European Journal of Endocrinology (2011) **164** 559–567 ISSN 0804-4643

CLINICAL STUDY

Lipid accumulation product: a powerful marker of metabolic syndrome in healthy population

Mariano J Taverna[1,2], María T Martínez-Larrad[3], Gustavo D Frechtel[1,4] and Manuel Serrano-Ríos[3]

[1]*Diabetes Genetics Section, Division of Genetics, Clinical Hospital of the University of Buenos Aires, Buenos Aires (C1120AAR), Argentina,* [2]*Humoral Immunity Institute 'Prof. Ricardo A. Margni' (IDEHU), National Research Council (CONICET) and School of Pharmacy and Biochemistry, University of Buenos Aires, Junín 956, Buenos Aires 1113, Argentina,* [3]*Department of Internal Medicine II, Hospital Clínico San Carlos, 28003 Madrid, Spain and* [4]*Laboratory of Molecular Biology, Department of Genetics and Molecular Biology, School of Pharmacy and Biochemistry, University of Buenos Aires, Buenos Aires (C1120AAR), Argentina*

(Correspondence should be addressed to M J Taverna at Humoral Immunity Institute, University of Buenos Aires; Email: taverna1@yahoo.fr)

Abstract

Objective: The metabolic syndrome (MS) is a cluster of cardiometabolic factors, which predisposes to diabetes and cardiovascular disease (CVD). Early detection of high-risk individuals for MS using accurate measures of insulin resistance (IR) could improve detection and prevention of CVD and diabetes. The aim of this study was to explore the ability of lipid accumulation product (LAP), compared with traditional measures of IR, to identify MS.

Design: In total, 768 Spanish adults were recruited. MS was assessed using the revised criteria of National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) and International Diabetes Federation (IDF). Measures of IR such as homeostasis model assessment of IR and LAP, an index of lipid accumulation based on a combination of waist circumference and serum triglycerides, were calculated. Receiver operating characteristic analysis was performed in order to detect the parameter with the best predictive capability for MS.

Results: The prevalence of MS-NCEP/ATP III and MS-IDF was 15.1 and 20.5% for men respectively, and 15.4 and 17.5% for women. LAP showed the highest diagnostic accuracy for MS-NCEP/ATP III (area under the curve 0.91 and 0.90 among males and females) and MS-IDF (0.88 for both males and females). This was confirmed by internal validation using 20 000 bootstrap samples. Among males and females, different LAP cut-off values exhibited high sensitivity (78–85%) and specificity (78–85%) for MS-NCEP/ATP III and MS-IDF identification with elevated efficiency (proportion of positives and negatives classified correctly by the test = 78–85%). When the sample was stratified according to decades of life, LAP exhibited a slightly lower performance among women than men, especially for MS-IDF detection.

Conclusions: In non-diabetic adults LAP has a strong and reliable diagnostic accuracy for MS-IDF and, especially, MS-NCEP/ATP III among females and, in particular, among males from Spain.

European Journal of Endocrinology **164** 559–567

Introduction

The metabolic syndrome (MS) is a cluster of cardiovascular and metabolic risk factors including central obesity, insulin resistance (IR), hypertension, prediabetes or diabetes, hyperinsulinemia, and dyslipidemia. These well-known risk factors cosegregate in a subject more often than might be expected by chance, and predispose to type 2 diabetes, and appear, albeit controversially, to be a risk factor for cardiovascular disease (CVD) (1).

The etiology of MS is not well understood, but predisposing factors include aging, inflammation, obesity, sedentary lifestyle, and genetics. Experimental and epidemiologic studies have suggested that IR and visceral adiposity are the basis of this syndrome (1).

Early and accurate identification of high-risk individuals for MS could be important to predict and prevent CVD and type 2 diabetes. Unfortunately, up until now, it has been quite difficult to detect robust and accurate predictors for MS. Recently, we reported a strong association between lipid accumulation product (LAP) and MS defined using the revised diagnostic criteria of National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III, area under receiver operating characteristic (ROC) curve 0.91) in healthy Argentinean adult males (2). LAP, a novel index of central lipid accumulation based on a combination of waist circumference (WC) and serum triglycerides (TG), has also been associated with risk for CVD (3) and type 2 diabetes (4). The aims of the present study were, first, to replicate the strong positive correlation reported

DOI: 10.1530/EJE-10-1039
Online version via www.eje-online.org

between LAP and MS-NCEP/ATP III, and, then, to explore the LAP's ability to diagnose MS defined according to the International Diabetes Federation criteria (MS-IDF), in a sample population integrated by healthy adult males and females from Spain.

Subjects and methods

Population

This study includes cross-sectional epidemiological analyses in a sample of 768 non-diabetic unrelated Caucasian men ($n=352$) and non-pregnant women ($n=416$) recruited by a simple random sampling approach from a target population of 63 417 inhabitants in rural and urban areas of the province of Segovia, in Central Spain (Castilla-León), aimed at investigating the prevalence of anthropometric and physiological variables related to IR, obesity, and MS (5). From an original sample of 2992 men and non-pregnant women, 1166 agreed to participate. Individuals with a previous diagnosis of type 1 diabetes, liver or heart failure, surgery or hospitalization in the past year, or body weight modifications >5 kg during last 6 months were excluded ($n=133$). In addition, 224 individuals refused to participate due to personal reasons. In the remaining sample ($n=809$), 41 individuals with known type 2 diabetes were excluded. The prevalence of diabetes was 8.9% ($n=72$; individuals with known diabetes under treatment $=41$, 5.1%).

The age of this sample population ranged between 36 and 77 years (mean age $54.3\pm$S.D. 11.7 years). Table 1 summarizes the clinical characteristics of the study population. All subjects gave their written consent to participate in the study. The study was carried out in accordance with the Declaration of Helsinki, and was approved by the ethic committee of our hospital.

Clinical measurements

Anthropometric measurements included body mass index (BMI), WC, hip circumference, and waist-to-hip ratio. Systolic (SBP) and diastolic blood pressures (DBP) were measured three times in the seated position after 10 min of rest by use of a sphygmomanometer.

After an overnight fast period, 20 ml of blood were obtained from an antecubital vein without compression, centrifuged, and frozen immediately at -20 °C. Plasma glucose was determined in duplicate by a glucose-oxidase method using an autoanalyzer Hitachi 704 (GLU Glucose GOD-PAP, Roche Diagnostics). Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TG were measured by enzymatic methods using commercial kits (TG Triglycerides GPO-PAP, CHOL Cholesterol CHOD-PAP and Phosphotungstate Precipitant, Roche Diagnostics) using an autoanalyzer Hitachi 704. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Serum insulin concentration was determined by a specific RIA (Human Insulin Specific RIA kit, Linco Research, Inc., St Louis, MO, USA) with a lower detection limit of 2 μU/ml, intra- and inter-assay coefficient of variation being <1 and $<7.43\%$ respectively. Cross-reactivity is $<0.2\%$ to intact human proinsulin.

