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INFLUENCES FROM PHYSICAL ACTIVITY AND GENDER ON THE METABOLIC SYNDROME AND LEFT VENTRICULAR HYPERTROPHY – CROSS-SECTIONAL AND LONGITUDINAL STUDIES

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Influences from Physical Activity and Gender on the Metabolic Syndrome and Left Ventricular Hypertrophy – Cross-sectional and Longitudinal Studies

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Kristina, Alice, Mauritz, Carla and Therese

ABSTRACT

Aims The overall aim was to investigate influences from physical activity (PA) and gender on the metabolic syndrome (MetS) and left ventricular hypertrophy (LVH).

Specific aims *Study 1*: To examine the prevalence of the MetS and its association to PA and other lifestyle factors. *Study 2*: To evaluate plausible links between the MetS and its components and LVH. *Study 3*: To investigate potential influences from insulin-like growth factor-1 (IGF-1) and IGF binding protein-1 (IGFBP-1) on the MetS-LVH relationship. *Study 4:* To prospectively study the potential effects from PA on cardiovascular (CVD) risk and total mortality in individuals with the MetS.

Methods In a population-based cross-sectional study (study 1-3)/prospective cohort study (study 4) of 60-year-old men (n 1822) and women (n 2049) participants underwent physical examination and laboratory tests, including ECG, and completed an extensive questionnaire at baseline 1997-99. In study 4, all participants were followed from the date of the baseline investigation until the date of their death or until 31 December 2012. Incident cases of first-time CVD event and death from any cause were ascertained through examinations of the National Cause of Death Registry and the National In-Hospital Registry.

Results *Study 1*: One out of four men and one out of five women met the criteria for the MetS. There was an inverse dose-response association between PA and the MetS. *Study 2*: In men and women with the MetS, the prevalences of LVH were 12.8 and 9.9%, respectively – compared with 7.9 and 3.3%, respectively, without the MetS. A dose-response relationship between the MetS components and the occurrence of LVH in both men and in women was seen. In women, LVH was associated with MetS beyond the influence of hypertension, i.e. contributions from impaired fasting glucose, hyperinsulinemia, and abdominal obesity, whereas the relation was fully explained by the effect of hypertension in men. *Study 3*: There were higher levels of IGFBP-1 in women than in men, and lower levels of IGFBP-1 in women with LVH, than without. There was an increased association to LVH in women with the lowest levels of IGFBP-1. Oestrogen-use was negatively associated to the occurrence of LVH. The association between IGFBP-1 and LVH was diminished in physically active men and women, as well as in women using oestrogen. *Study 4*: MetS was associated with an increased risk for incident CVD events, CVD mortality and total mortality. PA appeared to counteract the deleterious effects from the MetS.

Conclusions The metabolic syndrome is prevalent in 60-year-olds in Stockholm, and inversely related to physical activity. Left ventricular hypertrophy was more frequent in individuals with the metabolic syndrome, and possible gender differences were indicated concerning its development. Oestrogen may have a protective effect on the development of left ventricular hypertrophy. The metabolic syndrome was associated with a substantially increased risk for incident cardiovascular events, cardiovascular mortality as well as all-cause mortality during a follow-up of 13-15 years. Physical activity during leisure-time seemed to counteract the deleterious effects from the metabolic syndrome.

LIST OF SCIENTIFIC PAPERS

I. **Halldin M**, Rosell M, de Faire U, Hellénius ML. The metabolic syndrome: Prevalence and association to leisure-time and work-related physical activity in 60-year-old men and women. Nutr Metab Cardiovasc Dis. 2007 Jun;17(5):349-57.

II. **Halldin M**, Fahlstadius P, de Faire U, Vikström M, Hellénius ML. The metabolic syndrome and left ventricular hypertrophy – the influence of gender and physical activity. Blood Press. 2012 Jun;21(3):153-60.

III. **Halldin M**, Brismar K, Fahlstadius P, Vikström M, de Faire U, Hellénius M-L. The metabolic syndrome and ECG detected left ventricular hypertrophy – influences from IGF-1 and IGF-binding protein-1. PLoS ONE, accepted for publication.

IV. **Halldin M**, Vikström M, Leander K, Gigante B, de Faire U, Hellénius M-L. Beneficial effects from physical activity on cardiovascular risk and total mortality in individuals with the metabolic syndrome – a prospective cohort study of 60-year-old Swedish men and women. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

Apo	Apolipoprotein
BMI	Body mass index
BP	Blood pressure
Chol	Cholesterol
CI	Confidence interval
CVD	Cardiovascular disease
γGT	Gamma-glutamyltransferase
HDL	High-density lipoprotein cholesterol
IFG	Impaired fasting glucose
IGF-1	Insulin-like growth factor-1
IGFBP-1	Insulin-like growth factor binding protein-1
LDL	Low-density lipoprotein cholesterol
LVH	Left ventricular hypertrophy
M	Men
MetS	Metabolic syndrome
n	Number
OR	Odds ratio
PA	Physical activity
RR	Relative risk
SAD	Sagittal abdominal diameter
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
TG	Triglycerides
W	Women
WC	Waist circumference

1 BACKGROUND

1.1 METABOLIC SYNDROME

The metabolic syndrome (MetS) is a combination of metabolic and clinical features like abdominal obesity, insulin resistance and impaired glucose tolerance, hypertension, and atherogenic dyslipidemia with elevated levels of triglycerides, decreased levels of high-density lipoprotein cholesterol (HDL) and small dense particles of low-density lipoprotein cholesterol (LDL). Moreover, fatty liver, impaired fibrinolysis, proinflammatory activity, elevated levels of uric acid as well as a state of oxidative stress are established factors of the syndrome.

1.1.1 The definitions of the metabolic syndrome

There are different definitions and criteria of the MetS, and revisions have been made throughout the years. The most established definitions are those proposed by:

- The World Health Organization (WHO) in 1998 [1],
- The European Group for the Study of Insulin Resistance (EGIR) in 1999 [2],
- The National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP III) in 2001, revised 2005 and 2009 [3, 4, 5], and
- International Diabetes Federation (IDF) [6].

The definitions are based on different basic features of the MetS [5]:

- WHO emphasized insulin resistance (or impaired glucose tolerance or diabetes) as the major underlying risk factor, together with at least two of obesity, hypertension, high triglycerides, reduced HDL-cholesterol, or microalbuminuria [1].
- EGIR stated a modification of the WHO criteria, excluding people with diabetes and requiring hyperinsulinemia to be present. EGIR proposed the use of fasting insulin levels to estimate insulin resistance and impaired fasting glucose as a substitute for impaired glucose tolerance. Waist circumference was the measure of obesity [2].
- NCEP/ATP III focused on cardiovascular risk, and the definition was designed to facilitate diagnosis in clinical practice and therefore did not include a measurement of insulin resistance [3]. No single factor was required for diagnosis, but the presence of three of the five factors abdominal obesity, elevated triglycerides, reduced HDL-cholesterol, hypertension, and elevated fasting glucose (impaired fasting glucose or type 2 diabetes mellitus).

In 2005, both the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) attempted to reconcile the different clinical definitions [6, 4]. Their separate recommendations contained differences related to waist circumference: the IDF recommended that the threshold for waist circumference to define abdominal obesity in Europeans should be ≥94 cm for men and ≥80 cm for women; the AHA/NHLBI, in contrast, recommended cut points of ≥102 and ≥88 cm, respectively. The IDF also stressed the need to adopt different values for waist measurement in different ethnic groups.

- In 2009, IDF and AHA/NHLBI representatives held discussions to attempt to resolve the remaining differences between definitions of MetS [5]. Both sides agreed that abdominal obesity should not be a prerequisite for diagnosis but that one out of five criteria, so that the presence of any three of five risk factors constitutes a diagnosis of MetS.

The NCEP/ATP III definition (revised 2009), three or more of the following criteria are required:

- Fasting plasma glucose concentration of 5.6 mmol/l (100 mg/dl) or greater, or drug treatment for elevated glucose
- Triglyceride concentration of 1.7 mmol/l (150 mg/dl) or greater, or drug treatment for elevated triglycerides
- HDL concentration less than 1.03 mmol/l (40 mg/dl) in men and less than 1.29 mmol/l (50 mg/dl) in women, or drug treatment for reduced HDL
- Systolic blood pressure of 130 mmHg or greater, and/or a diastolic blood pressure of 85 mmHg or greater, or antihypertensive drug treatment in a patient with a history of hypertension
- Waist circumference of 102 cm or greater in men, and 88 cm or greater in women

1.1.2 The increasing prevalence of the metabolic syndrome

Swedish and international reports have demonstrated an increasing prevalence of the MetS worldwide – in adults as well as in children, in men as well as in women [7, 8]. One fourth – according to some reports up to one third – of the adult population in United States, Canada och Europe meets the criteria of the syndrome [9, 10]. This prevalence was observed in both men and women, according to studies in the USA [11, 12, 13]. According to population-based investigations in the USA, the age-adjusted prevalence of the MetS has been 23-26% in the adult population with minor fluctuations over the past decade [14]. The prevalence is substantially higher within some ethnic subgroups in the USA.

In the DECODE study, based on eleven prospective European cohort studies comprising 6156 men and 5356 women without diabetes and aged from 30 to 89 years, the age-standardized prevalence of the MetS varied between 14% in women and 16% in men, and the prevalence increased with age [15]. In a British cross-sectional study of 3770 women aged 60-79 years, the prevalence according to the NCEP definition was 29% [16].

The prevalence of the MetS among a number of Asian populations also has been on the rise, most dramatically in China [17]. From the China Multiprovince Study [18] the Beijing cohort reported an increase in the MetS prevalence from 9% to 21% during a period from 1992 to 2002. The DECODA [19] study estimated the prevalence of the MetS in East Asians using both the IDF and NCEP definition. The prevalence of IDF MetS in men (women) was 12.0% (15.0%) and 13.8% (2.5%) in Chinese and Japanese patients, respectively. The NCEP prevalence in men (women) was 7.9% (10.3%) and 5.1% (5.6%) in Chinese and Japanese patients, respectively. In spite of the fact that disparity in the criteria between the definitions of the MetS has yielded different prevalence of the MetS across East Asian populations, there is a definitive consensus that the prevalence of MetS is increasing in dangerous proportions.

In Africa, contrary to earlier thoughts, MetS is no longer rare. The prevalence is increasing, and it tends to increase with age [20].

Concerning the MetS prevalence in children and adolescents, the literature is relatively sparse, and standard definition of the syndrome for the pediatric population is not yet available. However, similar tendencies as in adults have been observed in various populations [21, 22]. In a Chinese study of a total of 8764 children aged 7-11 years, randomly selected from six cities, the proportion of children with at least one, two, and three risk factors of the MetS were 25, 5 and 1%, respectively. Metabolic abnormalities were also present in children under 10 years of age [23].

1.1.3 Metabolic syndrome and associated risks

When the metabolic and clinical variables, stated in the MetS definitons above, aggregate in individuals, the risk of developing type 2 diabetes, cardiovascular disease (CVD) and mortality as well as all-cause mortality considerably increases – to mention some of the most important consequences of the MetS [24, 25, 26, 27].

Several cross-sectional and prospective studies have demonstrated associations to CVD:s in individuals with the MetS [26, 27, 28, 29]. There is also a strong association between the MetS and dementia and other cognitive disorders [30, 31, 32, 33]. The risk of getting diabetes type 2 is substantially higher in individuals with the MetS, and the prognosis is worsened in diabetics with the MetS, compared to diabetics without it [29, 34].

Over the last years several epidemiological studies have also demonstrated associations between the MetS and different types of cancer, like prostate cancer, breast cancer, colon cancer, and liver cancer [35-45]. Furthermore, there is also an association between the MetS and sleeping disorders like obstructive sleep apnea [46].

Finally, each of the MetS components is known to increase several public health diseases and mortality – but the MetS itself seems to carry an additional risk, beyond the risk related to its individual components [47, 48, 49].

(Courtesy of Mai-Lis Hellénius)

1.1.4 The metabolic syndrome and physical activity

Although the MetS appears to be more common in people who are genetically susceptible, acquired underlying risk factors – being overweight or obese, physical inactivity, and an atherogenic diet – commonly elicit clinical manifestations [50].

