DISSERTATIONS IN
HEALTH
SCIENCES

Maarit Katariina Valtonen

Hopelessness, Depressive Symptoms, Physical Activity and Metabolic Syndrome

A Population-based Cohort Study in Men

Publications of the University of Eastern Finland
Dissertations in Health Sciences

UNIVERSITY OF
EASTERN FINLAND

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To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland
for public examination in the auditorium of Vanha Ortopedia in Jyväskylä
on Saturday, October 8th, at 12 noon.

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 72

Institute of Clinical Medicine,
Institute of Public Health and Clinical Nutrition,
Institute of Biomedicine/Physiology,
School of Medicine,
Faculty of Health Sciences, University of Eastern Finland
Kuopio Research Institute of Exercise Medicine, Kuopio
LIKES - Research Center for Sport and Health Sciences, Jyväskylä
Department of Medicine, Central Hospital Central Finland, Jyväskylä
2011

Kopijyvä Oy
Kuopio/Jyväskylä, 2011

Distributor:
University of Eastern Finland
Kuopio Campus Library
P.O.Box 1627
FI-70211 Kuopio, Finland
http://www.uef.fi/kirjasto

ISBN: 978-952-61-0530-7
ISBN: 978-952-61-0531-4 (PDF)
ISSN: 1798-5706
ISSN: 1798-5714 (PDF)
ISSNL: 1798-5706

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Valtonen, Maarit Katariina
Hopelessness, Depressive Symptoms, Physical Activity and Metabolic Syndrome. A Population-based Cohort Study in Men
University of Eastern Finland, Faculty of Health Sciences, 2011
Publications of the University of Eastern Finland. Dissertations in Health Sciences Number 72. 2011. 51 p.

ISBN: 978-952-61-0530-7
ISBN: 978-952-61-0531-4 (PDF)
ISSN: 1798-5706
ISSN: 1798-5714 (PDF)
ISSNL: 1798-5706

ABSTRACT:

The prevalence of metabolic syndrome is rapidly growing worldwide, increasing the risk for diabetes and cardiovascular disease. Hopelessness, determined as a system of negative expectancies concerning oneself and one's future, has shown to be a predictor of cardiovascular morbidity and mortality, independently of depression. Psychosocial factors have also been associated with features of metabolic syndrome. However, the direction of this association, possible mediating factors and the extent of psychosocial factors related with metabolic syndrome itself are not known.

The purpose of this study was to provide new information about the aetiology of metabolic syndrome and depressive symptoms, to disentangle the relationships among them and to clarify possible mediating factors, such as physical activity and low-grade inflammation, underlying the associations. To better target high-risk groups for treatment and prevention of metabolic syndrome, depressive symptoms and their consequences, such knowledge is necessary.

The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) is a population-based cohort study with a representative sample of 2682 middle-aged male participants. The data on the features and components of metabolic syndrome were collected on clinical examinations. Physical activity, feelings of hopelessness and depressive symptoms were estimated by detailed questionnaires. Follow-up data were collected 4 and 11 years after the baseline.

This study showed that non-diabetic men with high levels of hopelessness were twice more likely to have metabolic syndrome than men who were less hopeless, independently of traditional risk factors, body mass index and other depressive symptoms. In addition, non-diabetic men with both low-grade inflammation and depressive symptoms were more likely to develop abdominal obesity (waist girth at least 102 cm) and metabolic syndrome than men with neither of these risk markers even after adjusting for traditional risk factors.

The study also showed that those men exercising for at least 2.5 h per week moderate-to-vigorous leisure-time physical activity (LTPA) were 28% less likely to express feelings of hopelessness than physically inactive men even after adjustment for traditional risk factors and depressive symptoms. Men engaging in moderate-to-vigorous LTPA at least 2.5 hours per week had 35% lower risk to feel hopeless about their future and reaching goals 4 years later than inactive men at baseline. After 11 years the trend was still similar, indicating protective effect of LTPA.

This study indicates that that in addition to focusing on the traditional risk factors of cardiovascular disease, the emotional state and expectations of individuals should be taken into account in the prevention and treatment of metabolic syndrome and its consequences. This study also agrees with growing evidence that regular LTPA contributes to mental health. A physically active lifestyle may help one to maintain or gain more optimistic perspective on the future and oneself.

National Library of Medical Classification: WA 306, WG 120, WK 820, WM 171.5
Medical Subject Headings: Metabolic syndrome X; Cardiovascular Diseases; Depression; Men's Health; Life Style; Psychophysiologic Disorders; Risk Factors; Middle Aged; Cohort studies; Follow-Up Studies; Finland

Valtonen, Maarit Katariina
Toivottomuus, masennusoireet, liikunta-aktiivisuus ja metabolinen oireyhtymä miehillä
Itä-Suomen yliopisto, terveystieteiden tiedekunta, 2011
Publications of the University of Eastern Finland. Dissertations in Health Sciences Numero 72. 2011. 51 s.

ISBN: 978-952-61-0530-7
ISBN: 978-952-61-0531-4 (PDF)
ISSN: 1798-5706
ISSN: 1798-5714 (PDF)
ISSNL: 1798-5706

TIIVISTELMÄ:

Metabolinen oireyhtymä tarkoittaa tilaa, jossa esiintyy samanaikaisesti poikkeavuuksia sokeri-, insuliini- ja rasva-aineenvaihdunnassa, kohonnutta verenpainetta sekä keskivartaloon painottuvaa ylipainoa. Nämä altistavat oireyhtymän keskeisille komplikaatioille eli tyypin 2 diabeteksen kehittymiselle sekä sydän- ja verisuonisairauksille. Fyysisesti passiivinen elämäntapa ja epäterveelliset ruokatottumukset ovat keskeisiä tekijöitä metabolisen oireyhtymän kehittymisessä. Lisäksi psykososiaalisilla tekijöillä, kuten masennuksella, tiedetään olevan yhteys metaboliseen oireyhtymään, mutta yhteyden syy-seuraussuhde sekä välittävät mekanismit tunnetaan huonosti. Aiemmissa tutkimuksissa myös toivottomuudella eli kielteisillä odotuksilla itseään ja tulevaisuuttaan kohtaan, on todettu olevan itsenäinen, masennusoireista riippumaton yhteys sydän- ja verisuonitauteihin. Elimistön kudostulehduksen tiedetään liittyvän sekä masennuksen että sydän- ja verisuonitautien syntyyn ja etenemiseen.

Tämän tutkimuksen tarkoituksena oli lisätä tietoa metabolisen oireyhtymän ja psyykkisten oireiden etiologiasta ja näiden välisistä yhteyksistä. Lisäksi tavoitteena oli selventää mahdollisten välittävien mekanismien, kuten liikunta-aktiivisuuden ja tulehdustekijöiden roolia psyykkisten tekijöiden ja metabolisen terveyden välillä. Tätä ymmärrystä tarvitaan metabolisen oireyhtymän ja mielenterveysongelmien ehkäisyssä ja hoidossa.

Tämä tutkimus oli osa Itä-Suomen Yliopiston laajaa väestöpohjaista Sepelvaltimotaudin Vaaratekijätutkimusta. Tutkimuksessa kartoitettiin 2682 keski-ikäisen miehen masennusoireita kattavilla kyselylomakkeilla, määritettiin sydän- ja verisuonitauteihin liittyvät riskitekijät, arvioitiin liikunta-aktiivisuus sekä mitattiin kestävyyskunto. Seurantatutkimukset suoritettiin 4 ja 11 vuoden kuluttua.

Tutkimus osoitti, että miehillä, joilla oli toivottomuuden tunteita itseään ja tulevaisuuttaan kohtaan, metabolinen oireyhtymä oli yleisempää kuin miehillä, joilla toivottomuuden tunteita ei ollut, riippumatta muista masennusoireista. Tutkimus osoitti myös, että masennusoireiden esiintyminen yhdessä kohonneiden veren tulehdusarvojen kanssa lisäsi huomattavasti riskiä vyötärölihavuuden kehittymiseen 11 vuoden seurannassa. Toisaalta tutkimuksen keskeisenä löydöksenä oli vähäisen liikunta-aktiivisuuden ja toivottomuuden välinen selkeä yhteys muista masennusoireista riippumatta. Säännöllinen kohtuullisesti kuormittava liikunta suojasi toivottomuuden tunteilta seurantatutkimuksen aikana.

Tutkimustulosten mukaan kansanterveyden edistämistyössä tulisi ottaa huomioon perinteisten riskitekijöiden lisäksi yksilön henkiset voimavarat ja elämänasenne. Tutkimus vahvistaa aiempaa näyttöä liikunnan myönteistä vaikutuksista psyykkiseen terveyteen. Säännöllinen liikunta voi ehkäistä toivottomuuden tunteita ja näin edistää optimistista elämänasennetta ja mielenterveyttä.

Yleinen Suomalainen asiasanasto: metabolinen oireyhtymä; masennus; toivottomuus; elintavat; riskitekijät; miehet; keski-ikäiset; suomalaiset

To my parents
who taught me to believe
in the future and myself

Acknowledgements

This thesis was carried out in the Department of Medicine, Central Finland Central Hospital and in LIKES Research Center for Sport and Health Sciences, Jyväskylä, during the years 2006-2011. The data used in this thesis was collected by the Research Institute of Public Health, University of Kuopio, and Kuopio Research Institute of Exercise Medicine. I am very grateful to everyone involved for making it possible for me to use the data and to accomplish this thesis.

For the financial support I received for this work I wish to thank: LIKES Research Center for Sport and Health Sciences, the National Graduate School of Clinical Investigation, the healthcare district of Central Finland, Onni and Hilja Tuovinen Foundation, Orion Pharmos Foundation, Yrjö Jahnsson Foundation, Ida Montin Foundation and Juho Vainio Foundation.

I was fortunate to have the most intelligent group of supervisors to introduce me to the field of science and to guide me through this work. I am also lucky to be surrounded by people who help me to balance my days with medicine, science and life. I wish to express my deepest gratitude to all those who contributed to this work:

Professor Leo Niskanen, my principal supervisor and mentor, for his unending enthusiasm for science and the health of people. His wisdom, encouragement and guidance have been priceless during this work.

Docent David Laaksonen, my supervisor, for his patient assistance in the statistical analysis and in scientific writing. His excellent knowledge in cardiovascular epidemiology has been of great importance.

Professor Timo Lakka, my supervisor, for his knowledge in KIHD study data and important insight into the original articles and this thesis.

Professor Jussi Kauhanen, my supervisor, for his commitment to the KIHD study and this work.

Professor Olli J. Heinonen and Professor Matti Joukamaa, the official reviewers of this thesis, for their valuable comments and constructive criticism.

Professor Heimo Viinamäki for his enthusiastism and encouragement. His insight in the field of psychiatry has been extremely helpful during this work.

Other co-authors, Tommi Tolmunen, Jari Laukkanen, Rainer Rauramaa, Hanna-Maria Lakka, Kristiina Nyyssönen, Jaakko Mursu and Kai Savonen, for valuable contribution to this work.

The staff of the Research Institute of Public Health, University of Kuopio, and Kuopio Research Institute of Exercise Medicine for data collection in the KIHD study.

Docent Jouni Lauronen and the National Graduate School of Clinical Investigation for giving structure and guidance in the doctoral studies. I sincerely recommend this graduate school for medical post-graduate students in Finland.

The chief physicians Pekka Hannonen and Heikki Janhunen in Central Finland Central Hospital for allowing me to combine clinical and research work.

The director Eino Havas, Harri Selänne, Tuija Tammelin, Anu Kangasniemi, Kirsti Siekkinen, Martta Walker and all personnel in LIKES Research Center for creating such an exceptional working environment and for making this work possible for me in Jyväskylä. I am very grateful for encouragement and help I received in LIKES to finish this work.

My friend M. Greta Durant for her valuable advice and the English language revision of this thesis.

I also wish to thank Johanna, Jonna, Sini and Tiina for helping me with essential details of this work and all my girlfriends for keeping me sane in this craziness. The world is a better place because of you!

In addition, I owe deepest gratitude to my extended family in Finland and in America for life-long friendship and invaluable support during all these years. In particular, I want to thank my grand-parents Elli and Toivo Ahlgren, for being the idols of my life and my parents, Maire and Ahti Ahonen, for not only giving their time to our children but loving them so much.

Finally, I wish to express my love and gratitude to my dearest ones, Veera, Viljami and Verneri for making sure I know the priorities in life and my husband, Mikko Valtonen, for keeping up with my ambitions and making me feel I am worth it.

Jyväskylä September 12th, 2011

Maarit Valtonen

List of the original publications

This dissertation is based on the following original publications:

I Valtonen M, Laaksonen DE, Tolmunen T, Nyyssonen K, Viinamaki H, Kauhanen J, Niskanen L. Hopelessness -- novel facet of the metabolic syndrome in men. Scand J Public Health 2008;36,795-802.

II Valtonen M, Laaksonen DE, Laukkanen J, Tolmunen T, Viinamaki H, Lakka HM, Lakka T, Niskanen L, Kauhanen J. Low-grade inflammation and depressive symptoms as predictors of abdominal obesity. Submitted.

III Valtonen M, Laaksonen DE, Laukkanen J, Tolmunen T, Rauramaa R, Viinamaki H, Kauhanen J, Lakka T, Niskanen L. Leisure-time physical activity, cardiorespiratory fitness and feelings of hopelessness in men. BMC Public Health 2009;9,204.

IV Valtonen M, Laaksonen DE, Laukkanen J, Tolmunen T, Rauramaa R, Viinamaki H, Mursu J, Savonen K, Lakka T, Niskanen L, Kauhanen J. Sedentary lifestyle and emergence of hopelessness in middle-aged men. Eur J Cardiovasc Prev Rehabil 2010;17:524-529.

Contents

Abbreviations

AHA	American Heart Association
ATPIII	Adult Treatment Program III
BDI	Beck's Depression Inventory
BMI	Body Mass Index
CES-D	Center for Epidemiological Studies Depression Scale
CHD	Coronary Heart Disease
CRH	corticotrophin-releasing hormone
CVD	Cardiovascular Disease
CRP	C-reactive protein
DM	Diabetes Mellitus
EGIR	European Group for the Study of Insulin Resistance
HDL	High-density lipoprotein
HPA	Hypothalamus Pituitary Adrenal
HPL	Human Population Laboratory
5-HTTLPR	Serotonin-transporter-linked polymorphic region
hs-CRP	High sensitivity C-reactive protein
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IL	Interleukin
KIHD	Kuopio Ischaemic Heart Disease Risk Factor Study
LDL	Low density lipoprotein
LTPA	Leisure-time physical activity
MET	Metabolic Equivalent
MI	Myocardial infarction
NCEP	National Cholesterol Education Panel
NHLBI	National Heart, Lung, and Blood Institute
SES	Socio-economic status
S-ICAM1	Soluble intercellular adhesion molecule-1
TNF-α	Tumour necrosis factor-alpha
$V0_{2max}$	Maximal oxygen uptake
WHO	World Health Organization
WHR	Waist-to-hip ratio

1 Introduction

The prevalence of metabolic syndrome is rapidly growing worldwide (Zimmet et al. 2005), but the role of psychosocial issues in its development is poorly understood. Central obesity and associated insulin resistance are crucial factors in the pathogenesis of metabolic syndrome (Laaksonen et al. 2002a, 2004a). Suggestions that behavioral and psychosocial factors are associated with features of metabolic syndrome (Laaksonen et al. 2004a; Viinamäki et al. 2009) have been made. However, the time order of the associations, mediating factors underlying the associations and the role of psychosocial factors in the associations itself are not known.

