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MAIJA HASSINEN

Predictors and Consequences of the Metabolic Syndrome

Population-based Studies in Aging Men and Women

Doctoral dissertation

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Kuopio Research Institute of Exercise Medicine
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ABSTRACT

Several hundred million people throughout the world have the metabolic syndrome, a cluster of metabolic and cardiovascular disorders. Obesity is one of the main underlying risk factors for the metabolic syndrome. The increasing prevalence of obesity and the metabolic syndrome is alarming because they increase the risk of type 2 diabetes, coronary heart disease, cardiovascular disease and premature mortality. Increasing longevity prolongs exposure to metabolic and cardiovascular risk factors. Even so, older persons, especially women, have been underrepresented in epidemiological studies. The purpose of the present thesis is to expand knowledge on the predictors and consequences of the metabolic syndrome in aging men and women. The thesis is based on two population studies. The association of cardiorespiratory fitness with the metabolic syndrome was evaluated in a large cohort of men and women, 57 to 79 years of age. The associations of the metabolic syndrome and body adiposity with the progression of preclinical carotid atherosclerosis, and the associations of low-grade inflammation with the metabolic syndrome were evaluated in a 12-year follow-up study of elderly women, 70 to 80 years of age at the end of the follow-up.

Cardiorespiratory fitness had a strong, inverse, graded and independent association with the metabolic syndrome in older men and women. Those in the lowest third of directly measured maximal oxygen uptake (VO_{2max}) had a 10 times higher risk of having the metabolic syndrome than those in the highest third of VO_{2max} . Even a slight increment in high-sensitivity C-reactive protein (hsCRP) concentration in elderly women was associated with a 4 to 6 times higher risk of developing the metabolic syndrome than in those whose hsCRP concentration decreased during 12 years. The progression of carotid intima-media thickness (IMT) during 12 years was greatest in women with both a larger waist circumference and a smaller hip circumference. The mean increase in the carotid IMT was 2 times greater in women who developed the metabolic syndrome than in women who did not.

Cardiorespiratory fitness and hsCRP may be valuable additions to the definition of the metabolic syndrome. Identification of the metabolic syndrome may improve the prediction of preclinical atherosclerosis. When used in conjunction with other metabolic and cardiovascular risk factors, low cardiorespiratory fitness and elevated hsCRP may have additive predictive power in identifying individuals with multiple, often only mildly elevated cardiovascular risk factors, who are at increased risk of developing chronic and progressive diseases and who may benefit from lifestyle therapy targeting exercise and weight management. These findings emphasize the importance of ongoing efforts to identify and control the metabolic syndrome as early as possible to prevent atherosclerotic disease, also in the older population.

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Medical Subject Headings: Aged; Aging; Atherosclerosis; Body Fat Distribution; Body Mass Index; Carotid Arteries; Carotid Artery Diseases; C-Reactive Protein; Disease Progression; Exercise test; Female; Follow-Up Studies; Humans; Inflammation; Insulin Resistance; Men; Metabolic Syndrome X; Obesity; Physical Fitness; Risk Factors; Waist-Hip Ratio



To my family



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Kuopio, June 2008

Maija Hassinen

ABBREVIATIONS

AMPK	Adenosine monophosphate-activated protein kinase
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DR's EXTRA	Dose Responses to Exercise Training Study
HDL	High density lipoprotein
hsCRP	High-sensitivity C-reactive protein
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IGR	Impaired glucose regulation (IFG or IGT)
IL-6	Interleukin-6
IMT	Intima-media thickness
LDL	Low density lipoprotein
NCEP	National Cholesterol Education Programme
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
SD	Standard deviation
TNF- α	Tumor necrosis factor alpha
VO _{2max}	Maximal oxygen uptake
WHO	World Health Organization



LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which will be referred to in the text by the Roman numerals I-IV:

- I Hassinen M, Lakka TA, Savonen K, Litmanen H, Kiviaho L, Laaksonen DE, Komulainen P, Rauramaa R. Cardiorespiratory Fitness as a Feature of the Metabolic Syndrome in Older Men and Women. The Dose-Responses to Exercise Training Study (DR's EXTRA). *Diabetes Care*. 2008;31:1242-1247.
- II Hassinen M, Lakka TA, Komulainen P, Gylling H, Nissinen A, Rauramaa R. C-reactive Protein and Metabolic Syndrome in Elderly Women - a 12-year Follow-up Study. *Diabetes Care*. 2006;29:931-932.
- III Hassinen M, Lakka TA, Komulainen P, Haapala I, Nissinen A, Rauramaa R. Association of Waist and Hip Circumference with 12-year Progression of Carotid Intima-Media Thickness in Elderly Women. *International Journal of Obesity*. 2007;31:1406-1411.
- IV Hassinen M, Komulainen P, Lakka TA, Väisänen S, Haapala I, Gylling H, Alen M, Schmidt-Trucksäss A, Nissinen A, Rauramaa R. Metabolic Syndrome and the Progression of Carotid Intima-Media Thickness in Elderly Women. *Archives of Internal Medicine*. 2006;166:444-449.



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ORIGINAL PUBLICATIONS

1. INTRODUCTION

The metabolic syndrome, a cluster of metabolic and cardiovascular disorders, is typically characterized by abdominal obesity, insulin resistance, hyperglycemia, atherogenic dyslipidemia and hypertension (Figure 1). Several hundred million people throughout the world have the metabolic syndrome (1). In most European countries and in the United States the prevalence of the metabolic syndrome is up to one third of the adult population (2-6) and the prevalence is even higher in the elderly (2,6). Increasing longevity, overweight and obesity prolong exposure to metabolic and cardiovascular risk factors which increases the number of people who have the metabolic syndrome and its consequences, type 2 diabetes and cardiovascular diseases (CVD). The prevalence of these chronic diseases is still expected to increase, because the proportion of individuals above 65 years of age will almost double globally within the next years (7,8). Even so, older persons, especially women, have been underrepresented in epidemiological studies.

Sedentary lifestyle, unhealthy diet, genes and many other risk factors interact in the etiology of metabolic syndrome (Figure 1) (1,9,10). An abundant food supply and prepackaged fast-food with high caloric density together with every-day technologies that reduce the amount of physical activity have promoted the epidemic of obesity and the metabolic syndrome over the past several decades. Obesity, especially abdominal obesity, is frequently considered as the main underlying risk factor for the metabolic syndrome, accompanied with varying degrees and numbers of other risk factors (10). In early 2000, roughly half of the Finnish adult population was overweight and one fourth was obese (11). These prevalences are expected to increase in the future. The same trend has also been seen in other European countries (12) and in the United States (13). The increasing prevalence of obesity and the metabolic syndrome is alarming because they increase the risk of type 2 diabetes (5,14), coronary heart disease (CHD), CVD and premature mortality (15). Nearly 200 million people worldwide have diabetes and the prevalence is estimated to double by 2030 (16). Most cases will be type 2 diabetes. The rapid increase in prevalence is estimated to happen as a consequence of population aging and urbanization even if the prevalence of obesity remains stable (16,17).

Limited data are available, particularly in the elderly, on the associations of the metabolic syndrome with novel, non-traditional risk factors such as low-grade inflammation and low cardiorespiratory fitness and preclinical atherosclerosis. So far, these risk factors for CVD have not been included in any of the definitions of the metabolic syndrome, due to limited evidence and for practical reasons.

The purpose of the present thesis is to expand knowledge on the predictors and consequences of the metabolic syndrome in aging men and women. The thesis is based on two population studies. The association of cardiorespiratory fitness with metabolic syndrome and impaired glucose homeostasis was evaluated in a large cohort of older men and women. The associations of the metabolic syndrome and body adiposity with change in carotid intima-media thickness (IMT), a noninvasive marker of preclinical carotid atherosclerosis, and the associations of systemic low-grade inflammation with the metabolic syndrome was evaluated in a 12-year follow-up study of elderly women.

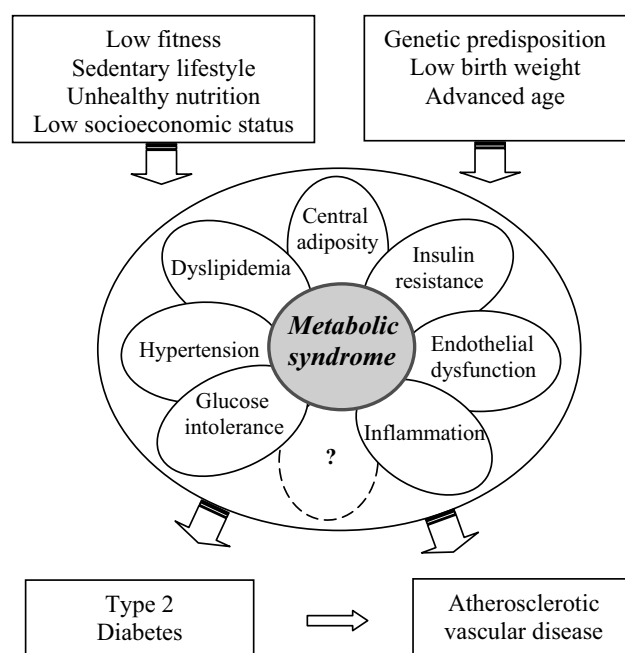


Figure 1. Predictors, components and consequences of the metabolic syndrome. The question mark refers to unknown risk factors. The upper boxes refer to modifiable (left box) and unmodifiable (right box) environmental and genetic factors that contribute to the metabolic syndrome.

2. REVIEW OF LITTERATURE

2.1 Metabolic syndrome

2.1.1 Definitions of the metabolic syndrome

In recent years, several working definitions have been developed for the metabolic syndrome. Most international expert groups agree that the syndrome is characterized by abdominal obesity, dyslipidemia, elevated blood pressure, glucose intolerance and insulin resistance (18-21).

To provide a tool for clinicians and researchers, the World Health Organization (WHO) introduced a definition for the metabolic syndrome in 1998 (22), and revised it in 1999 (18). The European Group for the Study of Insulin Resistance (EGIR) formulated their definition in 1999 (19), the National Cholesterol Education Program's Adult Treatment Panel III (NCEP) in 2001 (20), modified by an American Heart Association/National Heart, Lung and Blood Institute Scientific Statement in 2005 (23), and the International Diabetes Federation (IDF) in 2005 (21). The mostly used definitions, given by WHO and NCEP expert groups, and the latest one, IDF, are given in Table 1.

Table 1. Definitions of the metabolic syndrome

WHO 1999	NCEP 2001	IDF 2005
Diabetes, IFG, IGT or insulin resistance <i>Plus ≥ 2 of the following:</i>	<i>≥ 3 of the following:</i>	Waist circumference ≥ 80 cm in women, ≥ 94 cm in men <i>Plus any 2 of the following:</i>
Central obesity (WHR >0.85 in women, >0.9 in men) and/or BMI >30	Waist circumference >88 cm in women, >102 cm in men	
Elevated blood pressure ($\geq 140/90$ mm Hg)	Elevated blood pressure ($\geq 130/85$ mm Hg and/or drug treatment)	Elevated blood pressure ($\geq 130/85$ mm Hg and/or drug treatment)
Elevated triglycerides (≥ 1.7 mmol/l) and/or low HDL cholesterol (<1.0 mmol/l in women, <0.9 mmol/l in men)	Elevated triglycerides (≥ 1.7 mmol/l) Low HDL cholesterol (<1.29 mmol/l in women, <1.03 mmol/l in men)	Elevated triglycerides (≥ 1.7 mmol/l or specific treatment) Low HDL cholesterol (<1.29 mmol/l in women, <1.03 mmol/l in men or specific treatment)
Microalbuminuria (albumin excretion ≥ 20 $\mu\text{g}/\text{min}$ or albumin /creatinine ratio ≥ 30 mg/g)	Impaired fasting glycemia (≥ 6.1 mmol/l)	Impaired fasting glycemia (≥ 5.6 mmol/l) or diagnosed type 2 diabetes

WHO=World Health Organization (18), NCEP=National Cholesterol Education Program (20), IDF=International Diabetes Federation (21), BMI=body mass index, WHR=waist-to-hip ratio, IFG=impaired fasting glucose, IGT=impaired glucose tolerance.

2.1.2 Epidemiology of the metabolic syndrome

In majority of the 21 prospective cohort studies from Europe and the United States included in a recent meta-analysis, the prevalence of the metabolic syndrome according to NCEP or WHO criteria ranged from 23% to 46% among the general populations of countries with different levels of cardiovascular risk factors (15). The rates are comparable to those reported recently in 45-64 years old Finnish men and women (6). In a large study in United State citizens, the prevalence of the metabolic syndrome increased steeply since the age of 30 years in men and women, the increase continued until the age of 60 years in men and until 70 years in women and started to decline thereafter (24). The growing prevalence of the metabolic syndrome worldwide is undoubtedly a consequence of the global epidemic of obesity (12,13). The metabolic syndrome is an important risk factor for type 2 diabetes (14,15), which represents a steadily growing threat to human health in the 21st century (16). Insulin resistance contributes to impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). About 75% of those with combined IFG and IGT have metabolic syndrome (25). Because type 2 diabetes has a high morbidity and mortality the metabolic syndrome is a serious and growing public health problem (17). A meta-analysis indicated that individuals with the metabolic syndrome have a 61% increased risk of CVD compared to those without the syndrome (15). The metabolic syndrome might be even a stronger risk factor for CVD in women than in men (15,26). Individuals with the metabolic syndrome have also increased risk of coronary hearth disease, myocardial infarction, stroke and mortality (15,27). In a prospective study, women with metabolic syndrome, even without diabetes, had at least a 2-fold increased risk of ischemic stroke or transient ischemic attack (28).

2.2 Features of the metabolic syndrome

2.2.1 Overall and abdominal adiposity

Body composition can be indirectly estimated by body height and weight, body mass index as well as waist and hip circumferences, which are non-invasive, easy and inexpensive methods. Overweight and obesity have most often been defined by body mass index, calculated as the weight in kilograms divided by the square of the height in

meters. According to the WHO (29), overweight is defined as body mass index 25-29.9 and obesity as body mass index ≥ 30 .

Waist-to-hip ratio, calculated as the ratio of the waist circumference to the hip circumference, was previously acknowledged as the clinically accepted method of identifying patients with excess abdominal fat accumulation. However, recently waist circumference has been suggested as being a more practical measure of intra-abdominal fat mass, replacing body mass index and waist-to-hip ratio as a simpler indicator of visceral adipose tissue and successful weight management as well as for the assessment of cardiovascular risk (30,31). Because populations and ethnic groups may differ in the level of risk associated with a particular waist circumference (32), globally applicable cut-off points cannot be developed. Two 'action levels' for waist circumference have been suggested, in which individuals with a waist circumference over level 1 (men ≥ 94 cm and women ≥ 80 cm) should gain no further weight, and those with a waist circumference over level 2 (men ≥ 102 cm and women ≥ 88 cm) should reduce weight (31). For most definitions of the metabolic syndrome, waist circumference is included as a categorical variable indicating low risk or high risk (19-21).

Computed tomography (33) and magnetic resonance imaging (34) can be considered "golden standards" for the evaluation of abdominal adiposity. Because these techniques are laborious and expensive, and in addition computed tomography induces radiation exposure, their use in large epidemiological studies is usually not feasible. Waist circumference is associated with intra-abdominal fat measured by computed tomography (35) and with total adiposity measured by magnetic resonance imaging (34). Moreover, waist circumference correlates with abdominal obesity better than the waist-to-hip ratio (30).

Adipose tissue is a metabolically active endocrine organ in addition to its function in the storage of surplus energy (36). In the normal state, there is balance between adipose tissue lipolysis and triglyceride synthesis regulated by nutrients, hormones and autonomic nervous system (37). Body fat distribution, especially visceral adipose tissue accumulation, has harmful metabolic and medical consequences (38,39). Visceral fat is more resistant to the metabolic effects of insulin than peripheral fat, and the rate of lipolysis is higher (40-42). Insulin resistance in adipose tissue leads to an inability to

suppress release of fatty acids from adipose tissue and decrease in lipoprotein lipase activity induces decrease in clearance of triglyceride-rich lipoproteins (38). With an increase in visceral adipose tissue, a higher rate of flux of adipose tissue-derived free fatty acids to the liver may occur, which promotes an increased secretion of triglyceride-rich lipoproteins and glucose from the liver (1,39). An increase in abdominal subcutaneous fat increase release of lipolytic products into the systemic circulation and avoid more direct effect on hepatic metabolism (1).

Adipose tissue also contributes to systemic inflammation. Hyperplasia and hypertrophy of adipocytes as seen in obesity lead to an increased production of several adipokines such as tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) and reduced production of adiponectin (36). These adipokines include acute phase reactants and mediators of inflammation, thrombosis and insulin sensitivity (36). Visceral adipose tissue appears to be particularly active in the expression and secretion of adipokines. Adipokines and free fatty acids are involved in the regulation of insulin action in skeletal muscles and eventually induce insulin resistance (43).

Prospective studies indicate that abdominal obesity predicts the development of the metabolic syndrome (44) and cardiovascular events (45,46). Prospective (47) and cross-sectional (48) studies have found a direct association of body mass index, waist circumference or waist-to-hip ratio with carotid IMT in middle-aged individuals (Table 2). Other studies in middle-aged or older individuals have not shown clear associations (49-51). According to prospective studies in elderly individuals, intra-abdominal fat appears to be an independent risk factor for myocardial infarction (52) and a large waist circumference for mortality (53). On the other hand, a narrow hip circumference seems to have an independent and inverse association with the risk of type 2 diabetes (54) and CVD morbidity and mortality (55-57). Excess intra-abdominal fat has been associated with a greater risk of morbidity and mortality than overall adiposity (53). Obesity was an independent risk factor for CHD mortality among men and also contributed to the risk of CHD death among women in a study of over 8000 middle-aged Finnish men and women followed for 15 years (58). An increase in body weight of 1 kg increased the risk of CHD mortality by 1% to 1.5%, starting at a body mass index of 22.

Aging is associated with an increase and redistribution of body fat (59) and a decrease in skeletal muscle mass due to sarcopenia (60). In advancing age, intra-abdominal fat accumulates more rapidly than total fat, and that happens even in the absence of obesity (59). Already in pre-menopausal women, a selective accumulation of visceral fat as assessed by computed tomography occurs (61). Withdrawal of estrogen at menopause probably independently induces intra-abdominal fat accumulation (62-64).

