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Metabolic syndrome and coronary heart disease risk in a population-based study of middle-aged men from France and Northern Ireland

A nested case-control study from the PRIME cohort

V Bataille¹, B Perret², J Dallongeville³, D Arveiler⁴, J Yarnell⁵, P Ducimetière⁶, J Ferrières¹

SUMMARY

Metabolic Syndrome (MetS) was found associated with an increased CHD risk in several studies but data about this relationship in Southern Europe are lacking. We studied the association of MetS according to three different indexes (the National Cholesterol Education Program's definition (NCEP), a modified World Health Organization's definition (WHO) and the recent International Diabetes Federation's definition (IDF)) with CHD risk in a case-control study nested within the PRIME cohort, composed of subjects from France (Southern Europe) and Belfast (Northern Europe).

The PRIME prospective study is composed of 10 592 men, aged 50-59 at baseline and followed for 5 years. Subjects included in this nested case-control study were 296 cases of incident CHD and 540 controls, who remained free of CHD during the 5 years of follow-up of the PRIME cohort and matched for age, recruitment centre and recruitment date. All subjects had questionnaires and a medical examination at baseline, and a blood sample was taken.

Using the IDF's, the WHO's and the NCEP's definitions respectively, the frequency of MetS was 38.9%, 35.5% and 29.7% in cases and 32.4%, 28.7% and 22.6% in controls. After adjustment for physical activity, smoking and drinking habits, MetS was associated with CHD risk whichever the definition used ($OR_{IDF}=1.41$ [1.02-1.95], $P<0.04$, $OR_{WHO}=1.40$ [1.01-1.94], $P<0.05$ and $OR_{NCEP}=1.46$ [1.04-2.04], $P<0.04$). These results were homogeneous in France (low risk of CHD) and Belfast (high risk of CHD).

Our results add further evidence that MetS is predictive of CHD risk in middle-aged men from Northern and Southern Europe, and highlight differences between the three definitions studied.

Key-words: Metabolic Syndrome • CHD Risk • Male • Middle-aged • Prospective.

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RÉSUMÉ

Syndrome métabolique et risque coronaire chez l'homme d'âge moyen en France et en Irlande du Nord. Étude cas-témoins issue de la cohorte PRIME

Une association syndrome métabolique (SM) – risque de maladie coronarienne a été trouvée dans plusieurs études mais cette relation est peu décrite dans des études épidémiologiques prospectives menées en Europe du Sud. Dans cette étude, la relation entre risque de maladie coronarienne et SM, défini selon 3 définitions différentes (la définition du National Cholesterol Education Program (SMNCEP), la définition modifiée de l'OMS (SMOMS) et la définition récemment proposée par l'International Diabetes Federation (SMIDF)) a été étudiée dans une étude cas-témoins encastrée dans l'étude de cohorte PRIME, menée conjointement en France et en Irlande du Nord.

La cohorte PRIME est composée de 10 592 hommes, âgés de 50 à 59 ans à l'inclusion et suivis pendant 5 ans. L'effectif de notre étude cas-témoins intra-cohorte était composé de 296 cas incidents de maladie coronarienne (infarctus du myocarde ou angor) et de 540 témoins, demeurés indemnes de maladie coronarienne durant les 5 ans de suivi de la cohorte PRIME, et appariés pour l'âge, le centre et la date d'inclusion. À l'inclusion, tous les sujets ont été invités à remplir des questionnaires, ont été examinés et ont subi un prélèvement sanguin.

En utilisant respectivement la définition IDF, la définition OMS et la définition NCEP, la fréquence du SM était de 38,9 %, 35,5 %, et 29,7 % chez les cas, et de 32,4 %, 28,7 %, et 22,6 % chez les témoins. Après ajustement sur l'activité physique, la consommation d'alcool et la consommation de tabac, le SM était associé au risque de maladie coronarienne quelle que soit la définition utilisée ($OR_{SMIDF} = 1,41$ [1,02-1,95], $P < 0,04$, $OR_{SMOMS} = 1,40$ [1,01-1,94], $P < 0,05$ et $OR_{SMNCEP} = 1,46$ [1,04-2,04], $P < 0,04$). Ces résultats étaient comparables chez les sujets recrutés en France (Europe du Sud) et en Irlande du Nord (Europe du Nord).