Hope is an important determinant of subjective well-being (Scheier and Carver 1985). Hopelessness, a major symptom of depression, is defined as a cluster of negative expectancies concerning a person and his or her future (Stotland 1969). Lack of hope is associated with various manifestations of psychological morbidity (Haatainen et al. 2004). Hopelessness, independently of depression, is also associated with increased incidence of hypertension and myocardial infarction, accelerated progression of carotid atherosclerosis, as well as cardiovascular and overall mortality (Anda et al. 1997; Everson et al. 1996, 1997, 2000; Stern et al. 2001; Whipple et al. 2009; Do et al. 2010).

Higher levels of leisure-time physical activity (LTPA) and cardiorespiratory fitness protect against chronic diseases, such as metabolic syndrome (Laaksonen et al. 2002b; Lakka et al. 2003), type 2 diabetes (Laaksonen et al. 2005a), and cardiovascular disease (CVD) (Lakka et al. 1994; Lakka et al. 2002). Moreover, a physically active lifestyle may improve mental health (Mead et al. 2009). Experimental studies have shown that physical exercise seems to decrease symptoms of depression (Lawlor and Hopker 2001; Dunn et al. 2005; Dunn 2009). This evidence, however, comes mainly from cross-sectional studies on physical activity and depression. Prospective studies on physical activity and depression are scarce. In previous studies, psychological outcome has ranged from clinical depression to depressive symptoms and mood. The relationship between physical activity, cardiorespiratory fitness and feelings of hopelessness has not been previously studied. It is plausible that physical exercise has a stronger impact on certain depressive symptoms than on other mental symptoms. The purpose of the thesis is to provide new information about the aetiology of metabolic syndrome and depressive symptoms, especially hopelessness, to disentangle the relationships among them and to clarify possible mediating factors underlying the associations. The focus of the thesis was on middle-aged men and their physical activity and their mental and physical health. Although the health of Finnish men has improved during the past decades, we are not approaching an ideal state. The prevalence of obesity and associated type 2 diabetes continues to escalate. Psychiatric diseases are the leading cause of disability. Physical inactivity is the most common modifiable risk of public health, and most life-style interventions do not reach people who critically need them. Mental disorders often hamper the implementation of the healthier life-style. Health-care professionals need tools to identify high-risk individuals and to refer them to life-style interventions.

2 Review of literature

2.1 METABOLIC SYNDROME

2.1.1 Pathogenesis of metabolic syndrome

Metabolic syndrome is a cluster of different risk factors for diabetes and CVD. These risk factors, including dysglycemia, hypertension, dyslipidemia and abdominal obesity, share common pathogenetic processes. The underlying mechanisms of metabolic syndrome still remain unclear, but central obesity and associated insulin resistance nonetheless play an important role. It is not known whether visceral fat causes insulin resistance or is just associated with insulin resistance (Kirk and Klein 2009). According to one hypothesis, the release of fatty acids from visceral adipose tissue causes insulin resistance, because these fatty acids are delivered directly to the liver through portal vein (Nielsen et al. 2003). Free fatty acids decrease the ability of insulin to suppress hepatic glucose production resulting in inappropriate fasting and postprandial gluconeogenesis. In addition, an increase in the flux of non-esterified fatty acids enhances the production of very-low-density lipoprotein, causing higher triglyceride and lower high-density lipoprotein (HDL) concentrations in plasma. Ectopic accumulation of fat in skeletal muscle and liver is also associated with insulin resistance in these tissues (Krssak 1999; Seppälä-Lindroos et al. 2002). Free fatty acids themselves may also cause vasoconstriction (Tripathy et al. 2003) and increase sodium reabsorption (DeFonzo et al. 1975), leading to hypertension.

Furthermore, adipose tissue produces inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and IL-8, which can induce insulin resistance (Perseghin et al. 2003) and may play a critical role in the pathogenesis of metabolic syndrome. There are also many other factors that are associated with insulin resistance, such as increased serum concentrations of prothrombotic factors and uric acid, microalbuminuria, reduced low-density lipoprotein (LDL) particle size, increased serum concentrations of adiponectin, abnormal sex hormone metabolism, and disturbed cortisol metabolism, that are not included in the diagnostic criteria for metabolic syndrome (Laaksonen et al. 2004a, 2004b, 2004c; Eckel et al. 2005). Also considered is the role of prenatal and early-life influences as well as genetic factors in the development of metabolic syndrome (Alberti et al. 2009).

Behavioral and psychosocial factors are clearly associated with features of metabolic syndrome. A sedentary lifestyle (Laaksonen et al. 2002b, Lakka and Laaksonen 2007; Ilanne-Parikka et al. 2010), lower levels of cardiorespiratory fitness (Laaksonen et al. 2002b; Hassinen et al. 2010), unhealthy diet (Laaksonen et al. 2005a), low socio-economic status (SES) (Brunner et al. 1997), low birth weight (Laaksonen et al. 2003) and depression (Viinamäki et al. 2009) are all related to obesity or metabolic syndrome. However, the time order of the associations and mediating factors underlying the associations are poorly understood.

2.1.2 Definitions of metabolic syndrome

The clustering of hypertension, hyperglycemia and gout was already recognized in the early 20th century (Zimmet et al. 2005), but it took almost a century to first attempt a global

definition of metabolic syndrome (Zimmet et al. 2005). The different definitions of metabolic syndrome are presented in Table 1. The World Health Organization (WHO) definition was published in 1999 (Alberti and Zimmet 1998). This definition included measurement of insulin resistance by the euglycemic hyperinsulinemic clamp and was meant mainly for research purposes. The European Group for the Study of Insulin Resistance (EGIR) developed modified version of the WHO definition. The modified WHO definition (Laaksonen et al. 2002a; Lakka et al. 2002) includes hyperinsulinemia, impaired fasting glucose, or diabetes and the presence of at least two of the following: abdominal obesity (waist-to-hip ratio [WHR] >0.90 or body mass index [BMI] ≥30 kg/m^2), dyslipidemia (triglycerides ≥1.70 mmol/l or HDL cholesterol <0.9 mmol/l), or hypertension (blood pressure ≥140/90 mmHg or blood pressure medication) (Alberti and Zimmet 1998).

The National Cholesterol Education Panel (NCEP) published the Adult Treatment Program III (ATPIII) definition two years later to improve the clinical diagnosis of metabolic syndrome. The NCEP definition for men includes three or more of the following: fasting blood glucose levels ≥5.6 mmol/l, triglycerides ≥1.7 mmol/l, HDL cholesterol <1.0mmol/l, blood pressure ≥130/85 mmHg, waist girth >102 cm (NCEP 2001; Laaksonen et al. 2002a).

The International Diabetes Federation (IDF) published the definition in 2005, with an aim to identify people at high risk of CVD and diabetes throughout different ethnic groups. The IDF definition recognized that central obesity is a prerequisite for metabolic syndrome (Zimmet et al. 2005). In Europeans, the IDF definition is based on the following criteria: waist circumference ≥94cm in males and at least two of the following: triglycerides (≥1.7 mmol/l), HDL cholesterol (<1.0 mmol/l), blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg) and fasting plasma glucose (≥5.6 mmol/l) (Zimmet et al. 2005).

In recent years the IDF and the American Heart Association (AHA) have tried to unify a global definition for metabolic syndrome (Alberti et al. 2009). The newest update for the definition, released in 2009, uses the structure of the NCEP definition with the ethnic-specific waist-girth parameters. A diagnosis comprises the presence of any three of the five risk factors. Therefore, abdominal obesity is one of the five criteria; not the prerequisite part of the syndrome. Defining abdominal obesity, however, still remains unresolved (Alberti et al. 2009).

Table 1 Definitions of metabolic syndrome

NCEP	**IDF**	**WHO (modified)** [c]	**NHLBI/AHA**
≥3 of following	**Waist ≥94cm**[a] **and ≥2 of following**	**Insulin resistance**[ǁ], **DM or IFG and ≥2 of following**	**≥3 of following**
Central obesity: waist > 102cm	Hypertriglyceridaemia: Triglycerides ≥1.7 mmol/l	Obesity: WHR > 0.90 or BMI > 30 kg/m^2	Central obesity: waist ≥94 cm[a]
Hypertriglyceri-daemia: Triglycerides ≥1.7 mmol/l	Low HDL-cholesterol: HDL <1.0 mmol/l	Dyslipidaemia: Trigly-cerides ≥ 1.7 mmol/l or HDL< 0.9	Hypertriglyceri-daemia: Triglycerides ≥1.7 mmol/l
Low HDL-cholesterol: HDL <1.0 mmol/l	Hypertension: Blood pressure ≥130/85 mmHg or medication	Hypertension: Blood pressure ≥ 140/90 mmHg or medication	Low HDL-cholesterol: HDL <1.0 mmol/l
Hypertension: Blood pressure ≥130/85mmHg or medication	Fasting plasma glu-cose ≥ 5.6 mmol/l[b]or DM		Hypertension: Blood pressure 130/85mmHg or medi-cation
Fasting plasma glu-cose ≥6.1 mmol/l			Fasting plasma glu-cose ≥5.6 mmol/l[b]

[a]Ethnicity specific. [b]Fasting blood glucose ≥5.0 mmol/l. [c]In the original definition, microalbu-minuria was also a criterion.
NCEP = National Cholesterol Education Panel; IDF = International Diabetes Federation; WHO = World Health Organization; NHLBI = National Heart, Lung, and Blood Institute; AHA = Ameri-can Heart Association; DM = Diabetes Mellitus; IFG = Impaired Fasting Glucose; WHR = Waist-to-hip ratio; BMI = Body Mass Index; HDL = High-density lipoprotein

2.1.3 Public health importance of metabolic syndrome

The prevalence of metabolic syndrome is rapidly increasing worldwide (Zimmet et al. 2005). Metabolic syndrome forms a major public health issue by increasing the risk of type 2 diabetes (Laaksonen et al. 2002a, 2004a) and CVD (Lakka et al. 2002). The global preva-lence of diabetes is expected to double in the next two decades (IDF 2009). Diabetes will lead to approximately four million annual deaths globally in the age group of 20-79 (IDF 2009). Meanwhile, worldwide health care expenditures caused by diabetes are estimated to be at least 376 billion U.S. Dollars in 2010 (IDF 2009).

In Finland, the prevalence of overweight populations has been increasing (Helakorpi et al. 2005). As a consequence, in middle-aged and older Finns, up to 42% of men and 33% of women have impaired glucose tolerance or type 2 diabetes (Peltonen et al. 2006). Meta-bolic syndrome usually precedes abnormalities in glucose metabolism, likely increasing the syndrome's advancement.

2.2 PHYSICAL ACTIVITY

2.2.1 Assessment of physical activity

Physical activity has been defined as any bodily movement produced by skeletal muscles that increases energy expenditure beyond basal metabolic rate (Caspersen et al. 1985). A valid and reproducible assessment of physical activity is crucial in the investigation of relationship between physical activity and health. Physical activity is multidimensional and no single method is able to capture all subcomponents and domains in the investigated activity (Warren et al. 2010). Frequency, duration and intensity are fundamental dimensions of physical activity and allow calculation of energy expenditure associated with physical activity (Casparesen et al. 1985). Different types of physical activity exist, including LTPA, commuting physical activity, lifestyle physical activity, occupational physical activity, conditioning physical activity, as well as recreational and competitive sports.

Warren and coworkers recently published a review on the assessment of physical activity (Warren et al. 2010). They categorized the methods to assess free-living physical activity as self-reports (questionnaires, diaries, logs, recalls) and objective measures (motion sensors such as accelerometers, pedometers, heart rate monitors, direct observation, doubly labeled water). In observational studies, physical activity is traditionally assessed using self-reports. The accuracy of these methods is complicated by reactivity, recall bias and social bias (Ainsworth and Levy 2004). Objective measurements have been developed to solve these issues. They are, however, often too expensive or unpractical to use in large population studies and have other issues such as difficulties in capturing nonambulatory movements correctly (Warren et al. 2010).

Physical activity is typically classified by its intensity, expressed as metabolic equivalent (MET). One MET, the basal rate of oxygen consumption, is defined as metabolic expenditure at rest, corresponding to an oxygen uptake of 3.5 ml O_2/kg and energy expenditure of approximately 1 kcal/kg/hour. Other activities can be expressed as multiples of 1 MET: activities in range of 1.8-2.9 MET are considered low intensity activities, 3.0-5.9 MET moderate intensity and ≥ 6.0 MET vigorous (Warren et al. 2010).

2.2.2 Assessment of cardiorespiratory fitness

In population studies, cardiorespiratory fitness has been assessed by measuring maximal oxygen uptake ($V0_{2max}$), either directly by respiratory gas exchange analysis or indirectly in a graded exercise stress test (Åstrand and Rodahl 1986). Measuring $V0_{2max}$ indirectly is based on the assumption of a linear relationship between heart rate and oxygen uptake and the extrapolation of a submaximal heart rate to a known or predicted maximal heart rate. Direct measurement of oxygen consumption is the most accurate method for assessing cardiorespiratory fitness (Åstrand and Rodahl 1986). However, it is not often feasible or practical in large population studies. Therefore, indirect measurement of $V0_{2max}$ has been applied more frequently in epidemiologic studies.

2.2.3 Association between physical activity and cardiorespiratory fitness

Cardiorespiratory fitness is closely related to physical activity. Physical fitness is mainly determined by the frequency, duration and intensity of physical activity (Laukkanen et al. 2009) over the past weeks and months. However, the magnitude of response to exercise stimulus is genetically determined (Bouchard and Rankinen 2001; Blair et al. 2001). The direct genetic component of cardiorespiratory fitness is estimated to be 25% to 40% (Laukkanen et al. 2009). Therefore, the associations of cardiorespiratory fitness with health out-

comes should be estimated with caution when generalized to physical activity. Another distinction between cardiorespiratory fitness and physical activity is the intra-individual, day-to-day variability (Warren et al. 2010). Cardiorespiratory fitness stays relatively stable, taking time to adjust; whereas the level of physical activity constantly changes. Furthermore, $V0_{2max}$ is typically measured objectively in observational studies; whereas the assessment of physical activity is based on self-reports. This leads to a greater misclassification of physical activity and often to a weaker association with health outcomes than those of physical fitness (Blair et al. 2001).

