrillator might be implanted (Bardy *et al.*, 2005). A cardioverter defibrillator (Figure 6) is a pacemaker with the ability to detect life-threatening cardiac arrhythmias, such as ventricular tachycardia or fibrillation and treat them with tachypacing or a high-energy shock (Priori *et al.*, 2015). In selected cases an intracardiac electrophysiological study of the heart is performed and if the exact location of the "short circuit" is pinpointed it might be possible to treat with ablation (Priori *et al.*, 2015). SCD due to reasons other than CHD, such as arrhythmias caused of channelopathies and some myopathies, can be identified with a resting 12-lead ECG. Genetic information might help in a few diseases such as long QT-syndrome and dilated cardiomyopathy related to lamin A/C gene mutation.

Whole-population screening for SCD is not currently recommended, because its potential benefits are unclear and there is a possibility of false positive results (Priori *et al.*, 2015). However, it is recommended to screen family members of unexplained SCD victims (personal and family history, 12-lead resting ECG, 24-hour holter, exercise stress test, echo and targeted genetic testing if needed) (Priori *et al.*, 2015).

Implantable Cardioverter Defibrillator

Incision

Lead

Lead

Implantable
Cardioverter
Defibrillator

Tip of lead in right
ventricle of Heart
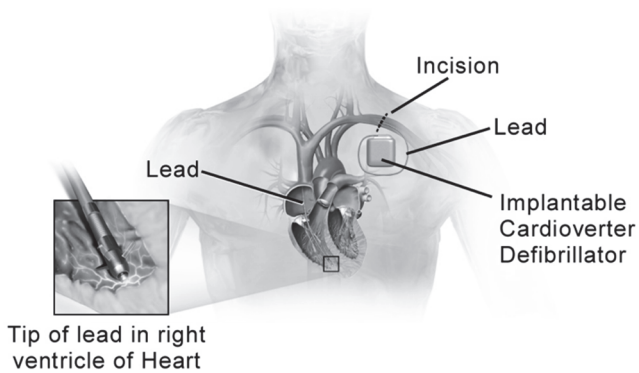
Fig. 6. An implantable cardioverter defibrillator. (By permission of Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436.)

2.3   Summary

– CHD is the most common cause of death.
– Deaths related to CHD are often sudden.
– Total risk factor burden is the cornerstone for the diagnosis and risk assessment of CHD.
– CRF seems to be one of the most important risk factor for CHD and it is underused in the clinical setting.
– Scarce data is available on how to combine the level of CRF with other risk factors for risk assessment of CHD related deaths.

3 Aims of the study

The aims of this study were to evaluate how an exercise stress test alongside assessments of CRF and ST segment depression and a questionnaire regarding LTPA can be used to predict the risk of CHD-related death.

More precisely the aims of this study were as follows:

1. To evaluate the prognostic value of CRF and exercise-induced ST segment depression with respect to death from CHD. (I)
2. To investigate whether combining an assessment of CRF with data on exercise-induced ST segment depression and conventional cardiovascular risk factors improves the prediction of SCD among middle-aged men. (II)
3. To find out how the level of CRF affects the association between LTPA and SCD. (III)

4 Methods

4.1 Study population

The study is based on the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), an ongoing epidemiological follow-up study designed to investigate risk predictors for atherosclerotic cardiovascular outcomes in men (T. A. Lakka *et al.*, 1994; J. A. Laukkanen *et al.*, 2001; R. Salonen, Seppänen, Rauramaa, & Salonen, 1988). The study population is a random sample of men living in Kuopio or the neighbouring rural communities of Eastern Finland, who were 42, 48, 54 or 60 years old at the baseline examination. This population is a representative sample of middle-aged men from an area known for its high incidence of CHD. Baseline examinations were conducted between March 1984 and December 1989.

4.2 Baseline examinations

4.2.1 Exercise testing

At baseline, maximal symptom-limited exercise stress tests were performed between 8:00 and 10:00 a.m. using an electrically braked cycle ergometer (T. A. Lakka *et al.*, 1994). Prior to June 1986 the testing protocol included a three-minute warm-up at 50 W followed by an increase in the workload of 20 W per minute (Tunturi EL 400, Turku, Finland). From June 1986, onwards the protocol specified a linear increase in the workload of 20 W per minute (Medical Fitness Quipment 400L, Mearn, Netherlands). All exercise tests were supervised by an experienced physician with the assistance of an experienced nurse. All exercise tests were performed at the Kuopio Research Institute of Exercise Medicine, Kuopio, Finland.

Cardiorespiratory fitness

During the exercise stress test the level of CRF was assessed directly from the collected respiratory gases and was expressed in METs. One MET corresponds to an oxygen uptake of 3.5 ml/kg per minute (Ainsworth *et al.*, 1993). Respiratory gas exchange was measured for the first 622 men by the mixing chamber method (Gebr., Mijnhart B.V., Netherlands), and for the remaining 1739 men by a breath-by-breath method (Medical Graphics, St. Paul, Minnesota, U.S.A.). The first method analysed

the maximal oxygen uptake as the average of values recorded over a 30-second period, and the second method analysed the average of values recorded over 8 seconds. Maximal oxygen uptake was defined as the highest value for, or the plateau in, oxygen uptake. It has previously been reported that these methods provide results that are closely correlated: one study found that the Pearson's coefficient for the correlation between simultaneous measurements with both systems in 13 men was 0.97 (T. A. Lakka *et al.*, 1994). The age-predicted MET during exercise test was computed as 14.7-0.11 x age (Morris *et al.*, 1993).

Exercise electrocardiogram

During the stress test a 12-lead ECG was recorded continuously with a Kone 620 electrocardiograph (Kone, Turku, Finland). The ECG was printed at 30-second intervals during exercise and after at least 5 minutes of recovery while the subject remained on the bicycle. The criteria for myocardial ischemia were exercise-induced horizontal or downsloping; at least 1.0 mm ST depression at 80 ms after the J point; or any ST depression of more than 1.0 mm at 80 ms after the J point in the ECG (Gianrossi *et al.*, 1989). The age-predicted maximal heart rate during exercise test was computed as 220 - age.

Exercise blood pressure

Blood pressure was measured manually immediately before the test, every two minutes during, and at least 5 minutes after the exercise test using cuff stethoscope method while the subject was on the cycle ergometer.

4.2.2 Biochemical analyses

Blood samples were collected after at least 12 hours' fasting and analysed according to standard protocol. The cholesterol contents of serum lipoprotein fractions and triglycerides were measured enzymatically (Boehringer Mannheim, Mannheim, Germany). Serum HDL cholesterol and its sub-fractions were separated from fresh serum samples using ultracentrifugation and precipitation (J. T. Salonen, Salonen, Seppanen, Rauramaa, & Tuomilehto, 1991). Fasting blood glucose was measured using the glucose dehydrogenase method (Merck, Darmstadt, Germany) after proteins had been precipitated with trichloroacetic acid. Type 2 diabetes was defined as fasting blood glucose of at least 6.7 mmol/l or a clinical diagnosis of

type 2 diabetes with dietary, oral or insulin treatment. Fasting serum insulin was measured with a radioimmunoassay (Novo, Biolabs; Novo Nordisk, Bagsvaerd, Denmark). Serum hs-CRP was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay, DPC, Los Angeles, CA, USA).

4.2.3 Resting measurements

Anthropometric measurements

Weight, height, and waist and hip dimensions were measured. BMI was calculated by dividing body weight with the square of height. Men with a BMI over 25 kg/m^2 were considered overweight.

Blood pressure

Resting blood pressure was measured by a nurse using a random-zero sphygmomanometer between 8:00 a.m. and 10:00 a.m. one week prior to the exercise stress test. The measurement protocol included six measurements at five-minute intervals in the supine, standing and sitting positions.

Electrocardiogram

A 12-lead ECG with paper speed 50 mm/sec was recorded during rest (Kone, Turku, Finland). The duration of the QT interval and resting heart rate were measured and were corrected for heart rate (QTc) according to Bazett's formula. The duration of the QRS complex was measured from the beginning of the Q wave to the end of the S wave. Left ventricular hypertrophy was estimated from the amplitude of the R and S waves.

Echocardiography

Echocardiographic studies were performed with an Advanced Technology Laboratories Ultramark IV device for randomly selected subsample of men (J. A. Laukkanen *et al.*, 2014; J. A. Laukkanen, Kurl, Eranen, Huttunen, & Salonen, 2005). Left ventricular function was assessed with fractional shortening in M-mode.

