

**The Metabolic Syndrome and Incident End Stage Peripheral Vascular Disease:
A 14-year Follow-up Study in Elderly Finns**

Jianjun Wang, MD¹; Sanna Ruotsalainen, MD¹; Leena Moilanen, MD¹; Päivi Lepistö, MD¹;
Markku Laakso, MD¹; Johanna Kuusisto, MD¹

¹Medicine; Kuopio University Hospital, P.O. Box 1777, FI-70211 Kuopio, Finland

Corresponding author:
Johanna Kuusisto, MD
Medicine,
Cardiology Unit,
Kuopio University Hospital
P.O.Box 1777
70211 Kuopio, Finland
E-mail: johanna.kuusisto@kuh.fi

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ABSTRACT

OBJECTIVE – We investigated the relationship of the metabolic syndrome (MetS) and its single components, defined by four different criteria, with peripheral vascular disease (PVD) in a prospective population-based study.

RESEARCH DESIGN AND METHODS – The MetS was defined according to the World Health Organization (WHO), the National Cholesterol Education Program (NCEP), the International Diabetes Federation (IDF) and the American Heart Association (updated NCEP) criteria. We investigated the relationship of the MetS defined by aforementioned four criteria with PVD (revascularization, amputation) with Cox regression analyses in a Finnish population of 1212 subjects with and without diabetes, aged 65 to 74 years during the 14-year follow-up.

RESULTS – The MetS defined by the WHO, NCEP and updated NCEP criteria was associated with a statistically significant risk for incident PVD (n=57) when adjusted for all confounding variables except for prevalent diabetes (hazards ratios, HRs from 1.91 to 2.62). After the adjustment for prevalent diabetes or after the exclusion of subjects with prevalent diabetes, there was no association between the MetS by any criteria and incident PVD. Of the single components of the MetS, elevated fasting glucose by the WHO and NCEP criteria (HR 2.35) and microalbuminuria by the WHO definition (HR 2.56) predicted PVD in multivariable models (prevalent diabetes included).

CONCLUSIONS– The MetS defined by the WHO, NCEP and updated NCEP criteria predicted incident end stage PVD in the elderly, but only when not adjusted for diabetes status. Two of the single components of the MetS, elevated FPG and microalbuminuria predicted PVD. We conclude that the MetS predicts PVD, but not above and beyond the risk associated with diabetes and microalbuminuria.

Abbreviations

ACE	American College of Endocrinology	IFG	impaired fasting glucose
ACR	the ratio of urinary albumin to urinary creatinine	IDF	International Diabetes Federation
BMI	body mass index	IGT	impaired glucose tolerance
CHD	coronary heart disease	MetS	metabolic syndrome
CVD	cardiovascular disease	MI	myocardial infarction
DBP	diastolic blood pressure	NCEP	National Cholesterol Education Program
EGIR	European Group for the Study of Insulin Resistance	OGTT	oral glucose tolerance test
FPG	fasting plasma glucose	2-hPG	2-h post glucose load
HDL	high-density lipoprotein	PVD	peripheral vascular disease
HR	hazard ratio	SBP	systolic blood pressure
		WHO	World Health Organization.
		WHR	waist-to-hip ratio

Peripheral vascular disease (PVD) refers to the atherosclerotic disease of peripheral arteries, most commonly in lower extremities. Smoking and diabetes are considered to be main risks of lower extremity PVD (1), but it is unclear whether other risk factors for coronary heart disease (CHD) are also risk factors for PVD. The metabolic syndrome (MetS), a clustering of cardiovascular risk factors that confer an increased risk of cardiovascular disease (CVD), has been defined by a variety of groups, including the World Health Organization (WHO) in 1999 (2), the European Group for the Study of Insulin Resistance (EGIR) in 1999 (3), the National Cholesterol Education Program (NCEP) Expert Panel in 2001 (4), American College of Endocrinology (ACE) in 2003 (5), the International Diabetes Federation (IDF) in 2005 (6) and the American Heart Association and the National Heart, Lung, and Blood Institute (updated the NCEP criteria) in 2005 (7). Since these different definitions were published, various prospective studies have reported that the MetS defined by the criteria is associated with incidence or mortality of CHD and CVD, and stroke (8-17). However, there are limited data on the effect of the MetS on PVD (18). Particularly, it is unknown whether the MetS predicts PVD beyond and above diabetes. Therefore, the aim of the present study was to investigate the relationship of the MetS and its single components, defined by the WHO, NCEP, IDF and updated NCEP criteria, with the risk of end stage lower extremity PVD in an elderly cohort of Finnish subjects during a 14-year follow-up.

