

**Cardiorespiratory Fitness as a Feature of the Metabolic Syndrome in Older
Men and Women:
The DR's EXTRA Study**

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ABSTRACT

Objective: We studied the associations of cardiorespiratory fitness with metabolic syndrome (MetS) in older men and women, because such data are limited in representative population samples.

Research Design and Methods: We studied a population sample of 671 men and 676 women aged 57-79 years at baseline of a randomized controlled intervention study. We assessed maximal oxygen uptake (VO₂max) by respiratory gas analysis during a maximal bicycle exercise test.

Results: VO₂max had a strong, inverse and graded association with the risk of having MetS as defined by the National Cholesterol Education Program criteria. Men and women in the lowest third of VO₂max had a 10.2 and 10.8-fold higher risk and those in the middle third had 2.9 and 4.7-fold higher risk ($P < 0.001$ all) of MetS than those with the highest VO₂max after multivariable adjustments. Factor analysis generated a principal factor that was strongly loaded by the main components of MetS and VO₂max (-0.68 in men, -0.70 in women).

Conclusions: Low cardiorespiratory fitness is associated with MetS in older men and women. Our findings suggest that low cardiorespiratory fitness could be considered a feature of MetS. (ISRCTN45977199).

The epidemic of the metabolic syndrome (MetS) is due in part to sedentary lifestyle, poor cardiorespiratory fitness, unhealthy diet and increased overweight and obesity (1). MetS is associated with an increased risk of type 2 diabetes, cardiovascular disease (CVD), and premature mortality (2,3). Higher levels of physical activity and cardiorespiratory fitness have been associated with a decreased risk of developing MetS (4-7) and its consequences type 2 diabetes, CVD and premature mortality (8-11).

Only a few population-based studies have been published on the association of cardiorespiratory fitness with MetS (4,5,7,12,13). Most have only included young and middle-aged individuals or men and have used indirect measurements of maximal oxygen uptake (VO₂max). We have previously found strong association of a low VO₂max, with an increased risk of having or developing MetS in middle-aged men (4,12). Based on factor analysis we have suggested that poor cardiorespiratory fitness could be considered a feature of MetS (12).

We assessed the association of directly measured VO₂max with MetS and impaired glucose metabolism in a large population sample of older men and women. Because MetS consists of highly correlated features, factor analysis was used as a complementary statistical approach. The present study extends our knowledge on the association of cardiorespiratory fitness with MetS in middle-aged men (12) to older men and women, the fastest growing segment of the population.

RESEARCH DESIGN AND METHODS

We used the baseline data of the Dose-Responses to Exercise Training Study (DR's EXTRA), which is an ongoing 4-year randomized controlled trial on the health effects of regular physical exercise and diet. The subjects were a representative population sample of 1500 men and 1500 women, aged 55-74 years, from the city of

Kuopio in Eastern Finland. Of these individuals 1479 participated in the baseline examinations in 2005-2006. The exclusion criteria were conditions that inhibit safe engagement in exercise training, malignant diseases and conditions considered to prevent co-operation. The present study population consisted of 1347 individuals (671 men, 676 women), aged 57-79 years, who had complete data on VO₂max, glucose metabolism and metabolic syndrome, and did not have type 1 diabetes. Of these individuals 564 men and 613 women did not have type 2 diabetes. The study protocol was approved by the Ethics Committee of the University of Kuopio and Kuopio University Hospital. All participants gave written informed consent.

Assessment of cardiorespiratory fitness. Cardiorespiratory fitness was assessed during symptom-limited maximal exercise stress test to exhaustion on an electrically-braked cycle ergometer (Sensor Medics, Germany). The tests were supervised by physicians according to a standardized test protocol with a warm-up of 3 minutes at 20 W and a 20 W-increase in the workload per minute. Participants were verbally encouraged to a maximal exertion. Oxygen consumption was measured directly by the breath-by-breath method using the VMax respiratory gas analyzer (Sensor Medics, USA). VO₂max was defined as the mean of the three highest values of the averaged oxygen consumption measured consecutively over 20 second intervals. A total of 98% of the subjects achieved the respiratory quotient of ≥ 1.1 . Electrocardiography was recorded throughout the exercise test using Cardiosoft software (GE Medical Systems, Germany).