Concering PA, one of the main theme for this thesis, there are a number of epidemiological studies, both cross-sectional and prospective, demonstrating an association between level of PA and prevalence of the MetS.

Two meta-analyses of prospective studies regarding the associations between PA level and prevalent MetS have recently been published. One stated, from five prospective studies, that recreational PA protects against the MetS [51]. Individuals with moderate or high PA had more than ten percent lower risk (OR 0.89, 95% CI 0.82-0.96) compared to physically inactive individuals, and the corresponding reduction in risk for individuals with high PA were more than forty percent lower risk (OR 0.58, 95% CI 0.38-0.98). The risk reduction from high PA was especially pronounced in women, representing an 80% reduction in risk (OR 0.20, 95% CI 0.08-0.49). The other meta-analysis included 17 prospective studies and

the results were similar [52]. On the basis of studies of a total of 64353 individuals and 11271 incident cases of the MetS it was concluded that a high level (compared to low level) of PA in leisure-time was associated with a significantly reduced risk of 20 % (OR 0.80, 95% CI 0.75-0.85).

Similar findings have also been reported from a cohort of 9007 men and 2826 women aged 20-84 in the USA [53]. Cardiorespiratory fitness was significantly and inversely associated with the occurrence of the MetS in both normal weight and overweight participants. Adjustments were made for age, sex, examination year, smoking, abnormal electrocardiogram, as well as dietary factors. Another trial examined the effects of six months of exercise training in sedentary, overweight, moderately hypertensive, postmenopausal women. The results showed significant improvements in components of the MetS [54].

1.1.5 Other conditions/components related to the metabolic syndrome

1.1.5.1 Left ventricular hypertrophy (LVH)

LVH is a potent independent predictor of cardiovascular morbidity and mortality, and blood pressure overload is the pivotal risk factor for its development – but many other factors, including gender, age, body mass index, diabetes mellitus and level of PA are potential determinants of LVH [55, 56, 57].

Previous studies have reported associations between MetS and LVH, and LVH may be a contributing factor to the increased CVD risk associated with the MetS [58, 59]. Furthermore, LVH has shown to be more prevalent among individuals with MetS [60]. Of above reasons, it was considered essential to include LVH in the analyses of MetS and its components.

1.1.5.2 Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-1 (IGBP-1)

IGF-1 is an endocrine hormone mainly stimulated by growth hormone, and structurally and functionally related to insulin. Being an important mediator of cell growth, it may also induce cardiac hypertrophy (LVH) – but contradictive studies have been published [61, 62].

Less than 1% of the total serum IGF-1is freely circulating; the remainder is bound to six high-affinity insulin-like growth factor binding proteins (IGFBPs), which play an important role in regulating IGF-1 activity, having both stimulatory and inhibitory effects. IGFBPs may also have IGF-independent effects [63].

2 OBJECTIVES

The main objective of this thesis was to, in cross-sectional and longitudinal studies, investigate influences from physical activity and gender on the metabolic syndrome and left ventricular hypertrophy, to further elucidate the prevalence as well as the pathogenesis of the metabolic syndrome and its consequences, and to identify potentially preventive efforts to apply in a public health setting.

The specific objectives were:

I. To examine the prevalence of the metabolic syndrome and its association to lifestyle factors, with special emphasis on physical activity.

II. To evaluate plausible links between the metabolic syndrome and its components and left ventricular hypertrophy, as well as potential influences of gender and physical activity.

III. To investigate potential influences from insulin-like growth factor-1 and IGF binding protein-1 on the relationship between the metabolic syndrome and left ventricular hypertrophy, also taking into account the role of physical activity, use of oestrogen and gender.

IV. To prospectively study the potential effects from physical activity on cardiovascular risk and total mortality in individuals with the metabolic syndrome.

3 MATERIAL AND METHODS

3.1 STUDY POPULATION

In order to study traditional as well as tentative new risk factor and lifestyle patterns, and their potential effects on cardiovascular morbidity and mortality, as well as all-cause mortality, a survey of 60-year-old men and women was conducted in Stockholm in the years 1997-99.

From August 1997 to March 1999, every third person (5460 individuals in total, 2681 men and 2779 women, living in Stockholm County, Sweden, born between 1 July 1937 and 31 June 1938, was randomly invited from population registers to participate in a health screening survey. Altogether, 4228 individuals participated (an overall response rate of 77%), 2036 men (response rate 73%) and 2192 women (response rate 82%). Immigrants constituted 19% of the total participating population of 60-year-old men and women, which corresponds to the percentage of immigrants among 60-year-olds in Stockholm County in December 1998 (21.5%). The response rate among all immigrants (n 787) in this study population was 68% [64].

In Paper I, 1829 men and 2035 women remained for further analysis after exclusion of 364 individuals with reported myocardial infarction (n 110), heart failure (n 53), stroke (n 60), and/or cancer (except basalioma) (n 141), in some cases overlapping diagnosis (i.e. one person could have more than one of the exclusion diagnoses).

The corresponding exclusion criteria of Paper II-IV were reported myocardial infarction (n 110), angina pectoris (n 148), heart failure (n 53), intermittent claudication (n 73) and/or stroke (n 60). After excluding 357 individuals, 1822 men and 2049 women were included in the studies.

3.2 MEASUREMENTS AND DATA COLLECTION

3.2.1 Anthropometric and blood pressure measurements

All participants underwent a physical examination collecting body weight, height, waist circumference and sagittal abdominal diameter (SAD). Waist circumference was measured in a standing position, midway between the lower rib margin and the iliac crest. SAD was determined to the nearest 0.1 cm using a ruler and a water level, with the participant lying horizontally with legs straight. Systolic and diastolic blood pressures were measured twice in sitting position, after five minutes of rest in supine position, and the mean of the measurements was calculated. An automatic device was used (HEM 711, Omron Healthcare, Bannockburn, IL, USA). In participants with an upper arm circumference above 32 cm, a wider cuff was used. A standard 12-lead resting electrocardiograms (ECG) was performed.

3.2.2 Blood analyses

Venous blood samples were drawn from an antecubital vein after overnight fasting. All blood samples were analysed online (continuously) by accredited methods.Triglycerides and cholesterol in serum were analysed using enzymatic methods (Bayer Diagnostics, Tarrytown, NY, USA) [65, 66]. HDL in serum was measured after isolation of LDL and VLDL (Boehringer Mannheim Gmbh, Germany) and LDL was estimated using the Friedewald equation [67]. Apolipoprotein A1 (Apo A1) and Apo B serum concentrations were determined by an immunochemical reaction (Bayer Diagnostics). Serum glucose was measured with an enzymatic colorimetric test (Bayer Diagnostics, Tarrytown, NY, USA), and serum insulin levels were determined using the ELISA technique (Boeringer Mannheim Gmbh, Diagnostica, Germany). Plasma fibrinogen was measured with a functional spectrophotometric test (Boehringer Mannheim) [68, 69]. Serum urate was measured using an enzymatic method (Bayer Diagnostics) [66, 70]. Gammaglutamyltransferase in serum was determined using an enzymatic colorimetric test (Bayer Diagnostics). For future analysis, blood samples (serum, plasma, and whole blood) were stored in freezers (-70 degrees Celsius) in two biobanks at Karolinska Institutet and Karolinska University Hospital.

3.2.3 Self-reported variables

A comprehensive questionnaire concerning lifestyle-related factors, for example, marital status, education, smoking, eating habits, alcohol consumption, quality of life, financial status, medication as well as occupation, health status, heredity, and physical activity (leisure-time and work-related) was completed on site. If needed, study nurses assisted with filling in the questionnaire.

Marital status was defined as married/living together or not, and education level as university educated or not. Current smoking was coded as yes or no. Dietary intake of fruit and vegetables was measured using a food frequency questionnaire, each question with four answer alternatives. Eating fruit ‘several times per day’ or ‘daily’ and vegetables ‘more than one portion daily’ or ‘almost daily’ were, respectively, rated as a moderate-to-high intake. Concerning alcohol, a weekly consumption of at least four to six bottles of strong beer (25-40 g ethanol), or two to three bottles of wine, or 0.35-0.75 l spirits were considered as a high intake.

The participants were asked to rate their general well-being (health) on a five-degree scale ranging from ’very bad’ to ’excellent’. A score of one to three was defined as ’bad’ and four to five as ‘good’ [71]. Self-rated financial status was based on a seven degree scale ranging from ’very bad’ to ‘excellent’. A score of one to four was considered as ‘bad’ and five to seven as ‘good’.

Concerning medication, the participants were asked to specify regularly prescribed medicine. Relevant for Paper I-IV were drug treatment for elevated glucose, elevated triglycerides, reduced HDL, and antihypertensive drugs as well as oestrogen (including both oral oestrogen replacement therapy (ERT) and locally/transdermally administered ERT).

3.3 PHYSICAL ACTIVITY

PA in leisure-time during the past year was asked for in a questionnaire, and the participants classified themselves into one of four groups:

1. low PA, a sedentary lifestyle with less than two hours of light PA per week (e.g. walking, cycling);
2. light PA, at least two hours per week without sweating (e.g. walking, cycling, gardening, fishing);
3. moderate PA, regular activity one to two times per week, at least 30 minutes each time (e.g. jogging, swimming, tennis); and
4. high PA, intensive regular activity more than three times per week, at least 30 minutes each time (e.g. running, swimming, aerobics or other strain exercise).

In the regression analyses of Paper II-IV, leisure-time PA group 1 and 2 were referred to as "low PA", and group 3 and 4 were referred to as "high PA".

Work-related PA was classified in the questionnaire as:

1. mainly sedentary/physically very light;
2. half work day sedentary/physically light;
3. less than half work day sedentary/physically intense; and
4. active/physically strenuous.

Work-related PA (only analyzed in Paper I) was determined as either "low" (group 1 and 2) or "moderate" (group 3 and 4).

3.4 METABOLIC SYNDROME

In Paper II-IV MetS was classified using the "updated" NCEP/ATP III definition (above) proposed by the American Heart Association/National Heart, Lung, and Blood Institute and the International Diabetes Federation Task Force on Epidemiology and Prevention (IDF) as well as World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity in a joint effort in 2009 [5]. In Paper I the "original" NCEP/ATP III definition was used, with a cut-off value for fasting plasma glucose concentration greater than 6.1 mmol/l(110 mg/dl) [3].

The NCEP/ATP III definition recognizes that the risk associated with a particular waist measurement will differ in different populations, and the cut-off values for waist circumference of 102 cm (men) and 88 cm (women) are suggested for people of European origin of AHA/NHLBI as well as European Cardiovascular Societies.

In this definition, three or more of the following criteria are applied:

1. fasting plasma glucose concentration of 5.6 mmol/l (100 mg/dl) or greater, or drug treatment for elevated glucose;
2. triglyceride concentration of 1.7 mmol/l (150 mg/dl) or greater, or drug treatment for elevated triglycerides;
3. HDL concentration less than 1.03 mmol/l (40 mg/dl) in men and less than 1.29 mmol/l (50 mg/dl) in women, or drug treatment for reduced HDL;
4. systolic blood pressure of 130 mmHg or greater, and/or a diastolic blood pressure of 85 mmHg or greater, or antihypertensive drug treatment in a patient with a history of hypertension; and
5. waist circumference of 102 cm or greater in men, and 88 cm or greater in women.

3.5 LEFT VENTRICULAR HYPERTROPHY

LVH was defined by standard 12-lead resting electrocardiograms (ECG) using two established criteria for LVH, the Minnesota Code and the Cornell voltage-duration product. ECG measurements were made with a ruler ("nomogram") on the resting ECG tracings.

The Minnesota Code for LVH was based on class 3:1, continuing to 3:3 if 3:1 was not fulfilled [72]. Either the Minnesota Code or Cornell voltage-duration had to be positive for LVH to qualify for LVH in this work.

Ten percent of the samples (n 400), randomly selected from the cohort of 60-year-old men and women were validated by Professor Sverker Jern's research group at Sahlgrenska University Hospital in Gothenburg, Sweden. The validation showed a correspondence of 83% between the two evaluations (Stockholm versus Gothenburg).

3.6 INSULIN-LIKE GROWTH FACTOR-1 AND INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-1

Total IGF-1 was determined in serum by an in-house radioimmunoassay (RIA) after separation of IGFs from IGFBPs by acid ethanol extraction and cryoprecipitation. To minimise interference of remaining IGFBPs, des (1-3) IGF-1 was used as radioligand [73].