RESEARCH DESIGN AND METHODS

Baseline study

The formation (19) and representativeness (20) of the study population have been described in detail previously. Briefly, the study was conducted in Kuopio, east Finland, between 1986 and 1988. Altogether 1910 subjects born between 1912 and 1921 were randomly selected from the population register including

all inhabitants of Kuopio. This random sample covered 35% of all residents in the age group of 65-74 years. The overall participation rate was 71%. All subjects with intermittent claudication and gangrene diagnosed by physicians at baseline examination, and with a previous history of leg amputation and peripheral revascularization surgery were excluded from the statistical analyses for incident PVD. The WHO criteria (2) for impaired glucose tolerance (IGT) and diabetes mellitus were used in the classification of subjects without previously known diabetes based on fasting plasma glucose (FPG) and 2-h post glucose load (2-h PG) values at baseline. The diagnosis of previously known diabetes was based on drug treatment for diabetes or a history of a diagnosis of diabetes made by a physician. A total of 1212 subjects aged 65-74 years were included in the current study. Among them, 962 were non-diabetic, 122 had known diabetes and 128 had newly diagnosed diabetes at baseline.

Previous verified definite and possible myocardial infarction (MI) prior the baseline study were defined according to the WHO MONICA project criteria (21) as modified by the FINMONICA AMI Register Study Group (22).

Weight, height, waist and hip circumference, and blood pressure were measured. Waist-to-hip ratio (WHR) was defined as waist circumference to hip circumference. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Smoking status was defined as current smoking. With respect to alcohol consumption, subjects were classified as alcohol users or nonusers. Physical activity during leisure time was classified as physically inactive (little and occasional activity) and physically active (regular exercise at least once a week and at least 30 minutes per time). Physical activity at work was classified as light physical work

(sedentary; standing and walking a little) and heavy physical work (exhausting workload; heavy manual work).

Blood samples were taken in the morning after a 12-hour overnight fast. All subjects, except for those receiving insulin, underwent an oral glucose tolerance test (75g glucose). Plasma glucose and insulin, serum lipids and lipoproteins, and urinary albumin were determined as previously described (19, 23). Ratio of urinary albumin (mg/L) to urinary creatinine (mmol/L) (ACR) was used as a measure of albumin excretion.

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Kuopio University Hospital. All study subjects gave informed consent.

Follow-Up Study

Medical records of all study subjects who participated in the baseline study in 1986-1988 were reviewed by 2 of the authors (S.R., J.K.). Clinical records for individuals who developed end stage PVD during 14-year follow-up were obtained from the medical records of the Kuopio University Hospital where all PVD cases are treated (S.R., J.K.). PVD was defined as lower extremity amputation (n = 26) due to ischemic vascular disease, or peripheral revascularization (n = 31, angioplasty or surgery), which were recorded until the end of June, 2001.

Definitions of the MetS

The WHO, NCEP, IDF, and updated NCEP definitions include diabetic individuals, and therefore, the present study was based on these definitions. Each component of the four definitions was defined according to the original criteria. Criteria for the four definitions of the MetS are shown in Table 1.

Statistical analyses

All statistics were performed with the SPSS 14.0 statistical programs. Because of the

skewed distribution of fasting insulin, triglyceride concentrations and ACR, these variables were log transformed for statistical analyses. Differences in baseline characteristics between subject with incident PVD and without were tested by chi-square test and univariate ANOVA adjusted for age and gender. The baseline variables not included in the definitions of MetS, showing a statistically significant association with incident PVD were added into the multivariable Cox regression models as covariates. The multivariable Cox regression analyses were applied to investigate the association of the MetS defined by the four criteria with incident PVD in adjusted models (model 1: adjusted for age and gender; model 2: adjusted for age, gender, history of MI, and physical activity of work; model 3: adjusted for age, gender, history of MI, physical activity of work and prevalent diabetes). A product term of gender \times each of four definitions was added to the model to represent interaction. The null hypothesis of no interaction was tested using the change in -2 log likelihoods between Cox models with and without the product term. The effect of the single components of the MetS on incident PVD was tested by the multivariable Cox regression models adjusted for other risk factors. A *p*-value less than 0.05 (two-sided) were considered as statistically significant. Exact *p*-values and confidence intervals (CI) are given in tables.