Other assessments. Blood samples were taken after a 12-hour fast. Serum total, low-density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, and triglycerides were measured by enzymatic photometric methods. Fasting plasma glucose was measured by the hexokinase

method. A 2-hour oral glucose tolerance test with a 75 g glucose load was carried out after a 12-hour fast excluding individuals with diagnosed type 2 diabetes. Body mass index (BMI) was calculated from the height and weight. Waist circumference was measured mid-distance between the bottom of the rib cage and the top of the iliac crest. Hip circumference was measured at the level of the trochanter major. Blood pressure was recorded in a sitting position after a five minute rest. Prevalent diseases, use of medications, alcohol consumption and smoking status were assessed by a questionnaire.

Classification of glucose tolerance. Based on the World Health Organization criteria, the subjects were classified as having normal glucose tolerance if the fasting glucose was <6.1 mmol/l and 2-hour glucose <7.8 mmol/l, impaired fasting glucose if the fasting glucose was 6.1-6.9 mmol/l and 2-hour glucose <7.8 mmol/l, impaired glucose tolerance if the fasting glucose was <7.0 mmol/l and 2-hour glucose 7.8-11.1 mmol/l and type 2 diabetes if the fasting glucose was ≥ 7.0 mmol/l or 2-hour glucose ≥ 11.1 mmol/l, or previously diagnosed type 2 diabetes. Impaired glucose regulation (IGR) was defined as the presence of impaired fasting glucose or impaired glucose tolerance.

Definition of metabolic syndrome. MetS was defined by the National Cholesterol Education Program criteria (14), based on the presence of elevated blood pressure ($\geq 130/85$ mm Hg or drug treatment), increased fasting plasma glucose (≥ 6.1 mmol/l), low serum HDL cholesterol (<1.03 mmol/l in men and <1.29 mmol/l in women), high serum triglycerides (≥ 1.7 mmol/l) and abdominal obesity (waist circumference >102 cm in men and >88 cm in women). The existence of at least three risk factors was defined as MetS.

Statistical analyses. VO₂max was used as a continuous variable and categorized into thirds separately in men and women. Differences in clinical and biochemical characteristics were analyzed using

independent-samples t-test, Mann-Whitney test or χ^2 -test as appropriate. The heterogeneity of the means of the components of MetS among the thirds of VO₂max was tested using analysis of covariance, adjusted for age, smoking, alcohol consumption and a prevalent CVD. CVD was considered present if the subject reported a history of angina pectoris, myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary artery angioplasty, stroke, transient ischemic attack or peripheral artery disease. The association of VO₂max with MetS or IGR was studied using logistic regression analysis.

As a complementary approach for assessing the associations of cardiorespiratory fitness with the risk of MetS, factor analysis was carried out using core components of or factors related to MetS and VO₂max. Principal component analysis was used for the extraction of the initial factors. Factors with eigenvalues >1.0 were retained to the analysis. The initial factors were then subjected to promax rotation. For interpretation, we considered variables with an absolute value ≥ 0.40 to be heavily loaded and 0.30-0.39 to moderately loaded on the factor. All statistical analyses were performed using SPSS for Windows, Release 11.5. $P < 0.05$ was considered significant.

RESULTS

Men and women with MetS had a lower VO₂max and more pronounced features of MetS than those without it (Table 1). As a continuous variable, a 1-SD decrease in VO₂max in men (6.3 ml/kg/min) and women (4.9 ml/kg/min) was associated with a 3.2-fold (95% CI 2.45-4.10, $P < 0.001$) increase in the risk of having MetS in men and a 3.1-fold (2.39-4.00, $P < 0.001$) increase in the risk in women adjusted for age, smoking, alcohol consumption and CVD. Further adjustment for waist circumference [OR (95% CI) 1.5 (1.09-2.03), $P = 0.012$, in men; 1.4 (1.00-1.90), $P = 0.053$, in women] or BMI [1.8 (1.31-2.36), $P < 0.001$, in men;

1.5 (1.12-2.07), $P=0.008$, in women] weakened the association. Further adjustment for other components of MetS had much more modest effects on the associations (OR 2.4-3.1 in men and 2.7-3.0 in women, data not shown). When VO₂max was expressed as L/min, a 1-SD decrease in VO₂max was associated with a 1.8-fold (1.37-2.31, $P<0.001$) increase in the risk of having MetS in men and a 1.4-fold (1.10-1.87, $P=0.007$) increase in women adjusted for age, smoking, alcohol consumption, CVD and body weight.