The intra- and interassay CV were 4% and 11%, respectively. Serum levels of IGF-1 are age dependent, decreasing which age, thus IGF-1 values are also expressed as standard deviation (SD) scores, calculated from the regression of the values of 247 and 448 healthy adult subjects, respectively [74, 75]. IGFBP-1 concentrations in serum were determined by an in-house RIA according to the method by Póvoa et al [76]. The sensitivity of the RIA was 3 µg/l and the intra- and interassays CV were 3% and 10%, respectively.

3.7 METHODOLOGICAL ASPECTS IN PAPER IV

In contrast to paper I-III, which all had a cross-sectional design, paper IV was a prospective cohort study, meaning that all participants were followed from the date of completion of the baseline investigation (1997-99) until the date of their death, or until 31 December 2012.

Incident cases of first-time CVD event (fatal or non-fatal myocardial infarction or ischemic stroke) and death from any cause were ascertained through regular examinations of the National Cause of Death Registry and the National In-Hospital Registry, using the International Classification of Diseases 10th revision (ICD-10) codes: I21, I25, I46, I63, I64, I65, and I66. We could guarantee registration of first CVD events only, as care was taken to exclude participants with a history of CVD in the analysis.

3.8 STATISTICS

3.8.1 Paper I

For between-group analysis, unpaired t-tests or, when data had a skewed distribution, the Mann-Whitney U test, were used. The chi-square test was used to test differences between groups for categorical variables. The association between the MetS and each of the PA groups was estimated by calculating odds ratios (OR) with 95% confidence intervals (CI) by means of logistic regression [77]. The “low PA” group (PA 1-2) was used as reference in all analyses. OR adjusted for gender, marital status, university education, smoking, and intake of fruit, vegetables and alcohol were also calculated. Statistical significance was considered to be $p < 0.05$. All statistical analyses were performed using SPSS for Windows software, version 12.1.

3.8.2 Paper II

For between-group analysis, t-tests or when data had a skewed distribution, the Mann-Whitney U test was used. In the regression analyses, PA group 3 and 4 were referred to as “high PA”. The “low PA” group (group 1 and 2) was set as a reference. Odds ratios were calculated crude and adjusted for waist circumference, blood pressure, triglycerides, HDL,

glucose, insulin and PA. All statistical analyses were performed using SAS ® statistical software system version 9.2.

3.8.3 Paper III

For between-group analysis, t-tests or, when data had a skewed distribution, the Mann-Whitney U test was used. Crude and adjusted (not presented) odds ratios were calculated for the MetS and its different components, as well as for insulin, IGF-1, IGFBP-1, oestrogen and PA. In the logistic regression models, PA group 3 and 4 (above) were referred to as "high PA". The "low PA" group (group 1 and 2) was set as a reference. All statistical analyses were performed using SAS statistical software system version 9.2.

3.8.4 Paper IV

For between-group analysis, t-tests or, when data had a skewed distribution, non-parametric Kruskal-Wallis test was used. In order to study if the risk over time varied between individuals with or without the MetS Cox regression was used. In the logistic regression models, PA group 3 and 4 were referred to as "high" PA. The "low" PA-group (group 1 and 2) was set as a reference.

Only first-time CVD events were modelled, assuming the risks to be proportional over time. Effects were presented as relative risk (RR) with 95% confidence interval (CI). In the analyses potential confounders were current smoking, alcohol consumption, education level, and dietary intake of fruit and vegetables. The outcomes (the individual risk factors and MetS at baseline, and CVD event and mortality of any cause after follow-up) were analysed one by one as the dependent variable. For CVD mortality we did not take competing risk into consideration. All statistical analyses were performed using SAS® statistical software system version 9.2.

3.9 ETHICAL CONSIDERATIONS AND INFORMED CONSENT

All studies were approved by the ethical committee at the Karolinska Institutet. All participants were fully informed about the details of the studies, and provided written informed consent.

4 RESULTS

In brief, Paper I focused on the relationship between the MetS and PA. Consequently, the major aim of Paper II was to relate the MetS and its variables to left ventricular hypertrophy (LVH), most obvious associated to hypertension and obesity – but also to deranged blood lipids and insulin resistance. On the basis of the gender differences in the association between LVH and the MetS observed in Paper II, potential influences from insulin-like growth factor-1 (IGF-1) and IGF binding protein-1 (IGFBP-1) on the MetS-LVH relationship were investigated in Paper III, also taking into account the use of oestrogen in women. Finally, the main aim of Paper IV was to prospectively study potential effects from PA on cardiovascular risk and total mortality in individuals with the MetS.

4.1 PAPER I

4.1.1 Characteristics of the study population

As previously reported, every third 60-year-old person in the Stockholm County was invited to a survey in 1997-99 (5460 individuals, 2681 men and 2779 women). Altogether, 4228 individuals participated (2036 men and 2192 women).

All men and women were investigated concerning anthropometric, metabolic, and lifestyle characteristics. The prevalence of the MetS in was 26% and 19% in men and women, respectively. After exclusions of 364 individuals with self-reported cardiovascular diseases and/or cancer (see Materials and Methods), the corresponding prevalences of the MetS in this sample were 24% and 19%. Anthropometric and metabolic characteristics are presented in Table 1, lifestyle characteristics in Table 2, and prevalence of the different components of the MetS and use of certain medication are shown in Table 3.

Body mass index (BMI) and waist as well as SAD differed significantly between individuals with and without the MetS. Even if individuals without the MetS naturally have more favorable anthropometric measures, baseline characteristics show that they still had a BMI over 25 kg/m² (compared to a BMI of 30 kg/m² in individuals with the MetS) and high measurements of waist as well. However, in men and women with the MetS, waist circumference was considerably higher (12-15 cm). In subjects with the MetS, the blood pressure levels were relatively high, and significantly higher than in individuals without the MetS. In general, individuals with the MetS demonstrated a typical dyslipidemia picture: higher levels of triglycerides and Apo B, and lower levels of HDL and Apo A1. In men, in contrast to women, total cholesterol and LDL levels were similar in individuals with and without the MetS. Both glucose and insulin differed significantly between subgroups with or without the MetS, and within gender groups. The highest glucose and insulin levels were seen in men. Levels of p-fibrinogen, s-urate, and s-gammaglutamyltransferase were generally within the upper normal ranges but significantly higher in individuals with the MetS (Table 1).

Table 1. Anthropometric and metabolic characteristics in relation to the metabolic syndrome.

Characteristics	M with MetS	M without MetS	W with MetS	W without MetS
	***n* 441 (24.1%)**	***n* 1388 (75.9%)**	***n* 380 (18.7%)**	***n* 1655 (81.3%)**
Body weight (kg)	93.9 (± 12.8) [a, b]	80.9 (± 11.2)[c]	81.1 (± 13.5)[c]	69.0 (± 11.2)
Height (cm)	176.8 (± 6.8)[b]	176.6 (± 6.6)[c]	163.0 (± 6.3)	163.8 (± 6.0)
BMI (kg/m^2)	30.0 (± 3.8)[a]	25.9 (± 3.1)	30.5 (± 4.7)[c]	25.7 (± 4.0)
Waist (cm)	106.5 (± 9.8) [a, b]	94.6 (± 8.7)[c]	98.3 (± 10.6)[c]	83.6 (± 10.4)
SAD (cm)	23.7 (± 2.6) [a, b]	20.6 (± 2.3)[c]	22.3 (± 2.7)[c]	19.2 (± 2.4)
SBP (mmHg)	150.5 (± 19.2) [a, d]	140.2 (± 20.2)[c]	145.8 (± 20.0)[c]	131.4 (± 21.7)
DBP (mmHg)	91.6 (± 10.0) [a, b]	86.4 (± 10.3)[c]	85.9 (± 8.9)[c]	80.5 (± 9.8)
TG (mmol/l)*	2.0 (1.1; 3.8) [a, f]	1.0 (0.6; 1.8)[c]	1.9 (1.1; 3.0)[c]	1.0 (0.6; 1.5)
Chol, total (mmol/l)	5.8 (± 1.1)[b]	5.8 (± 1.0)[c]	6.4 (± 1.3)[c]	6.1 (± 1.0)
HDL (mmol/l)	1.1 (± 0.3) [a, b]	1.4 (± 0.3)[c]	1.3 (± 0.3)[c]	1.7 (± 0.4)
LDL (mmol/l)	3.8 (± 0.9)[b]	3.9 (± 0.9)	4.2 (± 1.0)[c]	3.8 (± 0.9)
Apo A1 (g/l)	1.3 (± 0.2) [a, b]	1.5 (± 0.2)[c]	1.5 (± 0.2)[c]	1.7 (± 0.3)
Apo B (g/l)	1.2 (± 0.2) [a, b]	1.0 (± 0.2)[g]	1.2 (± 0.2)[c]	1.0 (± 0.2)
Glucose (mmol/l)*	6.1 (4.9; 9.9) [a, b]	5.3 (4.6; 6.0)[c]	5.6 (4.8; 8.6)[c]	5.0 (4.4; 5.7)
Insulin (pmol/l)*	13.9 (7.2; 27.0) [a, f]	8.3 (4.4; 15.2)[c]	12.5 (6.9; 22.1)[c]	7.8 (4.2; 13.6)
Fibrinogen (g/l)	3.2 (± 0.8) [a, b]	2.9 (± 0.7)[e]	3.4 (± 0.8)[c]	3.0 (± 0.7)
Urate (µmol/l)	356.4 (± 69.3) [a, b]	321.3 (± 59.9)[c]	304.4 (± 68.9)[c]	257.4 (± 53.9)
γGT (µkat/l)*	0.8 (0.4; 1.9) [a, b]	0.5 (0.3; 1.3)[c]	0.5 (0.3; 1.4)[c]	0.3 (0.2; 0.8)

Values are mean (± SD). M, men; W, women; MetS, metabolic syndrome; BMI, body mass index; SAD, sagittal abdominal diameter; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; Chol, cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; γGT, gamma-glutamyltransferase.

*Skewed value (median, percentiles).

a Significantly different from men without MS, $p < 0.001$
b Significantly different from women with MS, $p < 0.001$
c Significantly different from women without MS, $p < 0.001$
d Significantly different from women with MS, $p < 0.01$
e Significantly different from women without MS, $p < 0.01$
f Significantly different from women with MS, $p < 0.05$
g Significantly different from women with MS, $p < 0.05$

Concerning PA during leisure-time, men were less sedentary and more vigorously active in general than women. Regarding PA at work, more women than men reported a moderate degree of PA – very few participants reported high PA at work (the majority of both men and women was still fulltime employed: 72% of the men and 64% of the women). Regarding socioeconomic status, subjects with the MetS were to a lesser extent married or living together compared to subjects without the syndrome (67 vs. 78% in men, 61 vs. 67% in women), and fewer had a university education (21 vs. 29% in men, and 17 vs. 28% in women). The prevalence of smoking was generally rather low, with no clear difference in men with or without the MetS. The highest prevalence of smokers was found in women with the MetS (26%), who smoked significantly more than women without the MetS (20%).

Considering the reported intake of fruits, vegetables, and alcohol, there were significant gender differences favoring women, who generally reported a healthier habitual diet and less alcohol consumption. Finally, significantly fewer men and women with the MetS reported good health, and significantly fewer men with the MetS reported good finances than men without the syndrome (Table 2).

Table 2. Lifestyle characteristics in relation to the metabolic syndrome (numbers (%)).