4.2.4 Questionnaires

Subjects completed questionnaires regarding medical history, use of medication, family history of disease, smoking, use of alcohol and LTPA. A subject was classified as having CHD by the presence of one or more of the following criteria: previous myocardial infarction, angina pectoris, use of nitroglycerin for chest pain at least once a week, or chest pain as the reason for premature termination of the exercise test at baseline. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory (Kauhanen, Julkunen, & Salonen, 1992). Lifetime exposure to smoking was expressed in pack-years, which was calculated as the number of years smoked multiplied by the number of packs of tobacco products smoked daily at the time of the examination, or for ex-smokers, at the time when they had last smoked (J. T. Salonen *et al.*, 1991).

Leisure-time physical activity

LTPA was assessed with the KIHD LTPA Questionnaire, which was modified from the Minnesota LTPA questionnaire (T. A. Lakka *et al.*, 1994; Taylor *et al.*, 1978). The KIHD LTPA Questionnaire has been validated in the present study population and the Minnesota LTPA Questionnaire in other cohorts (Folsom, Jr, Caspersen, Gomez-Marin, & Knudsen, 1986; Timo A. Lakka, 2003). The KIHD questionnaire includes the most common physical activities of Finnish men. The participants reported the frequency (sessions per month), duration (hours and minutes per session) and intensity (translated into METs) of each physical activity. A trained study nurse helped the participants to complete the questionnaire and a physician corrected any errors. LTPA data from the questionnaire were calculated into energy consumption (kcal/day).

4.3 Follow-up

4.3.1 Mortality

All deaths were included by linkage to the National Death Registry. Participants enrolled in the study between 1984 and 1989 and the follow-up is ongoing. All events to the end of 2008 were included in the present analyses. Deaths from CHD were coded using the Ninth or Tenth International Classification of Diseases codes (410–414 and I20–I25, respectively). Deaths were classified by an independent

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event committee blinded to clinical data. The sources of information on causes of death consisted of interviews, hospital documents, death certificates, autopsy reports and medico-legal reports together with the clinical and ECG findings of the paramedic staff. A death was classified as SCD when it occurred within 24 hours of the onset of symptoms, when autopsy data did not reveal a non-cardiac cause of sudden death or unsuccessful resuscitation from ventricular tachycardia or ventricular fibrillation (J. A. Laukkanen *et al.*, 2010; J. A. Laukkanen, Makikallio, Rauramaa, & Kurl, 2009). Deaths due to aortic aneurysm rupture, cardiac rupture, cardiac tamponade or pulmonary embolism were not classed as SCD.

4.3.2 Coronary interventions

Information on coronary interventions was collected from the coronary intervention registry for Kuopio and combined with the study data. Coronary interventions were defined as percutaneous coronary intervention or coronary artery bypass surgery having been performed during follow-up. Interventions were performed for clinical reasons during the follow-up.

4.4 Ethical consideration

The study was approved by the Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland. Each participant provided written informed consent.

4.5 Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences for Mac, Versions 20–24 (IBM SPSS Inc, Chicago, Illinois, USA). Descriptive data are presented as mean and standard deviations or median and interquartile range for continuous data and as percentages for categorical data. Differences in continuous variables between groups were compared using a t-test and differences in categorical variables between groups using the Chi-square test. The associations and interactions between exercise stress test findings and risk factors and cardiac events were analyzed using Cox proportional hazards regression models. Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariable models. For most analyses we used age, serum LDL cholesterol, smoking, alcohol consumption, BMI, systolic

blood pressure, hs-CRP, type 2 diabetes and CHD as covariates, later referred to as conventional risk factors. These covariates were selected based on their previously established role as predictive factors for CHD death (Cahalin *et al.*, 2014; Conroy *et al.*, 2003; Eckel *et al.*, 2014; Wilson *et al.*, 1998). The proportional hazard assumption was verified for each risk factor by plotting Schoenfeld residuals against survival time transformed into natural logarithms. All covariates fulfilled the proportionality assumption. The cumulative incidence of events was calculated using the Kaplan-Meier method. The C-index was calculated to assess the ability of the model to correctly identify subjects with respect to SCD (model discrimination) and was used to evaluate the incremental value of combining low CRF with exercise-induced ST segment depression beyond other cardiovascular risk factors. Missing values for the conventional cardiovascular risk factors were replaced with the mean of the corresponding variable in the current study population (to a maximum of 3% of values in each group). All p-values were two sided and all associations and differences with p-values less than 0.05 were considered statistically significant.

4.5.1 Risk groups

For the statistical analyses in articles I and II the men were divided into four risk groups according to CRF and exercise-induced ST segment depression. The cut-off point for CRF was the even number nearest to the lowest tertile of MET 8. Forming the following risk groups:

1. High CRF (≥8 MET) without exercise-induced ST segment depression
2. High CRF (≥8 MET) with exercise-induced ST segment depression
3. Low CRF (<8 MET) without exercise-induced ST segment depression
4. Low CRF (<8 MET) with exercise-induced ST segment depression

For the statistical analyses in article III the men were divided into four risk groups according to CRF and LTPA. The cut-off points were at the lowest tertiles for CRF MET 7.9 and for LTPA 191 kcal/day. Forming the following groups:

1. High CRF (≥7.9 MET) and high LTPA (≥191 kcal/day)
2. High CRF (≥7.9 MET) and low LTPA (<191 kcal/day)
3. Low CRF (<7.9 MET) and high LTPA (≥191 kcal/day)
4. Low CRF (<7.9 MET) and low LTPA (<191 kcal/day)

5   Results

5.1   Baseline characteristics (Articles I–III)

A total of 3433 men were invited to participate and 3235 (94%) men were eligible
for the study. Altogether 2682 (83%) men participated in the baseline examinations.
Echocardiographic studies were performed for 905 randomly selected men. No
subjects were lost to follow-up. Autopsy findings were available for 80% of deaths.

The demographics, medical history and baseline characteristics of 2682 men
included in this study are presented in Table 3. Altogether 921 (34%) men were
considered having a low CRF (<8 METs) and 332 (12%) had exercise-induced ST
segment depression Table 4. The mean CRF was 8.6 METs and 1819 (68%) men
reached at least 85% of the age-predicted maximal heart rate. The most common
cause for discontinuing the exercise test was leg fatigue (Table 5).

Table 3. Baseline characteristics

Variable	Median / n	Interquartile range / Proportion
Age (years)	54.3	49–55
Height (cm)	172	168–177
Weight (kg)	79	72–87
Body mass index (kg/m^2)	26.5	24.5–28.9
Mean systolic blood pressure (mmHg)	132	123–144
Mean diastolic blood pressure (mmHg)	88	82–88
Resting heart rate (beats/minute)	61	55–68
Alcohol consumption (grams/week)	31	6–93
History of smoking (cigarette pack-years)	8.6[1]	11[1]
Smokers	865	32%
Leisure-time physical activity (kcal/day)	286	150–286
Hemoglobin (gram/l)	147	141–153
Serum total cholesterol (mmol/l)	5.8	5.2–6.5
Serum high density lipoprotein (mmol/l)	1.3	1.1–1.5
Serum low density lipoprotein (mmol/l)	4.0	3.3–4.7
Serum triglycerides (mmol/l)	1.1	0.8–1.6
Serum high sensitivity C-reactive protein (mg/l)	1.3	0.7–2.5
Type 2 diabetes	148	5.5%
Existing coronary heart disease	677	25%
Medication for hypertension	600	22%
Medication for high cholestrol	17	0.5%
β-blocker medication	485	18%

[1] Mean and standard deviation presented for history of smoking.

Table 4. Exercise stress test findings

Variable	Median / n	Interquartile range / Proportion
Maximal workload (watts)	221	190–259
Maximal oxygen uptake VO_{2peak}(ml/kg/minute)	30	25–35
Cardiorespiratory fitness (MET)	8.6	7.4–9.8
Low cardiorespiratory fitness (MET < 8)	921	34%
Reached 85% of age-predicted MET[1]	1968	73%
Exercise-induced ST segment depression	332	12%
Maximal heart rate (beats / minute)	159	141–172
Reached 85% of age-predicted maximal heart rate[2]	1819	68%

[1] The age-predicted metabolic equivalent (MET) during exercise test was computed as 14.7–0.11 x age.