In men and women, VO₂max was associated with all of the components of MetS (Table 2). VO₂max had a strong, inverse and graded association with MetS (Table 2). Men in the lowest third of VO₂max had a 10.2 times higher and women in the lowest third of VO₂max had 10.8 times higher risk of having MetS than those in the highest VO₂max after these adjustments (Table 2).

The association between VO₂max and the risk of MetS seemed to be stronger in men >70 years of age than in other men. The risk of having MetS in men aged <61, 61-65, 66-70 and >70 years increased 3.0 (95% CI 1.81-5.13, $P<0.001$), 2.6 (1.60-4.08, $P<0.001$), 3.0 (1.90-4.90, $P<0.001$), and 6.3 (3.07-13.16, $P<0.001$)-fold, respectively, with a 1-SD decrease in VO₂max. In women, age did not materially modify the association (OR 2.4-4.5, $P<0.001$ for all age groups).

In men and women without diabetes, there was an inverse association between VO₂max and the risk of having IGR. One-SD decrease in VO₂max was associated with a 1.4-fold (95% CI 1.15-1.78, $P=0.001$) increase in the risk of IGR in men and with a 1.6-fold (1.25-2.08, $P<0.001$) increase in the risk in women adjusted for age, smoking, alcohol consumption and CVD. Men and women in the lowest third of VO₂max had a 2.4-times higher risk of IGR than those in the highest third of VO₂max (Table 2).

In the factor analysis containing core components of MetS, cardiorespiratory

fitness, smoking and alcohol consumption, four first-degree factors with eigenvalues >1 were extracted and rotated using the promax method. These factors explained 62% of the total variance. The factor explaining the greatest proportion of the total variance (29% in men and 30% in women) had heavy loadings by the core components of MetS and VO₂max (Table 3). The second strongest factor had heavy loadings by measures of dyslipidemia in both men and women.

CONCLUSION

We found that cardiorespiratory fitness had a strong, inverse, graded and independent association with the risk of MetS in a population-based sample of older men and women. Men and women who were in the lowest sex-specific third of VO₂max had a 10 times higher risk of MetS than those who were in the highest third. Low cardiorespiratory fitness was also associated with IGR in men and women without diabetes, but the relationship was weaker than that for MetS.

The present results support the findings of cross-sectional (12,15,16) and prospective (4-7) studies concerning the association of cardiorespiratory fitness with MetS. In a cross-sectional population-based study, middle-aged men who were in the lowest third of directly measured VO₂max were almost seven times more likely to have MetS than those in the highest third (12). In a 4-year follow-up of these men, those who were in the upper third of directly measured VO₂max were 75% less likely to develop MetS than those in the lower third (4). In a 15-year population study, young adults with poor fitness were 3-6 times more likely to develop diabetes, hypertension and MetS than those with high fitness (7). In two studies cardiorespiratory fitness was only weakly associated with MetS or its development, (5,13).

Both low cardiorespiratory fitness and MetS are important and independent risk factors for type 2 diabetes (3,10), progression of carotid atherosclerosis

(17,18), CVD and all-cause mortality (2,8,9). MetS and type 2 diabetes may be a stronger predictor for future risk of CVD in women than in men (19). A sedentary lifestyle lowers cardiorespiratory fitness, impairs glucose homeostasis and increases the risk of type 2 diabetes (10,11), CVD and premature mortality (8,9).

The prevalence of MetS was 27% in men and 25% in women. These rates are comparable to those reported previously (1). Aging per se is associated with an increase and redistribution of body fat, a decrease in skeletal muscle mass, worsening of insulin resistance and hormonal alterations (20), all of which are important in the development of MetS (1). The association of cardiorespiratory fitness with MetS seemed to be stronger in men over 70 years, but otherwise age did not seem to influence the magnitude of the relationship.

The overall findings of the present study hold in men and women after adjustment for several important confounders. Of the individual components of MetS, waist circumference markedly weakened the association between cardiorespiratory fitness and MetS. Abdominal obesity is closely inverse related to cardiorespiratory fitness and is a core component of MetS (1). This is likely in part because a sedentary lifestyle predisposes to weight gain and increase central fat accumulation (7). Moreover, a sedentary lifestyle may reduce cardiorespiratory fitness. BMI attenuated the association of VO₂max with MetS less than waist circumference, which further suggests that waist circumference is a more useful measure of fat accumulation in the assessment of MetS. Other components of MetS explained only a small part of the association between cardiorespiratory fitness and MetS. Cardiorespiratory fitness was associated with MetS also when expressed as absolute values in L/min, controlled by body weight.