Table 2. Epidemiological studies on the association of body adiposity with carotid intima-media thickness (IMT)

Author	Study design	Adiposity determination	Result
<i>prospective</i>			
Hassinen M et al. 2007 (part of thesis, Study III)	102 women, age 60-70 y, population-based, 12 y	waist and hip circumference, BMI, WHR	Waist and hip were associated with IMT progression. Those with both larger waist and smaller hip had greatest progression.
Reed D et al. 2003 (51)	573 men and women, age 40-60 y, employees of company, 3 y	sagittal and transverse abdominal diameters, BMI	Baseline BMI predicted IMT progression but sagittal and transverse diameters did not.
Stevens J et al. 2002 (50)	9316 men and women, age 45-64 y, population-based, 9 y	BMI	BMI associated with IMT in cross-sectional analysis, but not in longitudinal after adjusted for age.
Lakka TA et al. 2001 (47)	774 men, age 42-60 y, population-based, average 4 y	waist circumference, WHR, BMI	Abdominal obesity (WHR, waist) was an independent risk factor for IMT independent of BMI.
<i>cross-sectional</i>			
Czernichow S et al. 2005 (65)	1014 men and women, mean age 59 y, from vitamin study	waist and hip circumference, WHR, BMI, bioimpedance	IMT was positively associated with BMI, fat mass, fat-free mass and waist circumference.
De Michele M et al. 2002 (48)	310 women, mean age 55 y, selected subjects	waist and hip circumference, WHR, BMI	There was a graded and independent association between obesity (BMI, WHR) and IMT.
Ebrahim S et al. 1999 (49)	7735 men and women, age 55-77 y, from general practice register	BMI	There were no association between carotid IMT or carotid plaques and BMI.

BMI=body mass index, WHR=waist to hip ratio, y=years.

2.2.2 Insulin resistance

Insulin resistance is believed to be a pathophysiological disturbance that underlies many of the components of the metabolic syndrome. The components of the metabolic syndrome occur more commonly in overweight or obese person, because excess adiposity increases the likelihood of having insulin resistance (66,67). One half to two thirds of the individuals with the metabolic syndrome (66,68,69) and half of overweight and obese persons (66) have insulin resistance whereas the prevalence of insulin resistance in those without metabolic syndrome is 10 to 30 per cent (68,69). There are individuals who are obese but otherwise metabolically normal with high levels of insulin sensitivity (70,71). On the other hand, insulin resistance can be present in normal weight individuals (72). A follow-up study of young children represents that hyperinsulinemia may predict weight gain and obesity (73). Both genes, age and lifestyle factors, like inactivity and overeating, contribute to the development of insulin resistance (67,74).

An overabundance of circulating free fatty acids, derived mainly from adipose tissue is a link between obesity and insulin resistance (67). A free fatty acid overload and following insulin resistance have metabolic consequences both in the liver, pancreas and peripheral tissues (Figure 2). In individuals with visceral adiposity, free fatty acids have direct access to the liver and result in increased hepatic glucose production and fasting hyperglycemia (74). Elevated levels of fatty acids in the peripheral circulation decrease the sensitivity of muscle tissue to the action of insulin (74). To counterbalance this insulin resistant state and maintain normal blood glucose levels, insulin secretion is increased resulting hyperinsulinemia (9). When insulin-resistant muscle is already overloaded with lipid, some of the excess fatty acids are diverted to the liver, which promotes the development of fatty liver and dyslipidemia (75). The lipoprotein abnormalities in insulin resistance are hypertriglyceridemia, low levels of high density lipoprotein (HDL) cholesterol and an increased amount of small low-density lipoprotein (LDL) particles (76).

The relationship between insulin and blood pressure is complex. Normally, insulin increases sympathetic nerve activity but dilates resistance arterioles in skeletal muscle (77), primarily by stimulation of nitric oxide release by endothelial cells. In insulin

resistance this effect is diminished (76). In addition, hyperinsulinemia may directly elevate blood pressure by raising renal sodium reabsorption (78). Although resistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia are common in patients with hypertension, not all hypertensive patients have insulin resistance and hyperinsulinemia, and hypertension does not develop in all subjects with insulin resistance (79). Insulin resistance may contribute to hypertension through other mechanisms, such as vascular damage caused by chronic abnormalities in lipid and glucose metabolism (76,80).

INSULIN RESISTANCE			
SKELETAL MUSCLES	LIVER	PANCREAS	VASCULAR SYSTEM
-Reduced effect of insulin -Reduced glucose uptake	-Increased glucose production -Dyslipidemia (HDL ↓, triglycerides↑, small dense LDL) -Inflammation	-Increased insulin secretion to compensate hyperglycemia -β-cell exhaustion in response to chronic hyperglycemia	-Endothelial dysfunction (NO↓) -Elevated blood pressure -Impaired thrombolysis

Figure 2. Adverse effects of insulin resistance in liver, pancreas, skeletal muscles and vascular system. (NO=nitric oxide)

Insulin resistance is associated with an increased risk of type 2 diabetes (67), and diabetes develops in many persons with metabolic syndrome (14,81). Insulin resistance may have an independent effect on atherogenesis (82) and be an independent risk factor for atherosclerotic CVD (83,84). Aging is usually associated with increased insulin resistance in parallel to increased production of proinflammatory cytokines (85,86). The loss of muscle mass (60) and increase in body adiposity (59) associated with aging promote insulin resistance. In a 6-year follow-up study among 208 initially healthy volunteers, insulin resistance was associated with an increased risk of developing age-related disease such as type 2 diabetes, hypertension and CVD, while these endpoints did not occur in the most insulin sensitive third (87).

2.2.3 Impaired glucose homeostasis

Elevated fasting glucose levels are an important component of metabolic syndrome, but neither IFG nor diabetes is an absolute criterion. Insulin resistance is one apparent factor in development of IFG, IGT, and type 2 diabetes (75,88). Increased free fatty acid levels are associated with resistance to insulin-mediated glucose uptake and metabolism in muscle and an increase in glucose production and release by the liver (67,89). Pancreatic β -cell dysfunction is a critical component in the pathogenesis of type 2 diabetes (89). Glucose intolerance develops when insulin secretion capacity of pancreatic β -cells declines, losing the ability to suppress hepatic glucose uptake and to compensate for insulin resistance in target tissue (76,89). Whereas insulin insensitivity is an early phenomenon partly related to obesity, in genetically susceptible individuals pancreatic β -cell function declines gradually over time already when the glucose level is still within the normal range, before the onset of clinical hyperglycemia (67,89). When insulin resistance is combined with β -cell defects in glucose-stimulated insulin secretion, IGT, IFG, or type 2 diabetes can result (90).

Peripheral insulin resistance is most characteristic of IGT, whereas insulin-mediated failure to suppress hepatic glucose output are more prominent feature in IFG (91). IFG is more common in men than women in virtually all ages, but up to eight times higher in European men aged 50 to 70 years (91). Conversely, the prevalence of IGT is higher in women than men, except in Europeans over the age of 80 (91). IFG and IGT are strong predictors of future diabetes (92,93) and represent intermediate stages in the progression from metabolic syndrome to type 2 diabetes (88). The incidence of subsequent diabetes is highest in individuals with combined IGT and IFG (91). The risk of CVD increases with the progress of glucose intolerance (94)

In a population-based prospective study, IGT and type 2 diabetes were strong independent predictors of advanced carotid atherosclerosis (95). In a metaregression analysis of 20 studies with a mean follow-up of 12 years, a continuous positive relationship was found between initial fasting and postprandial glucose levels and CVD events. The relationship was found even below the current thresholds for IFG and IGT (96). Both hyperglycemia and diabetes were predictors of all-cause and CVD mortality in a prospective study of young and middle-aged adults (97).

2.2.4 Dyslipidemia

Dyslipidemia among individuals with overweight or the metabolic syndrome is characterized by elevated triglycerides, low levels of HDL cholesterol and high level of small LDL cholesterol particles (98-100). Insulin resistance in fat cells leads to increased lipolysis with release of fatty acids (90). With an increase in free fatty acid flux to the liver, increased production of triglyceride-rich very low density lipoprotein cholesterol occurs (101,102). Triglyceride accumulation in the liver may decrease hepatic insulin sensitivity and contribute to dyslipidemia (100,103). Plasma LDL cholesterol levels are often normal in patients with the metabolic syndrome, but LDL particles are smaller than normal, making them more able to penetrate the endothelial wall and more susceptible to oxidation, a state associated with increased cardiovascular risk (104-106). HDL cholesterol has an established role in reverse cholesterol transport (107). HDL cholesterol also has anti-atherosclerotic and anti-inflammatory properties. Low plasma HDL cholesterol levels have been related to an increased risk of CHD and stroke (108-111). Middle-aged and elderly women with diabetes have a larger decrease in HDL cholesterol and greater decrease in LDL size than diabetic men relative to their nondiabetic counterparts (112).

2.2.5 Elevated blood pressure

Elevated blood pressure has been suggested to be a component of the metabolic syndrome (18,20). However, the associations of blood pressure with other components of the metabolic syndrome have been weaker than the associations between other components of the metabolic syndrome (79,113). In several studies using factor analysis, blood pressure has been identified as a factor distinct from the other metabolic syndrome components (81,114,115). Although the association between obesity and hypertension is documented (116), the mechanism supporting the association between insulin resistance and hypertension is partly unclear (80). Acute increases in plasma insulin within the physiological range elevate sympathetic neural outflow but produce vasodilatation and do not elevate arterial pressure in normal humans (77). In addition to insulin's direct action to kidney (sodium retention), insulin and increased levels of free fatty acids may stimulate the activity of the sympathetic nervous system causing

vasoconstriction, and may thus play an essential role in linking obesity and insulin resistance to hypertension (78).

Blood pressure, especially systolic, is associated with mortality from cardiovascular and other causes, and the incidence of stroke and coronary disease (117). According to a recent study, the contribution of metabolic syndrome components to the risk of CVD and all-cause mortality is mainly related to blood pressure along with glucose abnormalities, with no contribution of the other components (118). The result of a prospective study indicates that individuals with essential hypertension with high triglycerol and low HDL cholesterol are at greatest risk of CVD (119).

2.2.6 Poor cardiorespiratory fitness

Cardiovascular system responds to exercise with many adaptations to assure that active muscles blood supply is appropriate to metabolic needs, the generated heat is dissipated and blood supply to the brain and heart is maintained. Maximal oxygen uptake (VO_{2max}) is the commonly used measurement which describes the maximum volume of blood that the heart can pump (cardiac output) and the capacity of the lung to oxygenate the blood and the working muscle to use it at maximal physical exertion (120).

Physical activity is the principal determinant of cardiorespiratory fitness although non-modifiable factors, like genes, gender and age have also strong influence (121,122). Men have 10 to 20% greater VO_{2max} than women partly because a larger proportion of muscle mass and a smaller body fat content, a greater stroke volume and a higher hemoglobin concentration than women (123). Age-related decline in VO_{2max} is approximately 10% per decade between 25 and 75 years (124). Physical limitations resulting from sedentary lifestyle, disabling diseases, medication, loss of coordination and lack of familiarity of required exercise skill may limit VO_{2max} (124).

Cardiorespiratory fitness is associated with many components of the metabolic syndrome, like waist circumference, fasting glucose, insulin resistance, HDL cholesterol, triglyceride levels, and blood pressure (125-130). Cross-sectional studies have demonstrated an inverse association for cardiorespiratory fitness with the metabolic syndrome (131-135) or clustering of its abnormalities (125,126,130,136) (Table 3). Population-based studies and data from older individuals are limited. Also,

few prospective studies have assessed the relation of cardiorespiratory fitness to metabolic syndrome incidence (Table 3). In a 4-year study, middle-aged men in the upper third of VO_{2max} were nearly 75% less likely than unfit men to develop the metabolic syndrome (137). In a 15-year study, young adults with poor fitness were 3 to 6 times more likely to develop diabetes, hypertension and the metabolic syndrome than those with high fitness (127). In a 5-year study, the risk for metabolic syndrome was a half lower in men and women in the upper third of cardiorespiratory fitness than those in the lower third (138). In some studies no independent association between cardiorespiratory fitness and the metabolic syndrome was found (139,140).

Low cardiorespiratory fitness is associated with an increased risk of IFG and type 2 diabetes (141), CVD and mortality (142-145). Obese individuals with at least moderate cardiorespiratory fitness have lower rates of CVD or mortality than their normal-weight and unfit peers (144). In a prospective study of middle-aged men, even a small improvement in physical fitness was associated with a significantly decreased risk of death (143).

Table 3. Epidemiological studies on the association of cardiorespiratory fitness (CRF) and metabolic syndrome (MS)

Author	Study design	MS definition / Measure of CRF	Result
<i>prospective</i>			
La Monte M et al. 2005 (138)	9007 men 1491 women, mean age 44 y, selected subjects, 5.7 y	NCEP/ maximal treadmill time	Low CRF was a strong, independent predictor of MS in men and women.
Ekelund U et al. 2005 (140)	249 men 356 women, mean age 53 y, population-based, 5.6 y	MS risk score/ submaximal test (heart rate)	CRF was not an independent predictor of MS after adjusting for physical activity.
Carnethon M et al. 2003 (127)	2029 men 2458 women, age 18-30 y, population-based, 15 y	NCEP/ maximal treadmill time	Low CRF was associated with development of MS.
Laaksonen D et al. 2002 (137)	612 men, age 42-60 y, population-based, 4 y	WHO, NCEP/ directly measured VO _{2max}	Men in the upper third of VO _{2max} were 75% less likely to develop MS than unfit men.
<i>cross-sectional</i>			
Hassinen M et al. 2008 (part of thesis, Study I)	671 men 676 women, 57-79 y, population-based	NCEP/ directly measured VO _{2max}	Men and women with lowest third of VO _{2max} had a 10 times higher risk of MS.
Wijndaele K et al. 2007 (136)	571 men 448 women, mean age 46 y, random community sample	Continuous MS risk score/ directly measured VO _{2peak}	CRF was inversely associated with MS risk score independently of muscular strength in men and women.
Ekelund U et al. 2007 (130)	1709 boys and girls, age 9-16 y, population-based	MS risk score/ incremental cycle ergometer test	CRF and physical activity were independently associated with clustered risk factors.
Finley C et al. 2006 (135)	9007 men 2826 women, mean age 45 y, selected subjects	NCEP/ maximal treadmill time	CRF was inversely associated with the prevalence of MS.
Jurca R et al. 2004 (134)	8570 men, mean age 43 y, selected subjects	NCEP	CRF was inversely associated with prevalence of MS even after adjusting for strength.
Farrell S et al. 2004 (133)	7104 women, mean age 45 y, selected subjects	NCEP/ maximal treadmill time	Prevalence of MS was lower across progressively higher levels of CRF.
Franks P et al. 2004 (139)	874 men and women, mean age 54 y, population-based	MS risk score/ submaximal test (heart rate)	CRF had borderline association with MS after adjustment for physical activity.
Lakka TA et al. 2003 (132)	1069 men, age 42-60 y, population-based	WHO modified/ directly measured VO _{2max}	CRF was inversely associated with MS.
Kullo I et al. 2002 (131)	360 men, mean age 48 y, volunteers	NCEP/ maximal treadmill time	CRF was inversely associated with MS.
Carroll S et al. 2000 (126)	711 men, mean age 47 y, selected subjects	2 MS risk scores/ submaximal test (heart rate)	CRF was inversely associated with clustering of metabolic abnormalities.
Whaley M et al. 1999 (125)	15537 men 3899 women, mean age early 40s, selected subjects	Deadly quartet/ maximal treadmill time	Low CRF was associated with an increased clustering of metabolic abnormalities.

NCEP=National Cholesterol Education Program, WHO=World Health Organization, y=years
VO_{2max}/VO_{2peak}=Maximal/peak oxygen consumption.

2.2.7 Systemic low-grade inflammation

C-reactive protein (CRP) is an acute phase reactant and levels may increase up to 1000-fold in response to major infection or trauma (146). In normal clinical practice CRP values below 10 mg/l are considered normal. Higher values indicate infection, inflammation or necrosis. Increased serum concentration of high-sensitivity CRP (hsCRP) is a marker of low-grade inflammation, and sensitive immunoassays are capable to detect also very low serum CRP concentrations (<1 mg/l). Even slightly elevated serum concentrations of hsCRP predict clinical manifestations of atherosclerotic CVD (147-149). Although serum CRP concentrations may increase in response to acute illness concentrations are remarkably stable over long period of time when measured in asymptomatic adults (146).

CRP is primarily secreted by the liver in response to variety of inflammatory cytokines. Elevated plasma CRP concentrations have been reported in individuals with abdominal obesity, especially in the obese with large depots of visceral adipose tissue (150). Elevated CRP concentrations accompanying obesity may signify an increased concentration of adipocytokines and a proinflammatory state, which is associated also with insulin resistance (151). In obesity, white adipose tissue is characterized by an increased production and secretion of a wide range of inflammatory molecules including TNF- α and IL-6. These cytokines may have local effects on adipose tissue physiology and also systemic effects on other organs (152). Process linked to chronic inflammation decrease insulin action, whereas insulin resistance leads to worsening of inflammation (153).

TNF- α is a pro-inflammatory cytokine that is produced and secreted from adipocytes. TNF- α is increased in the adipose tissue and skeletal muscle of insulin resistant humans (154). Within adipose tissue, TNF- α causes adipocyte insulin resistance (152) and impairs insulin signaling (155). Via downregulation of lipoprotein lipase it inhibits lipid storage in adipose tissue (155). TNF- α has important effects on whole-body lipid metabolism, raising serum triglyceride levels by stimulating very low density lipoprotein cholesterol production (153).

IL-6 has been classified as a cytokine with both a pro- and an anti-inflammatory actions (156,157). On average 30 % of circulating IL-6 in resting conditions originate

from adipose tissue (158). Abdominal adipose tissue release more IL-6 than subcutaneous adipose tissue (159). During exercise, IL-6 is produced locally in working skeletal muscle, and low muscle glycogen content stimulates the production (157). During exercise, IL-6 contributes to the maintenance of glucose homeostasis, stimulates adipose tissue lipolysis, and may also inhibit the effect of TNF- α (157). On the other hand, it has been proposed that IL-6 alters insulin sensitivity, increases hepatic production of fibrinogen and CRP, is procoagulant and stimulates adhesion of circulating leucocytes to the vascular endothelium (156). IL-6 also stimulates the central and the sympathetic nervous systems and might result in hypertension contributing to higher concentration of angiotensin II, which is a potent vasoconstrictor (153). Data from population-based studies have shown that elevation of IL-6 predicts total and cardiovascular mortality (160,161).

AMP-activated protein kinase (AMPK) is a major regulator of energy balance and glucose and lipid metabolism at both cellular and whole body levels (162). AMPK switches cells from an anabolic state where nutrients are taken up and stored to a catabolic state where they are oxidized (162). IL-6 may mediate or modify some of AMPK actions in muscle and adipose tissue (163). As IL-6, also AMPK is activated by exercise and absence of glucose (163). In a recent animal study, IL-6 knockout mice had decreased AMPK activity and developed components of the metabolic syndrome, such as obesity, dyslipidemia and glucose intolerance (163).

Adiponectin is an anti-inflammatory cytokine produced by adipocytes that circulates at relatively high levels in the blood (164,165). Adiponectin activates AMPK (166), improves insulin sensitivity, inhibits inflammation and may have direct antiatherosclerotic effects (164,165). Adiponectin levels are reduced in obese individuals, especially in those with abdominal obesity (167). Reduced adiponectin levels contribute to insulin resistance, hyperglycemia and endothelial dysfunction (164,165). In a recent study, lower adiponectin levels were associated with most of the components of the metabolic syndrome and the metabolic syndrome itself (168). Cytokines and free fatty acids increase also the production of fibrinogen and coagulation factor, PAI-1, in the liver, which complements the overproduction of PAI-1 by especially visceral adipose tissue (1).