2.2.4 Physical activity and general health

Substantial evidence shows that physically active people are healthier and are less likely to develop many chronic diseases than people with a sedentary lifestyle. Lack of physical activity is a well-known risk factor for CVD and many other chronic diseases (Warburton et al. 2006). Regular exercise reduces blood pressure, systemic low-grade inflammation and adipose tissue, especially visceral fat, and enhances serum lipid profile, endothelial function, cardiac function, coronary blood flow, autonomic balance, insulin sensitivity and glucose homeostasis (Physical Activity Guidelines Advisory Committee Report, 2008). These health benefits of exercise lead to a reduced risk of type 2 diabetes, CVD, and premature death. Recent American guidelines recommend for all adults moderate physical activity 2.5 hours per week or one hour 15 minutes vigorous-intensity physical activity per week. Adults are also recommended to engage in muscle-strengthening activities on two or more says a week (Physical Activity Guidelines Advisory Committee Report, 2008). These guidelines were issued in Finland, as well (Physical Activity. Current Care guideline 2010). The guidelines are based on substantial systematic evidence. A total of 30 prospective studies in 7 different countries, including >141 000 men and >263 00 women in gender-specific analysis and >50 00 subjects in analysis of both genders combined, showed a 30-35% risk reduction in the development of coronary heart disease (CHD) for most active men and women (Physical Activity Guidelines Advisory Committee Report, 2008). Prospective studies published since the guidelines show similar results (Shiroma and Lee 2010). Considering that most of these results have been controlled for beneficial effects of physical activity on cardiovascular risk factors, such as BMI, hypertension, dyslipidemia and diabetes, the risk reduction is probably underestimated (Shiroma and Lee 2010).

The preventive effect of physical activity on the development of metabolic syndrome and type 2 diabetes is indisputable. In Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study, physically active men were 48% less likely to develop metabolic syndrome than physically inactive men over four years (Laaksonen et al. 2002b). A review of randomized controlled trials (Williamson et al. 2004) showed a 40-60% reduction in the incidence of type 2 diabetes over 3-4 years in high risk individuals with a modest weight loss through diet and exercise. In the Finnish Diabetes Prevention Study regular physical activity was associated with a 57% reduced incidence of type 2 diabetes even after adjusting for dietary changes. In the Da Qing Impaired Glucose Tolerance and Diabetes Study (Pan et al. 1997), incident type 2 diabetes decreased by 46% in the exercise group, 42% in the diet and exercise group, and 31% in the diet-treated group. The available evidence, although coming mostly from observational studies, strongly supports a causal relationship between increased physical activity and health benefits.

Importantly, the health benefits of regular physical activity exceed potential risks. The risk of sudden cardiac event is greater for people who stay inactive than for those who increase their physical activity (Warburton et al. 2006). The risk can be minimized by preferring moderate intensity physical activity and increasing the level of activity gradually.

Musculoskeletal injuries are the most common adverse events caused by physical activity (Aaltonen et al. 2007). The risk is highest in contact and team sports, ranging from 6.6 to 18.3 per 1000 hours of participation and lowest in commuting and lifestyle activities and some sports such as golf, walking and swimming, ranging from 0.19 to 1.5 per 1000 hours of participation (Parkkari et al. 2004). The risk of overuse injuries can be decreased by preferring a variety of activities, increasing activity gradually and giving time for body adaptation (Aaltonen et al. 2007).

2.2.5 Physical activity and mental health

A physically active lifestyle contributes to mental health (Penedo and Dahn 2005). Observational studies have shown an inverse relationship of physical activity with various psychological outcomes, including depressive symptoms, clinical depression and anxiety (Penedo and Dahn et al. 2005). However, wide variations in psychological variables and disease severity have lead to a wide diversity in outcome findings (Dunn 2009). The evidence on the psychological benefits of exercise comes mainly from over 100 observational studies, most of which have assessed a cross-sectional relationship between physical activity and depression (Ströhle 2008; Physical Activity Guidelines Advisory Committee Report, 2008). These studies suggest that physically active people have on average a 45% lower odds of having depressive symptoms than physically inactive people (Physical Activity Guidelines Advisory Committee Report, 2008). For instance, in American and Canadian population surveys among over 55,000 people, physical activity was associated with fewer depressive symptoms (Stephens 1988). In a study among over 16,000 participants from 15 different European countries, physical activity was associated with improved mental health (Abu-Omar et al. 2004). Two large cohort studies of Finnish men and women 60 years and over showed that lack of physical activity was associated with depressive symptoms (Kivelä and Pahkala 1991), and that intensive exercise was related to fewer depressive symptoms (Ruuskanen and Ruoppila 1995). However, in the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study, lower levels of cardiorespiratory fitness, rather than lower levels of physical activity, were associated with a higher risk of having depressive symptoms (Tolmunen et al. 2006).

Prospective studies on physical activity and mental health are still scarce. The Caerphilly Study found no relationship, after ten years, between leisure-time physical activity and incident of common mental disorders (Wiles et al. 2007). Neither did physical exercise predict a depression score, eight years after commencement, in the Rancho Bernardo Study (Kritz-Silverstein et al. 2001). In The Harvard Alumni Study, however, physically active men had lower depression rates over a 25-year follow-up time (Paffenbarger et al. 1994). The Alameda County study also showed that lack of physical activity predicted the development of depression five years later (Camacho et al. 1991). Other studies including only women or adolescents have shown similar results (Motl et al. 2004; Wise et al. 2006; Ströhle et al. 2007). The evidence supporting the American physical activity guidelines includes 28 prospective studies in nearly 40 000 adults from 11 nations with follow-up time ranging from 9 months to 37 years (Physical Activity Guidelines Advisory Committee Report, 2008). This review concluded that the odds of developing depressive symptoms was 15 to 25% lower among physically active than inactive people after adjustment for the risk factors of depression. Some studies used a clinical diagnosis to define depression, indicating that the association of physical activity with depression is not limited to self-reported symptoms of depression. Furthermore, this inverse association between physical activity and depression was independent of age, sex, ethnicity and medical condition (Physical Activity Guidelines Advisory Committee Report, 2008).

Existing evidence makes it tempting to believe the causal effect of physical activity on depressive symptoms. De Moor and colleagues investigated 8662 twins (of whom 2743 were identical) and their parents in a prospective study and reported common genetic factors explaining a lack of voluntary physical activity with a risk for depression and anxiety (De Moor et al. 2008). The authors caution against justifying exercise as treatment of depression without randomized-controlled trials. The finding of the study, however, does not exclude the possibility that physical activity may prevent and reduce symptoms of depression and have other beneficial effects on mental health.

Experimental studies have shown that exercise decreases symptoms of depression (Lawlor and Hopker 2001; Dunn et al. 2005; Dunn 2009). Blumenthal and colleagues showed in a randomized controlled trial that the magnitude of the effect of exercise is comparable to that of an antidepressant (Blumenthal et al. 1999). A controlled trial by Dunn and colleagues reported a 40 to 50% better response and remission rates in the exercise training group compared to the social interaction and sunlight exposure place groups. A recent comprehensive Cochrane review with a meta-analysis of 25 randomized controlled trials comparing exercise to standard treatment, no treatment or placebo in adults with depression, showed that exercise decreased symptoms of depression (Mead et al. 2009). However, the authors were unable to determine the magnitude of the effect of exercise and the most effective type of exercise. There was no difference in the magnitude of the effect of exercise and other interventions, such as antidepressants and psychotherapy. Although, evidence on the intensity of physical activity needed for the treatment of depression is limited, the American Physical Activity Guidelines Advisory Committee (2008) concluded that both moderate-intensity and vigorous physical activity equally protect against depressive symptoms compared to low intensity physical activity. Moreover, the committee concluded that any physical activity is better than physical inactivity. The protective effect of physical activity is independent of the mode and length of the exercise program. Furthermore, an increase in physical fitness is not required to reduce depressive symptoms.

Mechanisms underlying the relationship of physical activity with mental health are still unclear. Regular physical activity, certainly, has positive effects on several psychosocial factors, including self-esteem and self-efficacy, social isolation, self-image and self-worth (Camacho et al. 1991), distraction, a sense of mastery and self-concept (Ströhle 2008). Furthermore, physical activity is suggested to have positive influences on brain structure and function in humans (Dishman et al. 2006). The mechanisms behind these adaptations are not known, but several neurogenerative, neuroadaptive and neuroprotective processes have been suggested in animal models, including increased expression of brain growth factors, stimulation of growth and development of brain cells and protection from neurotoxic damage (Dishman et al. 2006). Other possible biological pathways include activation of the hypothalamic-pituitary-adrenocortical system (Ströhle and Holsboer 2003), increased neurotransmissions of central dopaminergic, noradrenergic and serotonergic systems (Meeusen and De Meirleir 1995), as well as increased biosynthesis of neurotransmitters, such as monoamines, catecholamines and endorphines (Wise et al. 2006).

Furthermore, depression has been associated with an increased release of inflammatory cytokines (IL-1, IL-2, IL-6, TNF-alpha) (Smith 1991; Shimbo et al. 2005). IL-6 induces the production of C-reactive protein (CRP), which has been related to depression (Smith 1991; Liukkonen et al. 2006). Acute physically activity is a well-known activator of inflammatory system, increasing the release of IL-6 from muscle up to 100-fold during exercise (Pedersen et al. 2003). Interestingly, the effects of such response seem to be anti-inflammatory and to improve lipid and glucose metabolism. In long run, regular physical activity can lead to

lower basal levels of inflammatory cytokines in circulation (Lakka et al. 2005; Beavers et al. 2010). How this relates to depressive symptoms is not known.

2.3 DEPRESSIVENESS AND HOPELESSNESS

2.3.1 Assessment of depressive symptoms

Depressive symptoms refer to wide range of mental problems, including emotional, cognitive, behavioral and physical symptoms. Most epidemiological studies use self-report questionnaires to assess depressive symptoms and to identify persons with perceived mental stress. Self-reports are less expensive and less time-consuming than interviews and therefore more practical for research use. The Beck Depression Inventory (BDI) and the Center for Epidemiologic Studies Depression Scale (CES-D) are the most widely used depression scales (Van Dam and Earleywine 2010). Depression scales are intended as screening instruments to identify individuals likely to have psychopathology rather than as specific diagnostic tools. These scales can also be used to provide quantitive assessment of depressive symptoms.

Assessment of depressive symptoms is complex. For many constructs in psychiatry, there is no absolute truth (Blacker and Endicott 2008). All self-report measures are susceptible to the questions of validity since individuals may exaggerate or minimize their degree of distress (Delman et al. 2008). Nevertheless, some measures give more valuable data than others. Data obtained from questionnaires have claimed to have weak associations with clinical diagnosis of depression and stress (Fechener-Bates et al. 1994). Questionnaires are, however, designed to measure several dimensions of psychopathology and functional behavior and to assess mental health among healthy individuals and to provide screening for symptoms of psychopathology in general populations.

2.3.2 Depressiveness in relation to physical health

Depression has become a leading cause of disability in the western world (Lopez and Mathers 2006). The lifetime prevalence of depression is estimated to be 10-15% in developed countries. Depression not only deteriorates subjective well-being but also weakens physical health. Depression has been implicated in the development of cardiovascular disease and all-cause mortality (Lett et al. 2004; Van der Kooy et al. 2007). According to a systematic meta-analysis by Van der Kooy and coworkers (2007) including 28 longitudinal and case-control studies with approximately 80 000 subjects, a depressed mood was moderately associated with an increased risk of myocardial infarction (MI), coronary heart disease, cerebrovascular diseases and other cardiovascular diseases. This evidence, however, suffers from heterogeneity, and only overall combined risk of depression for the onset of MI was homogenous. A clinically diagnosed major depression had the strongest association with the risk of CVD that was equal to the risk of smoking and diabetes (Van der Kooy et al. 2007).

Depression is also related to metabolic disorders. The association of depression with obesity (Luppino et al. 2010), insulin resistance (Timonen et al. 2005), metabolic syndrome (Viinamäki et al. 2009) and type 2 diabetes (Knol et al. 2006) have all been reported. A large meta-analysis showed that depressed persons had a 58% higher risk of developing obesity than those without depression (Luppino et al. 2010). The authors argued that depression had a stronger association with obesity than with overweight indicating a dose-response gradient in the association. Räikkönen and colleagues (2007) reported that women with high levels of depressive symptoms were at an increased risk of developing metabolic syndrome. A meta-analysis of nine longitudinal studies showed that adults with de-

pression or higher levels of depressive symptoms have a 37% higher risk of developing type 2 diabetes compared to those with lower levels of depressive symptoms (Knol et al. 2006).

Accumulating evidence supports the argument that emotional stress is the third key factor causing the obesity epidemic and the following outcomes, after "the big 2" (too much food, too little exercise) (Cuzza and Rother 2011). The mechanisms explaining the mind-body interrelations remain unclear. Several plausible factors may, however, mediate associations of depression with cardiovascular and metabolic health, including lifestyle, psychosocial, physiological and pharmacological factors. Depressed persons are more likely to follow an unhealthy lifestyle, such as physical inactivity and overeating, and therefore gain unfavorable health outcomes (Blumenthal et al. 1982). Van Oudenhove et al. (2011) recently published an interesting discovery: Sad emotions, assessed by neuroimaging, can be modified by food intake without the sense of taste, sight and smell. Fatty and salty food, given by an intragastric infusion, decreased sad emotions and experimentally induced sadness increased hunger. Not only do people seek comfort food to alleviate distress, but the intestinal system itself is capable of modulating the brain's activity. Mind-body-behavior interactions are fascinating and yet to be revealed.