Factor analysis reduces a large number of correlated variables to fewer factors that can be used to explain and reflect complex underlying phenomena (21), such as in

MetS (12,22,23). However, only a few studies have included cardiorespiratory fitness in the factor analyses (12). We found a principal factor that had heavy loadings by the main components of MetS and cardiorespiratory fitness in men and women aged 57-79 years. Taken together with our previous study among men aged 42-60 years from the same region in Eastern Finland (12) poor cardiorespiratory fitness could be considered a component of MetS.

Others have observed various separate factors with loadings by measures of obesity, dyslipidemia, glucose intolerance and blood pressure (22,23). These studies have used the varimax rotation, which generates uncorrelated factors that may not reflect the pathophysiological process underlying MetS (24). The promax rotation in the present study produced MetS factor which correlated strongly with VO₂max and the main components of MetS. The higher loadings of waist circumference compared with plasma glucose in the principal factor support evidence that central fat accumulation is a strong component of MetS and common to each of the other components of the syndrome. Lipids were included in more than one factor. LDL cholesterol is not considered a component of MetS (14) which may explain the small and negative loading in the principal factor and high positive loading on the second factor, which could be termed the lipid factor. The small negative loading of LDL cholesterol may also be in part because in the MetS LDL cholesterol particle size is small (14). If the decrease in LDL particle size is greater than the increase in particle number, this could be reflected in slightly lower LDL cholesterol concentrations, even though LDL concentrations have not been consistently associated with MetS. These findings suggest that while MetS may differ in its manifestations, there is still a common underlying pathophysiological process that explains the syndrome in most individuals. Abdominal obesity and poor cardiorespiratory fitness seem to be closely related to the underlying metabolic process.

The large representative population sample of older men and women is a strength of the present study. Few such data are available, particularly in women. VO₂max was assessed directly using a respiratory gas exchange analysis during a maximal cycle ergometer test, which is an accurate and highly reproducible measure of cardiorespiratory fitness (25). Factor analysis was used as complementary measures to assess the relationship of cardiorespiratory fitness with MetS. MetS was defined by widely used international criteria (14). We did not have a measure of insulin resistance, but detailed assessments of other features of MetS and glucose tolerance partly offsets this limitation. We observed a dose-response relationship across the thirds of VO₂max for the prevalence of MetS and IGR, but determinations of causality cannot be made because of the cross-sectional study design.

Low cardiorespiratory fitness is closely associated with the risk of MetS and IGR in older men and women and can be

considered a feature of MetS. The measurement of VO₂max even in individuals with relatively few metabolic risk factors may enable targeting of interventions to decrease the future risk of metabolic disturbances that eventually culminate in chronic and progressive diseases such as type 2 diabetes and CVD. Based on the present study, maintenance of good cardiorespiratory fitness by regular physical activity is likely to be important in the prevention of MetS.

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TABLE 1. Characteristics of men and women according to the presence of the metabolic syndrome