Les résultats de cette étude menée en France et en Irlande du Nord renforcent l'hypothèse que le SM est associé au risque coronaire chez les hommes d'âge moyen et soulignent les différences entre les 3 définitions utilisées.

Mots-clés : Metabolic Syndrome • CHD Risk • Male • Middle-aged • Prospective.

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Introduction

Metabolic syndrome (MetS) has been found associated with atherosclerosis [1,2] and risk of coronary heart disease (CHD) in the United-States [3-7] or in Northern-Europe [8-12], where cardiovascular incidence rates are elevated. There is in contrast much less information on the relationship between MetS and CHD risk in low risk populations from Southern-Europe, where the nutritional and environmental background is more favourable. Furthermore, recently, the International Diabetes Federation (IDF) has proposed a new definition of MetS [13].

Therefore, we assessed the risk of CHD associated with MetS in middle-aged men from France (Southern Europe) and Northern-Ireland (Northern Europe) in a nested case-control study from the PRIME cohort. To this end, we used three different definitions of the MetS proposed by the IDF [13], Laaksonen et al. (modified World Health Organisation's (WHO) definition) [14] and the National Cholesterol Education Program (NCEP) [15].

Methods

The PRIME cohort [16,17] is composed of 10 592 men, aged 50-59 and free of CHD at baseline, recruited in Northern-Ireland (Belfast) and France-Lille (North), Strasbourg (East) and Toulouse (Southwest)-between 1991 and 1994. Subjects were recruited in the general population through prevention and screening centres or in industry or administration through occupational medicine channels. Globally, in the French centres, two third of the subjects were recruited through prevention centres and one third through occupational medicine. In Belfast, all subjects were recruited in industry through occupational medicine.

After signing an informed consent, each subject had questionnaires and a medical examination including standardised measures of height, weight, waist and hip circumferences and blood pressure. A blood sample was taken after a 12-h fast. Plasma for lipid measurements was prepared immediately and was sent weekly at 4°C to Lille for a centralised measurement at the beginning of the study. All other aliquots were stored locally at -80°C and were regularly sent on dry ice to Lille for long-term storage in low-temperature banks. High density-lipoprotein cholesterol (HDL-C) was obtained after precipitation of apoprotein-B lipoproteins by phosphotungstate acid/polyanions and measured by cholesterol esterase-cholesterol oxydase techniques. Triglycerides were measured by enzymatic methods using triglyceride-lipase and glycerol-kinase.

Data about incident cases of CHD were obtained by an annual follow-up and details were obtained from hospitals and general practitioners. Each case of CHD was validated by an independent Medical Committee composed of one

member of the PRIME study group and three independent cardiologists. Details about endpoints in the PRIME study are detailed elsewhere [16]. Shortly, CHD cases in this work gathered "hard" CHD events (fatal or non-fatal myocardial infarction or coronary related death), and angina pectoris cases (defined by the presence of chest pain at rest and/or on exertion and at least one of the following criteria: angiographic stenosis over 50%, positive scintigraphy (if no angiographic data), positive exercise stress test (if no angiographic or scintigraphic data), electrocardiogram changes at rest (if no angiographic, scintigraphic or exercise stress test data), but without myocardial infarction and no evidence of a non-coronary cause in the clinical history).