[2] The age-predicted maximal heart rate during exercise test was computed as 220 - age.

Table 5. Causes of discontinuation of exercise stress test

Variable	Frequency	Proportion
Leg fatigue	1229	45.8%
Exhaustion	375	14.0%
Breathlessness	219	8.2%
Dyspnea	122	4.5%
Chest pain	88	3.3%
Severe arrhythmia	71	2.6%
Pain in joints	61	2.3%
Pain in leg muscles	53	2.0%
Change in diastolic blood pressure	41	1.5%
Ischemic changes in ECG	36	1.3%
Difficulty with the mask	34	1.3%
Co-operation difficulty	33	1.2%
Motivation difficulty	17	0.6%
Dizziness	14	0.5%
Change in systolic blood pressure	12	0.4%
Nausea	11	0.4%
Back pain	8	0.3%
Coordination disorder	4	0.1%
Headache	4	0.1%
Arrhythmia	3	0.1%
Symptoms of cardiac insufficiency	2	0.1%
Technical disorder	2	0.1%
Stomach ache	1	<0.1%
Missing data	242	9%

5.2 All-cause mortality

During a median follow-up time of 20.9 years (interquartile range 18.7–22.7) 753 (32%) men died (Figure 7). During this follow-up time an increase in CRF of one MET was associated with a 17% reduction in risk of all-cause death (95% confidence interval [CI] 13%–20%, p<0.001) after adjustment for the conventional risk factors (age, serum LDL cholesterol, smoking, alcohol consumption, BMI, systolic blood pressure, prevalent type 2 diabetes, serum hs-CRP and history of CHD).
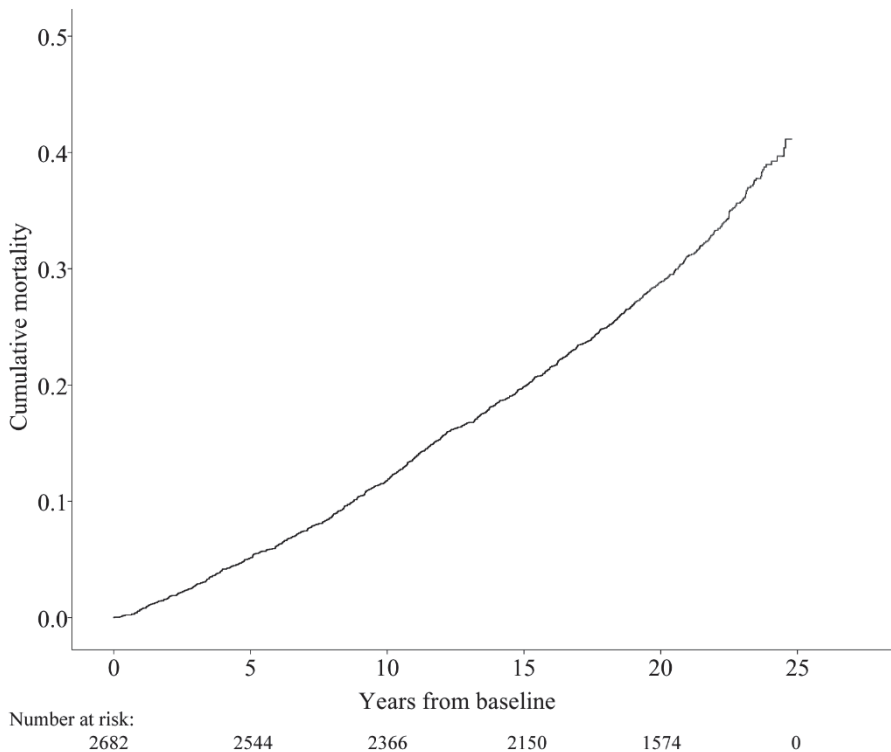

Fig. 7. Cumulative incidence of all-cause mortality

Men with low CRF (<8 MET) had a 1.7-fold (95% CI 1.4–2.0,) greater risk of all-cause death than men with high CRF after adjustment for exercise-induced ST segment depression in addition to conventional risk factors (p<0.001). After

adjusting for CRF and conventional risk factors, men with exercise-induced ST segment depression had a 1.6-fold (95% CI 1.2–1.8,) times higher risk of all-cause death than those without (p=0.002). After adjustment for conventional risk factors men with a low CRF (<8 MET) and exercise-induced ST segment depression had a 2.7-fold (95% CI 2.1–3.7) greater risk of all-cause death than men with a high CRF and without exercise-induced ST segment depression (p<0.001).

5.3 Coronary heart disease (Article I)

Of the 2328 men with complete exercise stress test data 243 (10.5%) died from CHD. The cumulative incidence of death from CHD divided into three same size groups of men with different level of CRF are presented in Figure 8. One MET increase in CRF was associated with a 22% (95% CI 16%–28%, p<0.001) decrease in the risk of CHD death with the aspect of this follow-up time and adjustment for conventional risk factors. Men with low CRF (MET < 8, n=867, 37%) had a 1.8 (95% CI 1.4–2.5, p<0.001) times higher risk of death from CHD than men with high CRF (MET ≥ 8) after adjustment for exercise-induced ST segment depression in addition to conventional risk factors. Among 169 men with very good CRF (≥ 12 METs), no deaths from CHD were observed. Men with exercise-induced ST segment depression had a 2.5 (95% CI 1.7–3.4, p<0.001) times higher risk of death from CHD after adjusting for CRF in addition to conventional risk factors.

After adjustment for conventional risk factors, men in group 4 had a 4.8-fold (95% CI 1.4–2.5, p<0.001) greater risk of death from CHD than men in group 1 (Table 6). The conventional risk factors in men divided into four groups according to CRF and exercise-induced ST segment depression are presented in Table 7. The interaction between CRF as a continuous variable and exercise-induced ST segment depression was statistically significant (p=0.010). The cumulative incidence of death from CHD in the four risk groups is shown in Figure 9.
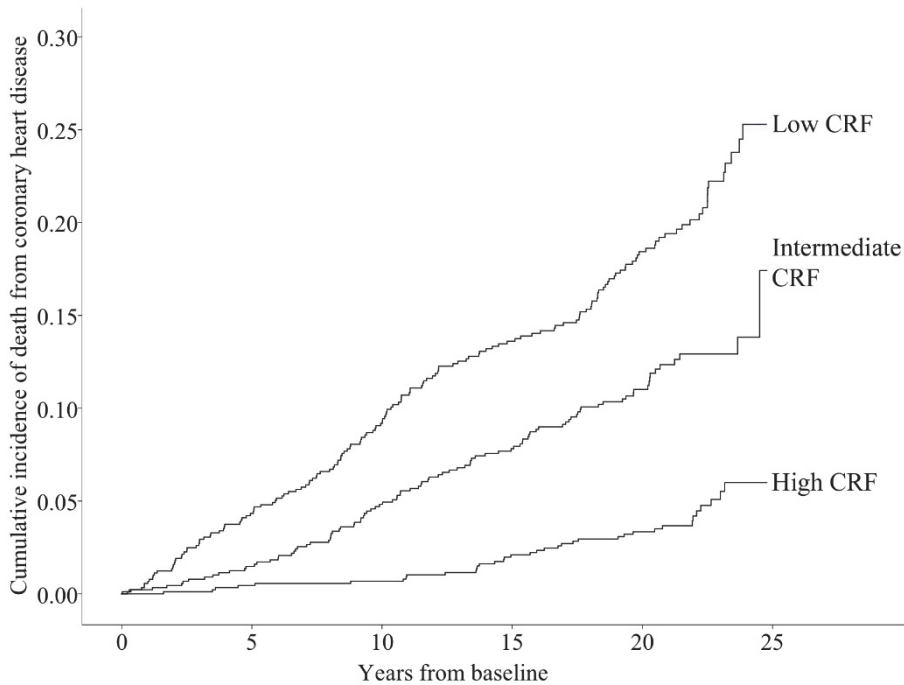
Fig. 8. The cumulative incidence of death from coronary heart disease according to cardiorespiratory fitness divided into groups of the same size. N=2628. Low CRF < 7.9 MET, Intermediate CRF 7.9–9.2 MET and high CRF > 9.2 MET.