Characteristics	**M with MetS** ***n* 441 (24.1%)**	**M without MetS** ***n* 1388 (75.9%)**	**W with MetS** ***n* 380 (18.7%)**	**W without MetS** ***n* 1655 (81.3%)**
Low PA, *n* (%)	61 (13.8) [a, e]	119 (8.6)	77 (20.3)[c]	161 (9.7)
Light PA, *n* (%)	227 (51.5)	749 (54.0)[c]	215 (56.6)	1005 (60.7)
Moderate PA, *n* (%)	121 (27.4)[b]	353 (25.4)[i]	62 (16.3)[f]	369 (22.3)
High PA, *n* (%)	24 (5.4)[a]	149 (10.7)[c]	17 (4.5)	104 (6.3)
Mod PA at work, *n* (%)	99 (22.4)	315 (22.7)	124 (32.6)	424 (25.6)
Married/living toget, *n* (%)	295 (66.9)[h]	1084 (78.1)[c]	232 (61.1)	1104 (66.7)
University educated, *n* (%)	93 (21.1)[g]	403 (29.0)	64 (16.8)[c]	466 (28.2)
Smoker, *n* (%)	75 (17.0)	272 (19.6)	98 (25.8)[i]	335 (20.2)
Mod intake of fruit, *n* (%)	198 (44.9)[b]	700 (50.4)[c]	242 (63.7)[i]	1237 (74.7)
Mod intake veget, *n* (%)	213 (48.3)[e]	799 (57.6)[c]	227 (59.7)	1143 (69.1)
High intake alcohol, *n* (%)	81 (18.4)[b]	238 (17.1)[c]	29 (7.6)	138 (8.3)
"Good" health, *n* (%)	307 (69.6) [a, h]	1146 (82.6)[f]	221 (58.2)[c]	1304 (78.8)
"Good" finances, *n* (%)	312 (70.7) [d, h]	1074 (77.4)[i]	265 (69.7)	1202 (72.6)

M, men; W, women; MetS, metabolic syndrome; PA, physical activity; Mod, moderate; toget, together; veget, vegetables.

a Significantly different from men without MS, $p < 0.001$
b Significantly different from women with MS, $p < 0.001$
c Significantly different from women without MS, $p < 0.001$
d Significantly different from men without MS, $p < 0.01$
e Significantly different from women with MS, $p < 0.01$
f Significantly different from women without MS, $p < 0.01$
g Significantly different from men without MS, $p < 0.05$
h Significantly different from women with MS, $p < 0.05$
i Significantly different from women without MS, $p < 0.05$

When analyzing the different components included in the metabolic syndrome, the most striking observation was the relatively high prevalence of hypertension in both genders (Table 3).

Table 3. Prevalence of the components of the metabolic syndrome as well as, diabetes and the use of antihypertensive, diabetes, and lipid-lowering medication.

Characteristics	**Men**	**Women**
	***n* = 1829**	***n* = 2035**
Waist (M >102 cm, W >88 cm)	505 (27.6)	795 (39.0)
Blood pressure (≥130/85 mmHg)	1356 (74.1)	1126 (55.3)
Triglycerides (≥1.7 mmol/l)	482 (26.3)	369 (18.1)
HDL (M <1.0 mmol/l, W <1.3 mmol/l)	284 (15.5)	378 (18.6)
IFG (glucose >6.1–7.0 mmol/l)	154 (8.4)	90 (4.4)
Diabetes (glucose ≥7.0 mmol/l)	148 (8.1)	82 (4.0)
Antihypertensive medication	327 (17.9)	336 (16.5)
Lipid-lowering medication	103 (5.6)	68 (3.3)
Diabetes medication	76 (4.2)	47 (2.3)

Values are numbers (%). IFG, impaired fasting glucose.

4.1.2 Associations between physical activity and the metabolic syndrome

There was an inverse and dose-response relationship between reported PA during leisure-time and the MetS, while no such pattern was noted for work-related PA. The crude odds ratio for having the MetS in the high PA group was 0.33 (95% CI 0.22-0.49) using the low PA group as reference. Adjusting for sex, marital status, university education, smoking, intake of fruit and vegetables as well as alcohol did not change the results (OR 0.33; 95% CI 0.22-0.51) (Figure 1).

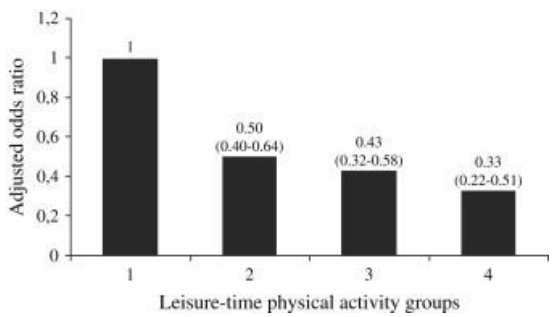


Figure 1. Adjusted odds ratio (95% CI) for the metabolic syndrome in different leisure-time activity groups (1=low, 2=light, 3=moderate, 4=high physical activity), using the low activity group as reference.

4.2 PAPER II

4.2.1 Characteristics of the study population

Characteristics of the study sample in relation to gender and occurrence of LVH are presented in Table 4. In general, both men and women with LVH showed an adverse cardiovascular risk profile, especially in women. Regarding blood pressure, systolic as well as diastolic, the differences between the groups with and without LVH were highly significant in both men and women. Of note is the relatively high systolic mean value in both genders (156 and 151 mmHg, respectively). In women with LVH, compared with women without LVH, significantly higher levels of body mass index (BMI), waist, SAD, total cholesterol and apolipoprotein B as well as glucose and insulin were noted. In general, irrespective of groups, the mean values indicated high prevalences of overweight and abdominal obesity.

Table 4. Study population: distribution of anthropometric characteristics and biochemical measurements in relation to gender and occurrence of left ventricular hypertrophy (LVH).

	Men			**Women**		
	No LVH (*n* 1649)	**LVH (*n* 173)**	***p*-value**	**No LVH (*n* 1936)**	**LVH (*n* 113)**	***p*-value**
BMI (kg/m^2)	26.8 (± 3.7)	27.3 (± 3.8)	0.089	26.4 (± 4.4)	28.3 (± 5.0)	< 0.001
Waist (cm)	97.2 (± 10.3)	98.4 (± 10.8)	0.178	85.9 (± 11.6)	91.0 (± 13.2)	< 0.001
SAD (cm)	21.3 (± 2.7)	21.7 (± 3.0)	0.088	19.7 (± 2.7)	20.6 (± 3.1)	0.002
SBP (mmHg)	141 (± 19)	156 (± 24)	< 0.001	133 (± 21)	151 (± 24)	< 0.001
DPB (mmHg)	87 (± 10)	93 (± 12)	< 0.001	81 (± 10)	89 (± 9)	< 0.001
Biochemistry						
TG (mmol/l)*	1.2 (0.8–1.7)	1.1 (0.9–1.8)	1.000	1.1 (0.8–1.5)	1.1 (0.8–1.6)	0.103
TChol (mmol/l)	5.8 (± 1.0)	5.9 (± 1.0)	0.266	6.1 (± 1.0)	6.4 (± 1.7)	0.008
HDL (mmol/l)	1.3 (± 0.3)	1.3 (± 0.4)	0.460	1.6 (± 0.4)	1.6 (± 0.4)	0.529
LDL (mmol/l)	3.8 (± 0.9)	3.9 (± 0.9)	0.496	3.9 (± 1.0)	4.0 (± 1.0)	0.185
ApoA1 (g/l)	1.42 (± 0.24)	1.43 (± 0.28)	0.666	1.63 (± 0.26)	1.64 (± 0.24)	0.731
ApoB (g/l)	1.06 (± 0.23)	1.09 (± 0.23)	0.140	1.06 (± 0.23)	1.12 (± 0.26)	0.008
Glucose (mmol/l)*	5.4 (5.0–5.9)	5.4 (5.0–6.0)	0.488	5.1 (4.7–5.5)	5.3 (4.9–5.8)	< 0.001
Insulin (μU/ml)*	8.9 (6.7–12.8)	9.8 (7.3–14.4)	0.042	8.4 (6.2–11.2)	10.6 (7.0–14.1)	< 0.001

Values are mean (± SD). BMI, body mass index; SAD, sagittal abdominal diameter; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TChol, total cholesterol; HDL, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.

*Skewed distribution (median, percentiles).

4.2.2 Prevalence of LVH in relation to the MetS

Overall, the prevalence of MetS in the study population (after exclusion of 357 participants with prior cardiovascular disease and stroke) was 27.0% (492/1822) in men and 20.3% (416/2049) in women. Figure 2 shows the prevalence of LVH in men and women in relation to the number of components of the MetS (including the "arbitrary" columns of any of two variables of the MetS). The prevalence of LVH was 12.8% in men with the MetS, and 7.9% in men without the MetS ($p \leq 0.003$). The corresponding prevalences of LVH in women were 9.9% with the MetS and 3.3% without ($p \leq 0.001$). The prevalence of LVH in the whole group (including both genders) was 11.5% with the MetS and 5.3% without the MetS ($p \leq 0.001$).

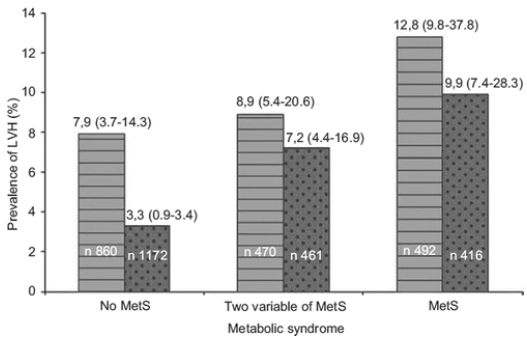


Figure 2. Prevalence of LVH in percentage (95% CI) in men (striped bars) and women (dotted bars) in relation to the number of components of the metabolic syndrome (MetS).

4.2.3 Relationships between LVH and MetS components

The MetS was associated with LVH in men with an OR of 1.63 (95% CI 1.17-2.26), whereas only two separate components, waist (with an OR 1.44; 95% CI 1.03-2.01) and hypertension (with an OR 3.52; 95% CI 2.11-5.87) yielded significant relations (Table 5). In women, the crude OR for LVH in relation to the MetS indicated a somewhat stronger relation with an OR of 2.37 (95% CI 1.59-3.54). As in men, abdominal obesity and hypertension were significantly associated (OR 2.21; 95% CI 1.50-3.24 and 4.61; 95% CI 2.77-7.70, respectively) with LVH. Furthermore, glucose and insulin were also associated to LVH (OR 2.79; 95% CI 1.87-4.15 and OR 2.30; 95% CI 1.57-3.38, respectively) in women.

Table 5. The risk of having left ventricular hypertrophy, assessed as crude odds ratio with 95% confidence interval, for the metabolic syndrome and its various components as well as insulin and physical activity.

	Men (*n* 1822)			Women (*n* 2049)		
	n	**Crude OR**	**95% CI**	***n***	**Crude OR**	**95% CI**
MetS	492	1.63	1.17–2.26	416	2.37	1.59–3.54
Waist (>102/88)	495	1.44	1.03–2.01	784	2.21	1.50–3.24
BP (>130/85)	1348	3.52	2.11–5.87	1128	4.61	2.77–7.70
TG (>1.7)	476	1.06	0.75–1.51	368	1.55	0.99–2.41
HDL (<1.03/1.3)	330	1.21	0.82–1.79	380	1.00	0.62–1.63
Glucose (≥5.6)	615	1.30	0.95–1.80	381	2.79	1.87–4.15
Insulin (>11.1/10.2)	617	1.37	0.99–1.89	689	2.30	1.57–3.38
PA (high)	611	1.1	0.85–1.66	547	1.04	0.67–1.61

BP, blood pressure; TG, triglycerides; HDL, high-density lipoprotein-cholesterol; PA, physical activity. The cut-off limits for insulin are based on the highest tertile.

In Table 6, the potential independent role of the various components of the MetS and insulin and the risk for LVH was analysed. In each of the separate analyses, adjustments were made for all of the other components of the MetS, one by one, to examine the independent association to LVH. The main findings of this analysis were that, in men, hypertension was the only component with a significant association (OR 3.40; 95% CI 1.99-5.82) with LVH, after adjustments. In women, however, not only hypertension (OR 4.41; 95% CI 2.51-7.76), but also waist circumference (OR 1.63; 95% CI 1.03-2.57), glucose (OR 1.77; 95% CI 1.13-2.79) and insulin (OR 1.67; 95% CI 1.06-2.62) seemed to be independently related to LVH. Adjustments for PA did not alter the above associations significantly.

Table 6. The risk of having left ventricular hypertrophy, assessed as adjusted odds ratio with 95% confidence interval, for the metabolic syndrome and its various components as well as insulin and physical activity.