Follow-up was completed for 98% of the subjects after five years, during which 335 cases of CHD (175 fatal or non-fatal myocardial infarction and 160 angina pectoris) occurred. For each of these incident cases of CHD, two controls were randomly selected from the participants in the PRIME cohort who remained free of CHD over the follow-up, matched for age (± 3 years), recruitment centre and examination date (± 3 days). Therefore, the sample of this nested case-control study was composed of 1005 subjects (335 cases and 670 matched controls). Glucose and insulin were assayed using plasma samples collected at baseline, immediately frozen and stored for 7-9 years at -80°C. Glucose was assayed by enzymatic methods (glucose oxydase). Insulin was assayed by a competitive radioimmunoassay (Sanofi-Diagnostic Pasteur, France). Subjects with incomplete data were excluded. If a case was excluded, his two matched controls were also excluded. If the two matched controls for a case were excluded, the corresponding case was also excluded. If one of the matched controls was excluded, both the other control and the corresponding case remained in the sample. Finally, 169 subjects were excluded, leading to a final sample composed of 836 subjects: 296 cases and 540 controls.

The IDF-defined MetS was defined by a waist circumference ≥ 94 cm plus any two of the four following criteria: triglycerides > 1.70 mmol/l (or self-reported treatment), HDL < 1.03 mmol/l, blood pressure $\geq 130/85$ mmHg (or self-reported treatment), fasting plasma glucose ≥ 5.6 mmol/l (or self-reported treatment). The WHO-MetS was defined as fasting plasma glucose ≥ 6.1 mmol/l (or self-reported treatment) or fasting insulin ≥ 13 IU/l (upper quartile of the non-diabetic population in controls) associated with at least two of the following abnormalities: obesity or central obesity (BMI ≥ 30 kg/m² or WHR > 0.90), dyslipidaemia (triglycerides ≥ 1.7 mmol/l or HDL-Cholesterol < 0.9 mmol/l) and arterial hypertension (blood pressure $\geq 140/90$ mmHg or self-reported treatment). The NCEP-MetS was considered as present if at least three of the following criteria were met: waist circumference > 102 cm, HDL-Cholesterol < 1.03 mmol/l, triglycerides ≥ 1.70 mmol/l, fasting plasma glucose ≥ 6.1 mmol/l and blood pressure $\geq 130/85$ mmHg.

Tobacco consumption was self-reported and adjustment for smoking habits was performed using three classes: non-

smoker, 1 to 10 cigarettes per day, up to 10 cigarettes per day. Self-reported alcohol consumption (number of glasses, detailed for each beverage and each day within a standard week) was used to compute the quantity of pure alcohol ingested by day (g/d). Alcohol consumption was categorised into three classes (teetotallers (0 g/d), mean consumption within a standard week under 40 g/d and more than 40 g/d). Physical activity was considered as present if at least a moderate physical activity of at least 20 minutes once or twice a week was reported by the subject.

χ^2 tests were used to test differences between cases and controls. A conditional logistic regression model, enabling to take into account the matching between cases and controls, was used to assess the CHD risk associated with MetS using either of these three definitions, after adjustment for physical activity, smoking and drinking habits (Crude odds-ratios were obtained by including only the variable considered in the model).

Results

Among the 836 subjects included in this study, 44.7% were from Belfast and 55.2% from France, and the mean age at baseline was 55.2 [± 2.8].

According to the IDF's, the WHO's and the NCEP's definitions respectively, the frequency of MetS was 38.9%, 35.5% and 29.7% in cases and was 32.4%, 28.7% and 22.6% in controls. These proportions seemed to deeply vary according to centre but differences were not statistically different neither in cases (31.8%, 39.5% and 30.2% in Belfast, 58.3%, 27.1% and 37.5% in Lille, 40.0%, 34.0% and 26.0% in Strasbourg, 37.7%, 34.7% and 26.1% in Toulouse) nor in controls (29.0%, 31.2% and 22.9% in Belfast, 46.2%, 28.2% and 28.2% in Lille, 46.6%, 35.2% and 26.0% in Strasbourg, 20.9%, 18.6% and 15.5% in Toulouse) whichever the definition used.