An oral glucose tolerance test using 75 g of glucose was carried out according to the WHO recommendations, and the results were interpreted in accordance with Genuth *et al.* (6).

IR was estimated by the homeostasis model assessment of IR (HOMA-IR) method using the software HOMA Calculator version 2.2.2 for Windows (Diabetes Trials Unit, University of Oxford, www.dtu.ox.ac.uk/homa/) (7).

The diagnosis of MS was established according to the revised criteria of the NCEP/ATP III (MS-NCEP/ATP III) (8): any three or more of the following criteria: i) WC >102 cm (men) or >88 cm (women), ii) fasting TG ≥ 150 mg/dl, iii) SBP ≥ 130 and/or DBP ≥ 85 mmHg, iv) fasting HDL-C <40 mg/dl (men) or <50 mg/dl (women), and v) fasting plasma glucose (FPG) ≥ 5.6 mmol/l. We have additionally classified individuals according to the IDF definition of the MS for Europid populations (MS-IDF) (9): central adiposity (defined as WC ≥ 94 cm for men and ≥ 80 cm for women) is a prerequisite factor for the diagnosis of the MS-IDF, and two of the following criteria are also necessary: TG ≥ 150 mg/dl or specific treatment for this abnormality, low HDL-C (<40 mg/dl in men and <50 mg/dl in women) or specific treatment, high BP (SBP ≥ 130 and/or DBP ≥ 85 mmHg) or treatment of diagnosed hypertension, and FPG ≥ 5.6 mmol/l or previously diagnosed T2DM.

LAP was defined as (WC (cm) -65) $\times$ (TG concentration (mmol/l)) for men, and (WC (cm) -58) $\times$ (TG concentration (mmol/l)) for women (3). LAP was created to describe the extent to which a subject had traveled the route of both increasing waist and TG. The formula includes the minimum WC values used to define sex-specific origin points (65 and 58 cm for men and women respectively) at Third National Health and Nutrition Examination Survey (NHANES III) (3). In our sample population, the minimum WC values for men (70 cm) and women (59 cm) were quite similar to those used in the original equation for the definition of LAP. The adjustment of LAP formula according to the minimum WC values of our sample population did not change findings (data not shown). For comparison purposes, we used the original formula (3).

The diagnosis of enlarged waist elevated TG syndrome (EWETS, TG ≥ 128 mg/dl, and WC ≥ 95 cm in men and ≥ 88 cm in women) and hypertriglyceridemic waist (HW, TG ≥ 176 mg/dl, and WC ≥ 90 cm in men and ≥ 80 cm in women) was established according to previous criteria (10).

Table 1 Clinical characteristics of the sample population.

		Men (n=352)				**Women** (n=416)			
Continuous variables	**Whole sample** (n=768) Mean±S.D.	MS-NCEP+ (n=53) Mean±S.D.	MS-NCEP− (n=299) Mean±S.D.	MS-IDF+ (n=72) Mean±S.D.	MS-IDF− (n=280) Mean±S.D.	MS-NCEP+ (n=64) Mean±S.D.	MS-NCEP− (n=352) Mean±S.D.	MS-IDF+ (n=73) Mean±S.D.	MS-IDF− (n=343) Mean±S.D.
Age (years)	54.0±11.6	56.9±11.5	52.8±11.6	56.6±11.6	52.6±11.6	61.0±10.3	53.3±11.3	60.7±10.0	53.1±11.4
BMI (kg/m^2)	27.43±3.97	30.40±3.31	27.06±2.97	30.01±3.01	26.94±3.01	31.84±4.04	26.48±4.05	31.22±4.19	26.48±4.09
WC (cm)	90.12±11.37	104.25±6.89	94.29±8.28	103.22±5.80	93.88±8.46	98.05±8.21	83.02±9.91	96.34±9.00	83.02±9.91
HC (cm)	100.23±7.96	103.2±6.2	98.00±6.49	102.7±5.8	97.8±6.6	108.52±9.20	100.19±7.99	107.43±9.26	100.20±8.05
WHR	0.90±0.10	1.01±0.05	0.96±0.08	1.01±0.05	0.96±0.08	0.90±0.07	0.83±0.07	0.90±0.07	0.83±0.07
SBP (mmHg)	124.6±17.1	136.0±14.2	123.7±15.1	133.9±14.7	123.4±15.1	140.21±16.99	120.82±16.87	140.33±16.35	120.28±16.66
DBP (mmHg)	78.3±8.9	83.6±9.0	78.0±8.3	82.7±9.2	77.9±8.3	85.03±9.04	76.40±8.35	84.62±9.02	76.26±8.30
FPG (mmol/l)	4.91±1.16	6.06±2.57	4.96±0.96	5.76±2.19	4.97±1.04	5.76±1.88	4.65±0.64	5.72±1.81	4.63±0.61
2 h glucose (mmol/l)	6.43±2.39	8.06±3.57	6.15±2.18	8.00±3.51	6.02±2.00	8.55±3.00	6.04±1.94	8.49±2.93	6.00±1.91
Fasting insulin (μU/ml)	13.21±8.65	19.02±9.83	12.44±6.74	17.99±9.09	12.26±6.77	22.38±15.32	11.31±6.61	21.24±14.88	11.29±6.65
2 h insulin (μU/ml)	76.41±66.16	116.22±114.28	68.20±55.20	110.41±100.45	65.66±53.50	130.57±92.67	69.42±54.87	122.08±90.46	69.66±55.32
Fasting proinsulin (pmol/l)	10.67±8.37	21.13±15.43	10.24±6.47	19.03±14.36	10.04±6.26	15.96±11.18	8.45±5.70	15.07±10.91	8.46±5.73
HOMA-IR	1.76±0.95	2.60±1.28	1.71±0.82	2.42±1.14	1.69±0.85	2.70±1.30	1.53±0.73	2.57±1.29	1.52±0.73
TC (mg/dl)	213.69±39.19	227.15±46.28	214.01±37.60	227.17±46.20	213.1±36.8	218.67±46.08	210.49±37.61	218.42±47.51	210.32±36.97
LDL-C (mg/dl)	133.20±34.28	145.71±40.25	136.20±33.62	146.04±39.06	135.43±33.31	140.06±36.18	127.64±32.67	139.92±36.77	127.34±32.38
HDL-C (mg/dl)	60.18±16.39	44.96±12.27	57.60±15.94	45.75±14.40	58.26±15.50	52.89±12.71	66.64±16.48	53.27±13.30	66.93±16.38
TG (mg/dl)	98.12±60.37	206.42±105.89	101.05±51.89	186.03±94.31	99.15±54.26	128.63±57.84	73.78±29.59	126.18±57.13	72.87±28.36
TG/HDL-C ratio	1.90±1.74	5.19±3.68	1.97±1.36	4.59±3.23	1.91±1.43	2.61±1.40	1.21±0.71	2.53±1.36	1.18±0.69
LAP	34.65±28.74	89.79±46.90	34.65±21.42	80.74±44.45	33.24±20.61	58.79±30.00	21.96±14.17	55.50±29.85	21.70±14.07
Dichotomic variables	%	%	%	%	%	%	%	%	%
Sedentary	33.1	24.5	40.5	26.4	41.1	34.4	27.8	31.5	28.3
Smoking	22.7	41.5	29.4	40.3	28.9	9.4	16.5	8.2	16.9
Obesity	24.8	60.4	15.6	51.4	14.6	64.1	19.6	56.2	20.1
HW	10.8	60.4	6.4	47.2	6.1	35.9	2.6	32.9	2.3
EWETS	14.2	66.0	13.7	68.1	9.6	39.1	2.3	34.2	2.3
FPG≥5.6 mmol/l	15.1	64.2	10.7	52.8	10.0	54.7	4.0	53.4	2.9
TG≥150 mg/dl	13.5	73.6	13.0	63.9	11.4	31.3	1.7	30.1	1.2
Low HDL-C[a]	14.3	41.1	5.7	44.4	2.5	50.0	11.1	47.9	10.5
High BP[b]	41.7	81.1	38.5	75.0	37.1	85.9	30.9	87.7	29.1
High WC (NCEP/ATP III)[c]	32.0	67.9	15.1	52.8	15.4	98.4	30.1	86.3	30.9
High WC (IDF)[d]	63.7	51.1	48.9	100.0	51.1	100.0	51.1	100.0	58.6
MS-NCEP/ATP III	15.2	NA	NA	66.7	1.8	NA	NA		
MS-IDF	18.9	90.6	8.0	NA	NA			NA	NA

BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EWETS, enlarged waist elevated triglyceride syndrome; FPG, fasting plasma glucose; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HW, hypertriglyceridemic waist; LAP, lipid accumulation product; LDL-C, low-density lipoprotein cholesterol; NA, non applicable; SBP, systolic blood pressure; SM-IDF, International Diabetes Federation-diagnosed metabolic syndrome; SM-NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III-diagnosed metabolic syndrome; TC, total cholesterol; TG, triglycerides; TG/HDL-C ratio, triglycerides-to-high-density lipoprotein cholesterol ratio; WC, waist circumference; WHR, waist-to-hip circumference.
[a]HDL-C<40 mg/dl (men) or <50 mg/dl (women).
[b]SBP≥130 and/or DBP≥85 mmHg or treatment of diagnosed hypertension.
[c]WC>102 cm (men) or >88 cm (women).
[d]WC≥94 cm (men) or ≥80 cm (women).

Statistical analysis

Data are presented as mean ± S.D. Prevalence rates are expressed as percentages. The areas under the curves (AUCs) for ROC curves were determined for each continuous variable to identify the predictors of MS-NCEP/ATP III and MS-IDF. AUCs are provided with S.E.M. and 95% confidence intervals (95% CI). ROC curves, a plot of the sensitivity (SEN) (true positive) versus 1-specificity (SP) (false positive) for each potential predictor tested, determine the ability of a screening measure for correctly identifying individuals based on their classification by a reference test. Values for each AUC can be between 0 and 1, with a value of 0.5 indicating that the diagnostic test is no better than chance. Therefore, values >0.5 are desirable, with 1 indicating perfect diagnostic accuracy, although this is rare in practice. A parameter possesses accurate diagnostic sensibility when the AUC value is >0.75 (11). Analyses of SEN, SP, correct classification rate or efficiency (EFF) and Youden's index (J) were performed using principal cut-off values for MS-NCEP/ATP III and MS-IDF diagnosis (SEN, SP, EFF, Youden's index, J). We defined the best cut-off value as the value with the highest EFF (proportion of positives and negatives classified correctly by the test) and J index (12). A bootstrapping procedure was used 20 000 times to validate best AUCs for MS (13). A P value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 11.5 (SPSS, Inc., Chicago, IL, USA), except for ROC analysis and bootstrapping (Simstat for Windows version 2.5.6, Provalis Research, Montreal, Canada), and analyses of SEN, SP, EFF and J (DAG_Stat – Diagnostic and Agreement Statistics) (14).

Results

Prevalence of MS and obesity

The average age of the subjects was 53.5 ± S.D. 11.7 years for men (range: 36–76 years) and 54.5 ± 11.5 years for women (range: 36–77 years). The general characteristics of the 768 subjects are shown in Table 1. The prevalence of MS-NCEP/ATP III and MS-IDF was 15.1 and 20.5% for men respectively, and 15.4 and 17.5% for women respectively. The frequencies of the MS components were as follows: high WC according to the IDF definition, 63.7%; high BP, 41.7%; high WC according to the NCEP/ATP III criteria, 32.0%; high FPG, 15.1%; low HDL-C, 14.3%; and high TG, 13.5%. The prevalence of obesity was 22.2 and 27.1% for men and women.

ROC analysis for MS

LAP exhibited the highest diagnostic accuracy for both MS-NCEP/ATP III (AUC 0.91 ± 0.02 (95% CI 0.86–0.95) for men and 0.90 ± 0.02 (0.86–0.94) for women) and MS-IDF (0.88 ± 0.02 (0.84–0.92) for both men and women). Among males, TG/HDL-C ratio showed the second highest diagnostic ability for both MS-NCEP/ATP III (0.86 ± 0.03 (0.81–0.91)) and MS-IDF (0.85 ± 0.03 (0.80–0.90)). Among females, WC showed the second highest diagnostic ability for MS-NCEP/ATP III (0.89 ± 0.02 (0.85–0.92)), while TG/HDL-C ratio exhibited the second highest diagnostic accuracy for MS-IDF (0.85 ± 0.02 (0.81–0.90)). Table 2 summarizes the ROC analysis for MS.

In age-adjusted ROC analysis, LAP also was the variable with the highest diagnostic accuracy for both MS-NCEP/ATP III (AUC 0.89 ± 0.02 (95% CI 0.86–0.93) for men and 0.88 ± 0.02 (0.85–0.91) for women) and MS-IDF (0.87 ± 0.02 (0.83–0.90) for men and 0.86 ± 0.02 (0.83–0.89) for women) (Table 3).