Table 6. Risk of death from coronary heart disease in four risk groups of men according to cardiorespiratory fitness and exercise-induced ST segment depression

Variable	High CRF without ST depression (Group 1)	High CRF with ST depression (Group 2)	Low CRF without ST depression (Group 3)	Low CRF with ST depression (Group 4)	Total
Participants (n)	1329	132	760	107	2328
Hazard Ratio[1]	1	1.9	1.7	4.8	
95% CI	Reference	1.1–3.4	1.2–2.3	3.2–7.4	
p-value	Reference	0.030	0.003	<0.001	
Deaths from CHD (n)	76	14	110	43	243
Deaths from CHD (%)	5.7%	10.6%	14.5%	40.2%	10.4%

The cut-off point for cardiorespiratory fitness (CRF) is at the approximate lowest tertile of 8 metabolic equivalents. [1]Adjusted for age, serum LDL cholesterol, smoking, alcohol consumption, BMI, systolic blood pressure, prevalent type 2 diabetes, serum hs-CRP and history of CHD.

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Table 7. Conventional risk factors among men in four risk groups according to cardiorespiratory fitness and exercise-induced ST segment depression

Variable	High CRF without ST depression (Group 1) Mean (SD) / proportion	High CRF with ST depression (Group 2) Mean (SD) / proportion	Low CRF without ST depression (Group 3) Mean (SD) / proportion	Low CRF with ST depression (Group 4) Mean (SD) / proportion
Participants (n)	1329	132	760	107
Age (years)	51.6 (5.3)	52.3 (5.2)	54.6 (4.3)	55.8 (3.3)
Type 2 diabetes	3.2%	4.6%	7.1%	14.0%
History of coronary heart disease	13.2%	18.9%	37.6%	65.4%
Smoking (cigarette pack-years)	7 (15)	5 (11)	12 (20)	9 (17)
Alcohol consumption (g/week)	71 (103)	80 (184)	84 (150)	65 (82)
Body mass index (kg/m^2)	26.1 (3.0)	25.5 (2.6)	28.2 (3.7)	27.4 (3.8)
Systolic blood pressure (mmHg)	132 (15)	136 (17)	136 (18)	139 (19)
High-sensitivity C-reactive protein (mg/l)	1.8 (2.4)	2.0 (4.1)	3.1 (4.4)	2.7 (2.4)
Serum LDL cholesterol (mmol/l)	4.0 (1.0)	4.1 (1.0)	4.0 (1.0)	4.5 (1.0)

The cut-off point for cardiorespiratory fitness (CRF) is at the approximate lowest tertile of 8 metabolic equivalents.

Subgroup analyses

Among men who achieved at least 85% of the age-predicted maximal heart rate during the exercise test, after adjustment for conventional risk factors the risk of death from CHD was 7.6-fold greater (95% CI 4.3–13.4) for the 45 men in group 4 than for the 1206 men in group 1 (p<0.001).

Among the 1772 men without history of CHD, after adjustment for conventional risk factors, the risk of CHD death was 5.7-fold greater (95% CI 3.0–10.7) times higher for 37 men in group 4 than for 1154 men in group 1 (p<0.001).

Among the 1232 men who did not use beta-blockers, after adjustment for conventional risk factors, the risk of CHD death was 6.7-fold greater (95% CI 3.9–11.5) for 54 men in group 4 than for 1232 men in group 1 (p<0.001).
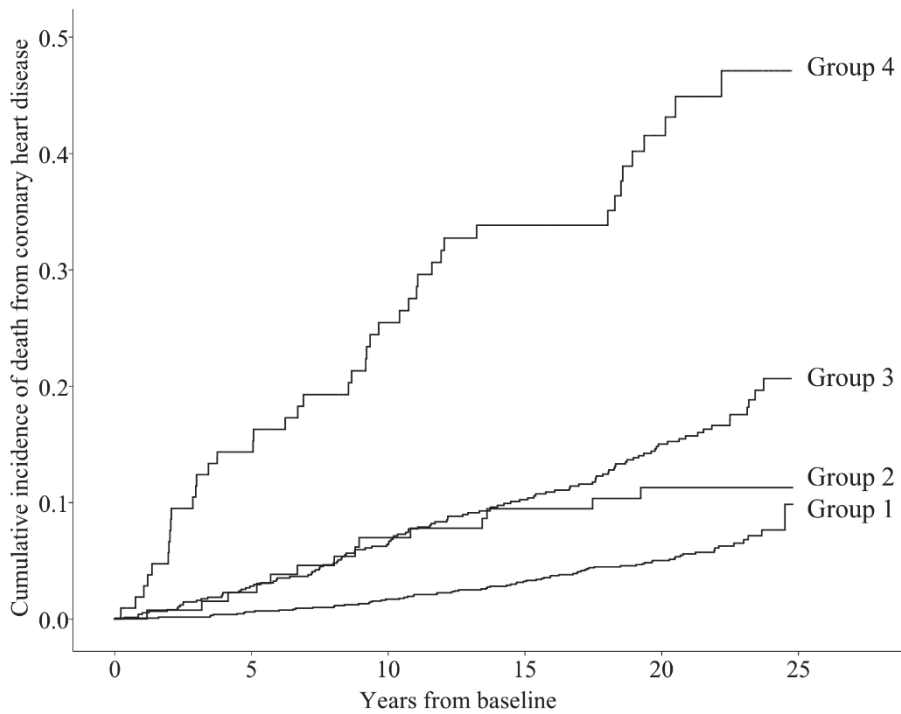
Fig. 9. Cumulative incidence of death from coronary heart disease in men divided into four risk groups according to cardiorespiratory fitness and exercise-induced ST segment depression. Group 1: High CRF without ST depression. Group 2: High CRF with ST depression. Group 3: Low CRF without ST depression. Group 4: Low CRF with ST depression

5.4 Sudden cardiac death (Article II)

Among the 2328 men with complete exercise stress test data 165 SCDs occurred (22% of all deaths; Figure 10). Of these, 135 (82%) occurred out of hospital. An increase in CRF of one MET was associated with a 19% decrease (95% CI 11%–26%) in the risk of SCD over this follow-up time and with adjustment for conventional risk factors (p<0.001).

After adjustment for conventional risk factors, men with low CRF (<8 METs) had a 1.6-fold (95% CI 1.1–2.3) greater risk of SCD than those with high CRF (p=0.012). After adjustment for conventional risk factors, men with exercise-induced ST segment depression had a 2.3-fold (95% CI 1.5–3.5) greater risk of SCD than those without (p<0.001). Thirty-two (47%) of all 68 deaths in group 4 were SCDs. After adjustment for conventional risk factors, men in group 4 had a 4.8-fold greater risk of SCD than those in group 1 (Table 8). The cumulative incidence of SCD in the four groups is presented in Figure 11.

The risk of SCD (Figure 12) was consistently highest in men with a combination of low CRF and any conventional cardiovascular risk factors. A discrimination analysis showed that when adding the combined variable of CRF and exercise-induced ST segment depression to a model that already included the conventional risk factors, the C-index increased from 0.757 (95% CI 0.723–0.789) to 0.769 (95% CI 0.736–0.808), indicating an improvement in the risk discrimination of SCD.

Table 8. Risk of sudden cardiac death among men divided into four groups according to cardiorespiratory fitness and exercise-induced ST segment depression.