Smoking was more frequent in cases than in controls both in the French centres ($P < 0.001$) and the Belfast centre ($P < 0.01$). Conversely, no significant difference was found between cases and controls for physical activity or drinking habits. In table I are summarised differences between cases and controls for each criteria contributing to the construction of the three MetS's definitions studied. WHO-defined and NCEP-defined MetS were significantly associated with CHD in univariate analyses ($OR_{WHO} = 1.38$ [1.01-1.88], $OR_{NCEP} = 1.45$ [1.05-2.01]), but significance was not reached for IDF-defined MetS ($OR_{IDF} = 1.34$ [0.99-1.83]).

After adjustment for physical activity, smoking and drinking habits, the OR estimates for the association of MetS with CHD ranged from 1.40 to 1.46 depending on the MetS definition and all three definitions of MetS were significantly associated with CHD (table II).

In sub-group analyses by country, the adjusted OR estimate for the NCEP-defined MetS was comparable in Belfast and in the French centres. Conversely, even if no

significant difference was existing, the OR estimate obtained using the WHO-defined MetS tended to be higher in Belfast than in the French centres, while the OR estimate obtained using the IDF-defined MetS tended to be slightly higher in the French centres than in Belfast.

Further analyses by type of event showed that adjusted OR estimates for myocardial infarction, ($OR_{IDF} = 1.24$ [0.79-1.96] $P = 0.35$, $OR_{WHO} = 1.44$ [0.91-2.28] $P = 0.12$, $OR_{NCEP} = 1.71$ [1.05-2.78] $P < 0.04$) tended to be higher than adjusted OR for angina ($OR_{IDF} = 1.63$ [1.02-2.60] $P < 0.05$, $OR_{WHO} = 1.36$ [0.85-2.17] $P = 0.20$, $OR_{NCEP} = 1.29$ [0.80-2.08] $P = 0.30$), except for the IDF's definition.

Discussion

In our work, in a cohort of men aged 50-59 from France and Belfast, MetS was significantly associated with CHD using IDF's, WHO's and NCEP's definitions with comparable OR, independently from usual confounders such as age, physical activity, smoking and drinking habits. Conversely, the frequency of MetS was higher using the IDF's than using the NCEP's definition of MetS.

These differences may be related to three major differences between IDF's and NCEP's criteria for MetS. Firstly, in the IDF's definition, abdominal obesity is a prerequisite whereas it is one among others factors in the NCEP's definition. Secondly, the thresholds defining abdominal obesity and hyperglycaemia are lower in the IDF's definition than in the NCEP's one, leading to an increase in the proportion of subjects responding to the IDF's criteria of MetS compared with NCEP's definition. Furthermore, the lowering of these thresholds of abdominal obesity and hyperglycaemia may have resulted in the inclusion of lower risk subjects in the IDF-MetS group, therefore diluting the relationship.

However, the association we found between MetS and CHD risk, with ORs around 1.5, was not as strong as the associations reported in previous prospective studies from the United-States [3,4,6,7] and Northern-Europe [9,11,12] in middle-aged men, displaying a 2 or 3-fold higher risk for subjects with MetS. Nevertheless, hazard risk estimates of 1.5 to 2 after adjustments, close to those we observed, were found in the USA in the Atherosclerosis Risk in Communities study (ARIC) [3].

Sub-group analyses reduce statistical power, but even if significance was not reached in sub-group analyses by country, these results were globally comparable in France (low risk of CHD) and Belfast (high risk of CHD).

In conclusion, our results indicate that the frequency of MetS may be higher using IDF's definition than using NCEP's one. However, IDF-defined, WHO-defined and NCEP-defined MetS were predictive of CHD risk in men in a population composed of subjects from France and Northern Ireland with comparable ORs.

Table I

Frequency of metabolic syndrome according to the three definitions and frequency of each criteria involved in these definitions.

