Annals of Human Biology, January – February 2012; 39(1): 46–53

ISSN 0301-4460 print/ISSN 1464-5033 online
DOI: 10.3109/03014460.2011.637512

informa
healthcare

RESEARCH PAPER

Prevalence of metabolic syndrome and related metabolic traits in an island population of the Adriatic

R. Deka[1], Z. Durakovic[2], W. Niu[1], G. Zhang[3], R. Karns[1], N. Smolej-Narancic[2], S. Missoni[2], D. Caric[4], T. Caric[4], D. Rudan[2], B. Salzer[5], R. Chakraborty[6] & P. Rudan[2]

[1]Department of Environmental Health, Center for Genome Information, University of Cincinnati, Cincinnati, Ohio, USA, [2]Institute for Anthropological Research, Zagreb, Croatia, [3]Human Genetics Division, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, [4]Health Center Hvar, Hvar, Croatia, [5]Labor Diagnostika, Zagreb, Croatia, and [6]Center for Computational Genomics, Institute of Investigative Genetics, University of North Texas Health Science Center, Fort Worth, Texas, USA

***Background*: Metabolic syndrome, a constellation of risk factors associated with cardiovascular disease and Type 2 diabetes, has reached epidemic proportions worldwide. Epidemiological studies in transitional societies will provide insight into the underlying factors that interact in its manifestation.**

***Aims*: To estimate the prevalence of metabolic syndrome, provide a comparative analysis of two metabolic syndrome definitions and assess clustering and association of metabolic traits and cardiovascular diseases in an Adriatic island population.**

***Subjects and methods*: In a cross-sectional study, data on four anthropometric, blood pressure and 11 biochemical traits were obtained from 1430 adults from the island of Hvar.**

***Results*: Prevalence of metabolic syndrome was 25% and 38.5% based on Adult Treatment Panel III and International Diabetes Federation definitions, respectively. Rates of abdominal obesity, elevated blood glucose and hypertension were high. Among the traits not included in the definitions, levels of LDL, total cholesterol and fibrinogen were markedly elevated. The majority of the phenotypes were significantly associated with the syndrome, the strongest being waist circumference.**

***Conclusion*: The Croatian islanders are characterized by a high prevalence of metabolic abnormalities. Central obesity is the strongest contributor of the syndrome. With a high prevalence of dyslipidemia and pro-inflammatory factors, the population is at substantial risk for cardiovascular diseases.**

Keywords: Metabolic syndrome, obesity, cardiovascular disease, Adriatic island population

INTRODUCTION

Metabolic syndrome, defined by a cluster of metabolic abnormalities including insulin resistance/carbohydrate intolerance, obesity, dyslipidemia and hypertension has emerged as a major public health problem on a global scale across societies, irrespective of economic development and state of affluence (Ford et al. 2002; Cameron et al. 2004; Song et al. 2004; Gu et al. 2005; Keighley et al. 2006). Since this assemblage of risk factors was first elucidated by Reaven (1988), a large body of data has confirmed that metabolic syndrome is associated with increased risk of Type 2 diabetes (T2D) and cardiovascular diseases (CVD) (Hanson et al. 2002; Lakka et al. 2002; Eckel et al. 2005; Galassi et al. 2006). The syndrome has, however, been defined variously based on specific cut points of the individual components. The two most commonly used definitions were proposed by the World Health Organization (1999) and National Cholesterol Education Program's Adult Treatment Panel III (ATPIII) (National Institutes of Health 2001). Yet, there has been a lack of consensus of the applicability of their prescribed trait cut points in both clinical settings and epidemiological studies (Eckel et al. 2005; Grundy et al. 2005; Kahn et al. 2005). Subsequently, a globally relevant definition was proposed by the International Diabetes Federation (IDF), taking into account ethnic variation of trait values, particularly that of central obesity (Alberti et al. 2005). Several studies have shown general agreement between the ATPIII and the IDF definitions with regard to prevalence rates of metabolic syndrome and their clinical predictability (Ford 2005; Nilsson et al. 2007; Boronat et al. 2009). However, more recently there have been disagreements on the utility of metabolic syndrome in clinical practice and its

Correspondence: Ranjan Deka, PhD, Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, OH 45267-0056, USA. Tel: 011-513-558-5989. Fax: 011-513-558-4397. E-mail: ranjan.deka@uc.edu

(*Received 28 March 2011; accepted 28 November 2011*)

value in epidemiological studies (Eckel et al. 2010; Simmons et al. 2010). Keeping these controversies in perspective, epidemiological studies could be more informative with the evaluation of additional metabolic traits, which are not included in the prescribed definitions of the syndrome, but are associated with cardiovascular disease risks.

We conducted a population-based cross-sectional study in a relatively isolated population of the eastern Adriatic coast of Croatia to estimate and compare the prevalence of metabolic syndrome using the ATPIII and IDF guidelines, and to evaluate additional metabolic traits associated with cardiovascular disease risks. The present-day Croatian islanders are predominantly of Slavic descent, who emigrated from the mainland interior of the Balkan peninsula at two time points, first during the 6th and 8th century AD and second between 15th and 18th centuries during the Turkish wars (Rudan et al. 1992). Since the time of their settlement, the island populations have remained relatively isolated with little emigration due primarily to geographic confinement. Although the Dalmatian islanders practice a largely traditional and active life-style based on farming and livestock, rates of obesity and arterial hypertension were found to be high in these populations (Smolej-Narancic and Zagar 2000; Rudan et al. 2003; Pucarin-Cvetkovic et al. 2006). Two later studies also reported a high prevalence of metabolic syndrome in several of these islands (Kolcić et al. 2006; Deka et al. 2008). The current study extends our previous work in the island of Hvar (Deka et al. 2008) with a substantially larger sample and inclusion of several metabolic traits, in addition to the phenotypes implicit in the definitions of the syndrome, involved in the cascade of cardiovascular diseases and impaired glucose metabolism. In all, data on 11 biochemical traits, blood pressure and four anthropometric measurements were obtained from over 1400 adult participants. The homogenous genetic background of the population due to limited population admixture (Martinovic et al. 1999), similarly active lifestyles due to an agricultural subsistence and predominantly Mediterranean diet (Smolej-Narancic 1999) were ideal to estimate the prevalence of metabolic syndrome and other metabolic traits without the confounding effects of population substructure and environmental heterogeneity.