Aging is associated with increased inflammatory activity (169,170). In a cohort of 81-year old men and women, aging was associated with increased circulating levels of TNF- α , and high inflammatory activity was associated with increased prevalence of clinical diagnosis of atherosclerosis (171). Limited data on the association of low-grade inflammation with the metabolic syndrome are available in the elderly (172), especially from long-term studies.

Cross-sectional studies have found associations of hsCRP with metabolic syndrome (172-179) (Table 4) and its components, including obesity (180), insulin resistance (172,173,180), dyslipidemia (180), elevated blood pressure (181) and endothelial dysfunction (180). Prospective studies in middle-aged individuals have observed that increased serum hsCRP concentrations predict the development of metabolic syndrome and type 2 diabetes (182-184) (Table 4).

Table 4. Epidemiological studies on the association of high-sensitivity C-reactive protein (hsCRP) and metabolic syndrome (MS)

Author	Study design	Definition	Result
<i>prospective</i>			
Hassinen M et al. 2006 (part of thesis, Study II)	103 women, age 60-70 y, population-based, 12 y	NCEP	Women with any increase in hsCRP during 12 years had a 4-6 times higher risk of MS than those whose hsCRP decreased.
Laaksonen D et al. 2004 (184)	680 men, age 42-60 y, population-based, 11 y	NCEP WHO	Men with hsCRP ≥ 3 mg/l had over 3 times higher risk of MS and 4 times higher risk of diabetes than those with hsCRP < 1.0 mg/l.
Ridker P et al. 2003 (183)	14719 women, mean age 54 y, selected subjects, 8 y	NCEP	hsCRP concentrations were higher in women with MS. There was a linear increase in hsCRP with the increase of MS components.
Han T et al. 2002 (182)	1244 men and women, mean age 46 y, population-based, 6 y	Own definition	Women with hsCRP in the highest third had 4 times higher risk of MS. In men hsCRP did not predict MS.
<i>cross-sectional</i>			
Ukkola O et al. 2007 (179)	1035 men and women, mean age 51 y, population-based	IDF	hsCRP increased with the increase of MS components. hsCRP was stronger indicator of MS in women.
Florez H et al. 2006 (178)	190 men and women, mean age 53 y, selected subjects	NCEP	Those with MS had higher hsCRP. Higher hsCRP concentrations were in those with abdominal obesity.
Wannamethee S et al. 2005 (172)	2722 men, age 60-79 y, from practice registers	NCEP WHO, modified	Men with MS based on NCEP and WHO had higher concentrations of hsCRP and markers of haemostasis.
Santos A-C et al. 2005 (175)	957 men and women, mean age 53 y, random digit dialing-one adult per household	NCEP	Those with MS had higher hsCRP. Central obesity and blood pressure were important determinants of inflammation in the MS.
Lim S et al. 2005 (176)	9773 men and women, age 40-69 y, from rural and urban community	NCEP for Asian	The highest quartile of hsCRP was independently associated with 2 times higher risk of having MS.
Ford E et al. 2005 (177)	1366 men and women, age 12-17 y, data from NHANES 1999-2000	NCEP	Those with MS had higher hsCRP. Of those with MS 38 % had hsCRP concentration > 3 mg/l.
Lee W-Y et al. 2004 (174)	767 men and women, mean age 47 y, selected subjects	NCEP	Those with MS had 2 times higher hsCRP. Of the MS components waist girth correlated best with hsCRP.
Rutter M et al. 2004 (173)	1356 men 1681 women, mean age 54 y, community-based	NCEP	Those with MS had higher hsCRP. hsCRP was higher in women with MS than in men with MS.
Browning LM et al. 2004 (185)	257 women, mean age 46 y, BMI > 25, community-based	WHO	hsCRP was not associated with MS independently of BMI.

CVD=cardiovascular disease, BMI=body mass index, y=years, NCEP=National Cholesterol Education Program, WHO=World Health Organization, IDF=International Diabetes Federation, NHANES=National Health and Nutrition Examination Survey.

2.2.8 Endothelial dysfunction

Several components of the metabolic syndrome impair endothelial function (186). A primary feature of endothelial dysfunction is the reduced bioavailability of nitric oxide which has an important role in vascular relaxation and important anti-atherogenic properties (187). Insulin resistance and systolic blood pressure are the principal determinants of endothelial dysfunction in the metabolic syndrome (186,188). Imbalanced production of fat-derived metabolic products, hormones and cytokines in obesity (especially visceral) decrease insulin sensitivity in the liver and skeletal muscle and impair endothelial function through direct or indirect mechanisms (186,189). In the insulin-resistance state, the ability of insulin to stimulate nitric oxide production in the endothelium is diminished (186). In obese individuals, endothelium-dependent vasodilatation may be reduced by up to 50% compared with lean subjects (190). High plasma levels of triglycerides (191) and total and LDL cholesterol, even at the levels with the normal range, may cause endothelial dysfunction (192). IGT and type 2 diabetes are also associated with impaired endothelium-dependent vasodilatation (193). Aging represents an independent risk factor for endothelial dysfunction (194,195).

2.3 Genetic susceptibility to the metabolic syndrome

Family studies suggest a significant genetic basis to individual components of the metabolic syndrome, such as abdominal obesity, insulin resistance, HDL cholesterol, triglycerides, and blood pressure (196,197). Clustering of the syndrome in families suggests also a genetic basis for the metabolic syndrome itself (197). Family studies demonstrate that clustering of metabolic risk factors are transmitted from parents to offspring (196,198). The thrifty gene hypothesis suggests that genetic selection has favoured energy-conserving genotypes in environment with an unstable food supply. Storage of energy as fat rather than glycogen would ensure energy during periods of starvation (197). To expose such genotypes to an abundance of food is detrimental, and may thus predispose to the metabolic syndrome and glucose intolerance (197). An alternative explanation, the thrifty phenotype, suggests that intra-uterine malnutrition leads to a low birth weight and increases the risk of the metabolic syndrome in later life (197). The risk of the metabolic syndrome associated with low birthweight has been

shown to increase particularly in families with the metabolic syndrome, suggesting that a low birthweight could be a phenotype for a thrifty gene (197)

2.4 Metabolic syndrome and preclinical atherosclerosis

Atherosclerosis is a progressive disease resulting from endothelial dysfunction, inflammation, lipid accumulation and thrombosis (199). The arterial intima-media represents the site for the development of atherosclerotic lesions. Although atherosclerosis is a generalized disease, specific arterial sites, such as bifurcations are prone to atherosclerotic plaque formation (199). High-resolution B-mode ultrasonography has been used to obtain measurements of the thickness of the intima and media of the carotid arteries. Carotid artery IMT is a surrogate measure of global preclinical atherosclerosis and predicts future risk of myocardial infarction and stroke (200,201). A change in carotid IMT has been validated as a vascular marker of the progression of preclinical atherosclerosis (202).

In prospective studies, individual components of the metabolic syndrome, such as abdominal obesity (47), elevated blood pressure (203-205), high triglycerides (204), low HDL cholesterol (204), and elevated blood glucose (206) have been found to associate with preclinical atherosclerosis as assessed by carotid IMT.

Many cross-sectional studies (106,207-214) (Table 5) have shown an association of metabolic syndrome with carotid IMT. In some, the effect was more pronounced in women than in men (210,212). Few prospective studies have assessed the relation of the metabolic syndrome to carotid IMT (Table 5). In a 5-year study, men and women with the metabolic syndrome had an increased risk of developing carotid atherosclerosis (215). In a 3-year study, men with the metabolic syndrome during the study had greater carotid IMT at both baseline and after 3 years (216). Also, individuals with multiple cardiovascular risk factors at baseline had a greater carotid IMT 15 years later (204). Because both cross-sectional and follow-up studies have been performed mainly in middle-aged individuals or had a wide age range, data from elderly population are warranted. Also, there is a lack of long term studies that focus on association of development of the metabolic syndrome with change in carotid IMT.

Table 5. Epidemiological studies on the association of metabolic syndrome (MS) with carotid intima-media thickness (IMT)

Author	Study design	Definition	Result
<i>prospective</i>			
Hassinen M et al. 2006 (part of thesis, Study IV)	101 women, age 60-70 y, population-based, 12 y	NCEP	The mean increase in carotid IMT was 2 times greater in those who developed MS than those who did not.
Fan AZ 2006 (217)	573 men and women, age 40-60 y, employees from a local utility company, 3 y	Factor analysis	The atherogenic effects of MS were mediated through its indicators. The association between MS variables and IMT differed between sexes.
Wallenfeldt K et al. 2005 (216)	316 men, age 58 y, selected based on obesity and insulin sensitivity, 3 y	WHO, modified NCEP	Both initial and final IMT was greater in men with MS according to WHO or NCEP. The annual change in IMT was greater in men with WHO MS both at baseline and after 3 years.
Bonora E et al. 2003 (215)	888 men and women, age 40-79 y, population-based, 5 y	WHO NCEP	Those with MS according to WHO or NCEP had an increased incidence of IMT plaque (WHO 51/NCEP 47%) and stenosis (WHO 34/NCEP 42%).
<i>cross-sectional</i>			
Vaudo G et al. 2007 (214)	234 men and women, mean age 53 y, 147 outpatients with MS, 87 controls from staff	NCEP	Patients with MS had greater carotid and femoral IMT and altered endothelial function.
Sandhofer A et al. 2007 (213)	1518 men (40-60 y) and women (50-70 y), population-based	NCEP WHO IDF	Subjects with MS had greater IMT than those without MS.
Kawamoto R et al. 2007 (212)	868 men and women, mean age 64 and 70 y, hospitalized patient	Own modified definition	Subjects with MS had greater IMT than those without MS. The effect was more pronounced in women.
Mohan V et al. 2006 (211)	3430 men and women, mean age 45 y, population-based	NCEP, modified	Subjects with MS had greater IMT than those without MS. IMT increased with severity of glucose intolerance.
Iglseder B et al. 2005 (210)	1588 men and women, age 40-65 y, unrelated, healthy; from a clinic	NCEP	Subjects with MS had higher IMT than those without MS. The effect of MS was more pronounced in women.
Scuteri A et al. 2004 (208)	471 men and women, age 21-96 y, volunteers	NCEP	Subjects with MS had 16 % higher IMT values than those without MS.
McNeill A et al. 2004 (209)	14502 men and women, age 45-64 y, population-based	NCEP	Subjects with MS had greater IMT and were 2 times more likely to have CHD than those without MS.
Golden S et al. 2002 (207)	11790 men and women, age 45-64 y, population-based	Six insulin resistance components	Those with all six risk factors had greater IMT than those without this grouping.
Hulthe J et al. 2000 (106)	391 men, age 58 y, population-based	WHO	Subjects with MS had greater IMT values and more small LDL particles than those without MS.

CHD=coronary heart disease, NCEP=National Cholesterol Education Program, WHO=World Health Organization, IDF=International Diabetes Federation, y=years.

2.5 Prevention and treatment of the metabolic syndrome

2.5.1 Physical activity

The NCEP Adult Treatment Panel III guidelines for the treatment of the metabolic syndrome recommended that after medical control of LDL cholesterol, the first-line treatment of the metabolic syndrome should be weight reduction and increased physical activity (218). Also other expert groups consider physical activity, diet and weight control as cornerstones in the prevention and treatment of the metabolic syndrome (219,220). Current evidence supports recommendation from the Centers for Disease Control and Prevention of the United States and the American College of Sports Medicine in 1995 (221), updated in 2007 with more accurate recommendations for different intensity and type of activities in all healthy adults aged 18 to 65 years (222) and in older adults (223). Based on these recommendations, to promote and maintain health, all healthy individuals should engage at least 30 minutes of moderate aerobic physical activity on five days each week or vigorous-intensity aerobic physical activity at least 20 minutes on three days each week and perform activities that maintain or increase muscular strength and endurance at least two days each week. In addition for older adults, the recommendations emphasize flexibility and balance exercises.

Randomized controlled trials indicate that exercise training has positive effects on individual components of metabolic and cardiovascular risk factors related to the metabolic syndrome such as body weight and fat (224-226), insulin sensitivity (226,227), lipid profile (228), blood pressure (229-231), low-grade inflammation (232,233), and diabetes (234). In all above mentioned trials, the follow-up periods were relatively short, 4-52 weeks, with the exception of the 6-year DNASCO (DNA Polymorphisms in Carotid Atherosclerosis) Study (230,232).

Current evidence on the effect of physical activity in the prevention of the metabolic syndrome itself is based mainly on cross-sectional (132,134,136,235,236) and prospective (137,140,237) epidemiological and short intervention (238) studies, suggesting that regular aerobic physical activity (137,140,235,236,238), muscular strength (134,136,237) and good cardiorespiratory fitness (132,137) are associated with or reduce the risk of developing the metabolic syndrome. In a randomized controlled trial of volunteers with IGT, a three-year lifestyle intervention including diet and

moderate intensity physical activity decreased the incidence of the metabolic syndrome by 41% compared with the placebo group (239).

The favorable effects of physical activity on most metabolic and cardiovascular risk factors are stronger if associated with weight loss (240). There are also individual differences of the effect of exercise on risk factors influenced by age, sex and genetic factors (122).

2.5.2 Nutrition

In addition to exercise, diet can also be beneficial for many of the components of the metabolic syndrome. In a recent meta-analysis of 44 randomized controlled trials, diet combined with exercise reduced body mass index and blood pressure, and the reduction of blood pressure was greater with diet alone than with exercise alone (231). In a randomized trial in obese men, adding structured exercise to diet counselling did not ameliorate the metabolic syndrome better than diet only (241). Another meta-analysis of randomized controlled trials found that combination of diet and exercise or solely dietary intervention was effective for reducing risk for type 2 diabetes in high risk individuals (242). Large cohort (243-245) and intervention (246) studies suggest that diets low in saturated fat, high in fiber, rich in fruits and vegetables, and with a low glycemic index may decrease the risk for diabetes or CVD. These findings give evidence that such diets may be effective for reducing the risk of the metabolic syndrome, but intervention studies are needed.

2.5.3 Weight reduction

Weight reduction is one of the key elements in preventing and treating of the risk factors of the metabolic syndrome. Epidemiological prospective studies and clinical trials have shown that even modest weight reduction of 5-10 %, due to either an increase in physical activity or a decrease in energy intake or both, can substantially lower blood pressure, improve blood lipid profile, insulin sensitivity and glucose tolerance (247) and decrease the incidence of diabetes (246). In a short-term randomized controlled trial, for each 1 kg of weight lost, the likelihood of the metabolic syndrome were reduced by 8 % in obese men and women (248).

2.5.4 Medication

At present, drug therapy for the metabolic syndrome focuses on correction of the individual risk factors i.e. hypertension, dyslipidemia, adiposity and hyperglycemia (1,25). Treatment guidelines have been given by the NCEP (20,218), the Sixth Joint National Committee for blood pressure (249) and the American Heart Association/American College of Cardiology (250). In a randomized trial of volunteers of the effect of metformin or lifestyle intervention on the metabolic syndrome, the incidence of metabolic syndrome was reduced by 41% in the lifestyle group and by 17% in the metformin group compared with the placebo group (239).

2.6 Summary of the review

The metabolic syndrome is a group of risk factors of metabolic origin accompanied by an increased risk for type 2 diabetes and CVD. The increasing prevalence of the metabolic syndrome is largely due to increasing obesity throughout the world. Several factors are likely to contribute to susceptibility to the metabolic syndrome, especially genes, aging, sedentary lifestyle and an atherogenic diet. The two putative main underlying risk factors for the metabolic syndrome are abdominal obesity and insulin resistance (Figure 3).

Insulin resistance can be secondary to obesity, but can have genetic components as well. Hyperinsulinemia may also be a risk factor for development of obesity. Metabolic syndrome is also characterized by elevated fasting plasma glucose levels. Another component of the metabolic syndrome, dyslipidemia, comprises elevated triglycerides and low levels of HDL cholesterol. Also, plasma LDL cholesterol particles are smaller than normal, making them more atherogenic. Elevated blood pressure is strongly associated with obesity and occurs more often in insulin-resistant individuals. Several other factors are postulated to contribute to the syndrome. A proinflammatory state is commonly present in the metabolic syndrome, largely due to obesity, and is characterized by elevation of cytokines and acute phase reactants, e.g. CRP. The prothrombotic state in the metabolic syndrome is characterized by elevation of fibrinogen and PAI-1. Several components of the metabolic syndrome have an adverse impact on the vascular endothelium, producing endothelial dysfunction and favoring the

progression of atherosclerosis. A better understanding of the non-traditional risk factors for the metabolic syndrome is still needed, especially in the elderly. For example, what is the additive value of low cardiorespiratory fitness, chronic low-grade inflammation and preclinical atherosclerosis in the prediction of the metabolic syndrome? Evidence from epidemiological and randomized trials supports the positive role of physical activity, healthy diet and weight control in prevention and treatment of the individual components of the metabolic and cardiovascular risk factors. The optimal prescription of physical exercise or diet is still unknown.

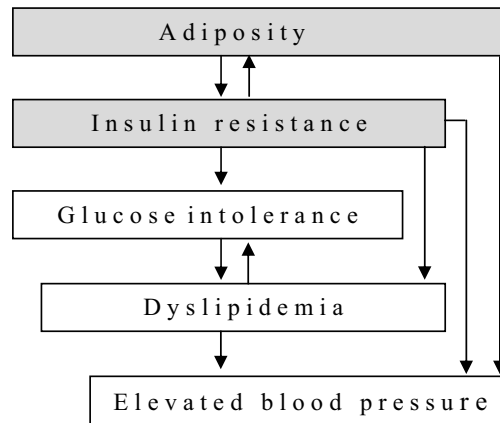


Figure 3. The interaction and timeorder of the individual components of the metabolic syndrome.

3. AIMS OF THE STUDY

The purpose of the present thesis based on two population studies is to increase the understanding of the predictors and consequences of the metabolic syndrome in aging men and women. Special emphasis is on the associations of physical fitness and low-grade inflammation with the metabolic syndrome and on the association of the metabolic syndrome with the progression of carotid IMT during 12 years.

The specific aims of the study are to investigate:

1. The association of poor cardiorespiratory fitness with the metabolic syndrome and impaired glucose homeostasis in older men and women (Study I).
2. The association of serum hsCRP with development of the metabolic syndrome in elderly women during a 12-year follow-up (Study II).
3. Associations of hip and waist circumferences with the progression of carotid atherosclerosis, quantitated ultrasonographically by carotid IMT, in elderly women during a 12-year follow-up (Study III).
4. The association of incident metabolic syndrome with the progression of carotid atherosclerosis as measured by carotid IMT, in elderly women during a 12-year follow-up (Study IV).