When four or five diagnostic criteria were present, the LAP's AUCs for MS-NCEP/ATP III and MS-IDF were even higher among males (0.94 ± 0.01 (0.92–0.97) and 0.93 ± 0.02 (0.90–0.96) respectively) and females (0.96 ± 0.01 (0.94–0.99) and 0.91 ± 0.05 (0.90–0.96) respectively). In these subgroups, age-adjusted ROC

Table 2 Areas under ROC curves for top five variables associated with metabolic syndrome.

MS-NCEP/ATP III AUC ± S.E.M. (95% CI)				**MS-IDF AUC** ± S.E.M. (95% CI)			
Variables	Men	Variables	Women	Variables	Men	Variables	Women
LAP	**0.91 ± 0.02**[a] (**0.86–0.95**)	LAP	**0.90 ± 0.02**[a] (**0.86–0.94**)	LAP	**0.88 ± 0.02**[a] (**0.84–0.92**)	LAP	**0.88 ± 0.02**[a] (**0.84–0.92**)
TG/HDL-C	0.86 ± 0.03 (0.81–0.91)	WC	0.89 ± 0.02 (0.85–0.92)	TG/HDL-C	0.85 ± 0.03 (0.80–0.90)	TG/HDL-C	0.85 ± 0.02 (0.81–0.90)
TG	0.85 ± 0.03 (0.78–0.91)	TG/HDL-C	0.85 ± 0.02 (0.81–0.90)	TG	0.83 ± 0.03 (0.77–0.88)	WC	0.84 ± 0.02 (0.80–0.89)
WC	0.83 ± 0.03 (0.77–0.89)	BMI	0.84 ± 0.02 (0.80–0.88)	WC	0.82 ± 0.02 (0.78–0.86)	SBP	0.82 ± 0.03 (0.77–0.87)
BMI	0.79 ± 0.04 (0.72–0.86)	HOMA-IR	0.83 ± 0.03 (0.78–0.88)	BMI	0.78 ± 0.03 (0.72–0.84)	TG	0.81 ± 0.03 (0.76–0.87)

AUC, area under the curve; BMI, body mass index; CI, confidence intervals; HOMA-IR, homeostasis model assessment of insulin resistance; LAP, lipid accumulation product; MS-IDF, International Diabetes Federation-diagnosed metabolic syndrome; MS-NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III-diagnosed metabolic syndrome; ROC, receiver operating characteristics; SBP, systolic blood pressure; TG, triglycerides; TG/HDL-C, triglycerides-to-high-density lipoprotein cholesterol ratio; WC, waist circumference.
[a]The highest AUCs are printed in bold.

Table 3 Age-adjusted ROC analysis for top five variables associated with metabolic syndrome.

MS-NCEP/ATP III AUC ± S.E.M. (95% CI)				**MS-IDF AUC** ± S.E.M. (95% CI)			
Variables	Men	Variables	Women	Variables	Men	Variables	Women
LAP	**0.89 ± 0.02**[a] **(0.86–0.93)**	LAP	**0.88 ± 0.02**[a] **(0.85–0.91)**	LAP	**0.87 ± 0.02**[a] **(0.83–0.90)**	LAP	**0.86 ± 0.02**[a] **(0.83–0.89)**
TG/HDL-C	0.84 ± 0.02 (0.80–0.88)	WC	0.85 ± 0.02 (0.82–0.99)	TG/HDL-C	0.83 ± 0.02 (0.79–0.87)	TG/HDL-C	0.84 ± 0.02 (0.81–0.88)
WC	0.83 ± 0.02 (0.79–0.88)	TG/HDL-C	0.85 ± 0.02 (0.81–0.89)	TG	0.80 ± 0.02 (0.76–0.84)	WC	0.81 ± 0.02 (0.77–0.85)
TG	0.82 ± 0.02 (0.78–0.86)	BMI	0.80 ± 0.02 (0.77–0.84)	WC	0.80 ± 0.02 (0.77–0.84)	TG	0.80 ± 0.02 (0.76–0.84)
BMI	0.82 ± 0.02 (0.77–0.86)	HOMA-IR	0.80 ± 0.02 (0.77–0.84)	BMI	0.79 ± 0.02 (0.75–0.83)	SBP	0.79 ± 0.02 (0.76–0.83)

AUC, area under the curve; BMI, body mass index; CI, confidence intervals; HOMA-IR, homeostasis model assessment of insulin resistance; LAP, lipid accumulation product; MS-IDF, International Diabetes Federation-diagnosed metabolic syndrome; MS-NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III-diagnosed metabolic syndrome; ROC, receiver operating characteristics; SBP, systolic blood pressure; TG, triglycerides; TG/HDL-C, triglycerides-to-high-density lipoprotein cholesterol ratio; WC, waist circumference.
[a]The highest AUCs are printed in bold.

analysis showed similar results among males (0.94 ± 0.02 (0.89–0.99) and 0.93 ± 0.02 (0.89–0.98) respectively) and females (0.95 ± 0.03 (0.90–1.00) and 0.89 ± 0.03 (0.83–0.96) respectively).

Most but not all findings were confirmed in ROC analysis when the sample was stratified according to decades of life. Specifically, LAP was ranked among the best top five variables for both MS-NCEP/ATP III and MS-IDF, among men (AUC-ROCs: 0.86–1.00 and 0.82–0.95 respectively) as well as among women (AUC-ROCs: 0.79–0.95 and 0.78–0.93). Among men, LAP exhibited the highest AUC-ROC for both MS-NCEP/ATP III and MS-IDF in the first (1.00 and 0.94 respectively), second (0.96 and 0.95 (together with WC) respectively), and fourth (0.89 and 0.84 respectively) decades, while among women, LAP was the top variable for MS-NCEP/ATP III in the third (0.91) and fourth (0.79 (together with TG/HDL-C)) decades, and was the top variable for MS-IDF in the third decade (0.86). The overall performance through decades showed that LAP was, among men, the best variable for both MS-NCEP/ATP III and MS-IDF identification, while among women, both LAP and TG/HDL-C were the best variables for detection of MS-NCEP/ATP III, and TG/HDL-C was the top variable for MS-IDF (Table 4).

Internal validation

The highest diagnostic accuracy of LAP for MS was confirmed using 20 000 bootstrap samples: MS-NCEP/ATP III = 0.93 ± 0.03 (0.88–0.98) for men and 0.91 ± 0.03 (0.85–0.96) for women, and MS-IDF = 0.90 ± 0.03 (0.84–0.95) for men and 0.90 ± 0.02 (0.84–0.94) for women.