Variable	High CRF without ST depression (Group 1)	High CRF with ST depression (Group 2)	Low CRF without ST depression (Group 3)	Low CRF with ST depression (Group 4)	Total
Participants (n)	1329	132	760	107	2328
Hazard ratio[1]	1	1.9	1.3	4.8	
95% CI	Reference	1.0–3.8	0.9–2.0	2.9–7.9	
p-value	Reference	0.063	0.156	<0.001	
SCDs (n)	54	10	69	32	165
SCDs (%)	4.1%	7.6%	9.1%	29.9%	7.1%

The cut-off point for cardiorespiratory fitness (CRF) is the approximate lowest tertile of 8 metabolic equivalents. [1]Adjusted for age, serum LDL cholesterol, smoking, alcohol consumption, BMI, systolic blood pressure, prevalent type 2 diabetes, serum hs-CRP and history of CHD.
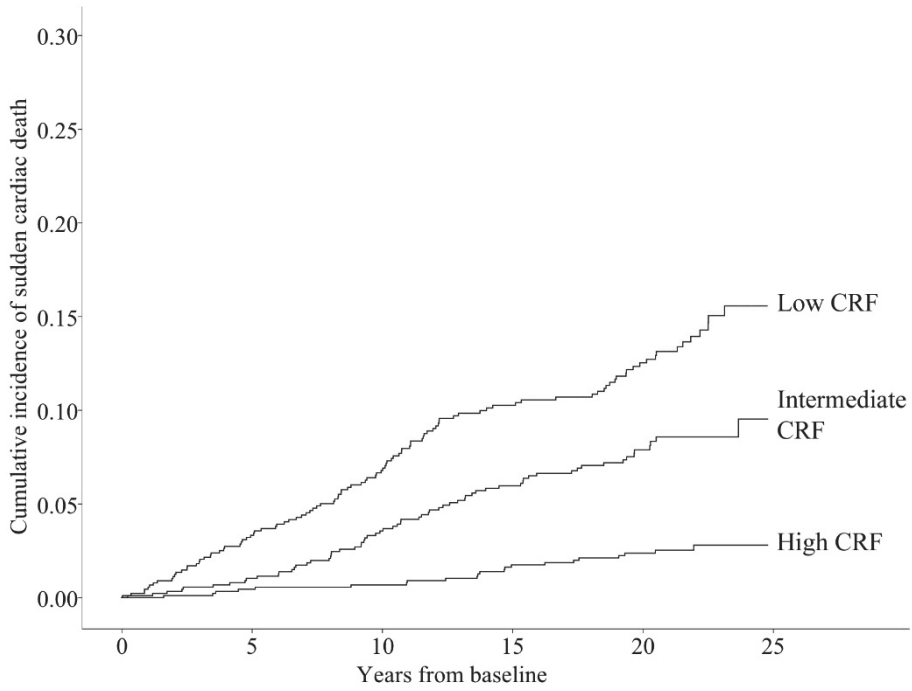
Fig. 10. Cumulative incidence of sudden cardiac death according to cardiorespiratory fitness divided into three groups of the same size. N=2628. Low CRF < 7.9 MET, Intermediate CRF MET 7.9–9.2 and high CRF MET > 9.2.
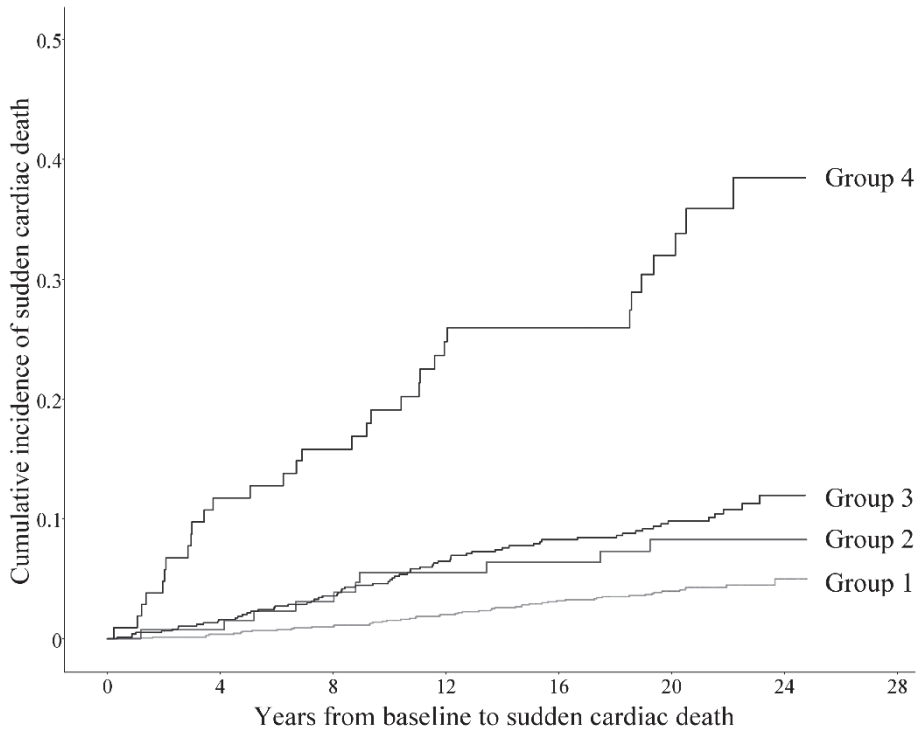
Fig. 11. Kaplan Meier plot of cumulative incidence of sudden cardiac death among men divided into four groups according to exercise test results. (Article II, published by permission of BMJ Publishing Group Ltd & BCS) CRF, Cardiorespiratory fitness; MET, Metabolic equivalents. Group: 1. Men with high CRF without exercise-induced ST depression 2. Men with high CRF and exercise-induced ST depression 3. Men with low CRF without exercise-induced ST depression 4. Men with low CRF and exercise-induced ST depression.

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HR (95% CI)   SCD

Younger <54 years and high CRF   1   2.7%
Older ≥54 years and high CRF   1.54 (0.84-2.81)   5.3%
Younger <54 years and low CRF   2.26 (1.00-5.09)   9.5%
Older ≥54 and low CRF   2.40 (1.32-4.39)   12.0%

No type 2 diabetes and high CRF   1   4.2%
Type 2 diabetes and high CRF   1.99 (0.80-5.00)   10.2%
No type 2 diabetes and low CRF   1.57 (1.08-2.29)   10.8%
Type 2 diabetes and low CRF   2.98 (1.59-5.59)   21.7%

No prevalent CHD and high CRF   1   3.6%
Prevalent CHD and high CRF   2.09 (1.21-3.60)   9.5%
No prevalent CHD and low CRF   1.49 (0.93-2.38)   7.2%
Prevalent CHD and low CRF   3.48 (2.28-5.31)   18.0%

No smoking and high CRF   1   3.1%
Smoking and high CRF   2.49 (1.63-3.82)   9.0%
No smoking and low CRF   1.98 (1.35-2.90)   9.5%
Smoking and low CRF   4.29 (2.90-6.35)   16.7%

Low alcohol consumption and high CRF   1   3.4%
High alcohol consumption and high CRF 1.51 (0.89-2.56)   5.5%
Low alcohol consumption and low CRF   1.91 (1.14-3.21)   10.5%
High alcohol consumption and low CRF   2.01 (1.18-3.42)   12.8%

Normal BMI and high CRF   1   3.4%
High BMI and high CRF   1.48 (0.86-2.55)   5.0%
Normal BMI and low CRF   2.11 (1.09-4.09)   11.7%
High BMI and low CRF   2.28 (1.35-3.89)   11.6%

Normal blood pressure and high CRF   1   3.5%
Elevated blood pressure and high CRF   1.74 (1.04-2.89)   6.9%
Normal blood pressure and low CRF   1.86 (1.19-2.93)   10.6%
Elevated blood pressure and low CRF   2.15 (1.31-3.52)   13.5%

No ST-segment depression and high CRF 1   4.1%
ST-segment depression and high CRF   1.91 (0.97-3.80)   7.6%
No ST-segment depression and low CRF   1.33 (0.90-1.99)   9.1%
ST-segment depression and low CRF   4.83 (2.94-7.93)   29.9%

Low LDL-cholesterol and high CRF   1   1.9%
High LDL-cholesterol and high CRF   2.24 (0.81-6.17)   4.8%
Low LDL-cholesterol and low CRF   2.73 (0.84-8.83)   9.9%
High LDL-cholesterol and low CRF   3.37 (1.22-9.35)   11.9%

Low CRP and high CRF   1   2.7%
High CRP and high CRF   1.81 (1.07-3.06)   6.5%
Low CRP and low CRF   2.43 (1.38-4.26)   10.1%
High CRP and low CRF   2.17 (1.28-3.69)   12.3%