4. METHODS

4.1 Study populations and design

The data used in this thesis are from two population-based studies from Eastern Finland (Table 6). In Study I, the men and women were 57-79 years of age. In Studies II-IV, the women were 60-70 years of age at baseline of the 12 years follow-up.

Table 6. Study population and design of the Studies I-IV

Study	Study population	Study design	Risk factor	Outcome
I	1347 men and women	baseline of a RCT ¹	Poor cardiorespiratory fitness	Impaired glucose tolerance and metabolic syndrome
II	103 women	prospective cohort, 12 years	Low-grade inflammation ²	Metabolic syndrome ³
III	102 women	prospective cohort, 12 years	Obesity	Carotid atherosclerosis ⁴
IV	101 women	prospective cohort, 12 years	Metabolic syndrome ³	Carotid atherosclerosis ⁴

¹ Ongoing randomized controlled trial, DR's EXTRA Study

² Change in high-sensitivity C-reactive protein during 12 years

³ Incident metabolic syndrome during 12 years

⁴ Change in carotid IMT during 12 years

Study I

The subjects were participants of the Dose-Responses to Exercise Training (DR's EXTRA, ISRCTN45977199) Study, the ongoing randomized controlled 4-year trial on the effects of regular physical exercise and diet on endothelial function, atherosclerosis and cognition. In the present study we used the baseline data of the study (Figure 4).

The original subject source was derived from a population register in 2002. The subjects were a representative sample of 1500 men and 1500 women, aged 55 to 74 years, from the city of Kuopio in Eastern Finland. Of these individuals, 2062 expressed their willingness to participate in the study. Altogether 1479 participated in the baseline examinations between April 2005 and November 2006, and 1410 of them participated in all the baseline study visits and were randomized into study groups (Figure 4). Exclusion criteria for the intervention study were conditions that inhibit safe engagement in exercise training, malignant diseases and other conditions preventing co-operation, as judged by the research physicians. The present study population consisted of 1347 subjects (671 men, 676 women) who had complete data on VO_{2max} , glucose homeostasis and the characteristics of the metabolic syndrome, and did not have type 1 diabetes. Of these individuals 564 men, 613 women did not have type 2 diabetes. The study protocol was approved by the Ethics Committee of Kuopio University and University Hospital. All participants gave written informed consent.

Those 37 men and 32 women who did not participate in all the baseline visits and were thus excluded based on partial data were older (69.7 vs. 66.5 years, $P<0.001$), less educated (8.9 vs. 11.2 years, $P<0.001$), shorter (163.2 vs. 166.7 cm, $P=0.02$), had a lower VO_{2max} (16.0 vs. 23.6 $ml\cdot kg^{-1}\cdot min^{-1}$, $P<0.001$), and serum HDL cholesterol (1.5 vs. 1.7 mmol/l, $P=0.002$), higher weight (81.9 vs. 77.1 kg, $P=0.05$), larger waist (102.2 vs. 93.9 cm, $P<0.001$) and hip circumference (107.4 vs. 100.9 cm, $P<0.001$), higher body mass index (30.7 vs. 27.7, $P<0.001$), fasting plasma glucose (6.3 vs. 5.8 mmol/l, $P=0.003$), serum triglycerides (1.6 vs. 1.3 mmol/l, $P=0.03$), and more metabolic risk factors (2.4 vs. 1.9, $P=0.001$). They were more likely to have metabolic syndrome (43 vs. 26%, $P=0.008$), CVD (50 vs. 22%, $P<0.001$), worse glycemic status (IGR 26 vs. 21% and type 2 diabetes 22 vs. 13%, $P=0.04$) and worse smoking status (never 40 vs. 55%; former smokers 36 vs. 35% and current smokers 24 vs. 11%, $P=0.003$).

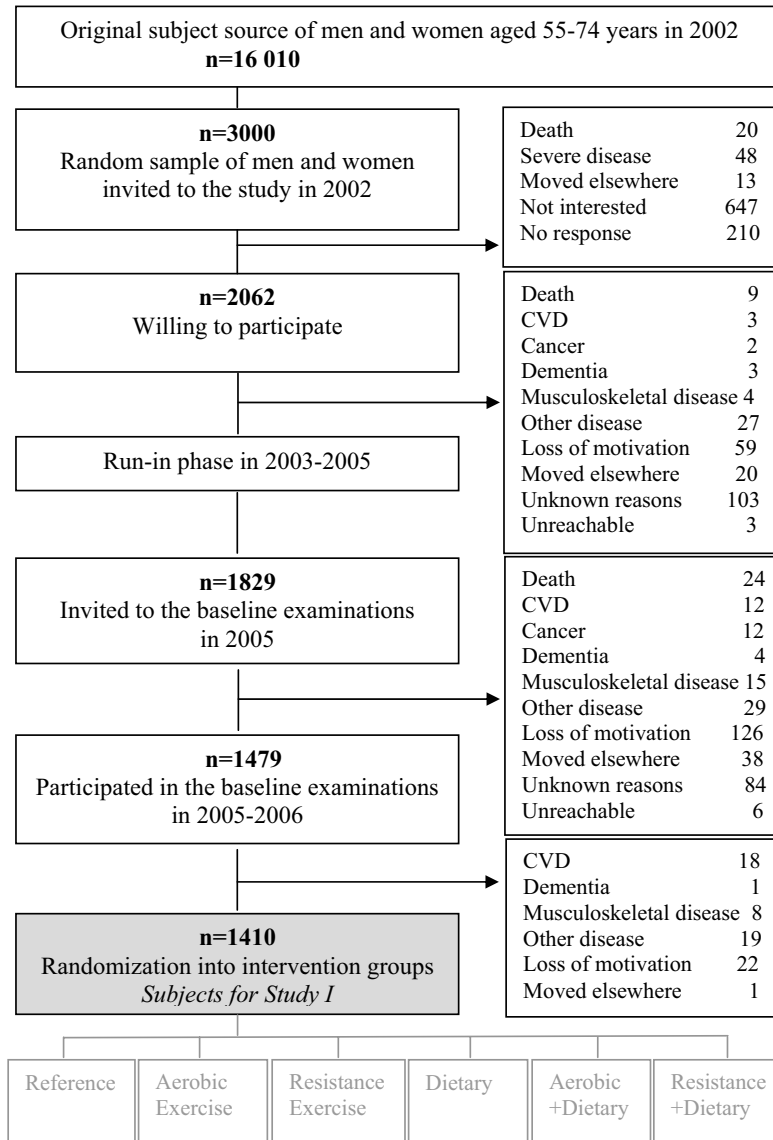


Figure 4. DR's EXTRA Study design (Study I)

Studies II-IV

The subjects were derived from a population-based, randomly selected sample of 299 women 50 to 60 years of age, initially examined as part of a large population-based risk factor study (FINMONICA) in 1982 (251) (Figure 5). The original study sample was stratified separately for men and women by ten year age groups to obtain even age and gender specific groups. For the baseline examinations of the present study in 1991-1992, we recruited only women, 60 to 70 years of age, living in province of Kuopio, one of the monitoring areas of the Finnish part of the WHO MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project. Of the 260 women who were invited, altogether 202 women completed the examinations between October 1991 and March 1992. Because 32 women had died or could not be contacted, 170 women 70 to 80 years of age were eligible for the 12-year follow-up study in 2003 (Figure 5). Of 170 women who were invited in the follow-up study, 57 did not participate.

All of the 113 women who participated in the study completed the examinations between March 2003 and June 2003. The same methods were used to assess study variables in study years 1991-1992 and 2003. The women who have participated in both study years were included in the analysis. Of the 113 women who completed all study visits in 2003, six had missing data on hsCRP at baseline or after follow-up and four had hsCRP concentrations >10.0 mg/l at baseline. Thus in Study II, the final study population included 103 women. Due to missing data on carotid IMT in either examination, the final study sample consisted of 102 women in Study III and 101 women in Study IV with complete data on study variables (Table 6). The study protocol was approved by the Ethics Committee of the University of Kuopio. All participants gave a written informed consent.

Those 89 women who participated in 1992, but did not participate in the 12 year follow-up in 2003 were older (65.6 vs. 63.9 years, $P<0.001$) and less educated (7.0 vs. 8.5 years, $P=0.004$) and had higher body weight (72.4 vs. 67.9 kg, $P=0.003$) and body mass index (29.2 vs. 27.4, $P=0.004$), a larger waist (88.0 vs. 83.4 cm, $P=0.002$) and hip circumference (102.0 vs. 98.8 cm, $P=0.03$), higher triglycerides (1.6 vs. 1.2 mmol/l, $P=0.008$), systolic blood pressure (161.3 vs. 155.5 mm Hg, $P=0.05$) and diastolic blood

pressure (91.9 vs. 88.5 mm Hg, $P=0.02$), lower HDL cholesterol (1.5 vs. 1.6 mmol/l, $P=0.02$), more metabolic risk factors (2.1 vs. 1.6, $P<0.001$) and a higher prevalence of type 2 diabetes (5 vs. 0 %, $P=0.02$) at baseline than the participants.

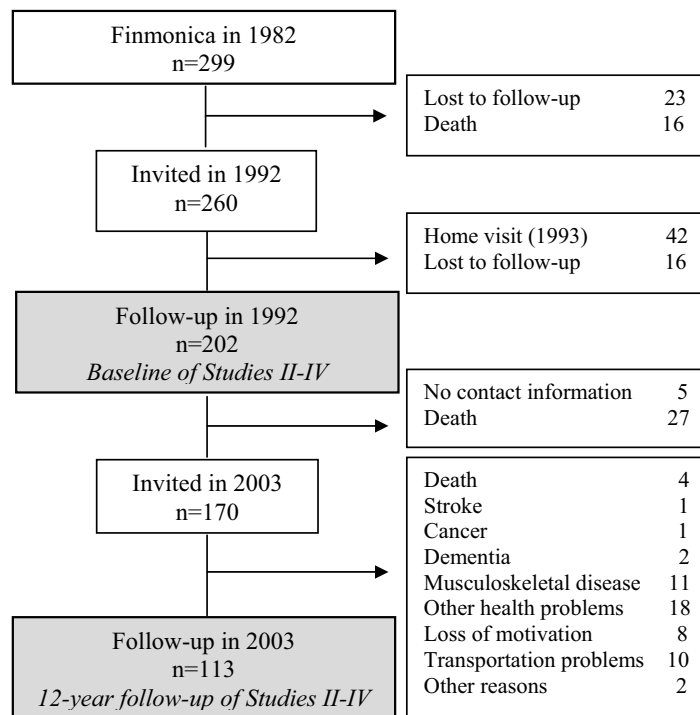


Figure 5. Formation of the cohort of the 12-year follow-up study (Studies II-IV)

EXAMINATION PROTOCOL

Study I

Examinations were carried out over three days, about seven days apart. The examination protocol consisted of a wide variety of examinations including anthropometry, biochemistry, measurement of blood pressure, endothelial function and cardiorespiratory fitness, carotid ultrasound, muscle and adipose tissue biopsies, assessment of cognitive function, depression, functional capacity and nutrition, and questionnaires on physical activity and background information. The invitation letter consisted general information about the study, instructions for laboratory measurements and a questionnaire on background information. For those who did not respond to the invitation letter, a phone call was made to determine the reason for non-participation.

The study visits and the measurements used in the Study I are presented here. At the first visit, the subjects gave blood samples for laboratory determinations. Before these measurements they were instructed to fast 12 hours and to abstain from drinking alcohol for three days, from smoking for 12 hours and from hard physical activity for a day. At the same visit anthropometry and blood pressure were measured and the subjects returned the self-administered questionnaire of background information. At the second visit, the returned questionnaire was checked and completed. At the third visit, a maximal cycle ergometer exercise test was performed. After these three visits, a 2-hour oral glucose tolerance test (OGTT) was performed to those who met specific criteria (see 4.3).

Studies II-IV

Baseline visits

Examinations were carried out over four days, at least eight days apart. The examination protocol consisted of a wide variety of examinations including anthropometry, biochemistry, measurement of blood pressure and bone mineral density, carotid ultrasound, assessment of cognitive function and functional capacity, and questionnaires on physical activity, nutrition, symptoms of depression and background information.

The study visits and the measurements used in the Studies II-IV are as follows. At the first visit, the women brought the completed questionnaire on background information, which was mailed before and a study nurse checked the questionnaire at that time. At the second visit, the women gave blood samples for laboratory determinations. Before these measurements the women were instructed to fast 12 hours and to abstain from drinking alcohol and using analgesics (except paracetamol) for a week. At the same visit, the questionnaire on physical activity was given to complete at home. At the third visit, a trained nurse measured carotid IMT, anthropometry and blood pressure and physical activity questionnaire was received.

12-year follow-up visits

Examinations were carried out over two days, at least eight days apart. The examination protocol consisted of a wide variety of examinations including anthropometry, biochemistry, measurement of blood pressure, carotid ultrasound, assessment of cognitive function and functional capacity, and questionnaires on depression, nutrition, physical activity and background information. Invitation letter consisted general information of the study. Among those who did not response an invitation letter, a phone call was made to determine the reason for non-participation.

At the first visit, the women gave blood samples for laboratory determinations. Before these measurements the women were instructed to fast 12 hours and to abstain from drinking alcohol using analgesics (except paracetamol) for a week. At the same visit, carotid artery ultrasonography was performed. A self-administered questionnaire of background information was given to complete at home. At the second visit antropometry and blood pressure were measured. A nurse received and checked the self-administered questionnaire and interviewed their physical activity during the last month.

4.2 Assessment of body composition

Anthropometric measurements were assessed based on the MONICA protocol (252) with the subject in light indoor clothing without shoes. Body height (accuracy 0.1 cm) was measured using a metal scaled height meter. Body weight (accuracy 0.1 kg) was

measured with a digital scale. Body mass index was calculated dividing body weight in kilograms by the square of body height in meters. Waist circumference (accuracy 0.5 cm) was measured on bare skin, mid-distance between the bottom of the rib cage and the top of the iliac crest. Hip circumference (accuracy 0.5 cm) was measured at the level of the trochanter major. Subjects stood with their feet 12 cm apart with their weight equally distributed on each leg. The mean of two measurements of the circumferences were used in the analyses. The waist-to-hip ratio was calculated as the ratio of the circumference of the waist to the hip.

In the 84 participants at follow-up visit in 2003 (Studies II-IV), intraclass correlation between the mean of two measurements of two measurers at the same study visit for body height was 0.999 ($P < 0.0001$), waist circumference 0.995 ($P < 0.0001$), and hip circumference 0.981 ($P < 0.0001$). Coefficients of variation were 0.7%, 0.7% and 0.5%, respectively.

4.3 Assessment of glucose homeostasis

Venous blood samples were taken without stasis into glass tubes in the morning after a 12 hour fast by 10 o'clock and the samples were analyzed daily. Hexokinase method (Glucose, Thermo Clinical Labsystems Oy, Finland) was used for fasting plasma glucose analyses in Study I and fasting blood glucose analyses in Studies II-IV. In Study I, a 2-hour OGTT with a 75 g glucose load was carried out in the morning after a 12-hour fast for individuals with no previously diagnosed diabetes. The blood samples were taken at fasting state, and after 30, 60 and 120 minutes of the glucose load. The maximum deviation from those time point allowed was ± 3 minutes.

Based on WHO criteria (18), the subjects were classified as having normal glucose tolerance if the fasting plasma glucose was < 6.1 mmol/l and 2-hour glucose was < 7.8 mmol/l, IFG if the fasting plasma glucose was between 6.1 and 6.9 mmol/l and 2-hour glucose was < 7.8 mmol/l, IGT if the fasting plasma glucose was < 7.0 mmol/l and 2-hour glucose was between 7.8 and 11.1 mmol/l and type 2 diabetes if the fasting plasma glucose was ≥ 7.0 mmol/l or a 2-hour glucose was ≥ 11.1 mmol/l. Impaired glucose regulation (IGR), defined as the presence of IFG or IGT, refers to an intermediate state between normal glucose homeostasis and type 2 diabetes (18). In addition, those

subjects who did not participate in the OGTT were classified as having normal glucose tolerance if the fasting plasma glucose level was <6.1 mmol/l, IFG if the plasma glucose level was between 6.1 and 6.9 mmol/l and diabetes if they reported to have type 2 diabetes diagnosed by a physician or the fasting plasma glucose level was ≥ 7.0 mmol/l.

4.4 Assessment of serum lipids and lipoproteins

Venous blood samples were taken without stasis into glass tubes in the morning after a 12 hour fast by 10 o'clock. Serum total cholesterol (Cholesterol, Thermo Electron Corporation, Finland in Study I; CHOD-PAP, Roche Diagnostics GmbH, Germany in Studies II-IV) and serum triglycerides (Triglycerides, Thermo Electron Corporation, Finland in Study I; GPO-PAP, Thermo Clinical Labsystems Oy, Finland in Studies II-IV) were analyzed by enzymatic photometric methods. Serum HDL cholesterol was analyzed using a direct enzymatic photometric method (HDL-Cholesterol, Thermo Electron Corporation, Finland) in Study I, and using an enzymatic photometric method (CHOD-PAP, Roche Diagnostics GmbH, Germany) in a supernatant after precipitation with dextran sulphate and $MgCl_2$ in Studies II-IV. Serum LDL cholesterol was calculated according to the Friedewald formula (253) in Studies II-IV and analyzed by a direct enzymatic photometric method (LDL-Cholesterol, Thermo Electron Corporation, Finland) in Study I. KONE Pro clinical chemistry analyzer (Studies II-IV) and KONELAB 20XTi (Study I) were used for analyses. In Study I, the samples were analyzed daily. In Study II-IV, the samples were stored in $2-8^{\circ}C$ and analyzed once a week at baseline and the 12-year follow-up, except for triglycerides in the 12-year follow-up, which were analyzed daily.

4.5 Assessment of low-grade inflammation

In Study II, serum hsCRP was analyzed by a commercial immunoassay (IMMULITE 2000 High-Sensitivity CRP, Diagnostic Products Corp., Los Angeles, CA, USA) using the IMMULITE 2000 Analyzer (Diagnostic Products Corp.). In the 103 participants, intraclass correlations between two hsCRP assays during the same study visit were 0.999 and 0.998 ($P < 0.0001$ both) and coefficients of variation were 2.8% and 3.4% at baseline and after follow-up in 2003, respectively. The within and between assay

variations of the hsCRP-method were at a low level (1.6 mg/l) 3.5 and 9.5% and at a medium level (4.7 mg/l) 3.9 and 6.2%. Serum samples for hsCRP were taken after 12 hour fast at baseline and 12-year follow-up and were stored at -80°C until analysis in 2005. To minimize confounding due to acute infections or other diseases that could increase hsCRP concentrations, four women with hsCRP >10.0 mg/l at baseline were excluded from analyses.