SEN, SP, EFF and J for MS detection

Analyses of SEN, SP, and EFF were performed in order to compare the ability of LAP and other metabolic categories (TG/HDL-C, HW, and EWETS) for MS-NCEP/ATP III and MS-IDF detection (Supplementary Table 1, see section on supplementary data given at the end of this article). Among men, the overall performance of LAP to detect MS-NCEP/ATP III was better in comparison with TG/HDL-C, HW, and EWETS, as indicated by the balance between SEN and SP (known as Youden's index, J). Specifically, LAP (cut-off value > 51.82) exhibited a high combination of SEN (0.85) and SP (0.85) together with a high efficiency or EFF (0.85) and an elevated J (0.70) for MS-NCEP/ATP, while TG/HDL-C (cut-off value > 2.86) showed the second highest performance (SEN, 0.74; SP, 0.82; EFF, 0.81; and J, 0.56). Even though HW and EWETS showed the highest SP (0.94 and 0.86 respectively) for MS-NCEP/ATP III, their SEN (0.60 and 0.66 respectively) and J (0.54 and 0.52 respectively) were poor.

In women also, the overall performance of LAP to detect MS-NCEP/ATP III was better in comparison with TG/HDL-C, HW, and EWETS. Specifically, LAP (cut-off value > 33.28) exhibited a high combination of SEN (0.81), SP (0.80), EFF (0.80), and J (0.61) for MS-NCEP/ATP, while TG/HDL-C (cut-off value > 1.64) showed the second highest performance (SEN, 0.67; SP, 0.81; EFF, 0.79; and J, 0.48). HW and EWETS showed the highest SP (0.97 and 0.98 respectively) for MS-NCEP/ATP, but their SEN (0.36 and 0.39 respectively) and J (0.33 and 0.39 respectively) were very poor.

In men, the overall performance of LAP to detect MS-IDF was better in comparison with TG/HDL-C, HW, and EWETS. Specifically, LAP (cut-off value > 48.09) exhibited a high combination of SEN (0.78), SP (0.81), EFF (0.81), and J (0.59) for MS-IDF, while EWETS showed the second highest performance (SEN, 0.68; SP, 0.90; EFF, 0.86; and J, 0.58). TG/HDL-C (> 2.60) and HW exhibited lower performance (SEN, 0.72 and 0.47; SP, 0.78 and 0.94; EFF, 0.78 and 0.84; J, 0.52 and 0.41 respectively) for MS-IDF.

Table 4 Areas under ROC curves for the best top five variables associated with metabolic syndrome according to decades of life.

Variables	**D1** (36–40 years)	Variables	**D2** (41–50 years)	Variables	**D3** (51–60 years)	Variables	**D4** (61–70 years)	Variables	**D5** (71–77 years)
MS-NCEP/ATP III AUC±S.E.M. (95% CI)									
Men									
LAP	**1.00±0.00 (1.00–1.00)**[a]	LAP	**0.96±0.02 (0.92–1.00)**[a]	FPG	**0.94±0.03 (0.88–0.99)**[a]	LAP	**0.89±0.04 (0.82–0.97)**[a]	WC	**0.93±0.04 (0.85–1.01)**[a]
TG	0.97±0.03 (0.92–1.03)	TG/HDL-C	0.95±0.02 (0.92–0.99)	Fasting proinsulin	0.88±0.05 (0.78–0.98)	BMI	0.85±0.05 (0.75–0.95)	BMI	0.91±0.06 (0.79–1.02)
TG/HDL-C	0.95±0.04 (0.86–1.03)	TG	0.95±0.02 (0.91–0.99)	LAP	0.86±0.06 (0.74–0.97)	TG	0.83±0.06 (0.71–0.95)	LAP	0.89±0.06 (0.77–1.01)
BMI	0.93±0.05 (0.83–1.04)	HDL-C[b]	0.85±0.06 (0.74–0.96)	TG/HDL-C	0.81±0.07 (0.67–0.96)	TG/HDL-C	0.83±0.05 (0.74–0.93)	DBP	0.86±0.07 (0.72–1.00)
SBP	0.93±0.05 (0.83–1.04)	BMI	0.84±0.05 (0.74–0.94)	TG	0.80±0.08 (0.65–0.95)	WC	0.82±0.05 (0.72–0.93)	TG/HDL-C	0.86±0.06 (0.73–0.98)
Women									
TG/HDL-C	**0.98±0.02 (0.93–1.03)**[a]	WC	**0.97±0.02 (0.94–1.00)**[a]	LAP	**0.91±0.03 (0.84–0.97)**[a]	LAP	**0.79±0.06 (0.69–0.90)**[a]	TG/HDL-C	**0.91±0.05 (0.82–1.00)**[a]
HDL-C[b]	0.96±0.04 (0.88–1.03)	LAP	0.95±0.03 (0.89–1.00)	WC	0.87±0.04 (0.79–0.96)	TG/HDL-C	**0.79±0.06 (0.67–0.90)**[a]	HDL-C[b]	**0.91±0.05 (0.81–1.01)**[a]
WC	0.96±0.03 (0.91–1.02)	BMI	0.91±0.03 (0.85–0.98)	BMI	0.85±0.05 (0.75–0.94)	WC	0.78±0.05 (0.68–0.87)	LAP	0.88±0.06 (0.76–0.99)
LAP	0.93±0.05 (0.84–1.02)	TG/HDL-C	0.88±0.04 (0.80–0.97)	TG/HDL-C	0.84±0.05 (0.74–0.94)	HDL-C[b]	0.76±0.06 (0.64–0.88)	TG	0.83±0.07 (0.69–0.97)
BMI	0.89±0.05 (0.80–0.98)	TG	0.88±0.06 (0.77–0.99)	Fasting proinsulin	0.77±0.05 (0.68–0.87)	BMI	0.74±0.06 (0.63–0.85)	Fasting proinsulin	0.80±0.07 (0.66–0.93)
MS-IDF AUC±S.E.M. (95% CI)									
Men									
LAP	**0.94±0.04 (0.87–1.01)**[a]	LAP	**0.95±0.02 (0.90–0.99)**[a]	WC	**0.89±0.04 (0.81–0.9)**[a]	LAP	**0.84±0.05 (0.74–0.93)**[a]	LAP	**0.91±0.05 (0.82–1.00)**[a]
WC	0.92±0.04 (0.84–1.01)	TG	**0.95±0.02 (0.91–0.99)**[a]	Fasting proinsulin	0.86±0.05 (0.77–0.95)	TG/HDL-C	0.81±0.05 (0.72–0.91)	TG/HDL	**0.91±0.05 (0.82–1.00)**[a]
TG	0.91±0.05 (0.82–1.00)	TG/HDL-C	0.94±0.03 (0.87–1.00)	BMI	0.85±0.05 (0.76–0.94)	TG	0.80±0.06 (0.68–0.91)	TG	0.86±0.07 (0.73–0.99)
TG/HDL-C	0.91±0.05 (0.80–1.01)	HDL-C[b]	0.85±0.07 (0.72–0.98)	LAP	0.82±0.06 (0.70–0.94)	FPG	0.78±0.07 (0.65–0.91)	WC	0.86±0.06 (0.75–0.97)
HDL-C[b]	0.87±0.08 (0.72–1.03)	BMI	0.78±0.05 (0.68–0.88)	2 h glucose	0.80±0.06 (0.68–0.92)	HDL-C[b]	0.75±0.06 (0.47–0.94)	WHR	0.85±0.07 (0.70–0.99)
Women									
TG/HDL-C	**0.98±0.02 (0.93–1.03)**[a]	WC	**0.94±0.03 (0.89–0.99)**[a]	LAP	**0.86±0.04 (0.78–0.95)**[a]	TG/HDL-C	**0.81±0.05 (0.71–0.91)**[a]	TG/HDL-C	**0.88±0.06 (0.77–0.98)**[a]
Fasting insulin	0.96±0.03 (0.90–1.02)	LAP	0.93±0.03 (0.88–0.99)	2 h insulin	0.84±0.05 (0.74–0.93)	LAP	0.78±0.06 (0.67–0.89)	HDL-C[b]	0.86±0.07 (0.73–0.97)
HDL-C	0.96±0.04 (0.88–1.03)	FPG	0.90±0.06 (0.78–1.02)	TG/HDL-C	0.84±0.05 (0.75–0.93)	HDL-C[b]	0.76±0.06 (0.65–0.88)	LAP	0.85±0.06 (0.74–0.99)
WC	0.96±0.03 (0.91–1.02)	BMI	0.88±0.04 (0.79–0.96)	TG	0.81±0.06 (0.70–0.92)	FPG	0.76±0.07 (0.61–0.90)	TG	0.81±0.07 (0.67–0.95)
LAP	0.93±0.05 (0.84–1.02)	TG/HDL-C	0.88±0.04 (0.79–0.96)	BMI	0.80±0.05 (0.70–0.91)	HOMA-IR	0.75±0.06 (0.64–0.86)	Fasting proinsulin	0.80±0.07 (0.66–0.93)