	Men (*n* = 1822)			Women (*n* = 2049)		
	n	**Adjusted OR**	**95% CI**	***n***	**Adjusted OR**	**95% CI**
Waist (> 102/88)	495	1.29	0.88–1.88	784	1.63	1.03–2.57
BP (> 130/85)	1348	3.40	1.99–5.82	1128	4.41	2.51–7.76
TG (> 1.7)	476	0.78	0.52–1.18	368	1.02	0.61–1.71
HDL (< 1.03/1.3)	330	1.09	0.69–1.71	380	0.65	0.37–1.14
Glucose (≥ 5.6)	615	1.09	0.76–1.55	381	1.77	1.13–2.79
Insulin (> 11.1/10.2)	617	1.08	0.75–1.57	689	1.67	1.06–2.62
PA (high)	611	1.28	0.91–1.80	547	1.41	0.90–2.22

BP, blood pressure; TG, triglycerides; HDL, high-density lipoprotein-cholesterol; PA, physical activity. Each component is adjusted for all other MetS components, insulin and physical activity to examine the independent association to LVH. The cut-off limits for insulin are based on the highest tertile.

4.3 PAPER III

4.3.1 Characteristics of the study population

The characteristics of the study population, in relation to gender and occurrence of LVH, are described in detail in Paper II. Anthropometric characteristics and biochemical measurements including IGF-1 and IGFBP-1 of men and women with or without LVH are presented in Table 7. In general, women with LVH revealed a more metabolically deranged status than men, while systolic as well as diastolic blood pressures were generally higher in men.

The levels of IGFBP-1 demonstrated a significant ($p < 0.001$) gender difference, with generally higher levels of IGFBP-1 in women (37.0 vs. 28.0 µg/l, on average). When discriminating between individuals with and without LVH, a significant difference in levels of IGFBP-1 was observed in women (31.0 vs. 37.0 µg/l, $p < 0.001$), but not in men. Concerning the levels of IGF-1, a significantly ($p < 0.001$) higher level was seen in men compared to women (161.8 vs. 151.1 µg/l, on average). No significant difference was observed between individuals with and without LVH, neither in men nor in women.

Table 7. Study population: anthropometric characteristics and biochemical measurements in relation to gender and occurrence of left ventricular hypertrophy (LVH).

	Men (n 1822)			**Women (n 2049)**		
	No LVH (n 1649)	**LVH (n 173)**	***p*-value**	**No LVH (n 1936)**	**LVH (n 113)**	***p*-value**
Waist (cm)	97.2 (±10.3)	98.4 (±10.8)	0.178	85.9 (±11.6)	91.0 (±13.2)	<0.001
SAD (cm)	21.3 (±2.7)	21.7 (±3.0)	0.088	19.7 (±2.7)	20.6 (±3.1)	0.002
SBP (mmHg)	141 (±19)	156 (±24)	<0.001	133 (±21)	151 (±24)	<0.001
DBP (mmHg)	87 (±10)	93 (±12)	<0.001	81 (±10)	89 (±9)	<0.001
TG (mmol/l)*	1.2 (0.8; 1,7)	1.1 (0.9; 1.8)	1.000	1.1 (0.8; 1.5)	1.1 (0.8; 1.6)	1.103
TChol (mmol/l)	5.8 (±1.0)	5.9 (±1.0)	0.266	6.1 (±1.0)	6.4 (±1.7)	0.008
HDL (mmol/l)	1.3 (±0.3)	1.3 (±0.4)	0.460	1.6 (±0.4)	1.6 (±0.4)	0.529
LDL (mmol/l)	3.8 (±0.9)	3.9 (±0.9)	0.496	5.1 (4.7; 5.5)	5.3 (4.9; 5.8)	<0.001
Glucose (mmol/l)*	5.4 (5.0; 5.9)	5.4 (5.0; 6.0)	0.488	5.1 (4.7; 5.5)	5.3 (4.9; 5.8)	<0.001
Insulin (µU/ml)*	8.9 (6.7; 12.8)	9.8 (7.3; 14.4)	0.042	8.4 (6.2; 11.2)	10.6 (7.0; 14.1)	<0.001
IGFBP-1 (µg/l)*	28.0 (20; 40)	26.0 (18; 41)	0.376	37.0 (28; 49)	31.0 (22; 46)	<0.001
IGF-1 (µg/l)	161.5 (±49.7)	164.5 (±51.0)	0.454	151.0 (±46.3)	152.4 (±46.3)	0.756

Footnote: Values are means (±SD). SAD, sagittal abdominal diameter; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TChol, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; IGFBP-1, insulin-like growth factor binding protein-1; IGF-1, insulin-like growth factor-1.

*Skewed distribution (median, percentiles).

4.3.2 The risk of having LVH

The risk for LVH in relation to the MetS and its different components, as well as insulin, level of leisure-time PA, use of oestrogen, and percentile levels of IGFBP-1 and IGF-1 are presented in Table 8.

Hypertension was most strongly and independently related to LVH in both men and women. In women, also abdominal obesity, high glucose levels and hyperinsulinemia were independently related to LVH. Oestrogen (in women) was significantly negatively associated with LVH, with a crude OR of 0.47 (95% CI 0.28-0.79).

In women, low percentile levels of IGFBP-1 were significantly associated with LVH. In men, no significant association between IGFBP-1 and LVH was observed. Although not significant, there were generally higher OR:s for the risk of LVH in women than in men throughout all percentile levels of IGFBP-1.

The analysis of IGF-1, also based on percentile levels, did not yield any significant association to LVH (except for a negative association in the 30th percentile in women), neither in men nor in women. Of that reason, the following analyses focus only on IGFBP-1, and not IGF-1.

Table 8. The risk of having left ventricular hypertrophy (crude odds ratio) for the metabolic syndrome and its different components and insulin as well as physical activity, oestrogen and percentile levels of insulin-like growth factor binding protein-1 and insulin-like growth factor-1.

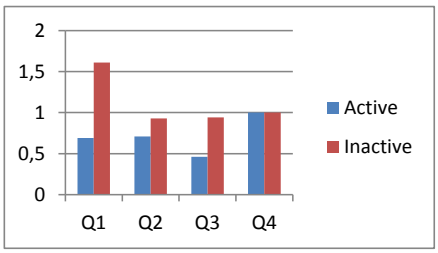
	Men (n 1822)			Women (n 2049)		
	N	**Crude OR**	**95% CI**	**N**	**Crude OR**	**95% CI**
MetS	492	1.63	**1.17-2.26**	416	2.37	**1.59-3.54**
Waist (>102/88 cm)	495	1.44	**1.03-2.01**	784	2.21	**1.50-3.24**
BP (>130/85 mmHg)	1348	3.52	**2.11-5.87**	1128	4.61	**2.77-7.70**
TG (>1.7 mmol/l)	476	1.06	0.75-1.51	368	1.55	0.99-2.41
HDL (<1.03/1.3 mmol/l)	330	1.21	0.82-1.79	380	1.00	0.62-1.63
Glucose (≥5.6 mmol/l)	615	1.30	0.95-1.80	381	2.79	**1.87-4.15**
Insulin (>11.1/10.2 µU/ml)	617	1.37	0.99-1.89	689	2.30	**1.57-3.38**
PA (high)	611	1.19	0.85-1.66	547	1.04	0.67-1.61
Oestrogen	-	-	-	549	0.47	**0.28-0.79**
IGFBP-1(10)	221	1.04	0.57-1.90	248	2.56	**1.23-5.83**
IGFBP-1(20)	180	0.70	0.35-1.38	195	2.43	**1.03-5.72**
IGFBP-1(30)	168	0.80	0.41-1.58	204	1.49	0.60-3.73
IGFBP-1(40)	165	0.88	0.45-1.71	196	1.42	0.56-3.61
IGFBP-1(50)	193	0.60	0.30-1.21	219	0.67	0.23-1.97
IGFBP-1(60)	209	0.55	0.28-1.11	179	1.12	0.41-3.04
IGFBP-1(70)	154	0.55	0.26-1.18	205	0.97	0.36-2.64
IGFBP-1(80)	201	0.66	0.34-1.30	211	1.44	0.58-3.60
IGFBP-1(90)	160	0.74	0.37-1.49	199	0.77	0.26-2.25
Ref (100)	**171**	**1**		**193**	**1**	
IGF-1(10)	189	0.91	0.45-1.85	201	1.09	0.51-2.33
IGF-1(20)	179	0.53	0.23-1.20	220	0.75	0.32-1.76
IGF-1(30)	197	0.97	0.50-1.90	207	0.30	**0.10-0.92**
IGF-1(40)	190	1.24	0.64-2.41	210	1.08	0.50-2.36
IGF-1(50)	175	0.91	0.45-1.85	212	0.90	0.40-2.03
IGF-1(60)	173	0.94	0.47-1.87	198	0.75	0.32-1.76
IGF-1(70)	181	1.01	0.50-2.04	193	1.15	0.53-2.49
IGF-1(80)	181	1.06	0.54-2.10	214	0.47	0.18-1.26
IGF-1(90)	179	0.96	0.48-1.91	192	0.97	0.44-2.14
Ref (100)	**182**	**1**		**202**	**1**	

Footnote: MetS, metabolic syndrome; BP, blood pressure; TG, triglycerides; HDL, high-density lipoprotein cholesterol; PA, physical activity; IGFBP-1, insulin-like growth factor binding protein-1; IGF-1, insulin-like growth factor-1.

When stratifying the risk of LVH on physical activity, presented as quartiles of IGFBP-1, there was a relatively weaker association (crude OR) to LVH in active men and women – especially in the lowest quartile of IGFBP-1 in both genders (Figure 3a and 3b). Furthermore, the risk of LVH was significantly higher in physically inactive women in the lowest quartile of IGFBP-1, compared to the highest quartile (set as reference).

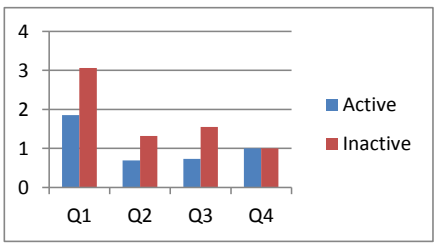
When stratifying the risk of LVH for oestrogen, we found a generally lower risk among users (Figure 4). The crude OR in the lowest quartile of non-users was significantly associated with LVH (OR 2.28, 95% CI 1.21-4.27).

Figure 3a. Risk of having LVH (crude OR) in different quartiles of IGFBP-1 in physically active and inactive men, respectively.



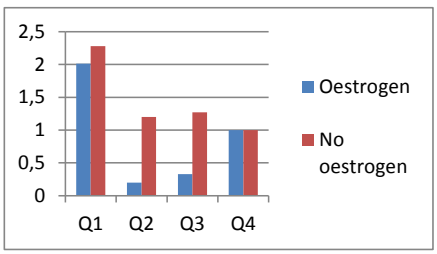
Active (95% CI)	**Inactive (95% CI)**
Q1 0.69 (0.34-1.41), n 145	1.61 (0.92-2.83), n 333
Q2 0.71 (0.35-1.45), n 142	0.93 (0.48-1.79, n 260
Q3 **0.46 (0.22-0.97), n 180**	0.94 (0.49-1.78), n 272
Q4 1 (ref), n 140	n (ref), n 256

Figure 3b. Risk of having LVH (crude OR) in different quartiles of IGFBP-1 in physically active and inactive women, respectively.



Active (95% CI)	**Inactive (95% CI)**
Q1 1.85 (0.70-4.87), n 125	**3.06 (1.48-6.31), n 375**
Q2 0.69 (0.21-2.24), n131	1.32 (0.58-3.02), n 350
Q3 0.73 (0.24-2.22), n 150	1.55 (0.69-3.47), n 343
Q4 1 (ref), n 128	1 (ref), n 327

Figure 4. Risk of having LVH (crude OR) in different quartiles of IGFBP-1 in women with and without reported use of oestrogen, respectively.



Oestrogen (95% CI)	**No oestrogen (95% CI)**
Q1 2.01 (0.68-6.00), n 107	**2.28 (1.21-4.27), n 411**
Q2 0.20 (0.02-1.71), n 123	1.20 (0.60-2.42), n 382
Q3 0.33 (0.06-1.66), n 153	1.27 (0.63-2.56), n 361
Q4 1 (ref), n 155	1 (ref), n 318

4.4 PAPER IV

4.4.1 Characteristics of the study population

The prevalence of the MetS in the study population was 23.2% (n 868), and 26.8% (n 468) of all male participants and 20.1% (n 400) of all females fulfilled the criteria for the MetS (Table 9). When characterizing the population based on occurrence of the MetS versus no MetS, there were significant differences in body weight, BMI, waist circumference, sagittal abdominal diameter, as well as for systolic and diastolic blood pressure in both men and women. Furthermore, all biochemical measurements, except for LDL in men, differed significantly in both genders. In general, the differences between individuals with and without the MetS tended to be more pronounced in women.