4.6 Assessment of blood pressure

Blood pressure in the right arm was recorded in a sitting position after a five minute rest using a mercury sphygmomanometer. The first appearance of the sounds (Korotkoff's 1st phase) was recorded as the systolic blood pressure and the disappearance of the sounds (Korotkoff's 5th phase) was recorded as the diastolic blood pressure. Two independent consecutive measurements of systolic and diastolic blood pressure were taken, and the mean of the measurements was used.

4.7 Assessment of cardiorespiratory fitness

In Study I, cardiorespiratory fitness was assessed during a maximal symptom-limited exercise test to exhaustion on an electrically-braked cycle ergometer (Ergoline, Bitz, Germany). From the final analyses, 59 from 1410 individuals were excluded. Five individuals were excluded due to measurement error in respiratory gases, 7 individuals with submaximal and 40 individuals with indirect testing. Seven individuals were not tested due to musculoskeletal or cardiac problems. Furthermore, because 4 individuals with type 1 diabetes were excluded from present analyses, the final study population was 1347 men and women with complete data on VO_{2max} . For safety reasons, and to obtain reliable information about exercise test variables, the tests were supervised by an experienced physician with the assistance of an experienced nurse. The test was performed using a standardized test protocol with a warm-up of 3 minutes at 20 W and a 20 W-increase in the workload per minute. Oxygen consumption was measured directly by the breath-by-breath method using the VMax respiratory gas analyzer (Sensor Medics, Yorba Linda, CA). VO_{2max} was defined as the mean of the three highest values of the average oxygen consumption measured consecutively over 20 second intervals

and expressed as milliliters of oxygen per kilogram of body weight per minute. A total of 98% of the subjects achieved the respiratory exchange ratio of ≥ 1.1 . Electrocardiography was recorded before, during and after the exercise test using Cardiosoft software (GE Medical Systems, Freiburg, Germany). Reasons for stopping the exercise test were recorded for all tested individuals. For those in the present analyses, the reasons were leg fatigue (n=694), breathlessness (n=508), exhaustion (n=41), joint pain (n=29), dyspnea (n=29), pain in leg muscle (n=20), arrhythmias (n=9), ST depression (n=8), a marked increase in systolic blood pressure (n=5), dizziness (n=1), signs of cardiac insufficiency (n=1), difficulties in co-operation (n=1), and lack of subject motivation (n=1).

4.8 Definition of metabolic syndrome

The metabolic syndrome was defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP) criteria (20), based on the presence of elevated blood pressure ($\geq 130/85$ mm Hg or drug treatment), increased fasting plasma (Study I) or blood (Studies II and IV) glucose (≥ 6.1 mmol/l), low HDL cholesterol (< 1.03 mmol/l in men and < 1.29 mmol/l in women), high triglycerides (≥ 1.7 mmol/l) and abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women). The existence of at least three risk factors was defined as the metabolic syndrome.

4.9 Assessment of carotid atherosclerosis

Carotid artery atherosclerosis was assessed noninvasively by ultrasonography (232,254) (Studies III-IV). Carotid IMT was used as a measure of carotid atherosclerosis in the present thesis. Certified sonographers measured carotid IMT while the subject was in the supine position, with the head turned 45° from the side being scanned. An ultrasound device with a high-resolution 10-MHz transducer was used, following a standardized and pretested protocol. In each examination, the sonographer used three different standardized scanning angles including lateral (45° from vertical axis), anterior ($20-30^\circ$) and posterior ($50-60^\circ$) projection. The scannings were recorded on super VHS videotape. The same sonographer read the scannings during both study years.

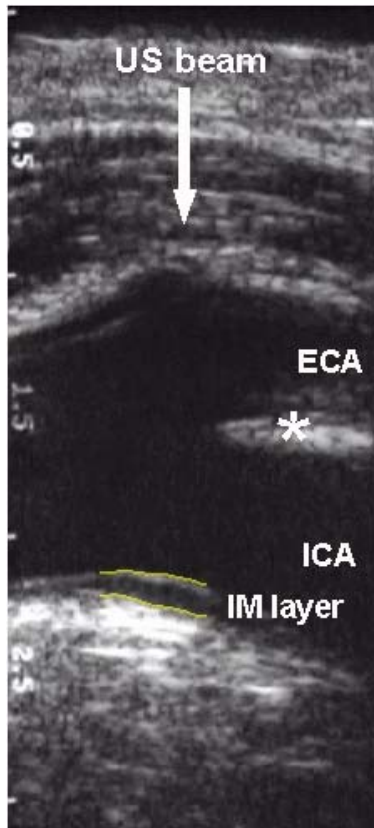


Figure 6. Measurement of intima-media (IM) thickness by ultrasound (US).
 ECA=external carotid artery
 ICA=internal carotid artery

The sonographer measured the IMT of the far wall of the right carotid artery. The IMT measurement extended to the longest wall region where the lumen-intima and media-adventitia boundaries could be clearly identified by an automated edge-detection program based on the active contour (255) (Figure 6). The mean carotid IMT of the traced region was used for the statistical analyses. We used IMT of the carotid bifurcation as the indicator of the progression of atherosclerosis because arterial bifurcations are prone to local plaque formation (199). Although we did not have data on the variability of carotid IMT measurements available for this particular cohort of elderly women, in another our study (232), using exactly the same methodology in middle-aged men, the mean difference between replicated carotid IMT measurements over six years was 0,0037 mm.

4.10 Other measurements

In Study I, the subjects completed a self-administered questionnaire on diseases diagnosed or treated by a doctor (no vs. yes), present medications, alcohol consumption (doses/previous week) and smoking status (never/former/current). CHD was considered present if the subject reported to have prevalent angina pectoris, myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal coronary artery angioplasty. CVD was considered present if the subject reported CHD, cerebrovascular

stroke, transient ischemic attack or lower extremity peripheral artery disease. Type 2 diabetes was defined according to OGTT or self-report (see 4.3).

In Studies II-IV, the women completed a self-administered questionnaire on diseases diagnosed by a doctor in previous year, family history of diseases, medications in previous week, smoking (no vs. yes) and alcohol consumption (doses/previous week). A subject was considered to have prevalent CHD if she reported to have angina pectoris or myocardial infarction. A subject was considered to have prevalent CVD if she reported CHD or cardiac insufficiency. Physical activity was assessed by an interview questionnaire. The weekly physical activity time (minutes per week) spent on the most common physical activities during the last month was estimated. The Framingham risk score (Study IV) was calculated by summing up risk points for age, LDL and HDL cholesterol, systolic and diastolic blood pressure, prevalent diabetes, and current smoking (256).

4.11 Statistical analyses

All statistical analyses were performed using SPSS for Windows, Release 11.5 and $P \leq 0.05$ was considered significant. For all analyses, the variables for adjustment were chosen based on their known association with the dependent and independent variables. In additional analyses, by adding individual metabolic risk factors or change in individual risk factors separately into the models we wanted to show which of the individual risk factors most strongly explained the association in question. Similarly, the change in physical activity was used as an additional adjustment in Studies III and IV. Differences between groups were analyzed using independent-samples t-test or analysis of variance for continuous variables and χ^2 -test for categorical variables as appropriate. To test changes between study years (Studies II and IV) the paired-samples t-test for continuous variables and the McNemar test for categorical variables were used. Appropriate transformation was used to normalize the distribution when required. When the variance and normality assumptions were not met, the Mann-Whitney U test or Wilcoxon-test was used. Data are presented as means \pm standard deviation (SD) or percentages.

In Study I, VO_{2max} was used as a continuous variable and as a categorical variable divided into thirds separately in men and women. The heterogeneity of the means of the components of the metabolic syndrome between the thirds of VO_{2max} was tested using analysis of covariance. The association of VO_{2max} with the risk of having IGR or the metabolic syndrome was estimated using logistic regression analysis, expressed as odds ratios (OR) and 95% confidence intervals (CI). As a complementary approach for assessing the associations of cardiorespiratory fitness with the metabolic syndrome, factor analysis was carried out using the core components of or the factors related to the metabolic syndrome and VO_{2max} . Principal component analysis was used for the extraction of the initial factors, which were then subjected to promax rotation to generate correlated factors. Only factors with eigenvalues >1.0 were retained in the analysis. Factors with an eigenvalue >1 indicate a factor accounting for more total variance than any original standardized variable.

In Study II, the trend in hsCRP concentration across groups of women with 0, 1, 2 or 3-5 metabolic risk factors at baseline was analyzed using the test for linearity. Logistic regression analysis was used to calculate OR for the development of metabolic syndrome in women with hsCRP concentration increases as compared with those with a hsCRP concentration decrease.

In Study III, waist and hip circumferences were categorized into thirds and body mass index according to generally used clinical cut-off points (<25 , 25-30, and >30) (29). Associations between measurements of body composition were analyzed with Pearson's correlation coefficients. The heterogeneity of the means of the 12-year increase in carotid IMT between the groups of baseline waist and hip circumferences, waist-to-hip ratio, and body mass index was tested using analysis of covariance, and expressed as means and 95% CI. For the analyses of interaction between waist and hip circumferences on the progression of carotid IMT, waist and hip circumferences were dichotomized at mean (83 cm for waist and 98 cm for hip) because of the limited number of subjects.

In Study IV, analysis of covariance was used to compare the change in mean carotid IMT in women with or without incident metabolic syndrome and also in women with no increase, an increase of one or an increase at least two metabolic risk factors during the

follow-up. Linear regression analysis was used to assess the independent association of individual metabolic risk factors at baseline with the change in carotid IMT.

5. RESULTS

5.1 Characteristics of the study populations

5.1.1 Study I

In the baseline of the DR's EXTRA Study, men had higher waist circumferences, VO_{2max} , triglycerides, diastolic blood pressure, alcohol consumption, lower HDL cholesterol, worse glucose tolerance and higher prevalence of smoking and CVD than women (Table 7). Women had a larger hip circumference and higher systolic blood pressure and total cholesterol.

Table 7. Basic characteristics for men and women and differences between sex (Study I)

	Men (671)	Women (676)	P for difference
Age, year	66.3 (5.4)	66.5 (5.3)	0.402
Height, cm	173.6 (6.1)	160.0 (5.8)	<0.001
Weight, kg	83.6 (13.6)	70.5 (12.9)	<0.001
Body mass index	27.7 (4.0)	27.5 (4.9)	0.544
Waist circumference, cm	98.9 (11.1)	88.6 (13.0)	<0.001
Hip circumference, cm	99.8 (8.0)	101.8 (9.7)	<0.001
VO_{2max} , ml·kg ⁻¹ ·min ⁻¹	26.4 (6.3)	20.9 (4.9)	<0.001
Alcohol consumption, doses/week	6.3 (8.1)	2.3 (4.3)	<0.001
Smoking, never/ past/ current, %	35 / 51 / 15	74 / 19 / 7	<0.001
Fasting plasma glucose, mmol/l	6.0 (1.0)	5.6 (0.8)	<0.001
Serum total cholesterol, mmol/l	4.9 (0.9)	5.3 (0.9)	<0.001
Serum LDL cholesterol, mmol/l	3.2 (0.8)	3.2 (0.8)	0.113
Serum HDL cholesterol, mmol/l	1.5 (0.4)	1.9 (0.5)	<0.001
Serum triglycerides, mmol/l	1.4 (0.8)	1.3 (0.6)	0.046
Systolic blood pressure, mm Hg	145.5 (18.9)	150.2 (21.1)	<0.001
Diastolic blood pressure, mm Hg	84.3 (9.4)	82.4 (9.1)	<0.001
IFG/ IGT/ type 2 diabetes, %	14 / 12 / 16	7 / 11 / 9	<0.001
Cardiovascular disease, %	27	18	<0.001
Lipid lowering medication, %	35	34	0.672
Antihypertensive medication, %	41	42	0.785
Metabolic risk factors, no.	1.9 (1.1)	1.8 (1.2)	0.284
Metabolic syndrome, %	27	25	0.312

Data are presented as means (\pm SD) or percentages (%). P-values from independent-samples t-test, Mann-Whitney test or χ^2 -test as appropriate. For glucose and triglycerides P-values were derived from log-transformed values. Body mass index was calculated as weight (kg) divided by height (m) squared. IFG; impaired fasting glucose, IGT; impaired glucose tolerance.

5.1.2 Studies II-IV

Basic characteristics of all 113 women who participated both in 1992 and after 12 years follow-up in 2003 are presented in Table 8. Whereas waist and hip circumference, body mass index, blood glucose, metabolic risk factors and the mean carotid IMT increased, LDL and HDL cholesterol and systolic and diastolic blood pressure decreased during 12 years. Simultaneously, use of lipid lowering and antihypertensive medication increased significantly as did the prevalence of metabolic syndrome. The amount of physical activity also increased. None of the 113 participants had diabetes diagnosed by a doctor at baseline, but 13 developed type 2 diabetes during 12 years.

Table 8. Basic characteristics in 1992 and 2003 of all 113 women who participated in both study years (Studies II-IV). P-value refers to the change during 12 years

	Baseline in 1992	Follow-up in 2003	P for difference
Age, year	63.9 (3.1)	75.3 (3.0)	<0.001
Height, cm	157.6 (5.3)	155.5 (5.5)	<0.001
Weight, kg	67.9 (10.7)	68.4 (12.1)	0.354
Body mass index	27.4 (4.4)	28.1 (4.9)	0.002
Waist circumference, cm	83.4 (10.6)	91.8 (11.6)	<0.001
Hip circumference, cm	98.8 (10.3)	102.9 (8.7)	<0.001
Physical activity, min/week	196.6 (109.9)	283.1 (142.2)	<0.001
Alcohol consumption, doses/week	0.6 (1.3)	0.7 (1.6)	0.685
Smoking, current, %	7	4	0.219
Fasting blood glucose, mmol/l	4.8 (0.6)	5.3 (1.0)	<0.001
Serum total cholesterol, mmol/l	6.2 (1.0)	5.3 (0.9)	<0.001
Serum LDL cholesterol, mmol/l	4.1 (0.9)	3.5 (0.8)	<0.001
Serum HDL cholesterol, mmol/l	1.6 (0.3)	1.3 (0.3)	<0.001
Serum triglycerides, mmol/l	1.2 (0.4)	1.2 (0.5)	0.399
High-sensitivity C-reactive protein, mg/l*	2.7 (7.2)	2.4 (3.4)	0.643
Systolic blood pressure, mm Hg	155.5 (21.9)	141.7 (19.5)	<0.001
Diastolic blood pressure, mm Hg	88.5 (10.1)	71.9 (9.6)	<0.001
Cardiovascular disease, %	17	30	0.001
Lipid lowering medication, %	6	34	<0.001
Antihypertensive medication, %	24	55	<0.001
Metabolic risk factors	1.5 (0.9)	2.4 (1.1)	<0.001
Metabolic syndrome, %	13	48	<0.001
Carotid intima-media thickness, mm**	1.05 (0.31)	1.26 (0.38)	<0.001

Data are presented as means (\pm SD) or percentages (%). P-values from paired-samples t-test, Wilcoxon-test or McNemar test as appropriate. For C-reactive protein P-value was derived from log-transformed value. Body mass index was calculated as weight (kg) divided by height (m) squared. *n=107, **n=103

5.2 Cardiorespiratory fitness and the metabolic syndrome (Study I)

Men and women with the metabolic syndrome had, by definition, a high risk factor profile (Table 9) and were also more likely to use antihypertensive and lipid lowering medication. Also, men with the syndrome were more likely to smoke than those without the syndrome.

Table 9. Basic characteristics according to metabolic syndrome status for men and women

	MEN			WOMEN		
	No metabolic syndrome	Metabolic syndrome	P for difference	No metabolic syndrome	Metabolic syndrome	P for difference
N	487	184		507	169	
Age, year	66.4 (5.4)	65.9 (5.6)	0.272	66.6 (5.3)	66.4 (5.3)	0.607
Height, cm	173.5 (6.0)	173.8 (6.2)	0.582	160.0 (6.0)	160.0 (5.4)	0.985
Weight, kg	79.7 (10.9)	93.8 (14.7)	<0.001	66.6 (10.0)	82.2 (13.6)	<0.001
Body mass index	26.4 (3.0)	31.0 (4.3)	<0.001	26.0 (3.8)	32.1 (4.9)	<0.001
Waist circumference, cm	95.3 (8.9)	108.6 (10.7)	<0.001	84.3 (10.4)	101.6 (11.1)	<0.001
Hip circumference, cm	97.7 (6.5)	105.4 (8.8)	<0.001	99.0 (7.9)	110.2 (10.0)	<0.001
VO _{2max} , ml·kg ⁻¹ ·min ⁻¹	27.8 (6.1)	22.7 (5.4)	<0.001	21.8 (4.9)	18.1 (3.6)	<0.001
Alcohol consumption, doses /week	6.3 (7.9)	6.5 (8.4)	0.510	2.4 (4.7)	1.8 (2.9)	0.398
Smoking, never/ past/ current, %	39 / 49 / 12	23 / 56 / 21	<0.001	74 / 19 / 7	73 / 19 / 8	0.778
Fasting plasma glucose, mmol/l	5.7 (0.6)	6.7 (1.3)	<0.001	5.4 (0.5)	6.3 (1.2)	<0.001
Serum total cholesterol, mmol/l	4.9 (0.9)	4.8 (1.0)	0.332	5.3 (0.9)	5.1 (1.0)	0.037
Serum LDL cholesterol, mmol/l	3.2 (0.8)	3.2 (0.9)	0.991	3.2 (0.8)	3.3 (0.9)	0.664
Serum HDL cholesterol, mmol/l	1.6 (0.4)	1.2 (0.3)	<0.001	2.0 (0.5)	1.5 (0.4)	<0.001
Serum triglycerides, mmol/l	1.2 (0.5)	2.0 (1.0)	<0.001	1.1 (0.4)	1.9 (0.8)	<0.001
Systolic blood pressure, mm Hg	144.7 (19.2)	147.5 (18.0)	0.090	148.9 (21.0)	153.9 (20.9)	0.007
Diastolic blood pressure, mm Hg	83.9 (9.2)	85.1 (9.8)	0.166	81.6 (8.7)	84.6 (9.8)	<0.001
IFG/ IGT/ type 2 diabetes, %	12 / 9 / 8	20 / 16 / 38	<0.001	4 / 9 / 3	15 / 17 / 28	<0.001
Cardiovascular disease, %	25	32	0.052	17	21	0.328
Lipid lowering medication, %	33	41	0.046	31	44	0.003
Antihypertensive medication, %	35	57	<0.001	33	69	<0.001
Metabolic risk factors, no.	1.3 (0.6)	3.5 (0.7)	<0.001	1.3 (0.7)	3.5 (0.7)	<0.001

Data are presented as means (\pm SD) or percentages (%). P-values for difference between groups are from independent-samples t-test, Mann-Whitney or χ^2 -test as appropriate. For glucose and triglycerides P-values were derived from log-transformed values. Body mass index was calculated as weight (kg) divided by height (m) squared. IFG; impaired fasting glucose, IGT; impaired glucose tolerance.

The prevalence of metabolic syndrome (Figure 7) and IGR (Figure 8) were higher in men and women in the two lowest thirds of $\text{VO}_{2\text{max}}$ than in those in the highest third.