AUC, area under the curve; BMI, body mass index; CI, confidence intervals; D, decade; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LAP, lipid accumulation product; MS-IDF, International Diabetes Federation-diagnosed metabolic syndrome; MS-NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III-diagnosed metabolic syndrome; ROC, receiver operating characteristics; SBP, systolic blood pressure; TG, triglycerides; TG/HDL-C, triglycerides-to-high-density lipoprotein cholesterol ratio; WC, waist circumference; WHR, waist-to-hip ratio.

[a]The highest AUCs are printed in bold.

[b]The scale orientation was inversed for visual purposes.

In women, the overall performance of LAP to detect MS-IDF was better in comparison with TG/HDL-C, HW, and EWETS. Specifically, LAP (cut-off value >31.77) exhibited a high combination of SEN (0.78), SP (0.78), EFF (0.78), and J (0.58) for MS-IDF, while TG/HDL-C (>1.63) showed the second highest performance (SEN, 0.66; SP, 0.80; EFF, 0.77; and J, 0.45), and both HW and EWETS exhibited very poor SEN (0.33 and 0.34 respectively).

When the sample was stratified according to decades of life, LAP exhibited the best overall performance for MS-NCEP/ATP III and MS-IDF among men, and lesser ability among women, especially to detect MS-IDF where the TG/HDL-C ratio showed equal or even a slightly better performance than LAP. The Supplementary Table 1, includes detailed information about these findings.

Correlation for components of MS and IR

In males, age- and BMI-adjusted correlation analysis showed that LAP was correlated with HDL-C ($r=-0.3397$, $P<0.0001$), WC ($r=0.3337$, $P<0.0001$), TG ($r=0.9519$, $P<0.0001$), FPG ($r=0.1739$, $P=0.001$), DBP ($r=0.1157$, $P=0.034$), fasting insulin ($r=0.2243$, $P<0.0001$), and HOMA-IR ($r=0.2555$, $P<0.0001$), but not with SBP ($r=0.1011$, $P=0.064$).

In females, age- and BMI-adjusted correlation analysis showed that LAP was correlated with HDL-C ($r=-0.2693$, $P<0.0001$), WC ($r=0.5543$, $P<0.0001$), TG ($r=0.9085$, $P<0.0001$), FPG ($r=0.4036$, $P<0.0001$), DBP ($r=0.1226$, $P=0.016$), fasting insulin ($r=0.2724$, $P<0.0001$), and HOMA-IR ($r=0.3083$, $P<0.0001$), but not with SBP ($r=0.0761$, $P=0.135$).

In men, LAP showed a slightly better performance (cut-off values >51.82 and LAP >48.09; SEN, 0.45 and 0.52 respectively; SP, 0.79 and 0.75; EFF, 0.71 and 0.70; and J, 0.24 and 0.28) to detect IR (HOMA-IR >2.35, 75th percentile) than the other metabolic categories such as TG/HDL-C (cut-off values >2.86 and >2.60; SEN, 0.42 and 0.47; SP, 0.78 and 0.74; EFF, 0.69 and 0.67; and J, 0.20 and 0.21), HW (SEN, 0.24; SP, 0.88; EFF, 0.72; and J, 0.12), and EWETS (SEN, 0.36; SP, 0.83; EFF, 0.71; and J, 0.19). However, all indexes showed poor SEN. In women, LAP showed a slightly better performance (>33.28 and >31.77; SEN, 0.62 and 0.64 respectively; SP, 0.80 and 0.78; EFF, 0.76 and 0.74; and J, 0.42 and 0.41), to detect IR (HOMA-IR >2.00, 75th percentile) than the other metabolic categories such as TG/HDL-C (cut-off values >1.64 and >1.63; SEN, 0.52 and 0.54; SP, 0.81 and 0.79; EFF, 0.73 for both; and J, 0.32 for both), HW (SEN, 0.19; SP, 0.96; EFF, 0.77; and J, 0.14), and EWETS (idem to HW). When the sample was stratified according to decades of life, the performance of LAP to detect IR remained similar. The Supplementary Table 2, (see section on supplementary data given at the end of this article), includes detailed information about these findings. In addition, LAP showed similar performance, among men and women, for detecting other indicators of IR (e.g. 75th percentiles for fasting and 2 h insulin levels, data not shown).