RESULTS

The median follow-up for incident PVD (non-diabetic subjects: 24 revascularizations and 2 amputations; diabetic subjects: 9 revascularizations and 22 amputations) was 14.0 years (the 25th and the 75th quartiles were 13.6 and 14.7 years, respectively). Of the 57 subjects with PVD during the follow-up, 31 had diabetes. Compared with subjects without incident PVD, more subjects with incident PVD had previous myocardial infarction and diabetes, and were physically active at work. Subjects with PVD had also higher levels of systolic blood pressure (SBP), ACR,

triglycerides, FPG and 2-h PG, and lower levels of HDL cholesterol (Table 2). Although there was a trend that more subjects with incident PVD were current smokers compared with those without PVD (12.3 vs 7.9%), no statistically significant difference in smoking was found.

Table 3 shows hazard ratios (HRs) of the MetS defined by the four different criteria to predict PVD during the 14-year follow-up among all studying subjects. The prevalence of the MetS at baseline varied from 51.1% (WHO criteria) to 61.1% (IDF criteria) depending on the MetS criteria. The MetS by the WHO, NCEP, IDF and updated NCEP criteria was associated with a 1.84- to 2.74-fold risk for incident PVD when adjusted for age and gender (Model 1). After further adjustment for history of MI, and physical activity at work (Model 2), the MetS defined by the WHO, NCEP, and the updated NCEP criteria was associated with a statistically significant 1.91- to 2.62-fold risk for future PVD. However, the MetS by the IDF criteria did not predict PVD when adjusted for all aforementioned factors in Model 2. When prevalent diabetes was added into the Model 2, none of the four definitions predicted future PVD (Model 3). Interaction terms between the gender and the MetS by the four definitions were not significant for PVD ($P>0.50$).

We also repeated statistical analyses by excluding subjects with prevalent diabetes ($n=250$), with previous MI ($n=107$), and with microalbuminuria ($n=277$), respectively. None of the four definitions predicted incident PVD in non-diabetic subjects and in subjects without microalbuminuria (data not shown). When excluding 107 subjects with previous MI, similar results to those given in Table 3 were obtained. When analyses were done separately in diabetic and non-diabetic subjects, the MetS was not a predictor of incident PVD due to a small number of events.

Table 4 shows HRs for the single components

of the MetS definitions for risk of PVD in multivariable Cox regression models after the adjustment for other risk factors in all subjects. In all subjects the following single components of the MetS predicted PVD after the adjustment for age, gender, history of MI, and physical activity at work (Model 1): elevated FPG (FPG ≥ 6.1 mmol, HR: 4.03) according to the WHO and NCEP criteria and elevated FPG (FPG ≥ 5.6 mmol, HR: 2.55) according to the updated NCEP criteria; low HDL cholesterol (HDL cholesterol <1.03 mmol/l in men or <1.29 mmol/l in women, HR: 1.90) according to the NCEP criteria, and microalbuminuria (ACR ≥ 3.39 mg/mmol, HR 3.23) according to the WHO definition. After further adjustment for prevalent diabetes (Model 2), the following single components of the MetS still predicted PVD: elevated FPG (FPG ≥ 6.1 mmol, HR: 2.35); and microalbuminuria (ACR ≥ 3.39 mg/mmol, HR 2.56). Of the single components, only low HDL cholesterol (HDL cholesterol <1.03 mmol/l in men or <1.29 mmol/l in women) according to the NCEP criteria predicted PVD risk in Model 2 (HR: 3.02) among non-diabetic subjects.