Neuroendocine and neuroimmune interactions may also explain the associations of depression, CVD and obesity. Neuroendocrinological studies of depression show that both metabolic syndrome and depression are associated with an increased activity of the hypothalamus-pituitary-adrenal (HPA) system and elevated glucocorticoid concentrations, which promote accumulation of visceral fat (Björntorp 2001). A hyperactive HPA axis is found in 75% of patients with major depression (Ahlberg et al. 2002). This hyperactivity may lead to hypercortisolaemia and increase accumulation of visceral fat (Weber-Hamann et al. 2002). A study by Vogelzangs and co-workers (2007) suggests that hyperactivity of HPA axis indentifies a specific subtype of depression that is related to metabolic syndrome, mediated by central obesity. Although cortisol is an anti-inflammatory hormone, there is evidence that in depressed patients cortisol fails to inhibit inflammatory responses by insufficient glucocorticoid signaling, called glucocorticoid resistance (Pace and Miller 2009). Inflammatory cytokines not only activate the HPA axis (Miller et al. 2009) but also independently stimulate the adrenal gland to secrete cortisol (Bornstein et al. 2008). Cortisol may initiate and worsen depressive symptoms (Howren et al. 2009). Depression could increase low-grade inflammation through decreasing parasympathetic activity (Howren et al. 2009). Inflammation, in turn, upregulates the HPA axis by increasing the release of corticotrophin-releasing hormone (CRH) (Howren et al. 2009). Hypothetically, this process may lead to vicious circle where central nervous system connects depression to systemic low-grade inflammation and vice versa. Ultimately this synergistic effect could result in unfavorable cardiovascular and metabolic outcomes.

Depression, obesity and cardiovascular diseases tend to cluster and observational studies indicate the link between them. Reduction of stress control often predisposes one to clinical depression, whereas lifestyle factors, such as physical activity and healthy diet, enhance coping with stress. More evidence is critically needed to fully understand the associations between these highly prevalent public health concerns. Whether some depressive symptoms relate more strongly than others to physical health is also undetermined.

2.3.3 Hopelessness – facet of depression or distinct entity?

Hopelessness, a major symptom of depression, has been determined as a system of negative expectancies concerning oneself and one's future (Stotland 1969). Hope is an important determinant of subjective well-being (Stotland 1969). Lack of hope is associated with

various manifestations of psychological morbidity (Haatainen et al. 2004). Psychological factors associated with hopelessness in the general population include depression, suicidal ideation and alexithymia, meaning a poor ability to recognize and verbalize emotions and externally oriented way of thinking (Haatainen et al. 2004). Some studies suggest that hopelessness might be even a more powerful risk factor of suicidality than depression (Beck et al. 1993, Salter and Platt 1990). Hopelessness has been seen as a trait that reflects person's attitude and increases vulnerability to react to certain environmental stimuli with depression (Henkel et al. 2002). These stimuli include unemployment, poor financial situation (Haatainen et al. 2003b), poor general health, dissatisfaction with life (Haatainen et al. 2004) and stress (Northouse et al. 2001), which all are associated with hopelessness in general populations.

Hopelessness has also been demonstrated to have a negative impact on physical health (Scheier and Carver 1985) and mortality (Stern et al. 2001). Everson and co-workers have shown that hopelessness is significantly associated with the incidence of hypertension, myocardial infarction, and cardiovascular mortality and with accelerated progression of carotid atherosclerosis in middle-aged men (Everson et al. 1996, 1997, 2000). In women, hopelessness was a strong and independent risk factor for subclinical atherosclerosis (Whipple et al. 2009). The National Health Examination Follow-up Survey also showed the relationship between hopelessness and the incidence of fatal and non-fatal ischemic heart disease during a 12-year follow-up (Anda et al. 1997). Recently, hopelessness was reported to associate with plasma levels of soluble intercellular adhesion molecule-1 (s-ICAM1) and e-selectin, that are adhesion molecules thought to be early markers of endothelial dysfunction (Do et al. 2010). Of interest, in all of these studies the association of hopelessness with the outcomes was stronger than that of depression.

Hopelessness is rather common in general populations. According to Haatainen and colleagues (2003a) the prevalence of hopelessness measured with the Beck Hopelessness Scale in a homogenous sample of Finnish adults was 11.4%. Hopelessness is often a major symptom of depression. However, after excluding those with any self-reported mental disorder diagnosed or treated by a physician during the preceding year the prevalence of hopelessness was still as high as 7.8%. Thus, although feelings of hopelessness and futility are common features of depression, hopelessness often exists in the absence of depression. Hopelessness has also been shown to have independent association with 5-HTTLPR s allele, proposing that hopelessness may be a distinct phenotype from depression (Kangelaris et al. 2010). Previous studies (Everson et al. 1996, 1997, 2000; Anda et al. 1997; Do et al. 2010) suggest that the correlation between hopelessness and depression scales is only moderate. Moreover, these studies suggest that the associations of feelings of hopelessness and depression can be disentangled, and that hopelessness may be a more powerful predictor of adverse cardiovascular outcome than depressive symptoms. Thus, although hopelessness is a facet of depression, it is nonetheless a distinct entity.

2.4 SYSTEMIC LOW-GRADE INFLAMMATION – COMMON SOIL HYPOTHESIS

Systemic low-grade inflammation has been implicated as part of the "common soil" leading to development of metabolic syndrome, type 2 diabetes and cardiovascular disease (Laaksonen et al. 2004b, 2005b, Mathieu et al. 2010). C-reactive protein, an acute phase protein delivered from the liver, rises in concentration as a response to infection or any tissue injury. This protein is also an important marker of systemic low-grade inflammation. According to the Centers for Disease Control and American Heart Association,

people with plasma levels of CRP over 3.0mg/l have a 2-fold risk of CVD compared with those with CRP levels below 1mg/l (Williamson et al. 2004). The KIHD Study showed that middle-aged men with plasma levels of CRP above 3mg/l had an increased risk of developing metabolic syndrome and type 2 diabetes during 11 years of follow-up than those with CRP levels below 1 mg/l (Laaksonen et al. 2004b). In addition, empirical evidence links low-grade inflammation to several other diseases, such as dementia, chronic, obstructive pulmonary disease, osteoporosis, arthritis, heart failure and cancer (Beavers et al. 2010).

Cross-sectional studies have shown that depression is linked with an increased release of inflammatory cytokines, and obesity may in part mediate the association (Howren et al. 2009). In previous studies, low-grade inflammation has been suggested to be the common denominator between depressive symptoms and cardiovascular and metabolic outcomes. Pollitt and coworkers (2005) reported that fibrinogen, a systemic marker of inflammation and thrombosis, partly mediated the relationship between hopelessness and the progression of carotid atherosclerosis. Frasure-Smith et al. (2007) followed patients with acute coronary syndromes for two years and found that depressive symptoms and plasma levels of CRP were associated with an increased risk of major adverse cardiac events but the combined effect was not additive. Only men with both low levels of CRP and no depression had a low risk of cardiac events, suggesting that CRP and depression are at least partially overlapping risk factors. On the other hand, a study by Ladwig and coworkers (2005) suggested that depressive mood increases the power of low-grade inflammation to predict myocardial infarction. Other studies also reported that inflammation did not explain the relationship between depressive symptoms and CVD incidence (Empana et al. 2005; Vaccarino et al. 2007; Nabi et al. 2010).

The few studies on depression, low-grade inflammation and obesity are cross-sectional. Ladwig and coworkers (2003) found a relationship between depressive mood and plasma CRP levels in obese but not in non-obese men. However, Olszanecka-Glinianowicz and colleagues (2009) did not observe differences in inflammatory markers between depressive and non-depressive patients with obesity. This finding could be explained by a very high BMI of all subjects and a small study population. Capuron and coworkers (2008) investigated the role of inflammation in the association of depressive symptoms with metabolic syndrome in 323 men. The cross-sectional relationship of neurovegetative depressive symptoms and metabolic syndrome was weakened after adjusting for CRP and IL-6, suggesting that inflammation mediates, in part, this association. A recently published review assessed the direction of the association between depression and inflammatory markers and suggested that the direct association could be the result of a complex, tridirectional relationship among adiposity, low-grade inflammation and depression (Howren et al. 2009).

Evidently, long term exposure to systemic low-grade inflammation may lead to the development of chronic diseases. The evidence explaining the nature of this relationship is limited. It is, however, hypothesized that behavioral interventions that control or reduce low-grade inflammation could be effective to prevent and treat chronic disease. Physical activity has been shown to be related to lower levels of inflammation in observational studies (Nicklas et al. 2005; Beavers et al. 2010). Promising data from randomized control trials exists as well, indicating that aerobic physical activity may be beneficial in reducing low-grade inflammation, especially for people with elevated inflammatory markers (Beavers et al. 2010).

2.5 SUMMARY OF THE REVIEWED LITERATURE

Metabolic syndrome forms a major concern for public health by predisposing people to type 2 diabetes and cardiovascular diseases. Depressive symptoms, such as hopelessness, also deteriorate physical health. Based on the reviewed literature, the association between metabolic syndrome and depression is very complex. Several behavioral, physiological and social factors may explain relationship between them. Systemic low-grade inflammation may provide "the common soil" in the development of several chronic diseases. However, understanding of mediating factors and the causality in the relationship between metabolic syndrome and depression is largely lacking. Whether some depressive symptoms are more harmful for metabolic health than the others is also unknown. Hopelessness, defined as system of negative expectations concerning oneself and one's future, has been shown to increase risk for cardiovascular morbidity and mortality, independent of depression. Some studies argue that hopelessness is more powerful risk factor for CVD than depression. Although hopelessness and depression overlap, they are still considered distinct phenomena. How feelings of hopelessness relate to metabolic syndrome has not been studied earlier.

Physical activity clearly has positive effects on both physical and mental health. Substantial evidence shows that physically active people are less likely to develop symptoms of depression than people with sedentary behavior. In addition, intervention studies report antidepressive effects of exercise. Majority of the existing data, however, are criticized to have methodological deficiencies. More prospective data is called for to further distinguish the association of physical activity with depression and depressive symptoms.

3 Aims of the study

The purpose of the doctoral thesis is to provide new information about the etiology of metabolic syndrome, depression and hopelessness, to disentangle their relationships, and to clarify possible mediating factors underlying the associations. The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) with its large database and long follow-up period offered a unique opportunity to study cross-sectional and longitudinal relations of psychosocial factors and metabolic syndrome. The aims of the study were to answer the following specific questions in middle-aged men:

1. Are depressive symptoms and hopelessness associated with metabolic syndrome, and what are the determinants of this association? (**Study I**)
2. Do psychosocial risk factors predict the development of metabolic syndrome and what are the mediating mechanisms of this association (e.g. life-style factors, markers of systemic low-grade inflammation)? (**Study II**)
3. Do higher levels of physical activity and cardiorespiratory fitness protect against the development of depressive symptoms and hopelessness? (**Study III and IV**)?

4 Materials and methods

4.1 STUDY POPULATION

The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) is a population-based, cohort study that was designed to investigate biological, behavioral, socioeconomic and psychosocial risk factors for ischemic heart disease, diabetes and related outcomes in a sample of middle-aged men in Eastern Finland (Salonen 1988). Baseline data were collected between 1984 and 1989 from 2682 (89.2% of those eligible) male participants aged 42, 48, 54 and 60 years old. This study group is a representative sample of Finnish male population from town of Kuopio and neighboring rural communities. For the KIHD 4-year and 11-year follow-up study, 1229 subjects who had undergone carotid ultrasound examination at baseline between 1987 and 1989 were eligible. Of these, 1038 underwent repeat examinations during 1991-1993 and 854 during 1998–2001 (Lakka et al 2001).

The Research Ethics Committee of the University of Kuopio approved the study. All study subjects gave their written informed consent. The different studies include approximately from 500 to 2500 men who had complete data on the main characteristics of metabolic syndrome and who completed questionnaires on depressive symptoms and physical activity. The participants who had complete data on all study variables were eligible for the present study. The study samples and designs are presented in Table 2.

Table 2. Description of the study populations and designs.

Study	Design	Size	Exclusions at baseline	Variable of interest	Main outcome
I	cross-sectional	1743	diabetes	Hopelessness	Metabolic syndrome
II a	11-year follow-up	726	diabetes, waist >102cm	Depressive symptoms, low-grade inflammation	waist >102cm
II b	11-year follow-up	689	diabetes, metabolic syndrome	Depressive symptoms, low-grade inflammation	Metabolic syndrome
III	cross-sectional	2428	none	Physical activity, cardiorespiratory fitness	Hopelessness
IV a	4-year follow-up	630	hopelessness	Physical activity	Hopelessness
IV b	11-year follow-up	509	hopelessness	Physical activity	Hopelessness

4.2 DEFINITION OF METABOLIC SYNDROME

In the present study definitions of metabolic syndrome were used as proposed by the World Health Organization (WHO), the National Cholesterol Education Program (NCEP) and the International Diabetes Federation (IDF). The criteria of these definitions are presented previously in detail (Table 1). When using WHO definition, insulin resistance was estimated based on the upper quartile of fasting insulin concentrations (Lakka et al. 2002). Impaired fasting glucose was defined as a fasting blood glucose 5.6-6.0 mmol/l, equivalent to plasma glucose of 6.1-6.9 mmol/l (Alberti and Zimmet 1998). Diabetes was determined as fasting blood glucose concentration ≥6.1 mmol/l (equivalent to plasma glucose ≥7.0 mmol/l) or a clinical diagnosis of diabetes with either dietary, oral or insulin treatment (Laaksonen et al. 2002a; Lakka et al. 2002). Waist circumference cut-offs were used as >102 cm for NCEP definition and ≥94cm for IDF definition.

4.3 ASSESSMENT OF COMPONENTS AND FEATURES RELATED TO METABOLIC SYNDROME

Body mass index was computed as the ratio of weight to the square of height (kg/m^2). WHR was defined as waist girth/hip circumference measured at the trochanter major.

Waist circumference was calculated as the average of two measurements taken at the midpoint between the lowest rib and the iliac crest after inspiration and expiration. Resting blood pressure was measured between 8 and 10 o'clock by two trained nurses with a random-zero mercury sphygmomanometer (Hawksley, Lancing, UK).

Fasting blood glucose was measured using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. Serum insulin was determined with a Novo Biolabs radioimmunoassay kit (Novo Nordisk, Bagsvaerd, Denmark). Plasma fibrinogen was measured based on the clotting of diluted plasma with excess thrombin. Serum high sensitivity C.reactive protein (hs-CRP) was measured with an immunometric assay (Immulite High Sensitivity C-reactive protein Assay, DPC, Los Angeles, CA, USA) (Laaksonen et al. 2004b). This C-reactive protein assay has been standardized against the WHO International Reference Standard for C-reactive protein Immunoassay 85/506. At the level of 3.2 mg/L, the within-run CV is 2.8% and the total CV is 3.1% (Laaksonen et al. 2005b).

4.4 ASSESSMENT OF PHYSICAL ACTIVITY

The validated KIHD 12-month LTPA Questionnaire was used in the present study to assess physical activity (Lakka and Salonen 1992; Lakka et al. 1994). This is a detailed quantitative questionnaire assessing the duration, frequency and mean intensity of the most common lifestyle and structured LTPA of middle-aged Finnish men as recalled over the previous 12 months. Physical activity was categorised according to type: 1) conditioning physical activity: walking, jogging, cross-country skiing, bicycling, swimming, rowing, ball games and gymnastics, dancing or weight lifting, 2) nonconditioning physical activity: crafts, repairs or building, yard work, gardening, farming or snow shovelling, hunting, picking berries or gathering mushrooms, fishing and forest work or forestry, 3) walking or cycling to work. Low-intensity LTPA was defined as <4.5 METs, moderate-to-vigorous LTPA as ≥4.5 METs and vigorous LTPA as ≥7.5 METs. The durations of LTPA were calculated in min/week.