In men, LAP (>51.82 and >48.09) showed higher performance (SEN, 0.60 and 0.68 respectively; SP, 0.84 and 0.80; EFF, 0.78 and 0.77; and J, 0.44 and 0.48) to detect obesity (BMI $\geq 30\,kg/m^2$) than TG/HDL-C (>2.86 and >2.60; SEN, 0.47 and 0.38 respectively; SP, 0.80 and 0.76; EFF, 0.72 and 0.65; and J, 0.27 and 0.14), HW (SEN, 0.32; SP, 0.91; EFF, 0.78; and J, 0.23), and EWETS (SEN, 0.51; SP, 0.87; EFF, 0.79; and J, 0.38). In women, LAP (>33.28 and >31.77) showed higher performance (SEN, 0.65 and 0.68 respectively, SP, 0.83 and 0.80; EFF, 0.78 and 0.77; and J, 0.48 and 0.49) to detect obesity (BMI $\geq 30\,kg/m^2$) than TG/HDL-C (>1.64 and >1.63; SEN, 0.45 and 0.42 respectively; SP, 0.78 and 0.79; EFF, 0.69 for both; and J, 0.23 and 0.21), HW (SEN, 0.16; SP, 0.95; EFF, 0.75; and J, 0.12), and EWETS (SEN, 0.18; SP, 0.96; EFF, 0.75; and J, 0.14). When the sample was stratified according to decades of life, the overall performance of LAP to detect obesity remained similar to that found from the whole sample (data not shown).

Discussion

We found that LAP was the parameter with the strongest diagnostic accuracy for MS in a sample of healthy, unrelated Spanish adults. Specifically, LAP's AUCs for MS-IDF and, especially, MS-NCEP/ATP III were notably elevated in females (AUC 0.88 and 0.90 respectively) and males (AUC 0.88 and 0.91 respectively), in particular when four or five diagnostic criteria were present in females (AUC 0.91 and 0.96 respectively) and males (AUC 0.93 and 0.94 respectively). The highest diagnostic performance of LAP was observed among males for MS-NCEP/ATP III (proportion of positives and negatives classified correctly by the test, EFF = 85%, Supplementary Table 1). The overall performance of LAP through decades of life was better for MS-NCEP/ATP III and MS-IDF detection among men, and lesser for MS-NCEP/ATP III and, especially, MS-IDF among women where the TG/HDL-C ability was similar or even slightly better.

Our findings are highlighted by several aspects. First, to the best of our knowledge, LAP is the parameter with the highest diagnostic accuracy reported so far for MS-NCEP/ATP III and MS-IDF. Second, the reliability of our findings was confirmed by internal validation using bootstrapping, a powerful statistical procedure (13). Third, LAP is simple, inexpensive, and easy to calculate (3, 4), and could be a useful obesity estimator where height and/or weight may be difficult to assess (for example, amputees). Fourth, LAP showed a good

efficiency to identify MS independently of the classification used to detect it (using either NCEP/ATP III or IDF criteria), although its ability was slightly lower for MS-IDF identification, especially among women. In addition, LAP's performance for MS identification was not affected among individuals with major hypertriglyceridemia, postmenopausal status, or major central obesity (data not shown). Fifth, in a previous short report, we found the same LAP's power to diagnose MS-NCEP/ATP III among Argentinean adult males (AUC 0.91) (2), despite the fact that clinical and ethnic characteristics of the Spanish sample population were different to those of the sample used in first report (i.e. older males with lower prevalence of both normal weight and MS).

LAP is based on a combination of WC and TG. The components of LAP tend to increase with age (15, 16). Therefore, LAP was defined to assess the extent to which an individual had traveled the path of increasing both TG and WC (3). LAP could be associated to a dysfunctional and highly lipolytic adipose tissue that is a central abnormality behind MS and associated conditions such as CVD and type 2 diabetes (17). In this sense, it was reported, using population-based data obtained from the NHANES III, that LAP performs better than BMI for identifying cardiovascular risk (3) and diabetes (4). In agreement, single components of LAP have been associated with risk for CVD, type 2 diabetes, and MS (1, 17). WC, a simple measure of truncal fat that reflects both abdominal subcutaneous adipose tissue and, especially, visceral adipose tissue, is a robust predictor for cardiometabolic risk, and represents the main component of MS (18). TG, also, is a reliable predictor for these cardiometabolic syndromes (1). Moreover, the index TG/HDL-C ratio (>3) has showed both high SEN and SP for diagnosis of MS (19) and together with TG (>1.47 mmol/l) are probably among the best measures available for clinical assessment of IR (20). However, some studies do not support this view (21), or suggested that diagnostic ability of these variables depends on ethnic background (10, 22).

Other surrogates of lipid overaccumulation are HW and EWETS (10). The first especially applies for men, and the second for postmenopausal women (22). In our study, the supremacy of LAP over HW and EWETS (and in lesser magnitude over TG/HDL-C), for detecting MS-NCEP/ATP III and MS-IDF, in men as well as in women through different decades of life, could be, at least in part, explained by the fact that the former exhibited superiority over the latter indexes for detecting IR as well as obesity. Indeed, it was suggested that accurate detection of discrete metabolic conditions such as prediabetes and diabetes requires models composed by continuous rather than dichotomous risk factors (23). Accordantly, LAP is a remarkable continuous index of lipid overaccumulation. With qualitative indexes, SEN, SP, and target population are 'fixed', while with quantitative parameters, such as LAP, all are flexible, thus improving the efficiency of the test.

This study has some limitations. First, the sample size was relatively small. However, this limitation was overcome by performing bootstrapping of principal findings using 20 000 bootstrap samples. Second, there is no standard measurement protocol for WC yet, a component of LAP. Indeed, relationship between WC, morbidity, and mortality could depend on the measurement site, although recent data refused any influence on the association between WC, all-cause and CVD mortality, CVD, and diabetes (24). In the present study, LAP's power to diagnose MS-NCEP/ATP III and MS-IDF remained quite similar when data were analyzed using WC measured at the smallest horizontal girth between the costal margins and the iliac crests (shown for comparison purposes with our previous report) (2) compared to the umbilical level (not shown). In addition, because of TG levels exhibit high biological variation, indexes which include one TG determination, such as LAP, could, at least in theory, be a source of bias. At last, because of the limited value of cross-sectional designs, additional evidence from prospective studies is necessary before a firm conclusion can be drawn in this area.

Of note, LAP has been recently associated with all-cause mortality in non-diabetic patients at high cardiovascular risk (25), and with liver steatosis (26), thus highlighting and enlarging specific key parts of the corpus of evidence on LAP.