Concerning lifestyle parameters, women with the MetS reported to significant extent higher rates of smoking, lower level of education, lower intake of fruit and vegetables, and lower level of PA as well, compared to women without the MetS. In men with the MetS, the significant differences encompassed only higher alcohol consumption and lower level of PA.

Table 9. Study population: distribution of anthropometric characteristics, biochemical measurement and lifestyle variables in relation to gender and occurrence of the metabolic syndrome (mean (±SD) or percentiles for binary (lifestyle) data.

	Men			*Women*		
	Metabolic syndrome (n 468)	**No metabolic syndrome (n 1280)**	**P-value**	**Metabolic syndrome (n 400)**	**No metabolic syndrome (n 1589)**	**P-value**
Body weight (kg)	93.7 (±12.3)	80.3 (±11.0)	<0.0001	80.7 (±12.1)	68.6 (±11.1)	<0.0001
Height (cm)	177.1 (±6.7)	176.6 (±6.5)	0.1692	163.2 (±6.4.)	163.9 (±5.9)	0.0646
BMI (kg/m^2)	29.9 (±3.6)	25.7 (±3.0)	<0.0001	30.3 (±4.5)	25.5 (±3.9)	<0.0001
Waist (cm)	106.4 (±9.2)	94.0 (±8.5)	<0.0001	98.0 (±10.4)	83.2 (±10.1)	<0.0001
SAD (cm)	23.6 (±2.5)	20.5 (±2.2)	<0.0001	22.2 (±2.7)	19.1 (±2.4)	<0.0001
SBP (mm Hg)	150.8 (±18.1)	139.5 (±20.2)	<0.0001	147.3 (±19.9)	130.7 (±21.3)	<0.0001
DPB (mm Hg)	91.6 (±9.7)	86.1 (±10.3)	<0.0001	87.8 (±8.9)	80.1 (±9.7)	<0.0001
TG (mmol/l)*	1.9 (1.4; 2.5)	1.0 (0.8; 1.40)	<0.0001	1.8 (1.4; 2.3)	1.0 (0.8; 1.3)	<0.0001
TChol (mmol/l)	5.9 (±1.1)	5.8 (±1.0)	0.0095	6.5 (±1.3)	6.0 (±1.0)	<0.0001
HDL (mmol/l)	1.1 (±0.3)	1.4 (±0.3)	<0.0001	1.3 (±0.3)	1.7 (±0.4)	<0.0001
LDL (mmol/l)	3.9 (±0.9)	3.9 (±0.9)	0.590	4.2 (±1.0)	3.8 (±0.9)	<0.0001
Glucose (mmol/l)*	5.9 (5.5; 6.7)	5.2 (4.9; 5.5)	<0.0001	5.7 (5.2; 6.2)	5.0 (4.7; 5.3)	<0.0001
Insulin (µU/ml)*	13.5 (9.4; 17.8)	8.1 (6.2; 10.8)	<0.0001	12.4 (9.5; 16.3)	7.7 (5.8; 10.2)	<0.0001
Smoking	20.2	20.2	0.9853	26.5	21.3	0.0283
Alcohol (%high)	23.0	17.2	0.0082	7.7	7.8	0.9621
Education (%univ)	25.6	30.3	0.0545	19.1	29.9	<0.0001
Fruit/veg (%high)	72.9	74.0	0.6264	81.9	87.2	0.0120
Physical activity (%high)	30.2	36.9	0.0108	20.3	29.7	<0.0001

Abbreviations: BMI Body Mass Index; SAD Sagittal Abdominal Diameter; SBP Systolic Blood Pressure, DBP Diastolic Blood Pressure, TG Triglycerides, TChol Total Cholesterol, HDL High-density Lipoprotein Cholesterol, LDL Low-density Lipoprotein Cholesterol.

* skewed distribution (median, percentiles)

4.4.2 New cases of cardiovascular disease and number of deaths during follow-up

During the follow-up period from 1997-1999 to 31 December 2012 there were 472 deaths (273 in men and 199 in women) due to all causes, whereof 116 (81 men and 35 women) due to CVD. Furthermore, there were 376 incident cases of CVD (in this study defined as myocardial infarction and ischemic stroke) during the period (231 men and 145 women).

As presented in Table 10, the relative risks for CVD, CVD mortality as well as all-cause mortality were significantly and substantially higher in men and women with the MetS compared to study participants without the MetS. That applied not only for the crude model, but also after adjustments for potential confounders have been made. The differences of the point estimates before and after adjustments were relatively small, indicating that the MetS itself was a strong determinant of the above outcomes, compared to the factors adjusted for (smoking, alcohol consumption, educational level, intake of fruit and vegetables, and PA level). The point estimates ranged from 1.41, 95% CI 1.03-1.94 (all-cause mortality in women) to 4.92, 95% CI 2.53-9.57 (CVD mortality in women).

Table 10. Relative risks for non-fatal and fatal myocardial infarction or ischemic stroke, as well as all-cause mortality in individuals with the metabolic syndrome compared to individuals without the metabolic syndrome.

CVD (MI, stroke)	**Total (n 376)**	**Men (n 231)**	**Women (n 145)**
Crude	1.88 (1.52-2.33)	1.57 (1.20-2.06)	2.21 (1.57-3.11)
Adjusted	1.66 (1.33-2.08)	1.48 (1.12-1.97)	1.97 (1.38-3.82)
CVD mortality	**Total (n 116)**	**Men (n 81)**	**Women (n 35)**
Crude	2.59 (1.80-3.75)	1.80 (1.15-2.82)	4.92 (2.53-9.57)
Adjusted	2.26 (1.53-3.32)	1.78 (1.12-2.84)	4.34 (2.15-8.74)
All-cause mortality	**Total (n 472)**	**Men (n 273)**	**Women (n 199)**
Crude	1.63 (1.34-1.97)	1.54 (1.20-1.97)	1.60 (1.17-2.18)
Adjusted	1.45 (1.19-1.77)	1.47 (1.14-1.90)	1.41 (1.03-1.94)

Adjustments were made for: smoking, alcohol consumption, educational level, intake of fruit and vegetables, and physical activity level.

4.4.3 The influence of physical activity on future cardiovascular risk and total mortality in individuals with the metabolic syndrome

In Table 11 the relative risks for non-fatal and fatal myocardial infarction or ischemic stroke, as well as all-cause mortality in relation to level of PA (high versus low) in individuals with the MetS are presented. There was a general risk reduction in men and women reporting high PA, especially concerning CVD mortality and all-cause mortality. For example, physically active women had 74% decreased risk for CVD mortality after adjustment for potential

confounding factors (mentioned above), although not significant. Regarding all-cause mortality there were significantly lower risks in men and women together (relative risk 0.65 after adjustments, 95% CI 0.41-0.97) as well as in men separately (relative risk 0.58 after adjustments, 95% CI 0.35-0.98).

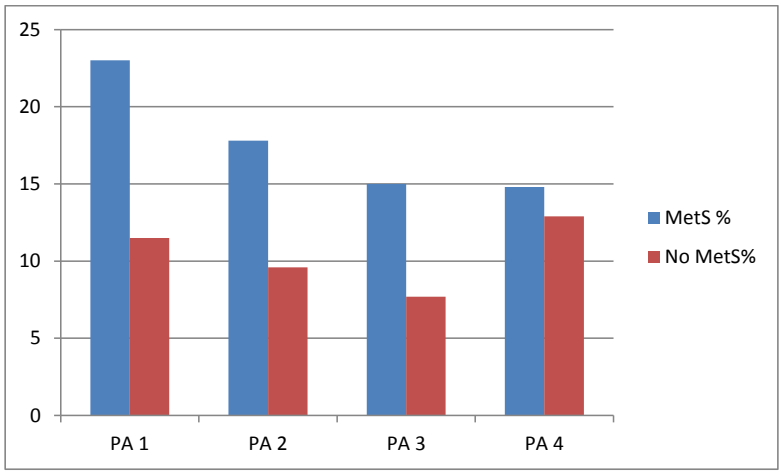
Table 11. Relative risks for non-fatal and fatal myocardial infarction or ischemic stroke, as well as all-cause mortality in individuals with the metabolic syndrome in relation to level of physical activity (high vs. low).

CVD (MI, stroke)	**Total (n 122)**	**Men (n 74)**	**Women (n 48)**
Crude	0.80 (0.52-1.23)	0.88 (0.52-1.46)	0.54 (0.23-1.26)
Adjusted	0.89 (0.57-1.38)	0.95 (0.57-1.58)	0.77 (0.32-1.89)
CVD mortality	**Total (n 47)**	**Men (n 29)**	**Women (n 18)**
Crude	0.47 (0.21-1.05)	0.53 (0.22-1.31)	0.22 (0.02-1.61)
Adjusted	0.50 (0.22-1.15)	0.61 (0.25-1.52)	0.26 (0.03-1.98)
All-cause mortality	**Total (n 147)**	**Men (n 93)**	**Women (n 54)**
Crude	0.60 (0.39-0.91)	0.53 (0.32-0.89)	0.65 (0.31-1.38)
Adjusted	0.65 (0.41-0.97)	0.58 (0.35-0.98)	0.73 (0.34-1.59)

Adjustments were made for: smoking, alcohol consumption, educational level, intake of fruit and vegetables, and gender (total column).

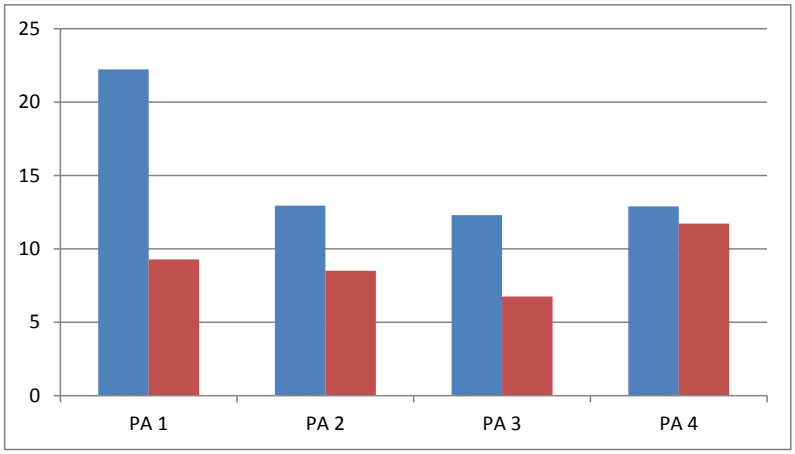
Figure 5 shows the probability of incident CVD (as proportions) in relation to PA in individuals with and without the MetS during the follow-up period (1997-2012). Overall, a considerably higher risk was seen in individuals with the MetS compared to individuals without the MetS regardless of level of PA. When analysing the probability that the proportion of incident CVD varied with level of PA, there was a significant ($p < 0.03$) decreased risk in individuals without the MetS, and a highly significant ($p < 0.0001$) risk reduction in individuals with the MetS in relation to levels of PA. In individuals with the MetS the CVD risk decreased gradually with activity level. Furthermore, almost a quarter (23%) in the inactive subgroup with the MetS developed CVD during the follow-up.

Figure 5. Probability of incident CVD (as proportions) in relation to physical activity (PA 1-4) in individuals with and without the metabolic syndrome during the follow-up period (1997-2012).