	MEN			WOMEN		
	No metabolic syndrome	Metabolic syndrome	P for difference	No metabolic syndrome	Metabolic syndrome	P for difference
N	487	184		507	169	
Age, year	66.4 (5.4)	65.9 (5.6)	0.272	66.6 (5.3)	66.4 (5.3)	0.607
Height, cm	173.5 (6.0)	173.8 (6.2)	0.582	160.0 (6.0)	160.0 (5.4)	0.985
Weight, kg	79.7 (10.9)	93.8 (14.7)	<0.001	66.6 (10.0)	82.2 (13.6)	<0.001
Body mass index	26.4 (3.0)	31.0 (4.3)	<0.001	26.0 (3.8)	32.1 (4.9)	<0.001
Waist circumference, cm	95.3 (8.9)	108.6 (10.7)	<0.001	84.3 (10.4)	101.6 (11.1)	<0.001
Hip circumference, cm	97.7 (6.5)	105.4 (8.8)	<0.001	99.0 (7.9)	110.2 (10.0)	<0.001
VO2max, ml/kg/min	27.8 (6.1)	22.7 (5.4)	<0.001	21.8 (4.9)	18.1 (3.6)	<0.001
Alcohol consumption, doses /wk	6.3 (7.9)	6.5 (8.4)	0.510	2.4 (4.7)	1.8 (2.9)	0.398
Smoking, never/ past/ current, %	39 / 49 / 12	23 / 56 / 21	<0.001	74 / 19 / 7	73 / 19 / 8	0.778
Fasting plasma glucose, mmol/l	5.7 (0.6)	6.7 (1.3)	<0.001	5.4 (0.5)	6.3 (1.2)	<0.001
Serum total cholesterol, mmol/l	4.9 (0.9)	4.8 (1.0)	0.332	5.3 (0.9)	5.1 (1.0)	0.037
Serum LDL cholesterol, mmol/l	3.2 (0.8)	3.2 (0.9)	0.991	3.2 (0.8)	3.3 (0.9)	0.664
Serum HDL cholesterol, mmol/l	1.6 (0.4)	1.2 (0.3)	<0.001	2.0 (0.5)	1.5 (0.4)	<0.001
Serum triglycerides, mmol/l	1.2 (0.5)	2.0 (1.0)	<0.001	1.1 (0.4)	1.9 (0.8)	<0.001
Systolic blood pressure, mm Hg	144.7 (19.2)	147.5 (18.0)	0.090	148.9 (21.0)	153.9 (20.9)	0.007
Diastolic blood pressure, mm Hg	83.9 (9.2)	85.1 (9.8)	0.166	81.6 (8.7)	84.6 (9.8)	<0.001
IFG/ IGT/ DM, %	12 / 9 / 8	20 / 16 / 38	<0.001	4 / 9 / 3	15 / 17 / 28	<0.001
Cardiovascular disease, %	25	32	0.052	17	21	0.328
Lipid lowering medication, %	33	41	0.046	31	44	0.003
Antihypertensive medication, %	35	57	<0.001	33	69	<0.001
Metabolic risk factors, No.	1.3 (0.6)	3.5 (0.7)	<0.001	1.3 (0.7)	3.5 (0.7)	<0.001

Data are presented as means (\pm SD) or percentages (%). P-values are from independent-samples t-test, Mann-Whitney or χ^2 -test as appropriate. For glucose and triglycerides P values were derived from log-transformed values.

IFG; Impaired fasting glucose, IGT; Impaired glucose tolerance, DM; type 2 diabetes. Body mass index was calculated by dividing body weight by body height squared.

TABLE 2. Components of metabolic syndrome and odds ratios (95% CI) for metabolic syndrome and impaired glucose regulation according to sex-specific thirds of maximal oxygen uptake

	Thirds in men (ml/kg/min)			P
	<23.3	23.3-29.1	>29.1	
Waist circumference, cm	107.2	98.7	90.9	<0.001
Body mass index	30.5	27.4	25.2	<0.001
Plasma glucose, mmol/l	6.3	5.9	5.8	<0.001
Serum triglycerides, mmol/l	1.7	1.4	1.2	<0.001
Serum HDL cholesterol, mmol/l	1.4	1.5	1.7	<0.001
Systolic blood pressure, mm Hg	148.0	145.8	142.7	0.027
Diastolic blood pressure, mm Hg	85.6	84.3	82.8	0.015
Odds ratio for metabolic syndrome	10.2 (5.79-17.96)	2.9 (1.68-4.96)	1	<0.001
Odds ratio for impaired glucose regulation	2.4 (1.45-4.03)	1.3 (0.85-2.14)	1	0.001
	Thirds in women (ml/kg/min)			
	<18.4	18.4-22.8	>22.8	P
Waist circumference, cm	96.9	89.1	79.8	<0.001
Body mass index	30.7	27.6	24.3	<0.001
Plasma glucose, mmol/l	5.9	5.6	5.4	<0.001
Serum triglycerides, mmol/l	1.5	1.4	1.1	<0.001
Serum HDL cholesterol, mmol/l	1.7	1.8	2.0	<0.001
Systolic blood pressure, mm Hg	153.0	151.0	146.4	0.005
Diastolic blood pressure, mm Hg	83.6	83.2	80.3	<0.001
Odds ratio for metabolic syndrome	10.8 (5.96-19.28)	4.7 (2.63-8.45)	1	<0.001
Odds ratio for impaired glucose regulation	2.4 (1.38-4.23)	1.6 (0.93-2.85)	1	0.002

Values are means and P values for differences among thirds from analysis of covariance, or odds ratios and P values

for trends across thirds from logistic regression analysis. Data are adjusted for age, smoking, alcohol consumption

and cardiovascular disease. For glucose and triglycerides P values were derived from log-transformed values. Body mass index was calculated by dividing body weight by body height squared.

TABLE 3. Loadings of 12 variables related to metabolic syndrome on the four factors extracted and rotated (promax) with factor analysis and the variance explained by each factor

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