4.5 ASSESSMENT OF CARDIORESPIRATORY FITNESS

A graded symptom-limited exercise test was performed on an electrically braked cycle ergometer (Tunturi EL 400 bicycle ergometer, Turku, Finland). Oxygen consumption was measured by respiratory gas analysis using either the mixing–chamber method (Mijnhardt, Odijk, the Netherlands) or the breath-by-breath method (Medical Graphics, St. Paul; MN, USA) as previously described in detail (Lakka et al. 1994, 2001). $V0_{2max}$ was defined as the highest value for or the plateau in oxygen uptake.

4.6 ASSESSMENT OF DEPRESSIVE SYMPTOMS

The Human Population Laboratory Depression Scale (HPL Depression Scale) was used to assess depressive symptoms. The HPL Depression Scale is a self-administered questionnaire that includes 18 items on conditions related to depression such as mood disturbances, a negative self-concept, loss of energy, problems with eating and sleeping, difficulty in concentrating, and psychomotor retardation or agitation (Roberts and O'Keefe 1981; Kaplan et al. 1987; Tolmunen et al. 2004a, 2004b, 2006). The score is generated by assigning one point for each true or false answer that corresponds to depressive symptoms.

The range of the HPL Depression Scale is 0-18 points. This scale has good internal consistency and demonstrated reliability (Kaplan et al. 1987) and it was specifically developed for screening general population samples (Roberts and O'Keefe 1981; Kaplan et al. 1987). A cut-off ≥5 has been used previously to classify men with depressive symptoms and to define clinically significant depression (Kaplan et al. 1987). The same cut-off point was used in the present thesis.

4.7 ASSESSMENT OF HOPELESSNESS

The subjects filled in several psychological questionnaires at baseline, at 4-year and 11-year follow-ups. The questionnaires included two items that measured hopelessness (Everson et al. 1996, 1997, 2000). These items were "the future seems to be hopeless, and I cannot believe that things are changing the better" and "I feel that it is impossible to reach the goal I would like to strive for". Participant responded using 5-point Likert scale (0 = absolutely agree, 1 = somewhat agree, 2 = cannot say, 3 = somewhat disagree, or 4 = absolutely disagree). Hopelessness score, with a range of 0 to 8, was created by reverse-coding and summing the items. The items were moderately correlated (r = 0.53) and the mean SD for hopelessness score at baseline was 2.73 (2.0). Cronbach's alpha for hopelessness score was 0.70. Scores on the hopelessness scale increased with age (P<0.001, means varied from 2.02 for 42-year olds to 2.93 for 54- and 60-year-olds) (Everson et al. 1996).

4.8 OTHER ASSESSMENTS

Participants filled in self-administered standardised questionnaires at baseline to record their medical history, adult socioeconomic status and lifestyle factors, such as smoking habits and alcohol consumption. Information on the amount of cigarettes, cigars and pipefulls of tobacco were ascertained by questionnaire. Smoking was categorized as none, 1 – 20 cigarettes/day or more than 20 cigarettes/day. A questionnaire on the quantity, frequency and type of alcoholic beverages was used to estimate alcohol intake. The average weekly consumption of alcohol was measured in pure ethanol (g/wk) (Kauhanen et al. 1997). Adult socioeconomic status was estimated using a summary index based on data collected by questionnaire on income, education, housing tenure and ownership of material goods (Lynch et al. 1994). The index ranged from 1 to 10, a higher value indicating lower socioeconomic status.

4.9 STATISTICS

SPSS 11.0-14.0 for Windows (SPSS, Inc., Chicago, IL) was used to perform all statistical analyses. Statistical significance was considered to be $P<0.05$.

Study I. Men were categorized into tertiles based on the scores for hopelessness. Differences in clinical and biochemical characteristics between men in hopelessness categories were tested for statistical significance with one-way ANOVA, and where indicated, the chi-squared test. The cut-off for the second tertile was 2 points and for the highest tertile 4 points. The associations of hopelessness with metabolic syndrome were estimated using logistic regression models adjusting for covariates.

Study II. Abdominal obesity was defined as waist girth >102cm and this was considered as endpoint at 11-year follow-up. To study the risk of developing abdominal obesity and metabolic syndrome, men with waist girth above the cut-off or men with metabolic syndrome at baseline were excluded from the prospective analyses. Men with diabetes and those using antidepressants were also excluded from these analyses.

Differences in characteristics between men who developed central obesity during the 11-year follow-up and those who did not were assessed with Student's t-test for continuous variables and the chi-squared test for categorical variables. A variable combining low-grade inflammation and depressive symptoms was created using the cut-offs serum hs-CRP ≥2mg/l and HPL Depression Scale ≥5 points. Participants were categorized into three groups according to these scores: men with no inflammation nor depressive symptoms, men with either inflammation or depressive symptoms and men with both inflammation and depressive symptoms. The association between low-grade inflammation and depressive symptoms and the risk of developing abdominal obesity at 11-year follow-up was estimated using logistic regression analysis adjusting for covariates. In separate analysis, the associations of low-grade inflammation and the risk of developing abdominal obesity, as well as depressive symptoms and the risk of developing abdominal obesity were tested. Variables with skewed distributions are presented as medians (interquartile ranges) and analysed using log-transformed values. Other data are presented as means ± standard deviations or percentages.

Study III. Participants were categorized by tertiles based on their scores for hopelessness. Differences between men in the highest third of hopelessness and men in the middle and lower thirds were assessed with one-way ANOVA, and where indicated, the chi-squared test. LTPA and VO_{2max} were categorized by tertiles for logistic regression analyses. The associations of LTPA and VO_{2max} with hopelessness were estimated using logistic regression models adjusting for age, smoking, alcohol consumption, presence of CVD, adult SES, low-grade inflammation, BMI and depressive symptoms. Durations of LTPA (in min/week) and triglyceride, insulin and hs-CRP concentrations are presented as medians (interquartile ranges); other data are presented as means ± SD or simple percentages. Triglyceride and insulin concentrations were corrected for skewing using log transformation for statistical analysis but are presented using untransformed values.

Study IV. At baseline men with a hopelessness score in the highest tertile, i.e. those with ≥ 4 points were excluded from the prospective analyses. Men who scored ≥ 4 points after follow-up were defined as having developed hopelessness. Differences in characteristics at baseline between men who developed hopelessness during the 11-year follow-up and those who did not were assessed with Student's t-test for continuous variables and the chi-squared test for categorical variables. The association between LTPA and risk of developing hopelessness at the 4- and 11-year follow-up was estimated using logistic regression analysis adjusting for covariates. Variables with skewed distributions are presented as medians (interquartile ranges) and analysed using log-transformed values. Other data are presented as means ± standard deviations or simple percentages.

5 Results

5.1 HOPELESSNESS AND METABOLIC SYNDROME (Study I)

Baseline clinical characteristics. Men in the highest third of hopelessness were physically less active, had lower socio-economic status and more commonly smoked than other participants (Table 2 of the Original Publications, **Study I**). They also had a higher BMI, larger waist girth and higher mean systolic blood pressure. The participants in the highest third had also higher CRP concentrations than the other men. The prevalence of metabolic syndrome as defined by the NCEP and the IDF increased in a graded fashion across hopelessness categories. The prevalence of elevated depressive symptoms also increased gradually with the hopelessness categories.

Hopelessness and metabolic syndrome. Men in the highest third of hopelessness were 2.2 times more likely to have metabolic syndrome by NCEP definition than men in the lowest category in models adjusting for age (Table 3 of the Original Publications, **Study I**, P<0.001). After further adjustment for traditional risk factors (SES, presence of CVD, smoking, alcohol consumption, physical activity) and BMI, the association remained statistically significant (P=0.002-0.009). After further adjustment for traditional risk factors and separate components of metabolic syndrome the association still persisted (e.g. plasma glucose P=0.002, serum insulin P=0.004, waist girth P=0.017).

Adjustment for traditional risk factors and adult socioeconomic position did not alter the association (upper vs. lower third, OR 2.1, 95% CI 1.3-3.2). Adjustment for other measures of socioeconomic status, such as income and years of education, also did not change the observed association between hopelessness and metabolic syndrome (data not shown).

Concentrations of serum CRP and plasma fibrinogen were also higher in men with more pronounced feelings of hopelessness. Adjustment for CRP and fibrinogen, however, did not alter the association of hopelessness with metabolic syndrome (data not shown).

The analysis by the IDF definition of metabolic syndrome showed similar results, but the association was somewhat weaker. The risk to have metabolic syndrome was 1.6 times higher for the men in the highest group than men in the lowest group of hopelessness after adjustment for age (Table 3 of the Original Publications, **Study I**, P=0.002). Adjustment for the traditional risk factors and BMI decreased this association slightly (P=0.039 - 0.065). The association persisted after further adjustment for depressive symptoms (P=0.017). Further adjustment for traditional risk factors and separate components of metabolic syndrome only waist girth decreased the association significantly.

In the analysis by WHO definition of metabolic syndrome there was no association between hopelessness and metabolic syndrome after adjusting for traditional risk factors (with adjustment only for age: OR 1.4, CI 95% 1.1-2.0, P=0.020; with adjustment for age and traditional risk factors: OR 1.3, CI 95% 1.0-1.9, P=0.105).

Hopelessness, depressive symptoms and metabolic syndrome. There was a direct association between hopelessness and depressive symptoms as continuous variables (r=0.38)). The prevalence of depressive symptoms increased in a graded fashion with the hopelessness categories (Table 1 of the Original Publications, **Study I**). However, adjustment for

depressive symptoms in the logistic regression analyses did not weaken the association of hopelessness with metabolic syndrome (upper vs. lower third, OR 2.1, 95% CI 1.4-3.4). Furthermore, there was no interaction between hopelessness and categories of depressive symptoms in the association with metabolic syndrome (e.g., for metabolic syndrome as defined by the NCEP, P=0.75 for the interaction). Use of different cut-offs for the dichotomization of depressive symptoms or use of the HPL Depression Scale as a continuous variable also did not change the overall results (data not shown).

5.2 DEPRESSIVE SYMPTOMS, LOW-GRADE INFLAMMATION AND DEVELOPMENT OF ABDOMINAL OBESITY AND METABOLIC SYNDROME (Study II)

Baseline clinical characteristics. Men with both low-grade inflammation and depressive symptoms had a lower socio-economic status and consumed more alcohol and smoked more commonly than other participants (Table 1 of the Original Publications, **Study II**). They also had a higher BMI, larger waist girth and more unfavourable lipid profile. While men with both low-grade inflammation and depressive symptoms had a lower cardiorespiratory fitness than others, their LTPA level was not significantly lower than the others'. The prevalence of cardiovascular disease increased in a graded fashion across the inflammation and depressive symptom categories.

The risk of abdominal obesity. CRP alone predicted the development of waist girth >102 cm (with adjustment for age: OR 2.43, Cl 95% 1.22-2.86, P<0.001; with adjustment for age, socioeconomic status, presence of cardiovascular disease, smoking, alcohol consumption, physical activity: OR 2.25, Cl 95% 1.44-3.51, P<0.001), but depressive symptoms did not (with adjustment for age: OR 1.54, Cl 95% 0.90-2.65, P=0.125; with adjustment for age and traditional risk factors OR 1.48, Cl 95% 0.83-2.63, P=0.207).

Men with both low-grade inflammation and depressive symptoms were nearly 5 times more likely to develop a waist girth over 102 cm during the 11 years of follow-up than men with neither of these risk factors after adjusting for age (Figure 1; Table 2 of the Original Publications, **Study II**, P<0.001). After further adjustment for potential risk factors the risk was still over 4-fold (P=0.005). When further adjusting for BMI the trend was no longer significant (P=0.859).

Similarly, when using a waist girth at least 94 cm, the risk of developing abdominal obesity was increased in men with both low-grade inflammation and depressive symptoms (with adjustment of age and traditional risk factors: OR 3.29, Cl 95% 0.95-11.43, P<0.001)

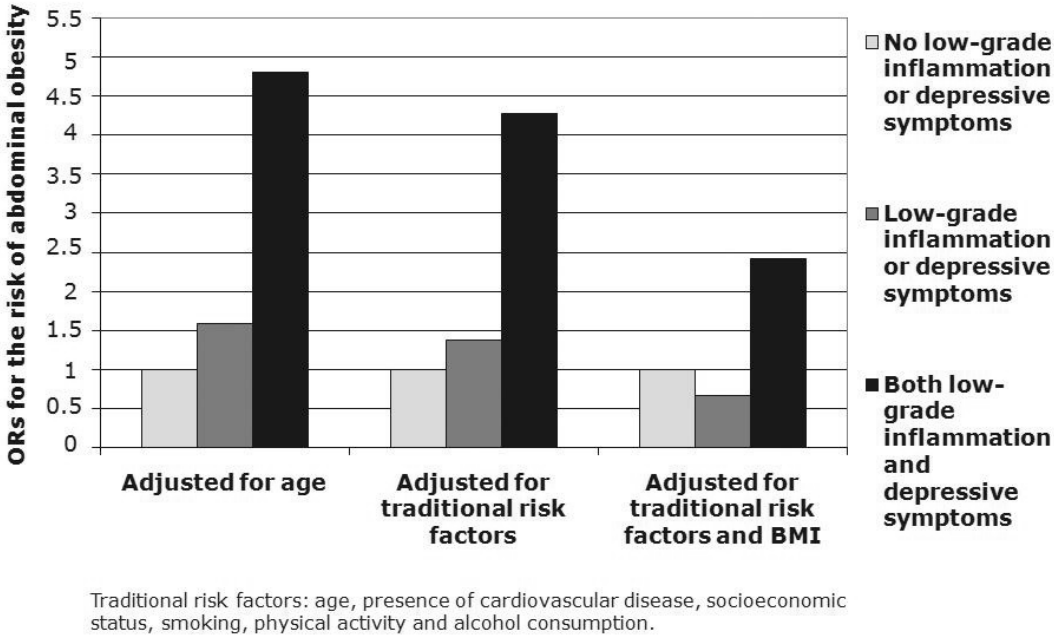

Figure 1. The risk (Odds Ratios) of developing abdominal obesity (waist girth >102 cm) in 11 years according to low-grade inflammation and depressive symptoms

The risk of developing metabolic syndrome. After adjustment for age and potential cardiovascular risk factors (SES, presence of CVD, smoking, alcohol consumption, physical activity), men with both low-grade inflammation and depressive symptoms were 4 times more likely develop metabolic syndrome during the 11 years (Figure 2; Table 2 of the Original Publications, **Study II**, P=0.001 and P=0.007, respectively). After further adjustment for BMI, the association was no longer significant (P=0.393).