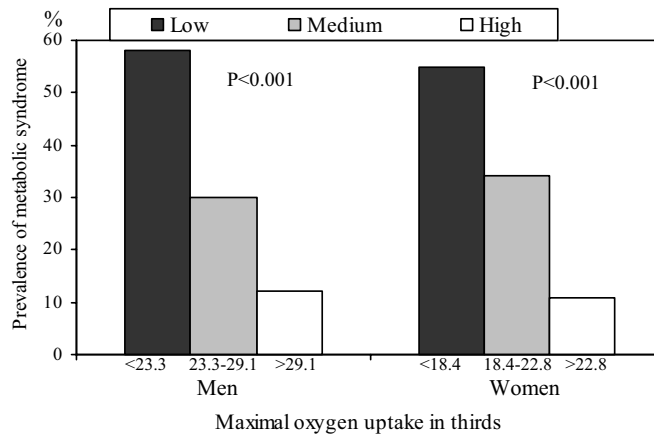


Figure 7. Prevalence (%) of metabolic syndrome across sex-specific $\text{VO}_{2\text{max}}$ thirds ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). P-value from χ^2 test.

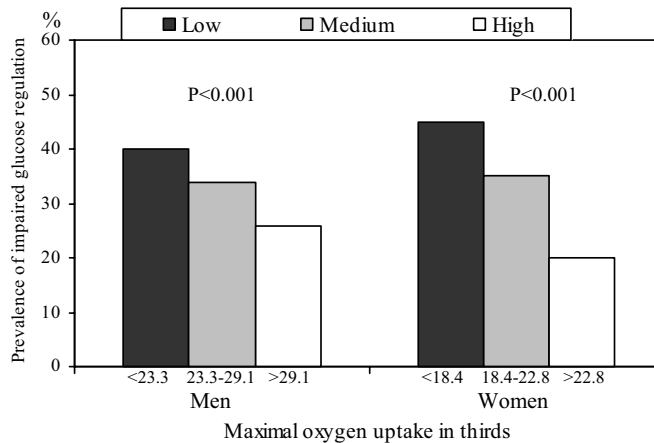


Figure 8. Prevalence (%) of impaired glucose regulation in non-diabetic men and women across sex-specific $\text{VO}_{2\text{max}}$ thirds ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). P-value from χ^2 test.

As a continuous variable, a decrease of 1 SD in VO_{2max} in men ($6.3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and women ($4.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was associated with a 3.2-fold (95% CI 2.45-4.10, $P<0.001$) and 3.1-fold (2.39-4.00, $P<0.001$) increase in the risk of having the metabolic syndrome after adjustment for age, smoking, alcohol consumption and CVD. Further adjustment for waist circumference [OR (95% CI) in men: 1.5 (1.09-2.03), $P=0.012$; women: 1.4 (1.00-1.90), $P=0.053$] and body mass index [men: 1.8 (1.31-2.36), $P<0.001$; women: 1.5 (1.12-2.07), $P=0.008$] weakened the association. Of other metabolic risk factors, the next strongest confounder after waist circumference was HDL cholesterol [2.4 (1.84-3.16), $P<0.001$] and triglycerides [2.6 (1.95-3.45), $P<0.001$] in men and glucose [2.7 (1.99-3.61), $P<0.001$] and triglycerides [2.7 (1.96-3.69), $P<0.001$] in women. When VO_{2max} was expressed as $\text{L}\cdot\text{min}^{-1}$, a 1-SD decrease in VO_{2max} was associated with a 1.8-fold (1.37-2.31, $P<0.001$) increase in the risk of having metabolic syndrome in men and a 1.4-fold (1.10-1.87, $P=0.007$) increase in women adjusted for age, smoking, alcohol consumption, CVD and body weight.

VO_{2max} in sex-specific thirds was associated with all of the components of the metabolic syndrome (Table 10).

Table 10. Components of metabolic syndrome according to sex-specific thirds of maximal oxygen uptake

	Thirds in men ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)				Thirds in women ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)			
	low <23.3	medium 23.3-29.1	high >29.1	P	low <18.4	medium 18.4-22.8	high >22.8	P
Waist circumference, cm	107.2	98.7	90.9	<0.001	96.9	89.1	79.8	<0.001
Body mass index	30.5	27.4	25.2	<0.001	30.7	27.6	24.3	<0.001
Fasting glucose, mmol/l	6.3	5.9	5.8	<0.001	5.9	5.6	5.4	<0.001
Triglycerides, mmol/l	1.7	1.4	1.2	<0.001	1.5	1.4	1.1	<0.001
HDL cholesterol, mmol/l	1.4	1.5	1.7	<0.001	1.7	1.8	2.0	<0.001
Systolic blood pressure, mm Hg	148.0	145.8	142.7	0.027	153.0	151.0	146.4	0.005
Diastolic blood pressure, mm Hg	85.6	84.3	82.8	0.015	83.6	83.2	80.3	<0.001

Data are presented as means. P for difference between groups from analysis of covariance. For glucose and triglycerides P-values were derived from log-transformed values. Body mass index was calculated as weight (kg) divided by height (m) squared.

In both men and women, VO_{2max} had a strong, inverse and graded association with the risk of having the metabolic syndrome (Figure 9, $P < 0.001$ for linear trend). Men and women in the lowest third of VO_{2max} had a 10.2 and 10.8-fold higher risk and those in the middle third had a 2.9 and 4.7-fold higher risk of the metabolic syndrome than those in the highest third, adjusted for age, smoking, alcohol consumption and CVD.

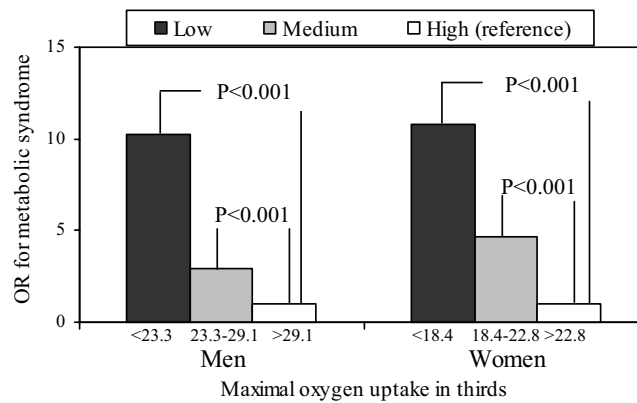


Figure 9. Odds of having metabolic syndrome in sex-specific thirds of VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$) adjusted for age, alcohol consumption and CVD. P for difference between groups.

The prevalence of the metabolic syndrome in men <61, 61-65, 66-70, and >70 years of age was 31%, 27%, 27%, and 25%, respectively. In women, these rates were 24%, 29%, 23%, and 23%. The association between VO_{2max} and metabolic syndrome seemed to be stronger in men >70 years of age than in other men (Table 11).

Table 11. The risk of the metabolic syndrome for a 1-SD decrease in VO_{2max} ($6.3 ml \cdot kg^{-1} \cdot min^{-1}$ in men and $4.9 ml \cdot kg^{-1} \cdot min^{-1}$ in women) in 5-year age categories.

Age	MEN			WOMEN		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
<61 year	3.0	1.81-5.13	<0.001	4.5	2.31-8.70	<0.001
61-65 year	2.6	1.60-4.08	<0.001	2.4	1.61-3.68	<0.001
66-70 year	3.0	1.90-4.90	<0.001	2.9	1.73-4.95	<0.001
>70 year	6.3	3.07-13.16	<0.001	3.8	2.14-6.85	<0.001

From logistic regression analysis. Adjusted for smoking, alcohol and CVD.

In men and women without diabetes, there was an inverse association between VO_{2max} and the risk of having IGR. A 1-standard deviation decrease in VO_{2max} was associated with a 1.4-fold (95% CI 1.15-1.78, $P=0.001$) increase in the risk of having IGR in men and with a 1.6-fold (1.25-2.08, $P<0.001$) increase in the risk in women, adjusted for age, smoking, alcohol consumption and CVD. Men and women in the lowest third of VO_{2max} had a 2.4-fold increased risk of IGR compared with the highest third of VO_{2max} (Figure 10, $P=0.001$ in men and $P=0.002$ in women for trend across the thirds).

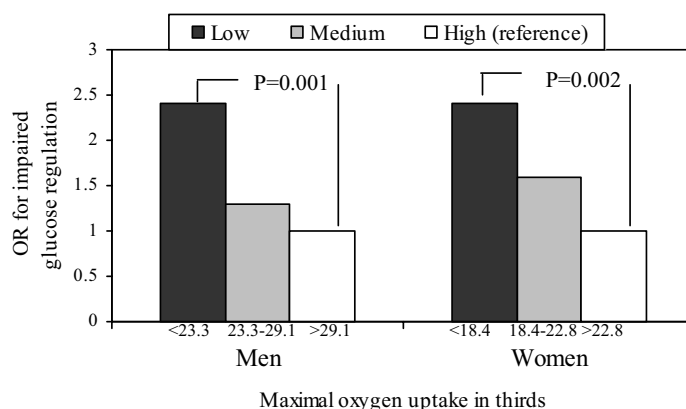


Figure 10. Odds of having impaired glucose regulation in sex-specific thirds of VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$), adjusted for age, alcohol consumption and CVD. P for difference between groups.

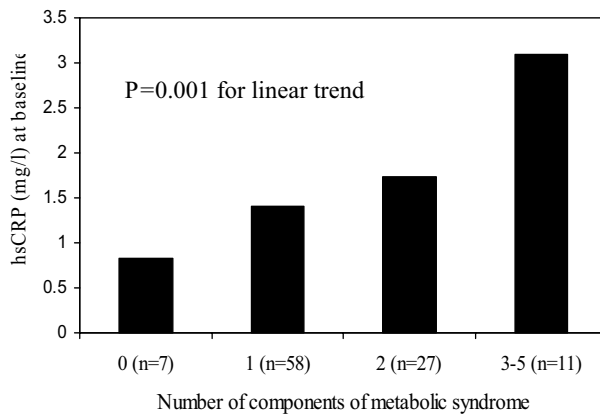
In the factor analysis containing core components of the metabolic syndrome, cardiorespiratory fitness, smoking and alcohol consumption, four factors with eigenvalues >1 were extracted and rotated using the promax method. These factors explained 62% of the total variance in men and women. Factor loadings of the variables with each factor are shown in Table 12. The factor explaining the greatest proportion of the total variance (29% in men and 30% in women) had heavy loadings on the core components of the metabolic syndrome and VO_{2max} . The second strongest factor had heavy loadings on triglycerides, LDL cholesterol and HDL cholesterol in both men and women.

Table 12. Loadings of 12 variables related to metabolic syndrome on the four factors extracted and rotated (promax) with factor analysis and the variance explained by each factor

Factor	MEN				WOMEN			
	1	2	3	4	1	2	3	4
Proportion of variance, %	29	12	11	10	30	12	10	10
Waist girth	0.79	0.19	0.19	0.003	0.93	-0.07	-0.10	0.11
Body mass index	0.78	0.20	0.14	0.04	0.93	-0.12	-0.04	0.10
Fasting plasma glucose	0.75	-0.17	0.03	0.23	0.64	0.01	0.18	0.05
2-hour glucose load	0.68	-0.09	-0.09	0.40	0.57	0.07	0.38	-0.03
Serum triglycerides	0.25	0.67	-0.02	-0.04	0.28	0.58	-0.08	-0.19
Serum HDL cholesterol	-0.28	-0.50	0.39	0.23	-0.30	-0.39	0.22	0.33
Serum LDL cholesterol	-0.40	0.79	0.18	0.28	-0.31	0.91	0.15	0.21
Systolic blood pressure	0.28	0.07	-0.05	0.84	0.26	0.15	0.65	0.21
Maximal oxygen uptake	-0.68	0.05	0.05	0.07	-0.70	0.03	-0.11	0.02
Alcohol consumption	0.09	0.04	0.85	0.03	0.14	0.06	-0.10	0.88
Smoking	0.17	-0.05	0.59	-0.44	0.04	0.09	-0.71	0.41

5.3 High-sensitivity C-reactive protein and the metabolic syndrome (Study II)

At baseline, the hsCRP concentrations increased significantly with increasing number of components of the metabolic syndrome (Figure 11). The mean hsCRP was twice as high in women with the metabolic syndrome as in those without it (3.1 vs. 1.5 mg/l).

**Figure 11.** High-sensitivity C-reactive protein (hsCRP) concentrations in women with 0, 1, 2 or ≥ 3 components of the metabolic syndrome at baseline.

Whereas hsCRP concentration increased markedly in 37 women who developed the metabolic syndrome during 12 years, it did not change in those 55 women who remained free of it or in those 11 with the metabolic syndrome already at baseline (Figure 12).

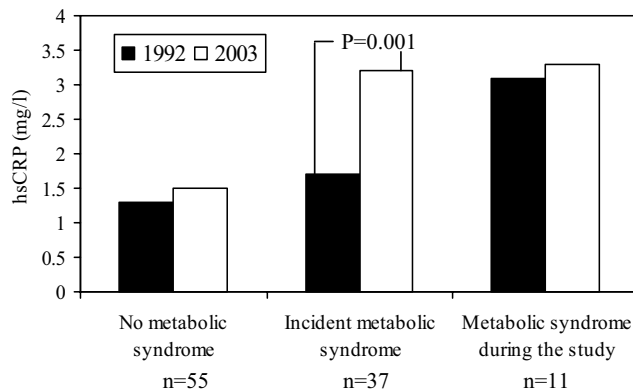


Figure 12. High-sensitivity C-reactive protein (hsCRP) at baseline (1992) and after 12-year follow-up (2003) in women with no metabolic syndrome during the study, incident metabolic syndrome or metabolic syndrome already at the baseline and after the 12 years.

Women with incident metabolic syndrome had higher waist circumference (87.8 vs. 77.4 cm), body weight (71.2 vs. 62.7 kg), and body mass index (28.8 vs. 25.4) at baseline than those who did not develop the metabolic syndrome ($P < 0.001$ all).

An increment of 1 mg/l in hsCRP concentration during 12 years was associated with a 37% ($P = 0.007$) increase in the risk of developing the metabolic syndrome after adjustment for age, smoking, the use of drugs for hypercholesterolemia, hormone replacement therapy, and prevalent CVD. A 1 mg/l increment in hsCRP was associated with a 26% ($P = 0.047$) increase in the risk after further adjustment for change in waist circumference and with a 31% ($P = 0.018$) increase after additional adjustment for change in triglycerides. Adjustment for changes in other components of metabolic syndrome had no effect on the association.

In women for whom hsCRP decreased, increased by 0-1 mg/l, or increased by >1 mg/l in 12 years, the metabolic syndrome developed in 22, 50, and 60%, respectively, during 12 years (P=0.005 for difference). Compared with women for whom hsCRP decreased, those with an increment in hsCRP of 0-1 mg/l had a 4.5-fold higher (P=0.011) and those with hsCRP increase of >1 mg/l had a 6.2-fold higher (P=0.002) risk of developing the metabolic syndrome after adjustment for baseline age, smoking, the use of drugs for hypercholesterolemia, hormone replacement therapy, and prevalent CVD (Table 13, Model 1). The association of hsCRP change with the risk of developing the metabolic syndrome was weakened after further adjustment for change in waist circumference or triglycerides, but changes in other components of the metabolic syndrome did not materially affect the association (Table 13, Models 2-6).

Table 13. Odd ratios (95% CI) for developing the metabolic syndrome during 12 years of follow-up in women without the metabolic syndrome at baseline stratified according to changes in high-sensitivity C-reactive protein (hsCRP) levels during 12 years of follow-up

hsCRP change	<0 mg/l	0-1 mg/l	>1 mg/l	P for trend
n	41	26	25	
Model 1	1	4.5 (1.4-14.3)	6.2 (1.9-19.9)	0.002
Model 2	1	2.7 (0.8-9.3)	4.4 (1.3-15.0)	0.018
Model 3	1	3.7 (1.1-12.3)	4.7 (1.4-15.6)	0.010
Model 4	1	3.9 (1.2-12.9)	5.8 (1.8-19.0)	0.003
Model 5	1	6.1 (1.6-23.8)	8.2 (2.2-31.5)	0.002
Model 6	1	5.2 (1.6-17.4)	7.5 (2.2-25.6)	0.001

From logistic regression analysis. Adjustments in Models 1-6:

Model 1: age, smoking, drugs for hypercholesterolemia, hormonal therapy, and CVD at baseline

Model 2: variables in Model 1 and change in *waist circumference* during follow-up

Model 3: variables in Model 1 and change in *triglycerides* during follow-up

Model 4: variables in Model 1 and change in *HDL* cholesterol during follow-up

Model 5: variables in Model 1 and change in *blood glucose* during follow-up

Model 6: variables in Model 1 and change in *systolic blood pressure* during follow-up

5.4 Waist and hip circumference and carotid atherosclerosis (Study III)

At baseline, waist circumference (in thirds; <77, 77-86, >86 cm) was directly associated with body weight (58.4, 65.8 and 77.8 kg), body mass index (23.4, 26.6, 31.2), hip circumference (89.3, 98.8 and 108.8 cm), triglycerides (1.0, 1.3 and 1.4 mmol/l) (in all, difference between groups $P<0.001$), and systolic blood pressure (150.5, 152.7 and 163.0 mm Hg, $P=0.04$) and inversely with HDL cholesterol (1.7, 1.6 and 1.5 mmol/l, $P=0.02$). Hip circumference (in thirds; <94, 94-101.5, >101.5 cm) was directly related to body weight (58.6, 66.4 and 77.8 kg), body mass index (23.4, 26.8, 31.4), waist circumference (73.6, 82.2 and 92.5 cm) (in all, difference between groups $P<0.001$), triglycerides (1.0, 1.3 and 1.3 mmol/l, $P=0.04$), hsCRP (0.9, 1.2 and 2.1 mg/l, $P=0.01$) and systolic (144.5, 157.8 and 164.4 mmol/l, $P<0.001$), and diastolic (85.8, 88.8 and 91.5 mm Hg, $P=0.07$) blood pressure and inversely to HDL cholesterol (1.7, 1.5 and 1.6 mmol/l, $P=0.005$).

There was a significant increase in the 12-year carotid IMT progression between the thirds of waist circumference after adjustment for conventional risk factors, including age, smoking, systolic blood pressure, serum LDL and HDL cholesterol, and blood glucose (Table 14). The association was not significant after further adjustment for hip circumference or body mass index (Table 14) or triglycerides (0.110, 0.272 and 0.249 mm, $P=0.11$). Although additional adjustment for hsCRP, family history of CHD and physical activity at baseline and the 12-year change in the amount of physical activity had no effect on the association (data not shown), adjustment for 12-year changes in LDL and HDL cholesterol, blood glucose and hsCRP weakened it slightly (0.093, 0.278 and, 0.260 mm, $P=0.06$).