0 1 2 3 4 5 6 7 8 9 10 11
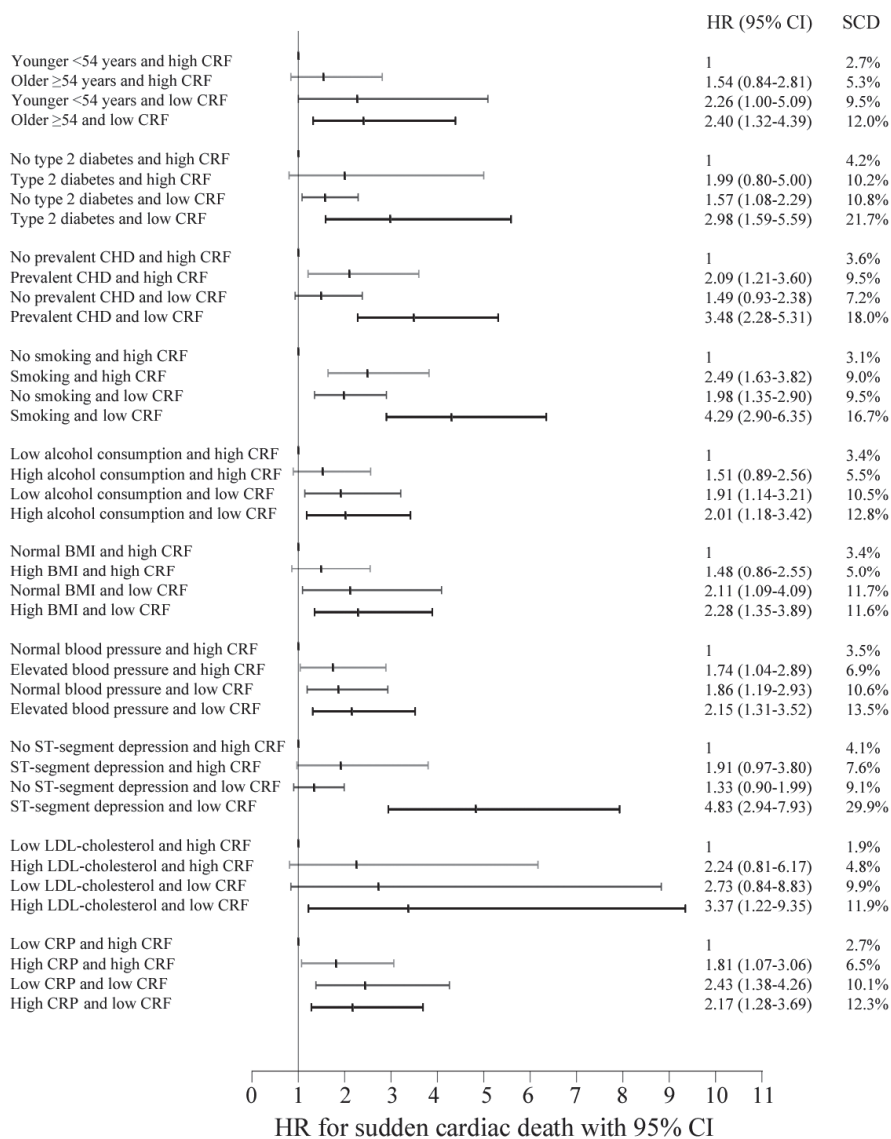
HR for sudden cardiac death with 95% CI

Fig. 12. Forest plot of risk of sudden cardiac death according to the level of cardiorespiratory fitness, risk factors and the incidence of sudden cardiac death in risk groups. (Article II, published by permission of BMJ Publishing Group Ltd &BCS) CRF <8 METs was considered low and CRF ≥8 METs was considered high. Hazard ratios were adjusted for age, presence of type 2 diabetes and CHD, smoking, alcohol consumption, body mass index (BMI), resting systolic blood pressure, LDL cholesterol and CRP. The

risk factors were dichotomized: hs-CRP at 1.26 mg/l, type 2 diabetes yes/no, coronary heart disease yes/no, smoking status smokers/non-smokers, alcohol consumption at 32 g/week, resting systolic blood pressure at 140 mmHg, 1mm ST segment depression observed/not, LDL cholesterol at 3 mmol/l, age at 54 years and BMI at 25 kg/m^2.

During follow-up, coronary interventions were performed in 314 (13%) of the men due to clinical reasons unrelated to this study. Further adjustments for coronary interventions during follow-up, the use of beta-blockers, QT-interval or left ventricular function at baseline had no significant effect on these results (data not shown).

5.5 Leisure-time physical activity (Article III)

Among the 2656 men with complete data on CRF and LTPA 193 SCDs occurred. The amount of LTPA among all participants is presented in Table 9. The baseline characteristics of the men divided into four risk groups according to CRF and LTPA are shown in Table 10. Men with low CRF had the highest burden of conventional CHD risk factors. The mean energy expenditure of LTPA was higher among men with high CRF than among men with low CRF (384 vs. 350 kcal/day, p=0.020).

After adjustment for conventional risk factors there was no significant difference in the risk of SCD between men with low LTPA and those with high LTPA. As continuous variables, the energy expenditure, frequency, duration and intensity of LTPA were not significantly associated with the risk of SCD when adjusted for conventional risk factors and exercise-induced ST segment depression (data not shown).

Table 9. Leisure-time physical activity

Variable	Median / n	Interquartile range / Proportion
Sessions/year (n)	239	135–383
Intensity (metabolic equivalents)	4.4	3.7–5.2
Duration (hours/year)	304	166–515
Energy consumption (kcal/day)	286	150–479
Men with an energy consumption <191 kcal/day (n)	899	33%

The cumulative incidence of SCD was highest among men in group 4 and second highest among men in group 3, whereas there was no difference in SCD occurrence between two other groups (Figure 13). After adjustment for conventional risk factors and exercise-induced ST segment depression, men in group 4 had a 2.2-fold
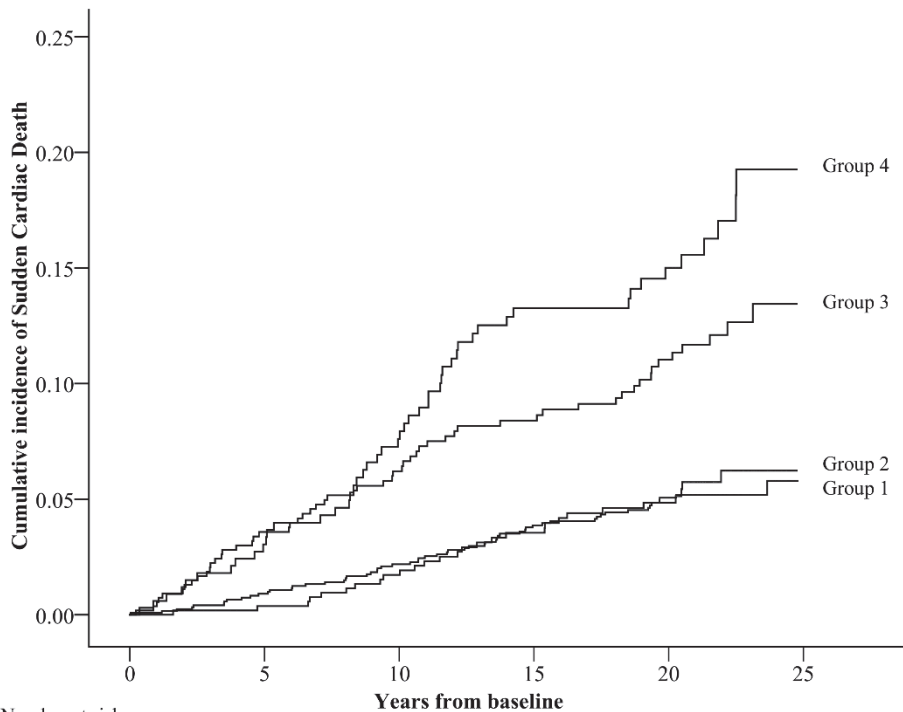
greater risk of SCD than those in group 1 (Table 11). After adjustment for conventional risk factors and exercise-induced ST segment depression, the risk of SCD was not significantly different in groups 2 and 3 when each was compared with group 1 (Table 11). The interaction between CRF and LTPA on the risk of SCD was significant (p=0.044).

Further adjustment for performed coronary interventions (percutaneous coronary intervention or coronary artery by-pass grafting) during follow-up or the use of β-blockers, left ventricular function, QT interval or estimated left ventricular hypertrophy at baseline had no significant effect on these results (data not shown). In a subsample of 1982 men without CHD at baseline, after adjustment for conventional risk factors, men with low CRF and low LTPA (n=202) had a 1.9-fold greater risk (95% CI 1.1–3.4, p=0.026) of SCD than men with high CRF and high LTPA (n=1013).