CONCLUSIONS

To our knowledge, this is the first study investigating the role of the MetS, defined by the WHO, NCEP, IDF and updated NCEP criteria, to predict incident end stage PVD. In the present study, the MetS defined by the WHO, NCEP and updated NCEP criteria predicted PVD in the elderly population. After taking the diabetes status into account none of the MetS definitions predicted incident PVD.

Only one previous prospective study has reported that the modified NCEP definition predicted PVD in Dutch subjects with familial hypercholesterolemia (18). However, this study did not use the original definition of the MetS because of the lack of waist circumference measurement. Moreover, the study did not investigate whether the MetS predicted PVD when taking the diabetes status and CHD into

account, or whether all risk factors included in the definition of the MetS are equally important in predicting PVD. Our study investigated the relationship between PVD and the MetS defined by the four originally proposed criteria and included all components of each definition. Given the fact that the risk of PVD is increased by the presence of CHD and diabetes (24, 25), we also controlled for the diabetes status and previous MI in statistical analyses.

We also investigated whether all single components of the MetS were equally important in predicting PVD, and whether the single components were better predictors of PVD than was the MetS. We found that of the single components of the MetS elevated FPG (FPG ≥ 6.1 mmol/l) and microalbuminuria were predictive of PVD with higher HRs compared with the MetS definitions. Although epidemiologic and experimental data show that microalbuminuria is associated with an increased risk for for-cause and CVD mortality, hypertension, and diabetes, there is a little information on relationship between microalbumin and PVD (26, 27). In this study, we found that the MetS did not predict PVD when excluding subjects with microalbuminuria, supporting the findings of previous studies (26-28), which have shown that microalbuminuria is associated with PVD and diabetes. Accordingly, the WHO and NCEP criteria for the MetS, which include FPG ≥ 6.1 mmol/l and microalbuminuria in their definitions, had the highest HRs in different statistical models. However, when adjusting for the diabetes status, the predictive power of the elevated FPG and microalbuminuria was significantly attenuated. Furthermore, low HDL cholesterol was predictive of PVD risk only when not adjusted for diabetes status. IGT was not a predictor of incident PVD in any model.

In the present study the MetS was not a statistically significant risk factor for PVD in nondiabetic and diabetic subjects, when analyzed separately. In contrast, our previous

study showed that the MetS was a predictor of CVD mortality in subjects without diabetes, although not above and beyond the risk associated with its individual components, such as impaired fasting glucose (IFG), IGT, low HDL cholesterol and microalbuminuria (17). The relationship between the MetS and PVD may be different from that of the MetS and CVD (17), but it is also possible that the number of PVD cases in subgroups was too small (26 in non-diabetic subjects, 31 in diabetic subjects) to demonstrate a statistically significant effect of the MetS on the risk of PVD.

Although smoking is probably the most important risk factor for the development of PVD in middle-aged men (29), we did not find this association in our study. Low percentage of smokers and a low number of PVD events (n=57) as well as elderly population may explain the results.

A major limitation of our study is a relatively low number of PVD events, even though the follow-up time was long. We restricted our analysis to end stage PVD, and thus milder cases of PVD (claudication, limb ischemia) were not included. Therefore, our findings may apply only to severe cases of PVD. The diagnosis of PVD was determined by strict clinically relevant criteria at both baseline and follow-up examinations similarly in diabetic and non-diabetic subjects, and the proportion of revascularizations of all cases of PVD was > 50 %. However, amputations do not necessarily result from atherosclerosis alone, since in diabetic subjects, neuropathy and concurrent infections may contribute to gangrene. Furthermore, the absence of middle-aged individuals in the cohort may lead to bias in the incidence of PVD. Finally, because of several definitions of the MetS, multiple testing increases the likelihood of false positive p values.

In conclusion, the MetS defined by the WHO,

NCEP and updated NCEP criteria predicts incident end stage PVD in elderly subjects but only when not adjusted for diabetes status. Two single components of the MetS, namely elevated FPG, and microalbuminuria predicted PVD with higher HRs compared to that of the MetS. Therefore, the MetS is a risk factor for

PVD, but not above and beyond the risk associated with diabetes and microalbuminuria.