The progression in carotid IMT over 12 years also increased across the thirds of hip circumference adjusted for conventional risk factors (Table 14). Further adjustment for waist circumference or body mass index had no effect on the association (Table 14). Adjustment for triglycerides, hsCRP, family history of CHD, physical activity at baseline or 12-year changes in LDL and HDL cholesterol, blood glucose, hsCRP and the amount of physical activity did not change the association either (data not shown).

The difference in the 12-year carotid IMT progression among the body mass index groups (<25, 25-30, >30) was significant after adjustment for conventional risk factors

(Table 14), but no longer after further adjustment for waist or hip circumference (Table 14) or triglycerides (0.112, 0.272 and 0.263 mm, P=0.07). Adjustment for hsCRP, family history of CHD, and physical activity at baseline and 12-year change in the amount of physical activity did not affect the association (data not shown), whereas adjustment for 12-year changes in LDL and HDL cholesterol, blood glucose, and hsCRP weakened it slightly (0.107, 0.278 and 0.260 mm, P= 0.07). The association between thirds of the waist-to-hip ratio and carotid IMT progression was not significant (data not shown).

Table 14. Increase in carotid intima-media thickness (IMT) at the 12-year follow-up. Waist and hip circumferences were categorized into thirds and body mass index according to generally used clinical cut-off points

Increase in IMT, mean (95% CI)			
Waist circumference			
<77 cm (n=33)	0.080 (-0.032-0.193) ^a	0.109 (-0.040-0.254) ^b	0.090 (-0.054-0.235) ^d
77-86 cm (n=35)	0.277 (0.170-0.383) ^a	0.281 (0.173-0.389) ^b	0.278 (0.171-0.385) ^d
>86 cm (n=34)	0.279 (0.166-0.391) ^a	0.241 (0.090-0.406) ^b	0.262 (0.113-0.411) ^d
P-value for difference	0.02 ^a	0.15 ^b	0.11 ^d
Hip circumference			
<94 cm (n=34)	0.030 (-0.079-0.140) ^a	0.063 (-0.079-0.205) ^c	0.037 (-0.106-0.180) ^d
94-101.5 cm (n=36)	0.342 (0.240-0.444) ^a	0.345 (0.243-0.448) ^c	0.342 (0.239-0.445) ^d
>101.5 cm (n=32)	0.260 (0.151-0.368) ^a	0.221 (0.068-0.374) ^c	0.251 (0.098-0.405) ^d
P-value for difference	0.001 ^a	0.004 ^c	0.003 ^d
Body mass index			
<25 (n=37)	0.095 (-0.009-0.200) ^a	0.130 (-0.008-0.268) ^c	0.124 (-0.008-0.256) ^b
25 - 30 (n=43)	0.281 (0.185-0.377) ^a	0.279 (0.182-0.375) ^c	0.280 (0.183-0.376) ^b
>30 (n=22)	0.274 (0.140-0.408) ^a	0.220 (0.025-0.414) ^c	0.229 (0.043-0.414) ^b
P-value for difference	0.03 ^a	0.19 ^c	0.16 ^b

From analysis of covariance. Body mass index was calculated as weight divided by height squared.

a Adjusted for age, smoking, systolic blood pressure, LDL and HDL cholesterol, and blood glucose

b Adjusted for model a and hip circumference

c Adjusted for model a and waist circumference

d Adjusted for model a and body mass index

In women with hip circumference ≤ 98 cm, the progression in carotid IMT over 12 years was significantly greater in those with waist circumference >83 cm than in those with a smaller waist circumference after adjustment for conventional risk factors (Figure 13, $P=0.003$ for interaction). Additional adjustment for body mass index, triglycerides, hsCRP, family history of CHD, physical activity at baseline or 12-year changes in LDL and HDL cholesterol, blood glucose, hsCRP and amount of physical activity had no effect on the difference (data not shown). In women with waist circumference >83 cm, there was a significant difference in carotid IMT progression between those with hip circumference >98 cm and those with lower hip circumference (Figure 13). This difference was not affected by additional adjustments. In women with hip circumference >98 cm, there was no significant difference in carotid IMT progression between women with waist circumference higher or lower than 83 cm (Figure 13).

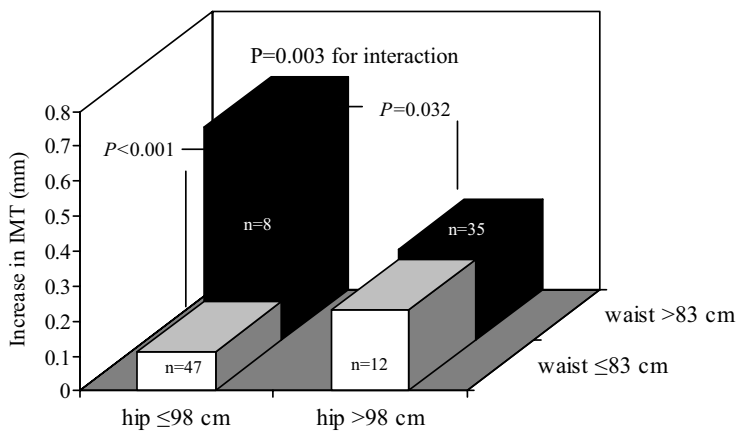


Figure 13. Increase in carotid intima-media thickness (IMT) according to baseline waist and hip circumference adjusted for age, smoking, systolic blood pressure, LDL and HDL cholesterol, and blood glucose. Waist and hip circumferences were dichotomized at the mean.

5.5 Metabolic syndrome and carotid atherosclerosis (Study IV)

At baseline, women with metabolic syndrome had an 18% greater mean carotid IMT than those without metabolic syndrome (1.21 vs. 1.03 mm, $P=0.06$). There was no difference in the change of carotid IMT during 12 years between 88 women without the metabolic syndrome at baseline and 13 women with it (+0.21 vs. +0.20 mm, $P=0.92$).

After the 13 women with metabolic syndrome already at baseline were excluded, 34 women who developed the metabolic syndrome during the 12 year follow-up had higher waist circumference (88.2 vs. 76.3 cm, $P<0.001$) and body mass index (29.1 vs. 25.0, $P<0.001$) at baseline than the 54 women without the metabolic syndrome after the 12 year follow-up. The mean increase in the mean carotid IMT was 2.0 times greater in those women who developed the metabolic syndrome than in those who did not after adjustment for age, CVD, physical activity, smoking, alcohol, LDL cholesterol, lipid lowering medication, carotid IMT, and metabolic risk score at baseline (Figure 14). Further adjustment for waist circumference at baseline reduced the difference in the carotid IMT progression by 23% ($P=0.19$) and adjustment for triglycerides by 19% ($P=0.10$). The difference remained significant after further adjustment for glucose, HDL cholesterol, systolic blood pressure, or Framingham risk score at baseline or change in the amount of physical activity during the follow-up.

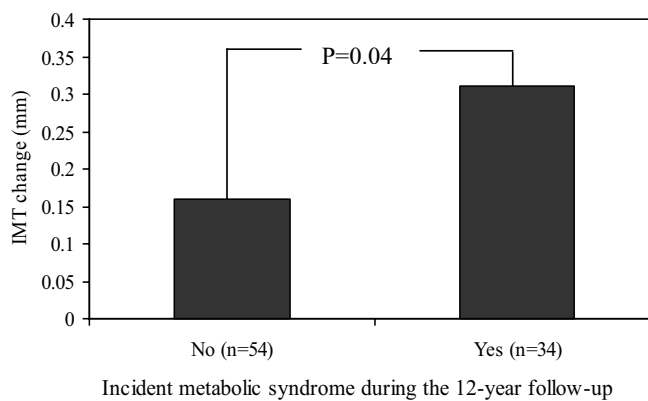


Figure 14. The change in carotid intima-media thickness (IMT) according to incident metabolic syndrome during the 12-years, after excluding women with the metabolic syndrome at baseline adjusted for age, CVD, physical activity, smoking, alcohol, LDL cholesterol, lipid lowering medication, carotid IMT, and metabolic risk score in 1992.

In the 88 women without the metabolic syndrome at baseline, the development of more metabolic risk factors during the 12-year follow-up was associated with a greater increase in the mean carotid IMT (Figure 15). The carotid IMT increase was 2.4 times greater in women who developed at least two metabolic risk factors than in those with no increase in risk factors after adjustment for age, prevalent CVD, physical activity, smoking, alcohol, LDL cholesterol, lipid lowering medication, carotid IMT and metabolic risk score at baseline. Adjustment for waist circumference at baseline reduced the difference in the carotid IMT increase by 21% ($P=0.10$) and triglycerides by 20% ($P=0.13$). Again, adjustment for glucose, HDL cholesterol, systolic blood pressure, or the Framingham risk score at baseline or change in amount of physical activity during the follow-up had no effect on the difference.

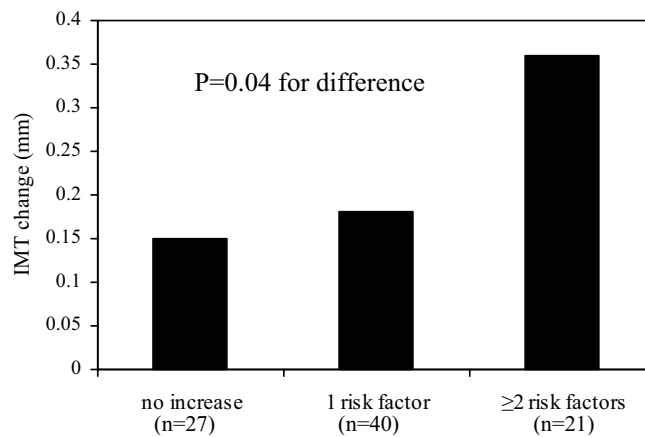


Figure 15. The change in carotid intima-media thickness (IMT) according to the increasing number of metabolic risk factors during the 12-year follow-up, after excluding women with the metabolic syndrome at baseline, adjusted for age, CVD, physical activity, smoking, alcohol, serum LDL cholesterol, lipid lowering medication, carotid IMT and metabolic risk score in 1992.

Of risk factors for the progression of carotid IMT, including baseline carotid IMT, age, triglycerides, LDL cholesterol, HDL cholesterol, glucose, waist circumference and systolic blood pressure, only baseline carotid IMT ($\beta=-0.295$, $P=0.003$), age ($\beta=0.196$, $P=0.05$), triglycerides ($\beta=0.248$, $P=0.01$) and waist circumference ($\beta=0.220$, $P=0.03$) were associated with the change in carotid IMT over 12 years in unadjusted linear regression analyses. When all risk factors were entered simultaneously into the model, only baseline carotid IMT ($\beta=-0.302$, $P=0.003$) and age ($\beta=0.193$, $P=0.05$) were independently associated with the change in carotid IMT.

6. DISCUSSION

6.1 Summary of the main findings

The purpose of the present thesis was to extend knowledge on the predictors and consequences of the metabolic syndrome in aging men and women.

❖ Cardiorespiratory fitness had a strong, inverse, graded and independent association with the metabolic syndrome in older men and women. Individuals in the lowest third of VO_{2max} had a 10 times higher risk and those in the middle third had 3 to 5 times higher risk of having the metabolic syndrome than those in the highest third of VO_{2max} . Low cardiorespiratory fitness was also associated with IGR in men and women without diabetes, but the relationship was weaker than that for the metabolic syndrome.

❖ Even a slight increment (<1 mg/l) in the serum level of high-sensitivity CRP was associated with 4 to 6 times higher risk of developing the metabolic syndrome during 12 years of follow-up in elderly women. The relationship was independent of abdominal obesity and other components of the metabolic syndrome.

❖ The progression of preclinical carotid atherosclerosis during 12 years was greater among elderly women in the two highest thirds of waist and hip circumferences and in women with overweight than in other women. Women with both a larger waist circumference and a smaller hip circumference had the greatest progression of carotid IMT.

❖ Incident metabolic syndrome and an increasing number of metabolic risk factors predicted the progression of preclinical carotid atherosclerosis during 12 years in elderly women. The mean increase in the carotid IMT was two times greater in women who developed the metabolic syndrome than in those who did not. The metabolic syndrome was a stronger predictor of carotid atherosclerosis progression than the individual components of the syndrome.

6.2 Methodological aspects

6.2.1 Study populations and design

In Study I, the baseline data of the ongoing randomized controlled trial, the DR's EXTRA Study, were used. The study population was a representative sample (nearly 20%) of 55 to 57 year old men and women from the city of Kuopio, Eastern Finland. About two thirds of the invited subjects were initially willing to participate in the study (Figure 4). About three fourths of them finally participated in the baseline examinations. Because of the age range and the relatively long run-in period, it is understandable that some of those who had expressed their willingness to the study were not able to participate due to different reasons (10% lack of motivation, 8% illness, 3% relocation, 2% death). This large study makes it possible to investigate the association of cardiorespiratory fitness with IGR and the metabolic syndrome in older men and women. Few studies of this topic are available in representative population samples of both men and women, especially in older individuals (Table 3). Because the baseline data of the ongoing study was available in the present study we had a cross-sectional study design, which limits deductions about causality and its direction. However, the notable strengths of the study are the representative population-based random sample, inclusion of both men and women, and focus on older age groups.

Studies II-IV consisted of a randomly selected population-based cohort of elderly women with a long follow-up period (Figure 5). Most previous studies of the associations of the variables of interest have included middle-aged individuals or have not specifically studied elderly individuals, especially women (Tables 2, 4, 5). Follow-up data are also scarce. The present data of this follow-up study are well-timed and important because women, especially elderly, have been underrepresented in epidemiological studies and represent a growing segment of the population. The study design provided an opportunity to investigate the predictive value of metabolic and cardiovascular risk factors in relation to the metabolic syndrome and preclinical carotid atherosclerosis in elderly women. Due to the long follow-up in older women, many of whom died or developed chronic diseases, the number of subjects in the 12-year follow-up visit was markedly reduced. Further, some subjects could not participate in the follow-up visits due to a long distance from home to the research institute and

transportation problems. Given these limitations, the participation rate can be considered fairly good. However, the relatively small study sample limits the statistical power and may lead to the underestimation of the true associations. A considerable increase in the use of antihypertensive and lipid lowering medications apparently decreased blood pressure and cholesterol during the 12 years. Also, a selection bias of healthier and slightly younger women in the follow-up complicates the generalization of the results to entire population. This may also lead to underestimation of the true associations, because of smaller differences in the variables of interest in population extremes.

6.2.2 Definition of the metabolic syndrome

The NCEP definition of the metabolic syndrome is simple to use in large epidemiological and intervention studies and in clinical practice. It has been one of the most widely used definitions during recent years, which helps in comparing the results with other studies. In contrast, the WHO definition requires clinical evidence of impaired glucose status, insulin resistance or diabetes mellitus in addition to two or more other risk factors, including microalbuminuria, which complicates its use in epidemiological studies and clinical practice. The latest definition, IDF, requires the presence of abdominal obesity, and the thresholds for abdominal obesity and impaired fasting glycemia are much lower than in the original NCEP definition. It is thus not surprising that IDF criteria classify a larger population as having metabolic syndrome than the NCEP.

Although the components of the metabolic syndrome occur more commonly in overweight and obese individuals, as postulated in IDF definition, there are individuals who are obese, but otherwise metabolically normal and individuals with normal weight with insulin resistance and other features of the metabolic syndrome (66,70,72). By using IDF criteria individuals with all other components of the metabolic syndrome except abdominal obesity are not defined as having the metabolic syndrome. Such individuals nonetheless have the metabolic syndrome, and therefore have an increased risk of type 2 diabetes and CVD. The NCEP definition considers central obesity as one of the five equally weighted criteria. A number of other metabolic and cardiovascular risk factors,

such as hsCRP, cytokines, fibrinogen, PAI-1, endothelial dysfunction, have been suggested as components of the metabolic syndrome (23,257). However, available data have not been sufficient to include them in the current definitions.

Although the NCEP and WHO definitions differ in their criteria, both have been considered useful for predicting diabetes, CVD and mortality (14,27,215,258-260). In contrast, evidence for the role of IDF definition in predicting these outcomes is limited (260). In a recent population-based study, the prevalence of the metabolic syndrome according to the IDF criteria was significantly higher than that according to the NCEP or WHO criteria, and the subjects identified in excess using the IDF criteria were less insulin resistant and have less carotid atherosclerosis (213). Inconsistent results exist of the current definitions regarding the ability to best predict diabetes and CVD. In Finnish men, the WHO definition seemed to predict CVD better than the NCEP (258). In another study, both definitions were predictive in a general population, but the NCEP was more predictive in lower-risk subjects (259). In a recent study, WHO, NCEP and IDF have a similar ability, even though different sensitivity, to predict incident diabetes and CVD (260). The sensitivity, but also the false positive rate, was somewhat higher by IDF definition. It is still under research whether the metabolic syndrome is a useful marker of CVD risk above and beyond the risk associated with its individual components. In general, the differences in the criteria of the metabolic syndrome definitions, including differences in the cut-offs of components and the way in which the components are combined, complicate comparability between studies.

We used the NCEP definition for the metabolic syndrome, because it is widely used in research and clinical practice, is useful in predicting type 2 diabetes, CVD and mortality, all variables needed were available, and the IDF criteria were only recently published.

6.2.3 Assessment of obesity

Overall obesity was assessed using the body mass index. Waist and hip circumferences were used to assess the distribution of body adiposity. Trained nurses carried out all the anthropometric measurements following a standard protocol. Waist and hip circumferences were measured twice, and the mean was used in the analyses. The

location of the measurement was selected carefully to increase precision. There are variations between studies in the site of especially waist circumference measurement, which complicates comparability. In some studies, waist circumference has been measured at the level of umbilicus, which may cause false estimates compared with measurement at a well-defined area between the rib cage and the iliac crest. The weakness of the current metabolic syndrome definitions is that they do not have instructions for waist and hip circumference measurements. In the present study, high intraclass correlations and small coefficient of variations (see 4.2) show a high reliability and repeatability between two consecutive measurements of waist and hip circumferences.

Waist circumference reflects mainly variation in subcutaneous and visceral fat, whereas hip circumference is also associated with bone structure in the pelvis, muscle mass in gluteo-femoral region, and subcutaneous fat mass (55). Compared with middle-aged individuals, hip circumference may reflect fat mass more than muscle mass in the elderly because of age-associated decrease in muscle mass. Body mass index provides a broad, nonspecific estimate of obesity, is easily obtained and commonly used in clinical practice. A potential limitation of body mass index measurement is that it does not take into account body fat distribution. For an equivalent body mass index, women have significantly greater amounts of total body fat than men do (261). Body mass index may not be the most appropriate measure of body composition in the elderly, in whom body height diminishes gradually after middle-age due to posture changes and osteoporosis, and lean body mass declines because of sarcopenia. Thus, in the elderly, the body mass index value may be in the normal-weight range despite muscle loss and excess body fat. Further, there are ethnic differences in the relations between various body mass index values and the risk of CVD (29). There is relative consensus about the classification for general adiposity based on WHO recommendations of body mass index (29). There is less consistency in the selection and cut-off points for indicators of abdominal obesity (262). Because each measure of body composition has its strengths and limitations, simultaneous assessment of waist and hip circumferences is reasonable in studies, especially among older individuals.