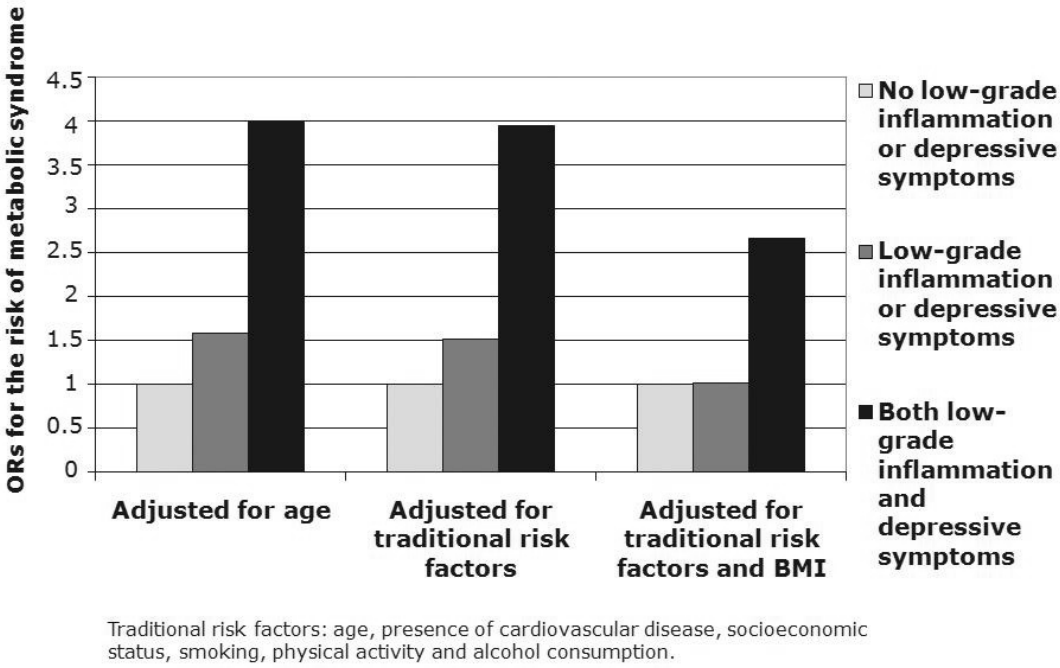

Figure 2. The risk (Odds Ratios) of developing metabolic syndrome in 11 years according to low-grade inflammation and depressive symptoms

5.3 PHYSICAL ACTIVITY, CARDIORESPIRATORY FITNESS AND HOPELESSNESS (Study III)

Cross-sectional association of LTPA with hopelessness. After adjustment for age, men with at least moderate LTPA more than 2.5h/week had a 41% lower risk of being hopeless than men with ≤60 min moderate LTPA/week (Figure 3a; Table 2 of the Original Publications, **Study III**, P<0.001). After further adjustment for potential confounding or mediating factors (age, SES, presence of CVD, smoking, alcohol consumption, low-grade inflammation, BMI and depressive symptoms), the association remained significant (P=0.001-0.003).

The association of vigorous LTPA with hopelessness was even stronger (Figure 3a; Table 2 of the Original Publications, **Study III**). Total LTPA was similarly associated with hopelessness, but low-intensity exercise was not (Table 2 of the Original Publications, **Study III**).

In additional analyses with separate adjustment of variables in Model 2 by VO_{2max}, diabetes and metabolic syndrome, none of these potentially mediating factors weakened the association (data not shown). Adjusting for the separate components of metabolic syndrome (fasting serum HDL, triglycerides or insulin, fasting blood glucose, waist girth and blood pressure) did not alter the association of moderate-to vigorous or vigorous LTPA with hopelessness either. Furthermore, in the association with hopelessness there was no interaction between moderate-to-vigorous LTPA and diabetes (P=0.290), CVD (P=0.641), or metabolic syndrome (P=0.225 for the interaction). There also was no interaction between high-intensity LTPA and these variables for the association with hopelessness.

The men were categorized by VO_{2max} tertiles to study whether cardiorespiratory fitness modifies the association between moderate LTPA and hopelessness (Figure 1 of the Original Publications, **Study III**). The association seemed to be stronger in the most fit group, but the interaction term for VO_{2max} and LTPA with respect to hopelessness was not significant (P=0.348). Physically unfit and physically inactive men were twice as likely to feel hopeless than fit and physically active men.

LTPA, hopelessness and depressive symptoms. HPL depression score and hopelessness score correlated moderately (r=0.38, P<0.001). The average HPL depression score in men in the highest third of hopelessness categories was higher than in the lower tertiles (Table 1 of the Original Publications, **Study III**). However, in the logistic regression analysis elevated depressive symptoms did not decrease the associations of moderate or vigorous LTPA and hopelessness (Figure 3b; Table 2 of the Original Publications, **Study III**, P=0.003 and P<0.001 respectively). Moreover, there was no interaction between LTPA and depressive symptoms in the association with hopelessness (moderate LTPA P=0.380, vigorous LTPA P=0.957 for the interaction). In separate analyses, depressive symptoms and LTPA were not associated.

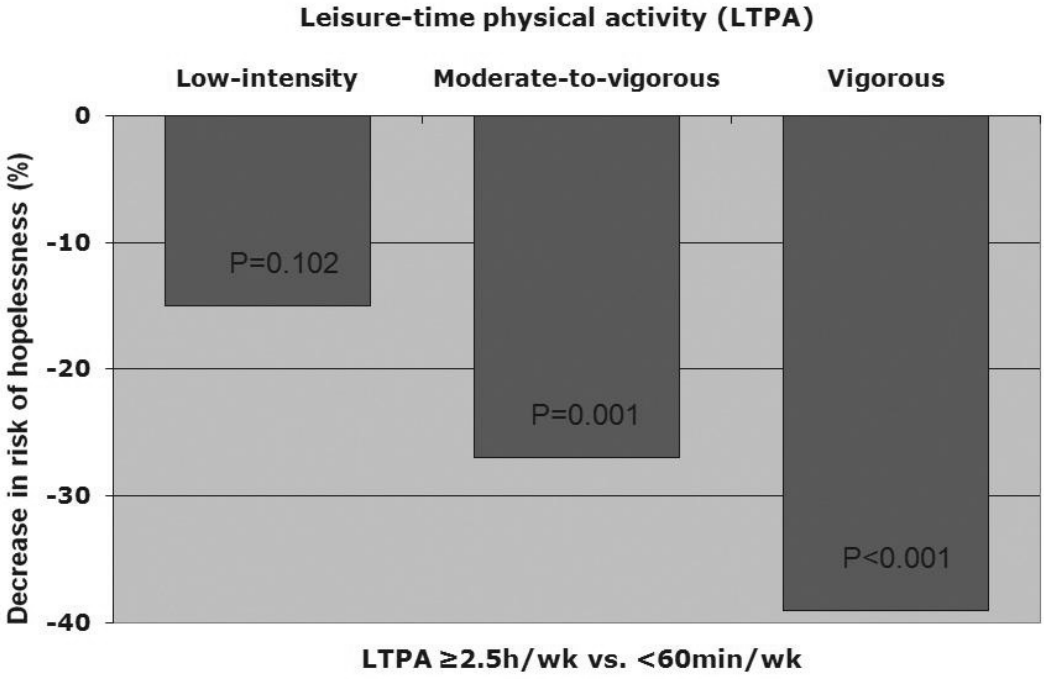

Figure 3a. Decrease in risk (in percentages) of hopelessness according to physical activity categories at baseline

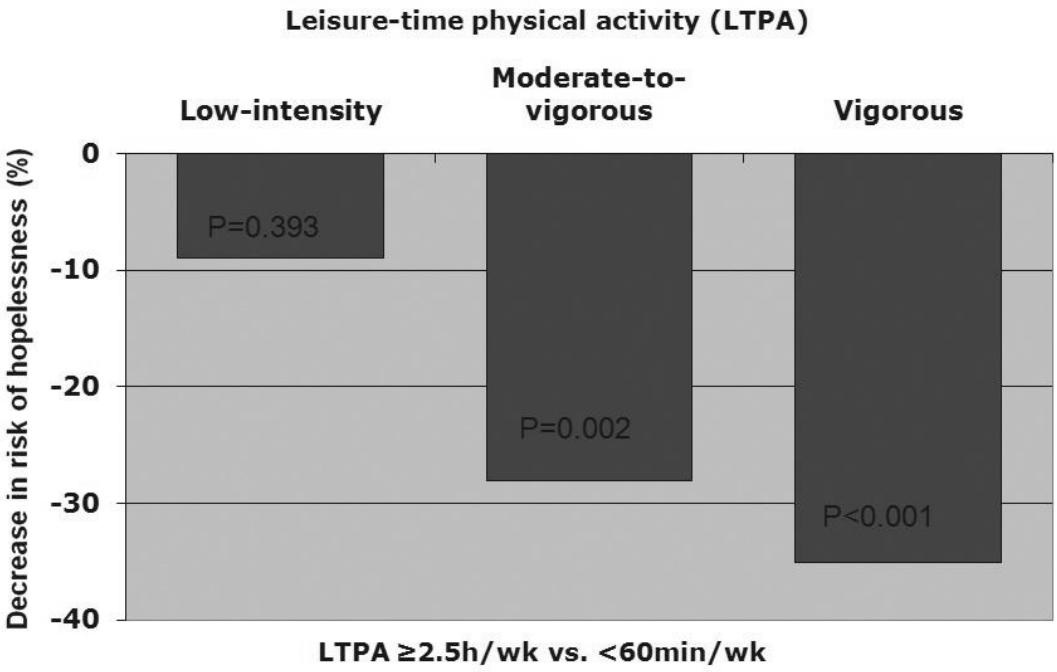

Figure 3b. Decrease in risk (in percentages) of hopelessness according to physical activity categories at baseline

Association of cardiorespiratory fitness with hopelessness. Men with VO_{2max} over 35.7 ml • kg^{-1} • min^{-1} were 47% less likely to express feelings of hopeless than those with VO_{2max} below 28.9. ml • kg^{-1} • min^{-1} after adjusting for age (Figure 4). After further adjustment for potentially confounding variables, cardiorespiratory fitness was still associated with hopelessness (Table 2 of the Original Publications, **Study III** P=0.003-0.037). After further adjustment separately for potential mediating factors, such as LTPA, diabetes, CVD and metabolic syndrome, the association remained significant (data not shown). Of the components of metabolic syndrome, only waist girth attenuated the association between VO_{2max} and hopelessness significantly (data not shown). Moreover, there were no interaction between VO_{2max} and diabetes (P=0.113), cardiovascular disease (P=0.196) or metabolic syndrome (P=0.785 for the interaction) in the association with hopelessness.

Cardiorespiratory fitness, hopelessness and depressive symptoms. Unlike with physical activity, after adjusting for depressive symptoms the association of cardiorespiratory fitness with hopelessness was no longer significant (Figure 4; Table 2 of the Original Publications, **Study III**). There was no interaction between VO_{2max} and depression in the association of VO_{2max} with hopelessness (P=0.109).

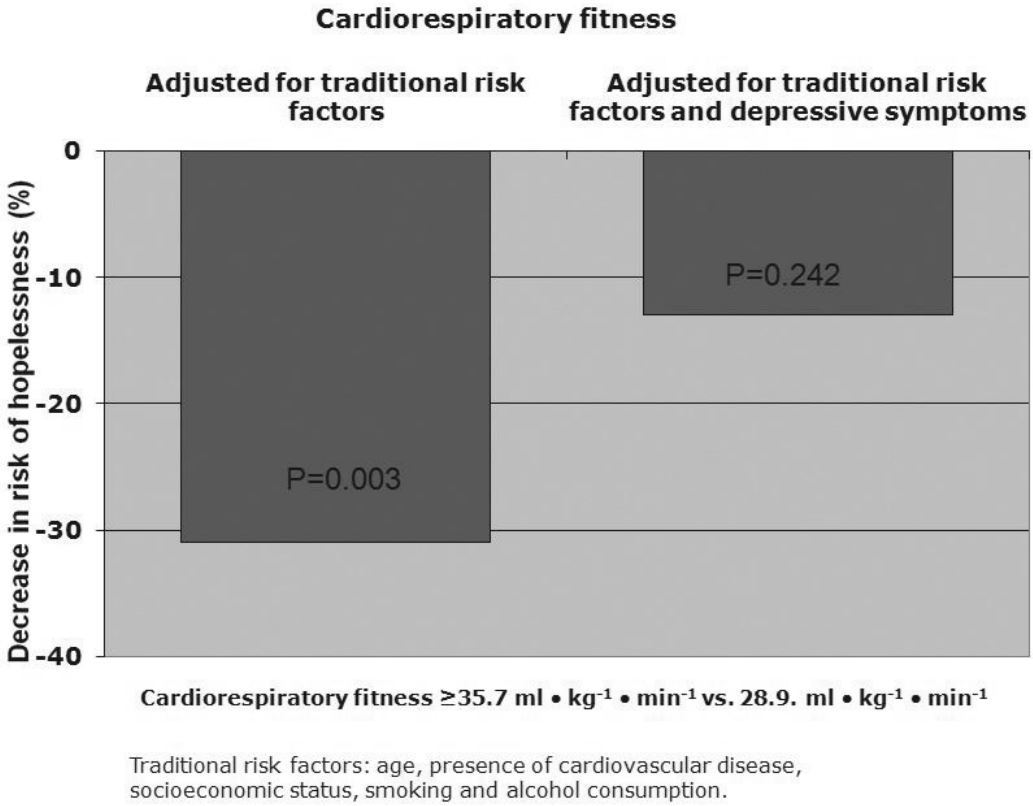

Figure 4. Decrease in risk (in percentages) of hopelessness according to cardiorespiratory fitness

5.4 PHYSICAL ACTIVITY AND RISK OF HOPELESSNESS (Study IV)

Baseline characteristics. Men who developed hopelessness at the follow-up had lower socioeconomic status and were more often smokers at baseline than the less hopeless men at baseline (Table 1 of the Original Publications, **Study IV**).

LTPA and hopelessness. Similarly to the baseline analysis, cross-sectional analyses at 4 years and 11 years of follow-up showed that LTPA and hopelessness were connected after adjustment for traditional risk factors (e.g. 4-year follow-up, total LTPA: OR 0.65, 95% Cl 0.45-0.94, P=0.015; vigorous LTPA: OR 0.70, 95% Cl 0.48-1.02, P=0.037; moderate-to-vigorous LTPA: OR 0.67, 95% Cl 0.47-0.95, P=0.008; 11-year follow-up, total LTPA: OR 0.76, 95% Cl 0.50-1.17, P=0.188; vigorous LTPA: OR 0.66, 95% Cl 0.43-1.01, P=0.042; moderate-to-vigorous LTPA: OR 0.52, 95% Cl 0.33-0.80, P=0.003). Low-intensity LTPA was not associated with hopelessness at any of the time points.