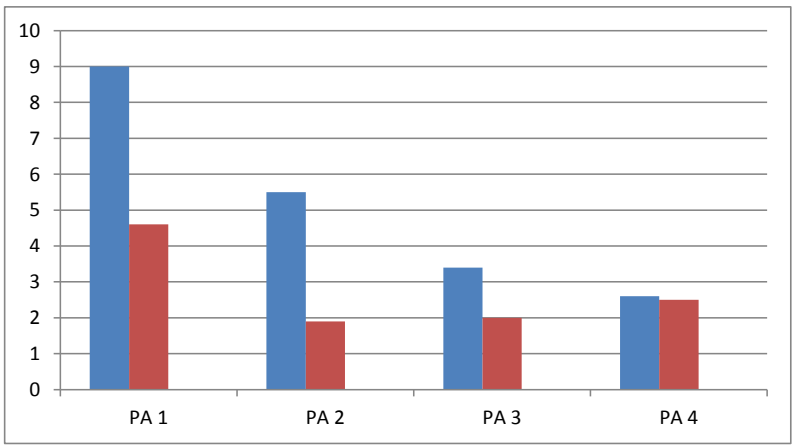
The proportions of CVD, CVD mortality, and all-cause mortality during the follow-up period (1997-99 to 2012), in individuals with and without MetS separated into the four levels of PA, are presented in Figure 6-8. A dose-response pattern was present for all three outcomes, particularly in the individuals with the MetS. However, a slight "U-shape" was noted, i.e. the proportion of CVD as well as CVD- and all-cause mortality were to some extent increasing in the most active subgroup. Individuals with the MetS seemed to always be at a higher risk compared to those without MetS – except for the most active subgroup (PA 4), where the risk differences almost were diminished.

Figure 6. Proportions (%) of myocardial infarction and ischemic stroke in individuals with (blue) and without (red) the metabolic syndrome during the follow-up from 1997-99 to 2012.



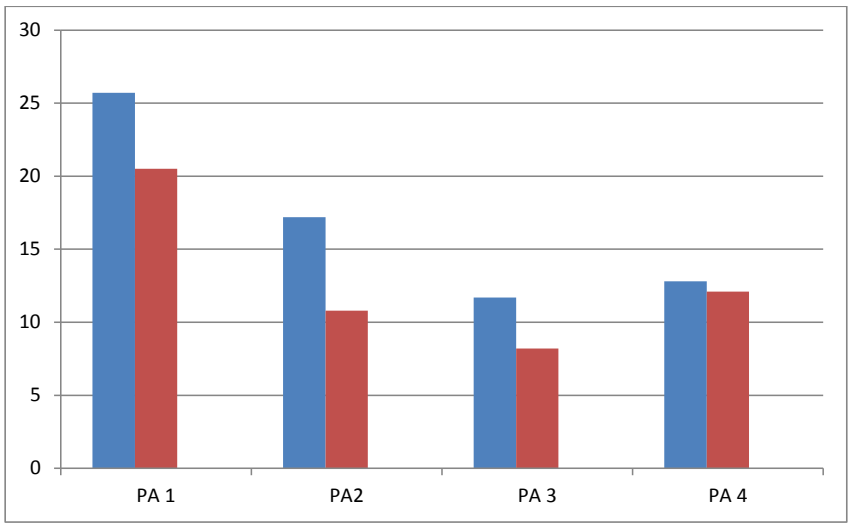
	MetS	No MetS
PA 1	22.2 (15.4-29.0), n 144	9.3 (5.7-12.8), n 259
PA 2	12.9 (10.0-15.9), n 487	8.5 (7.2-9.8), n 1646
PA 3	12.3 (7.5-17.1), n 179	6.8 (4.9-8.6), n 696
PA 4	12.8 (2.2-23.4), n 39	11.7 (7.6-15.8), n 239

Figure 7. CVD mortality (%) in individuals with (blue) and without (red) the metabolic syndrome during the follow-up from 1997-99 to 2012.



MetS		No MetS
PA 1	9.0 (4.3-13.7), n 144	4.6 (2.1-7.2), n 259
PA 2	5.5 (3.5-7.6), n 487	1.9 (1.2-2.5), n 1646
PA 3	3.4 (0.7-6.0), n 179	2.0 (1.0-3.1), n 696
PA 4	2.6 (0.1-13.5), n 39	2.5 (0.5-4.5), n 239

Figure 8. All-cause mortality (%) in individuals with (blue) and without (red) the metabolic syndrome during the follow-up from 1997-99 to 2012.



	MetS	**No MetS**
PA 1	25.7 (18.5-32.9), n 144	20.5 (15.5-25.4), n 259
PA 2	17.2 (13.9-20.6), n 487	10.8 (9.3-12.2), n 1646
PA 3	11.7 (7.0-16.5), n 179	8.2 (6.2-10.2), n 696
PA 4	12.8 (2.2-23.4), n 39	12.1 (8.0-16.3), n 239

5 DISCUSSION

During the last decades, changes in cardiovascular risk factor profiles in the Swedish population (as well as globally) have been observed, with decreasing levels of total cholesterol and blood pressure, increasing body weight and waist circumference, increasing levels of triglycerides, and in some areas in Sweden, a rise in the type 2 diabetes prevalence [78]. In the same time, longevity is still increasing (or at least at the same high level), and people tend to be more physically active in their older ages [79]. To be able to thoroughly investigate and follow cardiovascular risk factor patterns in the population, a survey was initiated in Stockholm 1997, collecting data from 60-year-old men and women living in Stockholm County at that time. Numerous of studies have emanated from this cohort, of which four constitute the basis of this thesis.

5.1 MAIN FINDINGS

The main findings from these four population-based studies of 60-year-old men and women living in Stockholm are concluded below. To note is, that individuals with prior or current cardiovascular disease (CVD), i.e. myocardial infarction, stroke, and heart failure were excluded from the analyses. Additionally, individuals with cancer (except basalioma) were excluded in Paper I, and those with intermittent claudication and angina pectoris were omitted in Paper II-IV.

One out of four men, and one out of five women in the cohort met the updated NCEP/ATP III criteria for the metabolic syndrome (MetS) [5] – figures supporting the established picture of a global epidemic of the MetS, comprising both men and women [15]. Furthermore, there were high prevalences of all single parameters contained in the MetS, in particular elevated blood pressures and central obesity.

A strong inverse dose-response association between leisure-time physical activity and the MetS was observed, while no such association was noted for work-related PA (see definitions in the Materials and Methods part of the thesis). A majority (approximately 70-80%) of the participants reported light-to-moderate PA, i.e. at least two hours of weekly activity.

The socioeconomic factors analyzed (marital status, education, smoking, intake of fruit and vegetables, alcohol consumption, reported health and financial status) confirm and add to the results from other studies, showing that the MetS is associated with lower social status and economic welfare [80].

Left ventricular hypertrophy (LVH), an independent cardiovascular risk factor associated with MetS, was detected by electrocardiogram (ECG) in 7.4% of the study participants. In men and women with the MetS, the prevalences of LVH were 12.8 and 9.9%, respectively – compared with 7.9 and 3.3%, respectively, in men and women without the syndrome.

In both men and in women, a dose-response relationship between the number of MetS components and the occurrence of LVH was observed. However, the LVH-MetS relationship seemed to rely entirely on hypertension in men, but in women also hyperglycemia, hyperinsulinemia, and abdominal obesity (waist circumference) were contributing factors, indicating gender differences behind the mechanisms of the development of LVH. The level of leisure-time PA did not significantly affect the associations between the MetS and LVH.

To further investigate the gender difference on the association between components of the MetS and LVH, the potential effects from insulin-like growth factor-1 (IGF-1) and its binding protein (IGFBP-1) were examined – having in mind the anabolic effects of IGF-1 together with the role of IGFBP-1 as regulating IGF-1 activity along with IGF-independent effects.

There were significantly higher levels of IGFBP-1 in women than in men, and significantly lower levels of IGFBP-1 in women with LVH compared to women without LVH. Furthermore, there was a significantly increased association to LVH among women with the lowest levels of IGFBP-1.

As being another potentially mediator of the observed disparity in gender, oestrogen-use was included in the LVH analyses – and was found negatively associated to the occurrence of LVH (statistically significant in the crude model).

Finally, leisure-time physical activity seemed to diminish the strong association between (especially lower) levels of IGFBP-1 and LVH in both men and women. Levels of total IGF-1 did not yield any firm relationships to LVH.

The occurrence of the MetS was associated with a substantially increased risk for incident cardiovascular events (myocardial infarction or ischemic stroke), cardiovascular mortality as well as all-cause mortality (the risk for CVD mortality was particularly high in women). Leisure-time PA appeared to counteract the deleterious effects from the MetS in a dose-response manner. The strongest preventive effects from PA were achieved when moving from sedentary to light activity.

5.2 METABOLIC SYNDROME

As previously mentioned, the components of the MetS are all established risk factors for a number of diseases and conditions, such as CVD (e.g. myocardial infarction, angina pectoris and stroke), type 2 diabetes and cancer (e.g breast, prostate, and colon cancer) as well as dementia and other cognitive disorders, and depression [27, 28, 30, 31, 35, 37, 38, 48]. A firm association to CVD mortality as well as all-cause mortality is also a part of the MetS picture [15].

5.2.1 The pathophysiology of the metabolic syndrome

The pathophysiology of the MetS is complex, with genetic predisposition and lifestyle factors interacting [50, 81, 82]. Overweight, particularly central obesity, is an essential and frequent clinical feature in the development of the MetS – together with insulin resistance in skeletal

muscles, adipose tissue and liver. Eventually, when the beta cell is no longer responsive, insulin resistance results in impaired glucose tolerance. A characteristic dyslipidemia with hypertriglyceridemia, low HDL levels, high Apo B levels, and small dense atherogenic LDL particles are also essential components of the MetS. Last years, postprandial hyperlipidemia and high levels of free fatty acids in serum and fatty liver have been recognized as potentially important contributing components of the MetS. Furthermore, hypertension is a well-established and frequent variable of the syndrome. Other important components are reduced fibrinolytic capacity, inflammatory activity, high levels of uric acid, impaired endothelial function, and oxidative stress [50, 83].

There is also evidence that an impaired non-esterified fatty acid (NEFA) metabolism could contribute to the insulin-resistant state observed among individuals with visceral obesity. Hypertrophied intra-abdominal adipocytes are characterized by a hyperlipolytic state that is resistant to the antilipolytic effect of insulin. The resulting NEFA flux to the liver may impair liver metabolism, leading to increased hepatic glucose production.

The proposed mechanism of hyperinsulinemia in association with cardiovascular disease has, furthermore, potentially been due to an increase in the hypercoagulable state, and the effect of insulin on thrombosis. With impaired glucose tolerance and hyperinsulinemia, there is impaired fibrinolysis, as seen with elevated levels of plasminogen activator inhibitor-1 antigen (PAI-1) and tissue plasminogen activator antigen (t-PA) [32].

Finally, insulin (i.e. insulin resistance) is not only a crucial variable of the MetS, but probably plays an important role in the pathogenesis of both CVD and some types of cancer as well.

5.3 LEFT VENTRICULAR HYPERTROPHY, IGF-1, IGF BINDING PROTEIN-1

LVH is an independent risk factor for CVD, and represents a powerful independent predictor of cardiovascular morbidity and mortality. LVH is a compensatory response of the myocardium to changes in loading conditions that can occur via several mechanisms. Most obvious are the direct effects of high blood pressure and obesity. However, deranged blood lipids as well as insulin resistance have also been reported as potential risk factors for LVH [84, 85]. There are numerous possible mechanisms to explain the impact from insulin resistance in the pathogenesis of LVH. Insulin may, for example, act as a growth hormone for cardiomyocytes, resulting in increased LV mass of the heart. Insulin also stimulates collagen synthesis in cardiac fibroblasts and plays an important role in sympathetic activation of the heart and vascular damage. The underlying mechanisms behind the association between abdominal obesity and LVH are still not fully understood. However, the production of different kinds of cytokines from intra-abdominal adipose tissue seems to be of importance [86].

Insulin may directly induce LVH by binding of insulin to the IGF-1 receptors expressed in the myocardium. Elevated plasma insulin is associated with LVH, and may play an important role in the development and progression of LVH, especially in females [87-89]. IGFBP-1 is regulated at transcriptional level by insulin and low fasting levels are a marker of

hyperinsulinemia. Furthermore, IGFBP-1 is the most important dynamic regulator of free IGF-1 activity [90].

Low IGFBP-1 per se may play an important role in the development of LVH, since it may enhance the effect of IGF-1, but also by its own direct effect on proliferation and migration through binding to the alpha 5 beta 1 integrin receptor [91]. These results are in line with our findings of significantly higher levels of IGFBP-1 in women than in men, and significantly lower levels of IGFBP-1 in women with LVH (compared to women without LVH). Furthermore, there was a significantly increased association to LVH among women with the lowest levels of IGFBP-1.