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Table 1– Definitions of the MetS by the WHO, NCEP, IDF and updated NCEP criteria

	WHO	NCEP	IDF	Updated NCEP
Required	Fasting insulin in top 25%; fasting glucose ≥ 6.1 mmol/l; 2- hour glucose ≥ 7.8 , type 2 diabetes (fasting glucose ≥ 7.0 mmol/l and/or 2-hour glucose \geq 11.1 mmol/l)	---	For Europeans: Waist ≥ 94 cm in men or ≥ 80 cm in women	---
No. of abnormalities	And ≥ 2 of:	≥ 3 of:	And ≥ 2 of:	≥ 3 of:
Fasting glucose		≥ 6.1 mmol/l	≥ 6.1 mmol/l; previously diagnosed type 2 diabetes	≥ 5.6 mmol/l
HDL cholesterol	<0.9 mmol/l in men or mmol/l in women	<1.03 mmol/l in men or <1.29 mmol/l in women	<1.03 mmol/l (men) or <1.29 mmol/l (women)	<1.03 mmol/l (men) or <1.29 mmol/l (women)
	or			
Triglycerides	≥ 1.7 mmol/l	≥ 1.7 mmol/l	≥ 1.7 mmol/l	≥ 1.7 mmol/l
Obesity	Waist/hip ratio >0.90 in men or >0.85 in women; BMI ≥ 30 kg/m ²	Waist ≥ 102 cm in men or ≥ 88 cm in women		Waist ≥ 102 cm in men or ≥ 88 cm in women
Hypertension	$\geq 140/90$ mmHg	$\geq 130/85$ mmHg	$\geq 130/85$ mmHg	$\geq 130/85$ mmHg
Microalbuminuria	Urinary albumin/urinary creatinine ratio ≥ 3.39 mg/mmol (30mg/g)			

Table 2 –Baseline characteristics of subjects with and without incident PVD during the 14-year follow-up in 1212 elderly subjects

	Incident (n=57)	PVD Non-PVD (n=1155)	P values
Male/Female, no.	24/33	402/753	0.266
Age (y)	69.6 ± 2.9	69.0 ± 2.9	0.087
Previous diabetes, no. (%)	24 (42.1)	98 (8.5)	<0.001
Prevalent diabetes, no. (%)	31 (54.4)	219 (19.0)	<0.001
Previous MI, no. (%)	11 (19.3)	96 (8.3)	0.013
Previous stroke, no. (%)	1 (1.8)	35 (3.6)	1.000
Current smokers, no. (%)	7 (12.3)	91 (7.9)	0.216
Alcohol user, no. (%)	15 (26.3)	327 (28.3)	0.880
Physically inactive at leisure time, no. (%)	10 (17.5)	300 (26.0)	0.139
Physically active at work, no. (%)	43 (75.4)	696 (60.3)	0.018
Body mass index (kg/m ²)	27.1 ± 4.5	27.5 ± 4.2	0.476
Waist circumference (cm)	93.3 ± 13.0	91.7 ± 11.1	0.274
Systolic blood pressure (mmHg)	166 ± 26	157 ± 24	0.004
Urinary albumin to urinary creatinine ratio (mg/mmol)	12.6 ± 25.2	3.9 ± 13.8	<0.001
Total cholesterol (mmol/l)	6.48 ± 1.15	6.52 ± 1.29	0.816
Triglycerides (mmol/l)	2.13 ± 1.15	1.79 ± 0.95	0.009
HDL cholesterol (mmol/l)	1.16 ± 0.28	1.28 ± 0.35	0.007
Fasting plasma glucose (mmol/l)	9.2 ± 4.2	6.3 ± 2.1	<0.001
2-h postload glucose (mmol/l)	13.7 ± 8.8	8.2 ± 4.7	<0.001

Data are means ± SD or no. (percentages).