Table 10. Baseline characteristics of the study population in the four risk groups according to cardiorespiratory fitness and leisure-time physical activity

Variable	High CRF with high LTPA (Group 1) Mean (SD) / proportion	High CRF with low LTPA (Group 2) Mean (SD) / proportion	Low CRF with high LTPA (Group 3) Mean (SD) / proportion	Low CRF with low LTPA (Group 4) Mean (SD) / proportion	Total
Participants (n)	1228	546	546	336	2656
Age (years)	52.3 (5.3)	51.9 (5.3)	54.4 (4.0)	54.3 (4.3)	53.1 (5.1)
Serum LDL cholesterol (mmol/l)	4.0 (1.0)	4.1 (1.0)	4.1 (1.0)	4.1 (1.1)	4.0 (1.0)
History of smoking (pack-years)	6.4 (14.3)	9.5 (17.0)	10.3 (19.1)	11.8 (19.6)	8.5 (16.8)
Alcohol consumption (g/week)	75 (141)	72 (124)	81 (151)	76 (114)	76 (137)
Body mass index (kg/m^2)	26.4 (3.3)	25.8 (3.3)	28.1 (3.8)	28.3 (3.8)	26.9 (3.6)
Systolic blood pressure (mmHg)	133 (16)	133 (17)	137 (18)	136 (18)	134 (17)
Type 2 diabetes	4.4%	3.8%	9.3%	6.3%	5.5%
High sensitivity C-Reactive protein (mg/l)	2.1 (4.2)	2.1 (3.3)	3.1 (4.3)	3.2 (4.2)	2.4 (4.1)
Exercise-induced ST depression	8.6%	5.8%	11.5%	7.3%	8.6%
History of coronary heart disease	17.5%	16.8%	41.9%	39.9%	25.2%

The cut-off points were at the lowest tertile for cardiorespiratory fitness (CRF) at 7.9 metabolic equivalents and for leisure-time physical activity (LTPA) at 191 kcal/day.

Fig. 13. Kaplan-Meier plot of cumulative incidence of sudden cardiac death divided into four risk groups according to cardiorespiratory fitness and leisure-time physical activity. The cut-off points were at the lowest tertiles, for cardiorespiratory fitness (CRF) at 7.9 metabolic equivalents and for leisure-time physical activity (LTPA) at 191 kcal/day. Group 1: High CRF and high LTPA. Group 2: High CRF and low LTPA. Group 3: Low CRF and high LTPA. Group 4: Low CRF with LTPA.

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Table 11. Risk for sudden cardiac death in men divided into four risk groups according to cardiorespiratory fitness and leisure-time physical activity

Variable	High CRF with high LTPA (Group 1)	High CRF with low LTPA (Group 2)	Low CRF with high LTPA (Group 3)	Low CRF with low LTPA (Group 4)	Total
Participants (n)	1228	546	546	336	2656
Hazard Ratio[1]	1	1.0	1.3	2.2	
95% CI	Reference	0.6–1.7	0.8–1.9	1.4–3.3	
p	Reference	1.000	0.250	0.001	
SCDs (n)	59	28	57	49	193
SCDs (%)	4.8%	5.1%	10.4%	14.6%	7.3%

The cut-off points were at the lowest tertiles, for cardiorespiratory fitness (CRF) at 7.9 metabolic equivalents and for leisure-time physical activity (LTPA) at 191 kcal/day. [1]Adjusted for age, serum LDL cholesterol, smoking, alcohol consumption, BMI, systolic blood pressure, prevalent type 2 diabetes, serum hs-CRP, history of CHD and exercise-induced ST segment depression.

6   Discussion

In this study, randomly selected middle-aged men with low CRF and exercise-induced ST segment depression or low LTPA had a higher risk of CHD related death. The main novel finding was that there is a significant interaction between CRF and exercise-induced ST segment depression as well as between CRF and LTPA in predicting SCD. This indicates that combining CRF with exercise-induced ST segment depressions and LTPA provides an additive prognostic value for assessing risk of CHD-related death including SCD beyond conventional cardiovascular risk factors. In addition, it seems that high CRF also reduces the risk for most other factors that themselves denote elevated risk of CHD-related death.

6.1   Coronary heart disease mortality

CHD is the most common cause of death in the world. In 20–30% of cases SCD is the first symptom of CHD and 25–50% of all deaths from CHD occur suddenly (Huikuri *et al.*, 2003). Present guidelines do not recommend screening of asymptomatic patients with an exercise stress test, mainly because of the possibility of false positive tests, and the potential economic benefits of such testing are unclear. However, on the basis of this and other studies, an exercise stress test could be used for CHD risk assessment (G. J. Balady *et al.*, 2004). It seems that the burden of risk factors should be combined with CRF for more accurate risk assessment. Identifying subjects at higher risk of CHD-death or SCD could give them a chance to improve their lifestyles and risk factors and possibly avoid sudden death.

6.2   Exercise-induced ST segment depression

An exercise-induced ST segment depression on ECG of more than 1 mm is considered a marker of myocardial ischemia (Montalescot *et al.*, 2013; Sharma *et al.*, 2012). However, this marker's mean sensitivity and specificity for detecting obstructive CHD is limited (68% and 77%, respectively) (Montalescot *et al.*, 2013). Although exercise-induced ST segment depression is a well-established predictor of CHD-outcomes, it has limited prognostic value as an isolated finding for premature death in general populations (Lauer *et al.*, 2005). This finding was confirmed in our study. We investigated how the risks of death from CHD and SCD are predicted by exercise-induced ST segment depression combined with different levels of CRF affects. Our findings are in line with those of previous studies: a

subject's pre-test probability and other exercise stress test findings should be considered when interpreting ST segment depressions.

6.3　Cardiorespiratory fitness

As a measure of the circulatory and respiratory systems, CRF shows the function of the heart and muscles and is therefore a good measure of the coronary system as well. There are compensatory mechanisms (i.e. coronary collaterals) that help maintain a good CRF even if there is a considerably occluded coronary system (for example, in left main vessel disease). However, CRF is often markedly impaired by the development of obstructive CHD. There are many factors that influence the level of CRF, such as age, gender, lifestyle, overweight, hereditary factors, diseases (including CHD) that affect the cardiorespiratory system, and mitigation of symptoms (Blair *et al.*, 2001; Bouchard *et al.*, 2011; A. S. Leon *et al.*, 1981; Wolfarth *et al.*, 2014).

Because of the many factors contributing to the level of CRF and relatively poor correlation between assessed LTPA and measured CRF a surrogate for measured CRF cannot be validated by asking subjects about their physical activity (Tager *et al.*, 1998). CRF seems to be the strongest risk factor for CHD outcomes (Kodama *et al.*, 2009). However, it seems that the accuracy of risk assessment can be improved by the introduction of low CRF in combination with other risk factors (Israel *et al.*, 2016). In this study, we evaluated how different levels of CRF and combinations of risk factors are associated with CHD outcomes.

6.4　Leisure-time physical activity

The health benefits of physical activity are well recognized and have been widely studied (Blair *et al.*, 2001; Pate *et al.*, 1995). Vigorous physical activity has been said to increase the risk of SCD momentarily. However, this risk is relatively low especially among active individuals and the consensus is that in the long-term physical activity decreases the risk of CHD events (M. A. Mittleman *et al.*, 1993; Murray A. Mittleman & Mostofsky, 2011).

It is possible that increasing CRF through aerobic physical activity such could be the key mechanism in reducing CHD mortality risk. CRF has been consistently shown to be strongly and robustly associated with reduced risk of all-cause mortality. CRF is largely determined by physical activity, it has been reported that genetic factors account for 22–57% of the variation in CRF (Karvinen *et al.*, 2015;

Perusse *et al.*, 2001; Zadro *et al.*, 2017). The response to exercise varies considerably between individuals (Bouchard *et al.*, 2011; Wolfarth *et al.*, 2014; Zadro *et al.*, 2017). Emerging evidence from both animal and human studies indicate that the same genetic factors influence physical activity levels, CRF, and the risk of mortality, leading to the suggestion that genetic pleiotropy might partly explain the observed associations between high baseline physical activity and reduced mortality in long-term observational follow-up studies.

6.5   Mechanism

Although the present study was not designed to investigate the mechanism behind these findings, some explanation can be postulated. Men with low CRF and exercise-induced ST segment depression might be more prone to develop severe CHD which, in turn, predisposes to ventricular arrhythmia, myocardial infarction and finally SCD. Men with high CRF tend to exercise more and have a healthier lifestyle than those with low CRF, which might have affected the long-term outcome in our study even though most other risk factors at baseline were adjusted for.