LTPA and the risk of developing hopelessness during 4-year follow-up. Men who reported at least 2.5 hours of moderate-to-vigorous LTPA per week were 42% more likely (Figure 5; OR 0.58, 95% Cl 0.35-0.96, P for trend=0.023) to feel hopeless 4 years later than physically inactive men adjusting for age (Table 2 of the Original Publications, **Study IV**). The association weakened slightly after further adjustment for smoking, alcohol consumption, cardiovascular disease and adulthood socioeconomic status as well as after additional adjustment for depressive symptoms (Figure 5). Further adjustment for $V0_{2max}$ and BMI had no effect on the association.

Total LTPA, vigorous LTPA, and low-intensity LTPA did not predict hopelessness at the 4-year follow-up (Table 2 of the Original Publications, **Study IV**). Furthermore, $V0_{2max}$ was not associated with the development of hopelessness during the 4-year follow-up.

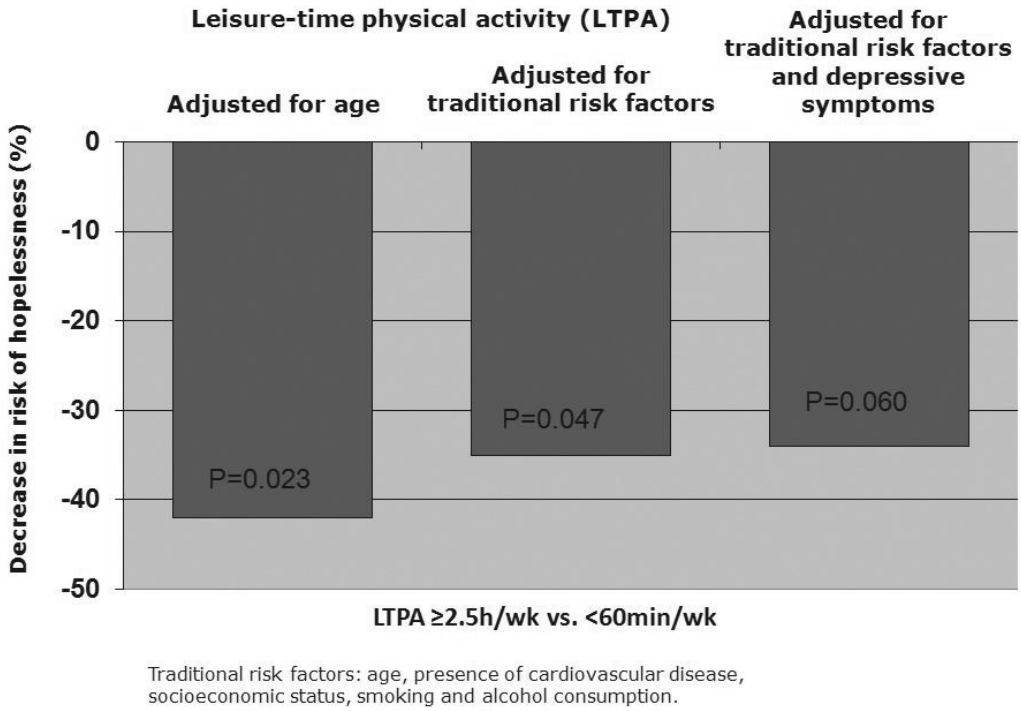

Figure 5. Decrease in risk (in percentages) of hopelessness during 4 years according to moderate-to-vigorous physical activity.

LTPA and the risk of developing hopelessness during the 11-year follow-up. An age-adjusted logistic regression model showed that moderate-to-vigorous LTPA at baseline reduced the risk to develop feelings of hopelessness during 11 years of follow-up (Figure 6; Table 2 of the Original Publications, **Study IV** with adjustment for age, OR 0.53, 95% Cl 0.29-0.99, P=0.049). After controlling for confounding variables the trend remained similar (OR 0.59, 95% Cl 0.32-1.12), but the association was no longer significant (P=0.108). Vigorous LTPA was similarly associated with hopelessness, but total LTPA and low-intensity LTPA did not predict hopelessness at the 11-year follow-up. $V0_{2max}$ also was not associated with the development of feelings of hopelessness at the 11-year follow-up (data not shown).

Furthermore, in the association with emergence of hopelessness there was no interaction between moderate-to-vigorous LTPA and diabetes (P=0.21), CVD (P=0.12) or metabolic syndrome (P= 0.29 for the interaction). There also was no interaction between high-intensity LTPA and these variables for the association with development of hopelessness.

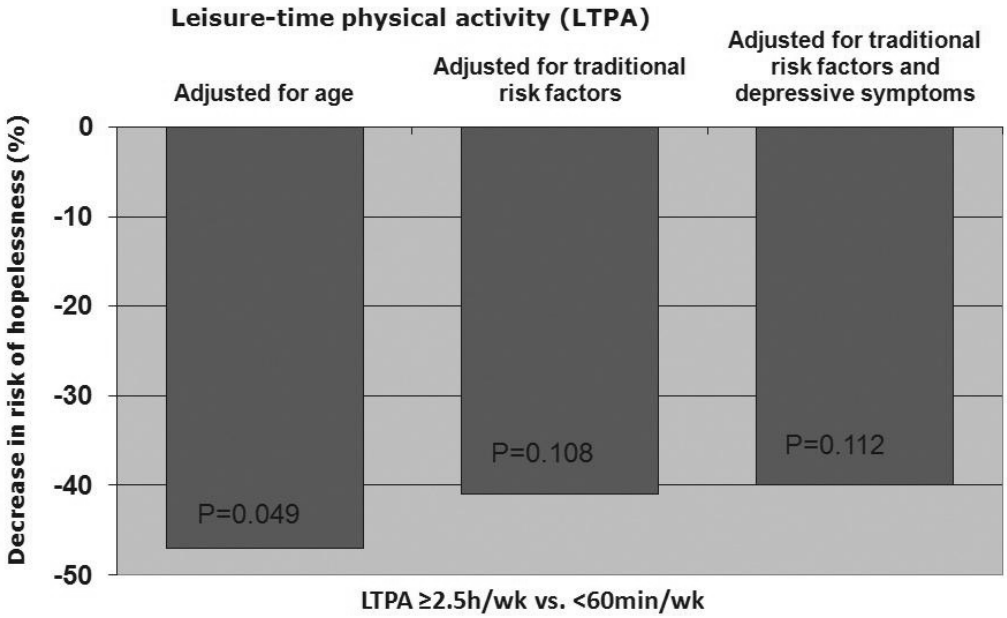

Figure 6. Decrease in risk (in percentages) of hopelessness during 11 years according to moderate-to-vigorous physical activity.

Hopelessness and the risk of becoming physically inactive during follow-up. Men who were hopeless at baseline were not at risk for becoming physically inactive during the 4-year follow-up (for ≥2.5 h/wk vs. <1 h/wk, moderate-to-vigorous LTPA, with adjustment

for age: OR 0.70, CI 95% 0.42-1.15, P for trend 0.15; with adjustment for age and traditional risk factors (presence of CVD, SES, smoking and alcohol consumption): OR 0.89, CI 95% 0.52-1.51, P=0.58) or during the 11-year follow-up (with adjustment for age: OR 0.57, CI 95% 0.29-1.11, P for the trend 0.14; with adjustment for age and traditional risk factors: OR 0.79, CI 95% 0.39-1.61, P=0.64). Those men already exercising less than hour per week moderate-to-vigorous physical activity at baseline (n=951, 36%) were excluded from this analysis. Moreover, there was no association between changes in LTPA and changes in hopelessness scores during the follow-up period (data not shown).

LTPA, hopelessness and depressive symptoms. Depression and hopelessness at baseline correlated moderately (r=0.38, P<0.001). The average depression score value at baseline was higher in hopeless men than in other men, although the difference was not significant (Table 1 of the Original Publications, **Study IV**). LTPA did not predict development of depressive symptoms (data not shown).

6 Discussion

6.1 METHODOLOGICAL ASPECTS

6.1.1 Study population and design

The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), with its large database and long follow-up period, offered a unique opportunity to study cross-sectional and longitudinal relations of psychosocial factors, physical activity, obesity and metabolic syndrome. The large study population represents a sample of middle-aged men from Eastern Finland, and the findings can be generalized to other male population of European background. Women were not included in the study. Therefore, further research is required to know how the findings apply for women or other ethnic groups.

The participation rate in the baseline examinations was high. However, cross-sectional design (**Study I** and **III**) does not allow conclusions of causality to be drawn. In the prospective studies (**Study II** and **IV**), the follow-up period was relatively long and the design enabled the consideration of temporality of the associations. Some statistical power was lost during the long follow-up. Adjustment for potential confounding and mediating variables was done, but residual confounding may remain.

6.1.2 Definitions of metabolic syndrome

In this thesis, the definitions of metabolic syndrome of the NCEP, the IDF and the WHO were used. Despite strong efforts by the global medical community, a unified definition of metabolic syndrome does not exist. This has lead to confusion and disagreement over its relevance as a clinical tool. However, there is consensus that abdominal obesity, high blood pressure, unfavorable lipid profile, and dysglycemia coexist and share a common underlying mechanism which increases the risk of CVD and especially diabetes (Alberti et al. 2009). The question whether metabolic syndrome predicts the increase in risk more than the sum of its components still remains debated. As Simmons et al. (2010) stated, the concept of metabolic syndrome also faces other limitations: The cut-offs of the continuous variables are artificial and therefore very controversial. The definition excludes many important risk factors for CVD and diabetes, such as sex, age, LDL cholesterol and behavioral variables. The WHO Expert consultation emphasizes that metabolic syndrome should not be used as a clinical diagnosis, but seen as a pre-morbid condition that increases the lifetime risk for CVD and diabetes (Simmons et al. 2010). Defining metabolic syndrome allows assessment of chronic disease risk within populations and comparisons between different countries and enhances understanding of the common pathogenesis of CVD risk factors. It also helps to predict relative risk of patients in clinical work and provides a clear public health message that underlines the importance of risk factor clustering in chronic disease prevention and management (Simmons et al. 2010).

6.1.3 Assessment of depressive symptoms and hopelessness

Depressive symptoms were measured using self-reported questionnaire instead of standardized interviews. Although the questionnaire is designed for epidemiological use rather than clinical diagnosis, it has been well validated (Roberts and O'Keefe 1981; Kap-

lan et al. 1987) and widely used in the prediction of various cardiovascular and metabolic outcomes and as an outcome itself (Roberts and O'Keefe 1981; Kaplan et al. 1987; Everson et al. 1998; Tolmunen et al. 2003, 2004a, 2004b, 2006). The Finnish version of the HPL Depression Scale has been used previously, as well (Tolmunen et al. 2003, 2004a, 2004b, 2006). The HPL depression scale is significantly correlated with the Beck Depression Inventory in an outpatient population (r=0.66), and it is also similar to other questionnaires, such as the Center for Epidemiologic Studies Depression scale (Kaplan et al 1987). A cut-off ≥5 has been used previously to classify men with depressive symptoms (Kaplan et al. 1987; Everson et al. 1998). Therefore the same cut-off point was used in this study. In a previous study, men who had five or more depressive symptoms from the HPL Depression Scale, 65% met the criteria for a current major depressive episode according to DSM-III-R criteria (Everson et al. 1998).

Unfortunately, depressive symptoms were only assessed at baseline and at 4-year follow-up. Therefore the bidirectional relationship between the variables of interest could not have been investigated at 11 year follow-up. Hopelessness was also measured using self-reported questionnaires instead of standard interviews. The hopelessness score was based on only two items. Therefore, this hopelessness scale is fairly simple, and it has not been compared with other hopelessness scales. Nevertheless, this scale has consistently predicted adverse outcomes, including development of hypertension, progression of carotid atherosclerosis, incident ischemic heart disease and overall mortality, independently of depressive symptoms (Everson et al. 1996, 1997, 2000, Whipple et al. 2009). Moreover, hopelessness assessed with only a single-item scale has predicted incident ischemic heart disease in 2800 men and women participating in the National Health Examination Follow-up Survey more strongly than depression (Anda et al. 1997). This suggests that feelings of hopelessness and futility can be assessed by a rather simple tool in a health care setting.

The HPL Depression scale does not include an item on hopelessness and correlation between these scales is only moderate (r=0.38). The correlation of this hopelessness scale with other depressive symptom questionnaires (Everson et al. 1996, 2000) is very similar, indicating that the scale measures feelings of futility that do not directly reflect depressive symptoms in general.

The hopelessness score was divided into tertiles, and the cut-off for the highest tertile was 4 points. In the prospective study, this cut-off was used to define men with high level of hopelessness. In previous studies, 5 and 6 points have also been used as cut-offs to indicate high level of hopelessness (Everson et al. 1996, 1997, 2000).

6.1.4 Assessment of low-grade inflammation

Cut-offs for CRP of 1 and 3 mg/l have been suggested to define low, moderate and high risk groups for cardiovascular disease. In this study an intermediate cut-off of 2 mg/l was used to define low and high-risk groups. Using 3 categories or cut-off of 3 mg/l resulted in too few individuals to allow for assessment of the combined effects of low-grade inflammation and depressive symptoms on the development of abdominal obesity.

CRP was the only marker used to assess low-grade inflammation. It is a well-known cardiovascular risk marker, however, with a long half-life and little diurnal variation (Laaksonen et al. 2005b; Pearson et al. 2003). The concentration of CRP in blood rises considerably in conditions like bacterial infection and large tissue injury. This needs to be taken into account when outcomes of low-grade inflammation are investigated.

6.1.5 Assessment of waist girth

Abdominal obesity was defined as waist girth >102cm. This cut-off was used for abdominal obesity as an endpoint at the 11-year follow-up. Using waist girth of ≥94cm lead to similar findings, but there was smaller number of participants in the outcome group. The NCEP definition of metabolic syndrome uses waist girth >102cm (NCEP 2001), whereas the IDF uses a cut-off of ≥94cm in their criteria (Zimmet et al. 2005). These two cut-offs have corresponded to BMI values of over-weight (>25kg/m^2) and obesity (>30kg/m^2) (Lean 2000). However, in this cohort BMI value of >25kg/m^2 corresponded to waist girth of 87cm (Laaksonen 2002a), indicating that this waist girth cut-offs correlate to considerably higher BMI values in non-diabetic Finnish male population.