Generally higher levels of IGFBP-1 in women have been described in previous studies [92, 93]. The levels were explained by insulin, body mass index (BMI) and waist circumference but also by oestrogens.

The beneficial effects on LVH in oestrogen-users that we observed, may have several possible reasons, besides the direct hormonal effects (i.e smooth muscle relaxant as well as antiproliferative effects). For example, key enzymes in glucose and fatty acid metabolism are regulated by oestrogens and, consequently, obesity-associated conditions such as diabetes are particularly associated with development of LVH. Moreover, menopausal hormone therapy users are likely to be better educated, more physically active, and have a lower BMI and blood pressure than untreated women because of a more health-conscious behavior.

5.4 PHYSICAL ACTIVITY

As already stated in the Background, there are firm associations between the beneficial effect of PA on the occurrence of MetS [51, 52, 94-96].

5.4.1 Acute effects of PA

Except for weight reduction, PA has acute effects on all other parameters in the MetS. The effects on insulin sensitivity, lipoprotein turnover, blood pressure regulation as well as anti-inflammatory and anti-oxidative mechanisms are immediate [102]. In sedentary individuals, PA equivalent to an hour of brisk walking results in positive effects on glucose-insulin and blood lipid turnover, and blood pressure. However, these effects are episodic and decline if the activity is not accomplished on regular basis.

5.4.2 Long-term effects of PA

A vast amount of literature, both epidemiological and interventional studies, is showing that the separate components of the MetS as well as the syndrome itself can be prevented and treated with regular PA [103-114].

5.5 STRENGTHS….

- The study population is a large (n 4228) and representative (every third man and woman) cohort with a high participation rate of 77%.

- Stockholm County is a relatively heterogeneous regarding socioeconomic conditions, health status, and ethnicity (21.5% immigrants among 60-year-olds in 1998), which makes the data more generalizable.
- The cohort is thoroughly characterized throughout a well-defined questionnaire and physical examinations, which allows adjustments for many factors of potential importance. As the cohort includes both men and women it allows a focus on gender perspectives.
- Although information from self-reports has been questioned, questionnaires to assess habitual PA may give valid and reliable data [97-98].
- Swedish national population registers are highly valid (Paper IV).

5.6 …AND LIMITATIONS

- Although the study population is representative, it represents only an urban population of 60-year-olds, and conclusions can only be drawn from that perspective.
- The cross-sectional design (Paper I-III) cannot prove causality, but only describe associations as they exist at a particular point in time, and hence generate hypotheses.
- PA level as well as smoking, alcohol consumption and dietary habits were self-reported in a questionnaire, which can be considered as a methodological limitation. Furthermore, the information on lifestyle is based on only one assessment at baseline.
- The electrocardiogram (ECG) has its limitations regarding detecting LVH, and echocardiography would of many reasons be preferable. However, ECG is one of the most important non-invasive imaging methods in the evaluation of cardiac morphology and dynamics, and is clinically relevant to apply (considering the limited possibilities to use echocardiography) [99], and many studies have confirmed the high specificity of ECG criteria for the diagnosis of LVH [100]. Moreover, obesity may limit sensitivity of ECG voltage criteria for LVH because of the attenuating effects of increased body mass on precordial voltages. However, Cornell product criteria for ECG LVH appear to provide a relatively accurate measure of LVH in obese and overweight individuals [101]. Furthermore, in Paper II and III, 10% of the ECG measurements were validated by experienced expertise showing a satisfyingly correspondence (83%).

5.7 CONCLUDING DISCUSSION AND CLINICAL IMPLICATIONS

Our findings suggest that individuals complying with the recommendations of regular leisure-time PA could decrease the risk of having the MetS by about two-thirds compared to sedentary individuals, even after adjustments for potential confounding factors. The robust

inverse dose-response relationships found between PA and the MetS emphasize the role of PA in the prevention and treatment of the MetS. In the same time, it is important to take into account data indicating a potential harmful effect of vigorous exercise in individuals at CVD risk.

Furthermore:

- Since waist circumference and SAD are relevant indicators of metabolic disturbances, our findings of high mean levels of BMI, waist circumference, and SAD is alarming and may call for action on a population level.
- The pathogenesis of LVH is complex and depends on both hemodynamic and metabolic conditions as well as gender. Therefore it is important to take into account not only MetS components, like blood pressure and glucose/insulin levels, when analyzing potential CVD risk factors – but also parameters like IGFBP-1, oestrogen and physical activity.
- The use of oestrogen and levels of PA, together with levels of IGFBP-1, are parameters to consider in the clinical setting, to be able to prevent deleterious consequences of LVH on CVD morbidity and mortality.
- The pathogenesis of the MetS has multiple origins, but obesity and sedentary lifestyle coupled with diet and still largely unknown genetic factors clearly interact and may determine the syndrome [32].

5.8 FUTURE PERSPECTIVES

According to recent figures from the World Health Organization (WHO), ischemic heart disease and stroke are the fast most prevalent causes of death. The top three causes of premature death are coronary (ischemic) heart disease, lower respiratory infections (such as pneumonia) and stroke [115]. Furthermore, in 2012 around 44 million (6.7%) of the world's children aged less than five years were overweight or obese. This number and proportion has increased from around 31 million (5%) in 1990.

Therefore:

- The promotion of PA has to be more high-lighted in prevention, as well as treatment of the MetS. The MetS is a common health threat of our time, associated with an increased risk of many non-communicable diseases like CVD:s, type 2 diabetes, dementia, common cancers and depression. PA has to be considered a cornerstone in preventive strategies in clinical practice as well as in the society.
- The relationship between lifestyle factors and the MetS is getting increasingly robust according to current research. Therefore, a future challenge may be to

screen individuals at risk, initially using a validated questionnaire focusing on PA and other lifestyle factors.

- Further elucidation of the biological processes linking the IGF-1/IGFBP-1 systems to risk of LVH will be important in facilitating the identification of people at risk for CVD.
- A fundamental policy shift is required to widen responsibility for the prevention of diet, activity and weight-related ill health across the whole of Europe's population to encompass non-health sectors such as culture, commerce, education, transport and planning. Only such a comprehensive approach offers any realistic prospect of averting a public health catastrophe for Europe and indeed for the whole world.
- The future challenge is to identify persons at risk (i.e with the MetS), measure all relevant variables (e.g. to be able to follow a progress), maybe initiate screening programs for MetS components and LVH (in risk groups), and, finally, encourage individuals to be physically active in a structured way, with tailored advice.

6 SAMMANFATTNING PÅ SVENSKA

För att kunna studera och följa kardiovaskulära riskfaktormönster, genomförde Stockholms läns landsting och Karolinska Institutet under 1997-99 en stor kartläggning av var tredje 60-årig man och kvinna boende i Stockholms län. Totalt deltog 4228 individer (77% deltagarfrekvens), varav 2036 män och 2192 kvinnor. Undersökningen omfattade en fysikalisk undersökning, blodprovstagning för direkta analyser samt för uppbyggnad av blodbank, vilo-EKG samt en utförlig frågeenkät. Denna kohort utgjorde studiepopulationen som denna avhandling baseras på.

Huvudsyftet med avhandlingen var att, i såväl tvärsnitts- som longitudinella studier, studera samband mellan grad av fysisk aktivitet på fritiden och det metabola syndromet (bukfetma, högt blodtryck, blodfettrubbning samt höga blodsockernivåer) och vänsterkammarhypertrofi (förstorad vänsterkammare, VKH), och samtidigt väga in könsaspekter. Även tillväxthormonet insulin-like growth factor-1 (IGF-1) och dess bindarprotein insulin-like growth factor binding protein-1 (IGFBP-1) studerades i relation till metabola syndromet och VKH.

Var fjärde man och var femte kvinna uppfyllde kriterierna för det metabola syndromet. Ett starkt omvänt dos-responssamband sågs mellan grad av fysisk aktivitet på fritiden och det metabola syndromet. En majoritet av deltagarna rapporterade lätt till måttlig fysisk aktivitet, det vill säga minst två timmar per vecka. Vänsterkammarhypertrofi, som är en oberoende kardiovaskulär riskfaktor associerad med metabola syndromet, identifierades med EKG hos 7% av studiedeltagarna. Hos män och kvinnor med det metabola syndromet var förekomsten högre (13% respektive 10%). Motsvarande siffror hos individer utan det metabola syndromet var 8% hos männen och 3% hos kvinnorna.

Hos både män och kvinnor sågs ett dos-responssamband mellan antalet komponenter i det metabola syndromet och förekomsten av VKH. Hos män berodde detta samband enbart på högt blodtryck, medan det hos kvinnor även orsakades av högt blodsocker, höga insulinnivåer och bukfetma. Detta indikerade att det kunde föreligga könsskillnader bakom upphovsmekanismerna till LVH.

För att knyta an till denna hypotes, studerades därefter potentiella effekter av IGF-1 och IGFBP-1 på sambandet mellan det metabola syndromet och VKH. Kvinnor uppvisade högre nivåer av IGFBP-1 jämfört med män, och kvinnor med VKH hade lägre nivåer av IGFBP-1 än kvinnor utan VKH. Vidare hade kvinnor med låga nivåer av IGFBP-1 en signifikant ökad risk för VKH.

Östrogenbruk (hos kvinnor) visade sig vara negativt associerat till VKH. Och vid stratifiering för fysisk aktivitet (en uppdelning i hög och låg aktivitet) respektive östrogenbruk sågs ett svagare samband mellan IGFBP-1 och VKH hos fysiskt aktiva män och kvinnor jämfört med mer inaktiva individer respektive hos kvinnor med östrogenbruk jämfört med icke-brukare.

Vid en långtidsuppföljning efter13-15 år, då uppgifter om insjuknande och död i hjärt-kärlsjukdom samt total dödlighet insamlats från slutenvårds- och dödsorsaksregistret fann vi, att både män och kvinnor med det metabola syndromet hade signifikant förhöjd risk att insjukna och dö i hjärtinfarkt och stroke, liksom en signifikant förhöjd risk för död av samtliga orsaker. Bland de som hade det metabola syndromet, tenderade de fysiskt aktiva att ha en lägre risk jämfört med de som var inaktiva. Tydligast var skillnaden när vi jämförde de inaktiva med de lätt aktiva.

Våra slutsatser är att det metabola syndromet är vanligt förekommande bland 60-åringar i Stockholms län och är starkt kopplat, på ett omvänt dosberoende sätt, till graden av fysisk aktivitet. Vidare verkar vänsterkammarhypertrofi, som var vanligare hos individer med det metabola syndromet, till en del ha olika uppkomstmekanismer hos män respektive kvinnor. Gällande östrogen, kan det möjligen ha en skyddande effekt mot utvecklingen av VKH.

Förekomsten av det metabola syndromet var förenat med kraftigt ökade risker för hjärt-kärlsjukdom och död under uppföljningstiden. Hos individer med det metabola syndromet som var fysiskt aktiva var dock risken lägre, varför fysisk aktivitet bör ha en central roll i såväl prevention som behandling av det metabola syndromet.

7 CONCLUSIONS

The conclusions from three cross-sectional studies and one prospective cohort study of 60-year-old men and women living in Stockholm, were that the metabolic syndrome (MetS) is prevalent, especially among men, and that it is inversely related to leisure-time physical activity (PA). No such association was noted for work-related PA. A majority of the participants reported light-to-moderate PA, i.e. at least two hours of weekly activity.

Furthermore, left ventricular hypertrophy (LVH) was more frequent in individuals with the MetS. Possible gender differences were indicated concerning the development of LVH, i.e the association between LVH and MetS was fully explained by hypertension in men, but in women hyperinsulinemia, hyperglycemia, and abdominal obesity were the determinants, in addition to hypertension. This was further emphasized by gender difference in levels of insulin-like growth factor binding protein-1 (IGFBP-1) and its associations to LVH. Furthermore, the use of oestrogen in women was negatively associated to LVH.

The metabolic syndrome was associated with a substantially increased risk for incident cardiovascular events, cardiovascular mortality as well as all-cause mortality during a follow-up of 13-15 years. The association was particularly evident for cardiovascular mortality among women. Leisure-time PA seemed to counteract the deleterious effects from the metabolic syndrome, especially for CVD mortality in females.

The above conclusions underline the importance of PA in the prevention and treatment of the metabolic syndrome, as well as to acknowledge gender differences in the pathogenesis of LVH.

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