Physical activity among subjects with CHD induces the growth of coronary collaterals, which have been shown to reduce the risk of death during myocardial infarction (Akin *et al.*, 2013). Another possible mechanism by which CRF may affect CHD outcomes is ischemic preconditioning, which occurs when the myocardium is subjected to repeated short-term ischemia without infarction. This leads to a protective reaction of the myocardium, the mechanism of which remains unclear (Yellon *et al.*, 1998). Since men with low CRF but higher levels of LTPA may have undiagnosed and asymptomatic CHD, the effect of ischemic preconditioning effect could be triggered more frequently during physical activity compared with men with low LTPA levels. Physical activity improves CRF as well as many risk factors for CHD-death: glycemic control, lipids, body weight, endothelial function, hemostasis and blood pressure (Glazer *et al.*, 2013; Arthur S. Leon & Sanchez, 2001; Lin *et al.*, 2015).

6.6   Methodological and ethical considerations

This study is based on the KIHD study, an ongoing epidemiological follow-up study designed to investigate risk predictors for atherosclerotic cardiovascular outcomes in men (T. A. Lakka *et al.*, 1994).

The risk of death was analyzed with a Cox regression test. The subjects were divided into four groups as previously described. The cut-off point for CRF has raised some questions. For articles I and II the cut-off point was at the approximate lowest tertile of the even number eight METs. For article III the cut-off point for CRF was at the exact lowest tertile of 7.9 METs, which is more statistically justifiable. Both cut-off points divided the men into appropriate size groups regarding the outcome and statistical analyses. Similar cut-off point has been used is previous studies and clinical practice.(Kodama *et al.*, 2009; Minkkinen *et al.*, 2009; Mora *et al.*, 2003) This cut-off point is also a clinically relevant as men with a CRF more than 7.9 or 8 METs can perform more vigorous physical activity such as running, manual forestry and shoveling.

This was a follow-up study, and therefore did not expose the participants to any considerable risks or affect their treatment. This study was approved by the Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland.

6.7 Strengths

At 2682, this was a large study population, with a very high participant rate (82% of those eligible), random selection of subjects and a long follow-up period. We employed reliable measures for most known risk factors, coronary interventions were performed during follow-up and some subjects underwent an echocardiography. We also had the possibility to take into account performed coronary interventions, including percutaneous coronary interventions and coronary artery by-pass grafting during follow-up.

A normal exercise stress test with the assessment of CRF calculated from the maximal workload is widely used. However, such testing has some confounding factors mainly due to the variables used in the mathematical equations. In this study, an accurate assessment of CRF was important and therefore a cardiopulmonary stress test was performed, and the level of CRF was calculated directly from the oxygen consumption of the respiratory gases, a method that is considered the gold standard. In this study, the exercise test was performed with a cycle ergometer which is more common in Europe rather than a treadmill, which is more common in the United States. The benefits of a cycle ergometer are that it is less expensive, occupies less space, and is less noisy. It also allows more accurate ECG recording compared with a treadmill because of less upper body movement.(Fletcher *et al.*, 2001)

The KIHD-LTPA Questionnaire has been validated and precisely filled in. There were no losses during the follow-up and the ascertainment of end points was accurate using all available data (up to 80% of SCD was evaluated with autopsy).

Some previous SCD risk of studies assessed the subject's LTPA level by questioning the spouse after the subject's death and might therefore be biased (Lemaitre *et al.*, 1999; Siscovick, Weiss, Hallstrom, Inui, & Peterson, 1982). As a randomized trial would be difficult to perform because of the relatively rare occurrence of SCD and problems with adherence to long-term exercise programs, a cohort study seems most suitable for this purpose. No previous cohort studies have considered both the direct level of CRF and the level of LTPA in the assessment of middle-aged men's risk of SCD.

6.8 Limitations

This study had several limitations, including that the population consisted only of middle-aged men and therefore the findings cannot be generalized to elderly or female populations. On the other hand, middle-aged men are at high risk for SCD and therefore these findings are of importance. At the time of study entry, middle-aged men had quite high morbidity and mortality from CHD and therefore the study has focused on risk factors among middle-aged men.

We were unable to correct for regression dilution bias which may have underestimated the associations demonstrated, as we only had a one-time assessment of CRF with exercise test. It would be interesting to know whether an increase in the level of LTPA among men with low CRF would result in an increase in CRF, unfortunately our data do not include information about changes in CRF over time. However, we have previously shown that long-term increases in CRF are associated with reductions in all-cause mortality (Jari A. Laukkanen *et al.*, 2016). Life-style habits and medical treatment may also have changed during follow-up e.g. smoking, diet and medication altering the results. Medical treatment including interventions (e.g. development of percutaneous coronary interventions techniques and stents) and medication (e.g. statins, antiplatelet therapy, ACE-inhibitors and AT2-blockers) has also improved during the follow-up, this can also alter the results especially among patients with diagnosed CHD. This study included performed coronary interventions during follow-up, however only interventions performed in the Kuopio region (which probably accounts for most). Additionally, the results might be affected by competing risk of death for other causes. It can also be argued that LTPA might be reduced prior to death because of

other factors which led to both a reduced level of LTPA and an increased risk of SCD, however the long follow-up reduces this confounding factor. There is a possibility that the higher CHD mortality and SCD rates in men who did not exercise regularly might be partly due to underlying atherosclerotic vascular diseases (diagnosed or undiagnosed) which are associated with an increased risk of fatal cardiac events.

This study was based on a randomly selected population including asymptomatic patients, which may have presented false-positive exercise-induced ischemic changes. The results of this study were adjusted for most known confounding factors; however, some residual confounding factors might remain. For example, we did not include serum creatinine level (a measure of kidney function) which has been considered an independent predictor of death for CHD and in some studies SCD as well (Deo *et al.*, 2016; Matts *et al.*, 1993). However, we adjusted these findings to hs-CRP another parameter analyzed from a blood sample which is considered to be a stronger predictor of CHD-death (Salim *et al.*, 2016). Additional feature of this study is the inability to adjust for all potential or undetected confounders as well use of medications which may have effect on outcomes. The current results are limited because of the observational nature of the long-term prospective study; the findings cannot be generalized to other kind of clinical populations; inability to correct for within-person variability in CRF and risk factor levels because of absence of data on repeat measurements in this study. Further studies are warranted to show if exercise interventions could improve prognosis in populations with different levels of risk factors. One limitation for cycle ergometer compared to treadmill exercise stress test is the tendency of the subject to experience leg fatigue, which can result in test cessation before maximal oxygen consumption has been reached (Fletcher *et al.*, 2001). The LTPA questionnaire was precisely filled in and checked by a physician, however, self-reported questionnaires include the risk of misinterpretations and missed information. However, self-reported physical questionnaires have been widely used in large population-based studies, and the assessment of the intensity, duration and frequency was based on a previously validated LTPA questionnaire (T. A. Lakka & Salonen, 1992).

Regardless of the possible limitations of the selected study population, our population consisted of men with a wide spectrum of backgrounds and with different stages of cardiovascular diseases and is therefore representative of a middle-aged male population undergoing clinical exercise testing.

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7 Summary of the findings and conclusions

The main findings of articles I–III were:

Article I:

Low CRF and exercise-induced ST segment depression are associated with an increased risk of death from CHD. The main finding is that men with the combination of a low CRF level and exercise-induced ST segment depression appear to be at a particularly high risk of death from CHD.

Article II:

The combination of low CRF and exercise-induced ST segment depression is associated with an elevated risk of SCD. This observation shows that combining information from these essential exercise test findings may improve the accuracy of SCD risk assessment among men.

Article III:

This study shows that the level of CRF is more important than the level of LTPA for SCD risk assessment in middle-aged men. The most important finding is that higher LTPA appears to be associated with a lower risk of SCD among the men with low CRF levels. However, the amount of LTPA performed did not affect the incidence of SCD among men with high CRF levels at baseline.

7.1 Conclusions and research implications

According to this study, exercise stress test findings, such as ST segment depression, CRF with the LTPA questionnaire could be used better to identify the subjects at high risk of death from CHD and SCD. The main results suggest that men with low CRF and exercise-induced ST segment depression or low LTPA are at a high risk of CHD-related deaths. It is not common in clinical practice that CRF levels are combined with information from other risk factors for the long-term assessment of CHD and SCD risk. These findings also emphasize the importance of regular physical activity and treatment of cardiovascular risk factors, especially among men with low baseline level of CRF.

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