Table 3 – Hazard ratios of the MetS defined by the WHO, NCEP, IDF and updated NCEP criteria for incident PVD (n=57) during the 14-year follow-up in 1212 non-diabetic (n=962) and diabetic (n=250) subjects (percentages in parentheses are the prevalence of the MetS according to different criteria in all subjects)

	All subjects (n=1212)			Non-diabetic (n=962)			Diabetic (n=250)		
	Models*	HR (95% CI)	P values	Models*	HR (95% CI)	P values	Models*	HR (95% CI)	P values
PVD events, no.		57			26			31	
WHO definition (51.1%)	1	2.74 (1.52-4.94)	0.001	1	1.59 (0.73-3.43)	0.242	1	2.07 (0.63-6.85)	0.233
	2	2.62 (1.45-4.72)	0.001	2	1.55 (0.72-3.36)	0.266	2	2.15 (0.65-7.12)	0.212
	3	1.68 (0.89-3.17)	0.110						
NCEP definition (51.1%)	1	2.28 (1.30-4.00)	0.004	1	1.43 (0.66-3.11)	0.366	1	1.23 (0.46-3.29)	0.681
	2	2.14 (1.21-3.77)	0.009	2	1.36 (0.62-2.96)	0.445	2	1.37 (0.50-3.74)	0.538
	3	1.36 (0.73-2.51)	0.331						
IDF definition (61.1%)	1	1.84 (1.02-3.32)	0.042	1	1.15 (0.52-2.54)	0.729	1	1.60 (0.59-4.35)	0.357
	2	1.74 (0.96-3.15)	0.067	2	1.09 (0.49-2.42)	0.828	2	1.76 (0.64-4.84)	0.273

	3	1.32 (0.72-2.43)	0.373						
<i>Updated NCEP definition (58.0%)</i>	1	2.04 (1.14-3.65)	0.017	1	1.39 (0.64-3.05)	0.409	1	1.14 (0.43-3.04)	0.798
	2	1.91 (1.06-3.44)	0.031	2	1.85 (0.62-5.48)	0.271	2	1.27 (0.47-3.47)	0.642
	3	1.29 (0.69-2.40)	0.420						

*Model 1: adjusted for age, gender; Model 2: adjusted for age, gender, history of MI, and physical activity of work; Model 3: adjusted for age, gender, history of MI, physical activity of work and prevalent diabetes.

Table 4 –Hazard ratios of the individual components of the MetS based on the WHO, NCEP, IDF and updated NCEP definitions for incident PVD in 1212 subjects

	Hazard ratio (95% CI)	
	Model 1	Model 2
Fasting plasma glucose ≥ 6.1 mmol/l	4.03 (2.26-7.20)***	2.35 (1.15-4.79)*
Fasting plasma glucose ≥ 5.6 mmol/l	2.55 (1.29-5.07)**	1.74 (0.80-3.75)
2-h postload glucose 7.8-11.0 mmol/l	0.64 (0.28-1.51)	1.18 (0.48-2.91)
Blood pressure $\geq 130/85$ mmHg or drug treatment	0.98 (0.39-2.47)	0.82 (0.32-2.09)
Blood pressure $\geq 140/90$ mmHg or drug treatment	1.39 (0.65-2.97)	1.21 (0.56-2.60)
Waist circumference ≥ 94 cm (women: ≥ 80 cm)	1.01 (0.55-1.84)	1.09 (0.59-2.02)
Waist circumference ≥ 102 cm (women: ≥ 88 cm)	0.94 (0.54-1.65)	0.83 (0.46-1.50)
Waist-to-hip ratio > 0.90 (women: > 0.85)	1.11 (0.56-2.19)	0.95 (0.47-1.91)
BMI ≥ 30 kg/m ²	0.93 (0.48-1.78)	0.65 (0.33-1.27)
Triglycerides ≥ 1.7 mmol/l	1.64 (0.96-2.80)	1.30 (0.75-2.25)
HDL cholesterol <0.9 mmol/l (women: <1.0 mmol/l)	1.70 (0.94-3.07)	1.63 (0.91-2.93)
HDL cholesterol <1.03 mmol/l (women: <1.29 mmol/l)	1.85 (1.09-3.17)*	1.55 (0.90-2.66)
Urinary albumin: urinary creatinine ≥ 3.39 mg/mmol	3.22 (1.90-5.46)***	2.56 (1.49-4.40)**

Model 1: adjusted for age, gender, history of MI, and physical activity of work; model 2: adjusted for age, gender, history of MI, physical activity of work and prevalent diabetes. * $P<0.05$, ** $P<0.01$, *** $P<0.001$