In conclusion, in non-diabetic adults LAP, a continuous variable associated with lipid overaccumulation, has a strong and reliable diagnostic accuracy for MS-IDF and, especially, MS-NCEP/ATP III in females and, particularly, in males from Spain. Our results are supported by previous studies (2–4) and should be viewed as a basis for future prospective studies in larger sample sizes and different ethnic groups.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-10-1039.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research was supported by grants FEDER 2FD 1997/2309 from the Fondo Europeo para el Desarrollo Regional, Red de Centros RCMN (C03/08), FIS (Fondo de Investigación Sanitario) 03/1618, and from Instituto de Salud Carlos III-RETIC RD06/0015/0012; CIBER de Diabetes y Enfermedades Metabólicas Asociadas is an ISCIII project (Madrid, Spain).

References

1 Gallagher EJ, LeRoith D & Karnieli E. The metabolic syndrome – from insulin resistance to obesity and diabetes. *Endocrinology and Metabolism Clinics of North America* 2008 **37** 559–579. (doi:10.1016/j.ecl.2008.05.002)

2 Tellechea ML, Aranguren F, Martínez-Larrad MT, Serrano-Ríos M, Taverna MJ & Frechtel GD. Ability of lipid accumulation product to identify metabolic syndrome in healthy men from Buenos Aires. *Diabetes Care* 2009 **32** e85. (doi:10.2337/dc08-2284)

3 Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. *BMC Cardiovascular Disorders* 2005 **5** 26. (doi:10.1186/1471-2261-5-26)

4 Kahn HS. The lipid accumulation product is better than BMI for identifying diabetes. *Diabetes Care* 2006 **29** 151–153. (doi:10.2337/diacare.29.01.06.dc05-1805)

5 Martinez-Larrad MT, Fernandez-Perez C, Gonzalez-Sanchez JL, Lopez A, Fernandez-Alvarez J, Riviriego J, Serrano-Rios M & Grupo de Estudio de Atencion Primaria de Segovia. Prevalence of the metabolic syndrome (ATP-III criteria). Population-based study of rural and urban areas in the Spanish province of Segovia. *Medicina Clinica* 2005 **125** 481–486. (doi:10.1157/13080210)

6 Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P & Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003 **26** 3160–3167. (doi:10.2337/diacare.26.11.3160)

7 Levy JC, Matthews DR & Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 1998 **21** 2191–2192. (doi:10.2337/diacare.21.12.2191)

8 Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr & Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004 **109** 433–438. (doi:10.1161/01.CIR.0000111245.75752.C6)

9 Alberti KG, Zimmet P & Shaw J. The metabolic syndrome – a new worldwide definition. *Lancet* 2005 **366** 1059–1062. (doi:10.1016/S0140-6736(05)67402-8)

10 Sumner AE & Cowie CC. Ethnic differences in the ability of triglyceride levels to identify insulin resistance. *Atherosclerosis* 2008 **196** 696–703. (doi:10.1016/j.atherosclerosis.2006.12.018)

11 Hanley JA & Mcneil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983 **148** 839–843.

12 McKenzie D, Vida S, Mackinnon AJ, Onghena P & Clarke D. Accurate confidence intervals for measures of test performance. *Psychiatry Research* 2007 **69** 207–209. (doi:10.1016/S0165-1781(96)02952-6)

13 Mossman D. Resampling techniques in the analysis of non-binormal ROC data. *Medical Decision Making* 1995 **15** 358–366. (doi:10.1177/0272989X9501500406)

14 Mackinnon A. A spreadsheet for the calculation of comprehensive statistics for the assessment of diagnostic tests and inter-rater agreement. *Computers in Biology and Medicine* 2000 **30** 127–134. (doi:10.1016/S0010-4825(00)00006-8)

15 MacLean DR, Petrasovits A, Connelly PW, Joffres M, O'Connor B & Little JA. Plasma lipids and lipoprotein reference values, and the prevalence of dyslipoproteinemia in Canadian adults. Canadian Heart Health Surveys Research Group. *Canadian Journal of Cardiology* 1999 **15** 434–444.

16 Dobbelsteyn CJ, Joffres MR, MacLean DR & Flowerdew G. A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The Canadian Heart Health Surveys. *International Journal of Obesity and Related Metabolic Disorders* 2001 **25** 652–661. (doi:10.1038/sj.ijo.0801582)

17 Després JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodés-Cabau J, Bertrand OF & Poirier P. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2008 **28** 1039–1049. (doi:10.1161/ATVBAHA.107.159228)

18 Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, Kahn R & Association for Weight Management and Obesity Prevention; NAASO; Obesity Society; American Society for Nutrition; American Diabetes Association. Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *Diabetes Care* 2007 **30** 1647–1652. (doi:10.2337/dc07-9921)

19 Cordero A, Laclaustra M, León M, Casasnovas JA, Grima A, Luengo E, Ordoñez B, Bergua C, Bes M, Pascual I, Alegría E & MESYAS Registry Investigators. Comparison of serum lipid values in subjects with and without the metabolic syndrome. *American Journal of Cardiology* 2008 **102** 424–428. (doi:10.1016/j.amjcard.2008.03.079)

20 McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C & Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. *Annals of Internal Medicine* 2003 **139** 802–809.

21 Kannel WB, Vasan RS, Keyes MJ, Sullivan LM & Robins SJ. Usefulness of the triglyceride-high-density lipoprotein versus the cholesterol-high density lipoprotein ratio for predicting insulin resistance and cardiometabolic risk (from the Framingham Offspring Cohort). *American Journal of Cardiology* 2008 **101** 497–501. (doi:10.1016/j.amjcard.2007.09.109)

22 Kim-Dorner SJ, Deuster PA, Zeno SA, Remaley AT & Poth M. Should triglycerides and the triglycerides to high-density lipoprotein cholesterol ratio be used as surrogates for insulin resistance? *Metabolism* 2009 **59** 299–304. (doi:10.1016/j.metabol.2009.07.027)

23 Stern MP, Williams K & Haffner SM. Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? *Annals of Internal Medicine* 2002 **136** 575–581.

24 Ross R, Berentzen T, Bradshaw AJ, Janssen I, Kahn HS, Katzmarzyk PT, Kuk JL, Seidell JC, Snijder MB, Sørensen TI & Després JP. Does the relationship between waist circumference, morbidity and mortality depend on measurement protocol for waist circumference? *Obesity Reviews* 2008 **9** 312–315. (doi:10.1111/j.1467-789X.2007.00411.x)

25 Ioachimescu AG, Brennan DM, Hoar BM & Hoogwerf BJ. The lipid accumulation product and all-cause mortality in patients at high cardiovascular risk: a PreCIS database study. *Obesity* 2010 **18** 1836–1844. (doi:10.1038/oby.2009.453)

26 Bedogni G, Kahn HS, Bellentani S & Tiribelli C. A simple index of lipid overaccumulation is a good marker of liver steatosis. *BMC Gastroenterology* 2010 **10** 98. (doi:10.1186/1471-230X-10-98)

Received 11 January 2011
Accepted 24 January 2011