6.2.4 Assessment of cardiorespiratory fitness

Cardiorespiratory fitness is an objective measure of recent physical activity. It is stronger than self-reported physical activity as a predictor of many health outcomes, at least in part because fitness measurements are less prone to misclassification than self-reported physical activity (263). VO_{2max} can be measured directly or estimated from the treadmill or cycle ergometer work load or exercise time. In the present study, VO_{2max} was assessed directly using a respiratory gas exchange analysis during a symptom-limited maximal cycle ergometer test, which is an accurate and highly reproducible measure of cardiorespiratory fitness (123,264). Although VO_{2max} is measured in liters per minute, it is commonly expressed as milliliters of oxygen per kilogram of body weight per minute to facilitate comparison of values among individuals of different body size.

There are different protocols in use with different magnitude of increments in work rate. We used a standardized test protocol with a warm-up of 3 minutes at 20 W and a 20 W-increase in the workload per minute. Predicting VO_{2max} from the treadmill or cycle ergometer work load is common clinically. This can be misleading especially in persons with heart disease, because the protocol will overpredict their exercise capacity (120). Inaccuracy occurs also if the subject does not have treadmill experience or is untrained. Because joint and balance disorders are common in older individuals, the cycle ergometer test may be a better choice than walking on the treadmill, which requires weight-bearing and balance. On the other hand, directly measured VO_{2max} is time-consuming, expensive, requires specialized equipment and considerable physical effort and motivation. Thus it is rarely used in large studies and is not considered very suitable for clinical practice. However, as the present study showed, directly measured VO_{2max} is a suitable test even for the older population. Even though the oldest individuals were almost 80 years, the tests were carried out without serious problems.

6.2.5 Assessment of low-grade inflammation

CRP is currently considered to be the most reliable and widely available inflammatory marker for clinical use (265). In the present study, CRP was measured with a high-sensitivity assay, in which case CRP levels are considered to have a long-term

predictive value (146). hsCRP concentrations <1, 1-3, and >3 mg/l refer to low, moderate and high cardiovascular risk (265). We used an immunoassay system that is capable of detecting very low concentrations of CRP, starting from 0.1 mg/l. In contrast, the measurement range for many clinically used and less expensive CRP starts from 1 mg/l. Intraclass correlations and coefficients of variation in baseline and after follow-up show a high reliability of hsCRP measurements (see 4.5). Baseline serum samples were stored at -80°C during 12 years which can be considered the best available way to ensure the quality of the stored samples. Because baseline and follow-up samples were analyzed at the same time and with the same method, potential measurement errors that may occur due to changes in analysis methods over time are decreased.

6.2.6 Assessment of carotid atherosclerosis

High-resolution B-mode ultrasonography together with automated analyzing software was used to detect early changes in the arterial intima-media layer of the carotid bifurcation (254). Three certified sonographers performed the ultrasound scannings in both study years with the same ultrasound device, following a standardized and pretested protocol. IMT was measured at the carotid bifurcation, because area is prone to plaque formation (199) and is considered the best site along the carotid tree for use as a marker of atherosclerosis (266). Although there is also some disagreement as to what is the best site of the carotid tree as a marker of atherosclerosis (267) or as to whether carotid IMT is a surrogate marker of coronary atherosclerosis (268), carotid IMT is widely considered to be a useful measure of preclinical atherosclerosis.

Carotid IMT reflects generalized atherosclerosis (266), and an increase in carotid IMT has been validated as a vascular marker of the progression of preclinical atherosclerosis (202). However, carotid IMT is not synonymous with atherosclerosis, but is rather a marker of hypertrophy of intima and media layers of the artery wall (266). Carotid ultrasonography is a more suitable technique for assessing the progression of preclinical atherosclerosis than the quantification of coronary calcium, especially in the elderly, most of whom have coronary calcification. High-resolution magnetic resonance imaging is another non-invasive method for imaging atherosclerosis, but the prognostic value of cardiovascular magnetic resonance needs

more evidence (269). Angiography is used clinically for detecting coronary atherosclerosis. However, early atherosclerosis can not be reliably detected using angiography (202).

As a noninvasive measure, carotid IMT is a safer and cost effective method for assessing preclinical atherosclerosis than angiography (202). The present study is one of the few population-based long-term studies of the association of metabolic syndrome with carotid IMT from which data on the progression of carotid IMT are available.

6.3 Results

6.3.1 Cardiorespiratory fitness and the metabolic syndrome

The main finding of this study in older men and women was a strong, inverse, graded and independent association of cardiorespiratory fitness with the risk of having the metabolic syndrome. The present results support the findings of cross-sectional and prospective studies concerning the association of cardiorespiratory fitness with metabolic syndrome (Table 3). Low cardiorespiratory fitness was also associated with impaired glucose homeostasis in non-diabetic men and women, but the relationship was weaker than that with the metabolic syndrome. Findings from factor analysis suggest that low cardiorespiratory fitness could be considered a component of metabolic syndrome, which confirms an earlier study in middle-aged men from the same area in Eastern Finland (132).

The weakness of the most previous studies on the association of cardiorespiratory fitness with the metabolic syndrome (Table 3) is that the subjects were not individuals randomly selected from a general population. Only a few population-based studies have been published. Most have included only young and middle-aged individuals or men. Further, directly measured VO_{2max} was not used as a measure of cardiorespiratory fitness, but instead was estimated based on duration of the treadmill time or using a submaximal test. In two studies in which cardiorespiratory fitness was only weakly associated with the metabolic syndrome or its development, VO_{2max} was estimated with a submaximal exercise test (139,140).

Of the single components of the metabolic syndrome, waist circumference markedly weakened the association between cardiorespiratory fitness and metabolic syndrome.

Abdominal obesity is closely related to cardiorespiratory fitness and is a core component of the metabolic syndrome. This is likely in part because a sedentary lifestyle predisposes to weight gain and increases central fat accumulation (127). Body mass index attenuated the association of VO₂max with the metabolic syndrome less than waist circumference, which further suggests that waist circumference is a more useful measure of fat accumulation in the assessment of metabolic syndrome. Also, as discussed earlier (see 6.2.3) body mass index may not be the most appropriate measure of body composition in the elderly. In a recent study, the poor metabolic risk profile of middle-aged men with low cardiorespiratory fitness was associated with more visceral adipose tissue accumulation, defined by computed tomography, even after controlling for body mass index (270).

One fourth of men and women had the metabolic syndrome. The rate is somewhat lower than comparatively aged men and women previously in Finland (3,6) and United States (4). The prevalence did not differ in the 5-year age categories. Also, the association of cardiorespiratory fitness with metabolic syndrome was materially similar in all 5-year age groups. The only exception was the group of men over 70 years, in which the association seemed to be stronger.

Factor analysis reduces a large number of correlated variables to fewer factors that may explain or reflect complex underlying phenomena (271), such as in the metabolic syndrome (114,115,132). We found a principal metabolic syndrome factor that had heavy loadings by the main components of the metabolic syndrome and cardiorespiratory fitness. The loading was particularly high for waist circumference, which supports the central fat accumulation as a major component of the metabolic syndrome. Few previous studies have included cardiorespiratory fitness in the factor analyses with conventional metabolic risk factors (132).

Lipids were included in more than one factor. LDL cholesterol is not considered a component of the metabolic syndrome, which may explain the small and negative loading in the principal factor and high positive loading on the second factor, which could be termed the lipid factor. The small negative loading of LDL cholesterol may also be in part because in the metabolic syndrome LDL cholesterol particle size is small. If the decrease in LDL particle size is greater than the increase in particle number, this

could be reflected in slightly lower LDL cholesterol concentrations, even though LDL concentrations have not been consistently associated with the metabolic syndrome.

These findings suggest that while the metabolic syndrome may differ in its manifestations, there is still a common underlying pathophysiological process that explains the syndrome in most individuals. Abdominal obesity and poor cardiorespiratory fitness seem to be closely related to the underlying metabolic process.

6.3.2 High-sensitivity C-reactive protein and the metabolic syndrome

Inflammation plays a major role in the development of diabetes and CVD and is associated with several components of the metabolic syndrome, like obesity, insulin resistance, dyslipidemia, blood pressure, impaired fibrinolysis and endothelial dysfunction. The reason for a link between inflammation and the metabolic syndrome may be central adiposity. Abdominal obesity may increase cytokine release into the circulation, which in turn may increase the hepatic production of CRP (see 2.2.7). On the other hand, insulin resistance and aging are both associated with increased low-grade inflammation. Some previous studies indicate that hsCRP might be a valuable addition to the definition of the metabolic syndrome to predict cardiovascular events (183,272), while other studies do not support this idea (173).

Previous evidence of the association between elevated hsCRP levels and the metabolic syndrome derives mainly from cross-sectional studies, while only few prospective and population studies are available (Table 4). In an 11-year study, middle-aged men with increased hsCRP levels were over three times more likely to develop the metabolic syndrome than those with low hsCRP levels (184). In a 6-year study, the association between hsCRP levels and the risk of developing the metabolic syndrome was present in middle-aged women, but not in men (182).

The present 12-year follow-up study in elderly women provides new information because it shows that changes in hsCRP concentration are associated with the development of the metabolic syndrome. An important finding is that even a slight increment in hsCRP concentration in elderly women was associated with a 4 to 6 times higher risk for developing the metabolic syndrome than in those whose hsCRP concentration decreased during 12 years. The association held even after controlling for

abdominal obesity, a major correlate of serum hsCRP levels and crucial component of the metabolic syndrome. hsCRP was doubled in women who developed the metabolic syndrome during follow-up and reached the same level as in those who had the metabolic syndrome already at baseline. These findings are important, because even moderately elevated hsCRP concentration have been associated with an increased risk of future cardiovascular events among middle-aged women (148).

In the present study, the direct association between hsCRP and the risk for the metabolic syndrome was partly explained by changes in waist circumference and triglycerides, major components of the metabolic syndrome. Adipose tissue may be partly responsible for a mild, chronic inflammatory state, which may induce insulin resistance. Furthermore, TNF- α increases the serum concentration of triglycerides (see 2.2.7). The aging-associated increase in fat mass and decrease in lean body mass may both accelerate the inflammatory process and development of the metabolic syndrome in the elderly. Moreover, in elderly women decreased estrogen levels have been associated with inflammation (170). It has also suggested that in women who are obese, but otherwise metabolically healthy with high insulin sensitivity, a lower inflammatory state could be associated with a lower risk of CVD (71).

6.3.3 Waist and hip circumference and carotid atherosclerosis

In the present study, the progression of carotid atherosclerosis during 12 years was greater among elderly women in two highest thirds of waist and hip circumferences and in women with overweight than in other women. Hip circumference was associated with the increase in carotid IMT independently of waist circumference and body mass index, while waist circumference and body mass index had no significant association with carotid IMT increase after taking into account other measures of body adiposity. A small hip circumference was related to carotid IMT progression in women with a large waist circumference, whereas waist circumference did not provide additional information in women with a large hip circumference. Our results agree with those from a previous cross-sectional study in which the prevalence of atherosclerotic disease was highest among individuals with a large waist circumference and a small hip circumference (273).

A number of previous studies have evaluated the relationship between obesity and CVD, but limited evidence exists for the association of different measures of body adiposity with preclinical atherosclerosis (Table 2), especially in the elderly. Few if any studies have assessed the association between hip circumference and atherosclerosis. In a 4-year follow-up study in middle-aged men, waist-to-hip ratio and waist circumference were associated with an accelerated increase in carotid IMT independently of body mass index, while body mass index had no independent association with the increase in carotid IMT (47). A graded and independent association of waist-to-hip ratio and body mass index with carotid IMT was found in a cross-sectional study in middle-aged women (48). There are also conflicting results regarding the independent association of body mass index (49) or measures of abdominal obesity (51,65) with carotid IMT.

In previous studies, inconsistent results exist which adipose tissue regions confer the greatest increase in morbidity and mortality. There is evidence that abdominal adipose tissue influences more disease risk than overall adiposity (52,53). Some studies indicate that lower body adiposity, which is predominant in most women, may be in fact protective against some disease, such as type 2 diabetes and CVD, rather than being harmful (55-57). In postmenopausal women, trunk fat was a strong independent predictor of insulin resistance and dyslipidemia, whereas leg fat had protective effects against metabolic dysfunction (274). In a cross-sectional study in 4000 men, hip circumference was inversely associated with metabolic risk factors (275).

The different associations of the measures of fat distribution on CVD risk may be due to regional variations in the lipolytic activity of human adipose tissue. In the visceral region, the rate of lipolysis is high and fat is also more resistant to the metabolic effects of insulin compared with peripheral fat cells (see 2.2.1 and 2.2.2). The association of visceral fat with inflammation (see 2.2.7) and impaired endothelial function (276) support findings that visceral fat is an important risk factor for early atherosclerosis. A lesser sensitivity to lipolytic stimulation may explain the greater tendency for women to accumulate fat in lower body regions (277). Adipose tissue in this region is more likely to take up free fatty acids from the circulation and store them, thereby protecting other organs such as liver and skeletal muscle from high free fatty

acids (278). Moreover, the favorable metabolic effect of large hip circumference may be due to increased gluteal muscle mass and a high lipoprotein lipase activity (279). In conclusion, accumulation of fat in the visceral area may increase the risk of metabolic and vascular disease more than the amount of total fat.

6.3.4 Metabolic syndrome and carotid atherosclerosis

Evidence of the association of metabolic syndrome with carotid IMT is derived mainly from cross-sectional studies, of which only a few are population-based (Table 5). Data are mainly from middle-aged individuals or have a wide age-range. The present study shows that incident metabolic syndrome and an increasing number of metabolic risk factors predict the progression of carotid IMT during 12 years in elderly women. The mean increase in the carotid IMT was two times greater in those who developed the metabolic syndrome than in those who did not. Incident metabolic syndrome was a stronger predictor for the progression of carotid IMT than the individual components of the syndrome. Of the components, waist circumference and triglycerides contributed most to the association between the metabolic syndrome and the change in carotid IMT.

The present results support the findings of population-based follow-up studies which report a direct relationship of the metabolic syndrome (215) or metabolic risk factors (204) with carotid IMT or the risk of CVD (258). An important finding is that incident metabolic syndrome was associated with the progression of carotid IMT even after controlling for Framingham risk score, an international risk assessment tool for estimating 10-year risk of developing CHD. This observation suggests that incident metabolic syndrome provides additional information for the progression of preclinical atherosclerosis beyond conventional risk factors, and thereby improves the prediction of clinical CVD.

The progression rate of carotid IMT in the elderly women in the present study was comparable to that recently reported in men 10 years younger from the same area in Finland (232). In women, the progression of atherosclerosis increases clearly after menopause (280), and CVD is the primary cause of death in women (281,282). The prevalence of stroke increases with age in both genders, but women have been reported to have a two times higher lifetime risk of dying of stroke than men (283). Also, women

with the metabolic syndrome, even without diabetes, were found to have at least a two-fold higher risk of ischemic stroke or transient ischemic attack (28).

In these elderly women, the prevalence of the metabolic syndrome increased from 13% to 46% during 12 years. While body weight remained the same during the follow-up, waist circumference increased by 10%. This may reflect an aging-associated progressive decrease in skeletal muscle mass and increase and redistribution of body fat particularly in the abdominal area, worsening of insulin resistance and hormonal alterations, all of which are important in the development of the metabolic syndrome. In addition to metabolic syndrome, abdominal obesity has been found to predict atherosclerosis and clinical cardiovascular events (45-47). In the present study, women with incident metabolic syndrome had a higher waist circumference and body mass index at baseline than those who did not develop the metabolic syndrome. These findings suggest that abdominal obesity is of major importance in the development of the metabolic syndrome and also partly explained the association between incident metabolic syndrome and the progression of carotid IMT.

6.4 Conclusions and future perspective

Cardiorespiratory fitness and hsCRP may be valuable additions to the definition of the metabolic syndrome (Figure 16). The metabolic syndrome in and of itself may improve the prediction of preclinical atherosclerosis. When used in conjunction with other metabolic and cardiovascular risk factors, low cardiorespiratory fitness and elevated hsCRP may have additional predictive power in identifying individuals with multiple, often only mildly elevated cardiovascular risk factors, who are at increased risk of developing chronic and progressive diseases and who may benefit from lifestyle therapy targeting exercise and weight management.

The increasing number of aging individuals in the future will bring along different demands to the health care system. Maintaining independent and active living as long as possible is a crucial factor for quality of life in aging. The present thesis expands the knowledge of the predictors and consequences of the metabolic syndrome in the older population. The study also included elderly women, a part of the population that has been historically underrepresented in epidemiological studies. These findings emphasize the importance of ongoing efforts to identify and treat the metabolic syndrome as early as possible to prevent atherosclerotic disease, even in the older population.

Further long-term population studies in elderly men and women are needed to clarify key factors to be included in the definition of the metabolic syndrome, the relative importance of the different components of the metabolic syndrome and the combinations of risk factors that are most useful in predicting disease outcomes. Randomized controlled clinical trials are needed to find out the dose-dependent effects of exercise training and diet on suppression of inflammation and prevention of the metabolic syndrome, type 2 diabetes and CVD in population-based samples, including older individuals. After finalizing the present thesis I will focus on these issues in the ongoing randomized controlled physical exercise and diet intervention study in older men and women that forms part of this thesis.

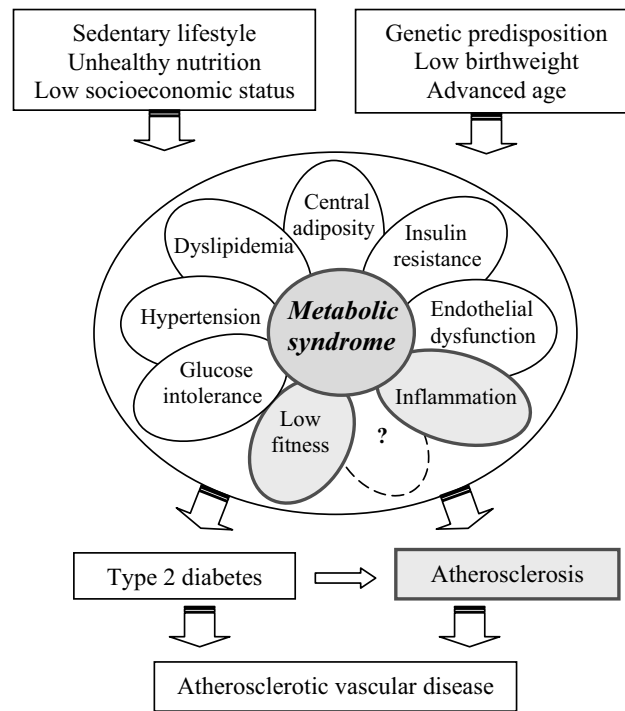


Figure 16. Updated view of predictors, components and consequences of the metabolic syndrome based on the present thesis.

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