	France (n=462)		Belfast (n=374)		All centres (n=836)	
	%	p	%	p	%	p
Waist circ. >102 cm ^{NCEP}						
Cases	28	ns	12	ns	21	ns
Controls	28		10		20	
Waist circ. >=94 cm ^{IDF}						
Cases	62	ns	42	ns	53	ns
Controls	55		39		48	
BMI >=30 kg/m ² or WHR >=0.9 ^{WHO}						
Cases	95	ns	84	ns	90	0.01
Controls	87		79		83	
FPG >5.6 mmol/l or treatment ^{IDF}						
Cases	28	ns	18	ns	24	ns
Controls	31		16		24	
FPG >=6.1 mmol/l or treatment ^{WHO}						
Cases	19	ns	9	ns	15	ns
Controls	15		6		11	
FPG >=6.1 mmol/l ^{NCEP}						
Cases	18	ns	9	ns	14	ns
Controls	14		6		10	
FPG >=6.1 mmol/l or treatment, or fasting insulin >=13 IU/l ^{IDF}						
Cases	37	ns	42	ns	39	ns
Controls	33		41		37	
TG >=1.7 mmol/l or treatment ^{IDF}						
Cases	47	ns	57	ns	51	ns
Controls	40		51		45	
TG >=1.7 mmol/l ^{NCEP}						
Cases	37	ns	57	ns	46	ns
Controls	34		50		41	
HDL-c <=1.03 mmol/l ^{NCEP IDF}						
Cases	40	<0.001	47	ns	43	<0.001
Controls	24		40		31	
TG >=1.7 mmol/l or HDL-c <=0.90 mmol/l ^{WHO}						
Cases	46	ns	63	ns	53	<0.05
Controls	38		56		46	
BP >=130/85 mmHg or treatment ^{IDF}						
Cases	76	<0.01	70	ns	73	<0.01
Controls	64		60		62	
BP >=130/85 mmHg ^{NCEP}						
Cases	74	<0.03	69	<0.04	72	<0.01
Controls	63		58		61	
BP >=140/90 mmHg or treatment ^{WHO}						
Cases	55	<0.02	53	<0.01	54	<0.001
Controls	42		38		40	
WHO-defined MetS						
Cases	32	ns	40	ns	36	<0.05
Controls	26		32		29	
NCEP-defined MetS						
Cases	29	ns	30	ns	30	<0.03
Controls	22		23		23	
IDF-defined MetS						
Cases	44	ns	32	ns	39	ns
Controls	35		29		32	

WHO: criterion involved in the WHO's definition of metabolic syndrome, NCEP: criterion involved in the NCEP's definition of metabolic syndrome, IDF: criterion involved in the IDF's definition of metabolic syndrome.

Table II

OR of coronary heart disease in France and Belfast according to the IDF, WHO and NCEP definitions of MetS.

	France			Belfast			Whole sample		
	MetS (%)	OR [95% CI]	p	MetS (%)	OR [95% CI]	p	MetS (%)	OR [95% CI]	p
IDF-defined MetS (%)									
Cases	44.3	1.47 [0.94-2.29]	0.09	31.8	1.28 [0.79 - 2.09]	0.31	38.9	1.41 [1.02 - 1.95]	<0.04
Controls	35.3			29.0			32.4		
WHO-defined MetS (%)									
Cases	32.3	1.33 [0.85-2.08]	0.22	39.5	1.52 [0.94 - 2.48]	0.09	35.5	1.40 [1.01 - 1.94]	<0.05
Controls	26.1			31.8			28.7		
NCEP-defined MetS (%)									
Cases	29.3	1.50 [0.93 - 2.39]	0.09	30.2	1.46 [0.88 - 2.43]	0.14	29.7	1.46 [1.04 - 2.04]	<0.04
Controls	22.4			22.9			22.6		

Odds-ratio and 95% confidence interval adjusted on physical activity, smoking and drinking habits. Cases and controls are matched for age, recruitment centre and recruitment date.

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