6.1.6 Assessment of physical activity and cardiorespiratory fitness

Precise assessment of LTPA by self-reports is complicated. Previous studies using objectively assessed estimates of physical activity show remarkably lower levels of physical activity compared with self-reports (Hagströmer et al. 2007). The KIHD Risk Factor study begun in the early 1980's when objective measurements of physical activity were not feasible. The validated KIHD 12-month Leisure-time Physical Activity Questionnaire provides, however, detailed information on frequency, duration and intensity of physical activity recalled for the preceding 12 months. The test-retest reliability of the questionnaire was accurate when readministered 12 months later (Lakka et al. 1992). Duration of vigorous LTPA also correlated well with age-adjusted cardiorespiratory fitness (Lakka et al. 1992). Nevertheless, the long time-frame makes the questionnaire vulnerable to recall bias. The subjective intensity classification may also allow participants to overestimate the true intensity of exercise (Lakka et al. 1994).

A major strength of the studies is that VO_{2max} was measured directly by a maximal symptom-limited cycle ergometer exercise test with analysis of respiratory gas exchange, which is an accurate and highly reproducible measure of cardioresipiratory fitness (Åstrand and Rodahl 1986).

6.2 HOPELESSNESS AND METABOLIC SYNDROME

This study showed for the first time that hopelessness is strongly associated with metabolic syndrome (**Study I**). Men with a hopelessness score in the highest third were 2.2 times more likely to have metabolic syndrome than men in the lowest third, and nearly two times more likely even after adjusting for BMI and traditional risk factors. After controlling depressive syndromes in general the risk was still 2.1 times higher. Similar findings were seen with the use of IDF definition of metabolic syndrome instead of the NCEP definition. The association with metabolic syndrome as defined by the WHO did not reach significance, however. The WHO criteria emphasize insulin resistance, or in this study, its proxy hyperinsulinemia, rather than abdominal obesity, as in the NCEP and IDF criteria (Laaksonen et al. 2004a). Furthermore, the less commonly used WHO definition is not generally applicable clinically because of its emphasis on a more or less direct measure of insulin resistance. It is not clear why hopelessness was not associated with metabolic syndrome as defined by the WHO, but it is conceivable that hopelessness plays a more important role in some phenotypes of metabolic syndrome than others. The importance of hopelessness on physical and mental health has been recognized. In previous studies hopelessness has been found to predict various cardiovascular outcomes, independently of depression (Everson et al. 1996, 1997, 2000, Do et al. 2010, Whipple et al. 2009).

In this study the association of hopelessness and metabolic syndrome seemed to be explained mostly by waist girth. Nevertheless, after adjusting for traditional risk factors and waist girth the association of hopelessness and metabolic syndrome defined by NCEP remained significant.

6.3 DEPRESSIVE SYMPTOMS, LOW-GRADE INFLAMMATION AND ABDOMINAL OBESITY

The association between depression and obesity has been well studied. The overall body of evidence suggests that the association is bidirectional, although discrepancies exist, probably due to methodological differences (Luppino et al. 2010; Atlantis et al. 2009). A previous prospective study in this cohort reported that low-grade inflammation increases the risk of metabolic syndrome and diabetes (Laaksonen et al. 2004b). The present study showed a similar prognostic effect of CRP level on development of unfavorable circumference (**Study II**). Thus, elevated serum CRP level alone predicted central obesity, but in the presence of depressive symptoms the risk was increased considerably. Men with both low-grade inflammation and depressive symptoms were 4.3 times more likely to develop waist girth over 102 cm during 11 years than men with neither of these risk markers even after adjusting for traditional risk factors. However, after adjustment for BMI the association was no longer significant. Similar findings were seen when using metabolic syndrome as outcome.

It is expected that a hopeless or depressed person is more likely to follow an unhealthy life-style and be less likely to make favorable behavioral changes (Blumenthal et al. 1982). In this study, however, traditional life-style risk factors such as smoking, alcohol consumption and physical inactivity did not change the relationship between depressive symptoms and metabolic outcomes.

The evidence of possible mechanisms explaining these associations comes from neuroendocrine studies of depression. It is plausible, however, that these mechanisms also apply to separate depressive symptoms such as hopelessness. Activation of the HPA system and elevated glucocorticoid concentrations may be underlying factors in the association of depressive symptoms and obesity (Luppino et al. 2010).

Low-grade inflammation may also mediate the correlation between depressive symptoms and obesity. In this study a graded increase in the concentrations of C-reactive protein was found across the hopelessness categories, even though adjustment for CRP and fibrinogen did not alter the association between hopelessness and metabolic syndrome. In addition, men with both low-grade inflammation and depressive symptoms were more likely to develop abdominal obesity over long period of time than men with neither of these risk markers. Thus, although low-grade inflammation certainly has consequences on metabolism of adipose tissue, independent of mood disturbances, together with depressive symptoms the effect may be even more damaging.

As expected, BMI weakens the association of CRP and depressive symptoms with development of waist girth due to the interrelationship of central obesity and overall obesity. On the other hand, attenuation of the association when adjusting by BMI suggests that obesity partly mediates the association.

Several behavioral factors and biological factors are connected in this complex, multidirectional relation of depression, low-grade inflammation and abdominal obesity. Physical inactivity and high alcohol consumption are well known to increase the accumulation of visceral fat (Laaksonen 2002b). Both factors are also associated with low-grade inflammation and depression (O'Connor and Irwin 2010; Mead et al. 2009). However, in this

study, lifestyle risk factors did not entirely explain the role of inflammation and depressive symptoms in the development of central obesity. Use of psychotropic medication is also suggested to result in weight gain (Luppino et al. 2010). In this study, those using antidepressants at baseline were excluded from the study. Furthermore, physical and psychological health may interact together in a biological level that is yet to be discovered.

6.4 PHYSICAL ACTIVITY AND HOPELESSNESS

All adults are recommended to engage in at least 30 min of moderate-intensity exercise 5-7 days per week to prevent chronic diseases (Physical Activity Guidelines Advisory Committee Report, 2008). Cross-sectional analyses of the baseline study (**Study III**) and at 4 years and 11 years of follow-up (**Study IV**) showed that men following the recommended physical activity guidelines had fewer feelings of hopelessness than physically inactive men after adjustment for traditional risk factors and potential mediating factors. Importantly, men engaging in moderate-to-vigorous LTPA at least 2.5 hours per week at baseline had 35% lower risk to feel hopeless about their future and reaching goals 4 years later than physically inactive men at baseline, after adjustment for confounding factors (**Study IV**). After 11 years the trend was still similar, indicating protective effect of LTPA. However, the association was no longer significant, possibly due to loss of statistical power. It is important to note that hopelessness at baseline did not predict physically inactive lifestyle 4 or 11 years later. The results of the present study suggest that physically inactive lifestyle predisposes to hopelessness, rather than vice versa.

The effect of depressive symptoms on the cross-sectional associations of LTPA and VO_{2max} with hopelessness was distinctly different. Odds ratios for total, moderate and vigorous LTPA for hopelessness were not attenuated in logistic models adjusting further for depressive symptoms, whereas the association of VO_{2max} and hopelessness was no longer significant. Cardiorespiratory fitness was strongly associated with elevated depressive symptoms even after adjustment for various potential confounding and mediating factors. The relationship between LTPA and depression, however, was not found in this cohort, as reported previously (Tolmunen et al. 2006). This suggests that hopelessness and depression are overlapping, but distinct entities. The findings also suggest that moderate or vigorous LTPA may ameliorate or protect against feelings of hopelessness even if VO_{2max} does not improve. Considering that physical activity did not protect against depressive symptoms in general, it is plausible that physical activity has stronger impact on certain depressive symptoms than the others.

Furthermore, in the prospective analysis, cardiovascular fitness did not protect against hopelessness. The distinction between hopelessness and depression could explain the difference in the associations of hopelessness with LTPA and VO_{2max}. It is important to note, however, that cardiorespiratory fitness is only partly a reflection of physical activity. Although moderate and vigorous LTPA obviously has an effect on VO_{2max}, it is also determined partly by genetic factors (Bouchard and Rankinen 2001). How this may relate to feelings of hopelessness and depression is still unclear.

Interestingly, Thirlaway and Benton (1992) reported that subjects who were physically inactive and fit had poorer mood that those who were inactive and unfit in a cross-sectional setting. They argued that fitness could be reflection of a former active lifestyle, and therefore to quit exercising may be stressful and depressing. Lampinen et al. (2000) showed that older adults who reduced their intensity of physical exercise during 8 years had more depressive symptoms at follow-up than those who remained active or increased their physical activity. Also a study by Motl et al. (2004) indicated that changes in physical

activity were associated with risk of depression in 2 years among adolescents. Hypothetically, a fit person, however, may be especially in need of physical activity to maintain positive mood, and a temporary lack of exercise could be especially damaging for their mental health.

This study agrees with growing evidence that regular LTPA contributes to mental health. Prospective studies are still scarce, however. While a few large cohort studies suggest that physical activity protects against depressive symptoms (Camacho et al. 1991; Paffenbarger et al. 1994; Strawbridge et al. 2002; Motl et al. 2004; Wise et al. 2006; Ströhle et al. 2007), others do not (Cooper-Patrick et al. 1997; Kritz-Silverstein et al. 2001, Wiles et al. 2007). In previous studies psychological outcome has been measured in various ways, varying from clinical depression to depressive symptoms and mood. Conflicting results could be partly caused by diversity in measurements of effects of physical activity on different depressive symptoms

Previous studies have shown that long-term exposure to systemic low grade inflammation may lead to progression of chronic diseases (Beavers et al. 2010). Inflammation is hypothesized to play a role in the development of depression (Howren et al. 2009), as well as metabolic diseases (Laaksonen et al. 2004b, 2005b). Physical activity is also related to lower systemic inflammation (Nicklas et al. 2005, Beavers et al. 2010). Future research will reveal whether systemic low-grade inflammation is the common denominator explaining the relationship between depressive symptoms, physical activity and metabolic syndrome.

7 Summary and Conclusions

1. Non-diabetic, middle-aged men with high levels of hopelessness were more likely to have metabolic syndrome than men who are less hopeless, independently of traditional risk factors, BMI and other depressive symptoms. This finding brings a new perspective to the only partly understood pathogenesis of metabolic syndrome and adds to the growing evidence of negative impacts of hopelessness on physical health.
2. Non-diabetic men with both low-grade inflammation and depressive symptoms were more likely to develop abdominal obesity (waist girth at least 102 cm) during 11 years than men with neither of these risk markers even after adjusting for traditional risk factors. These men were also more likely to develop metabolic syndrome. The findings suggest that the presence of both low-grade inflammation and depressive symptoms identify men at an especially high risk to develop abdominal obesity and metabolic syndrome.
3. Physically active middle-aged men were less likely to feel hopeless about their future and reaching goals than physically inactive men. Cardiorespiratory fitness was also related to reduced feelings of hopelessness, but this association was partially explained by depressive symptoms. Considering that hopelessness is an important determinant of mortality, cardiovascular morbidity and low subjective well-being, this study provides additional evidence for the health benefits of physical activity and fitness.
4. After adjusting for potential confounding factors, men engaging in moderate-to-vigorous LTPA had lower risk to feel hopeless about their future and reaching goals 4 years later than physically inactive men at baseline. After 11 years the trend was still similar, indicating protective effect of LTPA. However, the association was no longer significant. This study agrees with growing evidence that regular LTPA contributes to mental health. The new finding of this study is that a physically active lifestyle helps people to maintain or gain more optimistic perspective on the future and oneself.

These studies suggest that following the recommended physical activity guidelines may help to confront challenges in life and to enhance optimism and subjective well-being. Therefore moderate to vigorous physical activity should be promoted to improve mental health. These studies also suggest that in addition to focusing on the traditional risk factors of cardiovascular disease, the emotional state and expectations of individuals should be taken into account in the prevention and treatment of metabolic syndrome and its consequences. Physical and psychological health and performance are interdependent, possibly to an even greater extent than science currently understands.

8 Future Directions

This study brings a new perspective to the only partly understood pathogenesis of abdominal obesity and metabolic syndrome. In addition to focusing on the traditional risk factors of cardiovascular disease, the emotional state and expectations of individuals should be taken into account in the prevention and treatment of metabolic syndrome and its consequences. Feelings of hopelessness and futility can be rather easily assessed in a primary care setting. Assessment of hopelessness may allow targeting of individuals in whom more intensive lifestyle and pharmacological treatment of metabolic, cardiovascular and psychosocial risk factors could improve long-term cardiovascular outcome and quality of life. In addition, the presence of both low-grade inflammation and depressive symptoms seem to identify men at an especially high risk to develop abdominal obesity and metabolic syndrome. Screening depressive men with high low-grade inflammatory markers could also help to target high risk subjects for prevention and treatment of metabolic syndrome and its consequences.

This study adds to the growing evidence that regular LTPA also contributes to mental health. A physically active lifestyle not only helps one live a healthier life, but it may also improve well-being by helping to maintain a positive attitude and optimistic perspective on the future and oneself. In the future, more research should be carried out by utilizing recent technological advances, motor sensors and physiological monitoring, to allow greater accuracy and precision of the assessment of physical activity. Furthermore, more evidence-based data from randomized controlled trials are needed on the effects of physical activity on mental health.

Traffic safety, vaccinations and preventing secondary smoking are public health issues that have become social norms, the importance of which most people do not question in everyday decisions. By contrast, governmental programs to enhance physical activity are still inadequate. The prevalence of physical inactivity is higher than any other modifiable risk factor for cardiovascular and metabolic diseases (Warburton et al. 2006). Based on self-reported measures, 45-62% of the western populations reach the recommended physical activity level at least 30 min of moderate-intensity exercise per day. Objectively assessed estimates of physical activity show remarkably lower values (Hagströmer et al. 2007). Therefore, physical inactivity is a major public health risk factor that still has a great potential to be modified and gain enormous health benefits. Policy makers, corporations, employers and public health workers must work in tandem to support and promote an active environment, as both an essential method of disease prevention and as an investment in future productivity and wellbeing. Most essential, however, is that everyone acknowledges the individual responsibility in personal well-being and accepts a physically active lifestyle as the social norm.

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A Population-based Cohort Study in Men

Hopelessness, determined as a system of negative expectancies concerning oneself and one's future, has been shown to be a predictor of cardiovascular morbidity and mortality, independently of depression. This study indicates that hopelessness is also associated with metabolic syndrome. Additionally, physical activity is inversely associated with feelings of hopelessness. Regular physical activity may protect one from an emergence of hopelessness, and thus enhance subjective well-being and an optimistic perspective in life.

UNIVERSITY OF EASTERN FINLAND

Publications of the University of Eastern Finland
Dissertations in Health Sciences

ISBN 978-952-61-0530-7