METHODS

Study participants and measurements

The study was conducted in the middle Dalmatian island of Hvar on the eastern Adriatic coast of Croatia (Figure 1). According to the 2001 census, the total population was 11,103 individuals, living in 24 settlements consisting of 21 villages and three townships. A non-probability study sample was obtained by advertising through village officials and community leaders. Although the participants comprised of volunteers, they are representative of the general population of the island as the sample was drawn from eight different villages with similar genetic background, lifestyle and dietary patterns as described above (Martinovic et al. 1999; Smolej-Narancic 1999). Anthropometric data, blood pressure measurements and blood samples were collected from 1430 volunteers (602 men and 828 women) aged 18–97 years from eight settlements (Figure 1). After excluding subjects below 20 years of age and those without relevant demographic information, data on 1403 individuals were included in computations of descriptive statistics of the metabolic traits. Metabolic syndrome was assessed in a sample of 1394 subjects who had complete data on all traits for the ATPIII and IDF definitions. Additional data on coronary heart disease, gout, diabetes, hypertension and medication for any of these conditions were obtained through a self-administered questionnaire, medical chart review and clinical diagnostic data (e.g. measured fasting plasma glucose over ATPIII or IDF cut points for diagnoses of type-2 diabetes). Field work was conducted in two seasons of May 2007 and May 2008. This study was approved by the Ethics Committee of the Institute for Anthropological Research in Zagreb, Croatia and the Institutional Review Board of the University of Cincinnati.

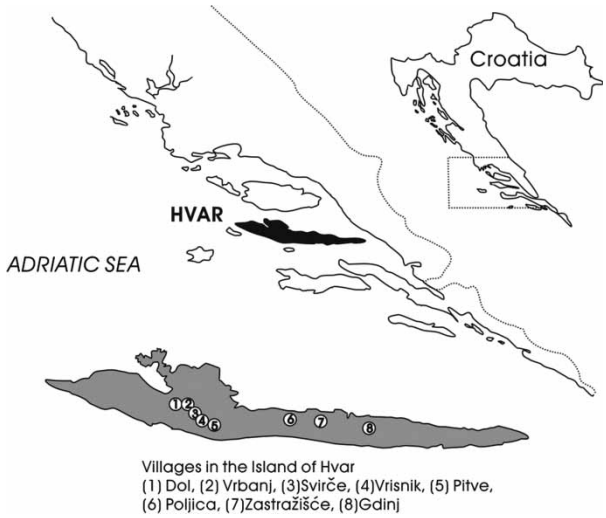

Figure 1. Map of the island of Hvar in the Adriatic coast of Croatia showing the locations of the study villages.

Anthropometric measurements of height (Ht), weight (Wt), waist circumference (WC) and hip circumference (HC) were obtained following techniques described by Weiner and Lourie (1981). Arterial blood pressure was measured three times in a resting position using a mercury sphygmomanometer; the second and the third measurements were used to calculate mean systolic (SBP) and diastolic (DBP) blood pressures. Blood samples were collected after a 12-hour fast; serum was separated and kept frozen until shipped for biochemical tests performed at the clinically accredited biochemical laboratory, Labor Centar, in Zagreb. Methods used were enzymatic hexokinase assay CHOD-PAP for fasting plasma glucose (FPG), homogeneous enzyme inhibition assay for high-density lipoprotein (HDL), FRIEDWALD calculation for low-density lipoprotein (LDL), photometric colour test CHOD-PAP for total cholesterol (TC), photometric colour

test GPO-PAP for triglycerides (TG), chemiluminescence immunoassay ECLIA for insulin, kinetic colorimetric Jaffe method for serum creatinine, enzymatic colour test for uric acid, Clauss method for fibrinogen, photometric colour test with ARSENAZO for calcium and immuno-inhibition assay for glycosylated haemoglobin (HbA1c).

ATPIII defines metabolic syndrome as the co-occurrence of three or more of the following five risk factors: (i) WC $>$ 102 cm in men and $>$ 88 cm in women; (ii) TG $\geq$ 1.69 mmol/L; (iii) HDL $<$ 1.03 mmol/L in men and $<$ 1.29 mmol/L in women; (iv) blood pressure $\geq$ 130/85 mmHg; and (v) FPG $\geq$ 6.1 mmol/L. The IDF definition includes central obesity as the core criterion with population-specific cut points of WC ($\geq$94 cm for men and $\geq$ 80 cm for women in Europeans) and two or more of the following: (i) TG $\geq$ 1.69 mmol/L or treatment for hypertriglyceridemia; (ii) HDL $<$ 1.03 mmol/L in men or $<$ 1.29 mmol/L in women or treatment for hypercholesterolemia; (iii) blood pressure $\geq$ 130/85 mmHg or treatment for hypertension; and (iv) FPG $\geq$ 5.6 mmol/L or treatment for T2D.

Data analysis

Descriptive statistics (mean and standard deviation) of all traits were computed using SPSS software version 15.0.1. Age-adjusted prevalence of metabolic syndrome and its components were computed by using cut-offs of ATPIII and IDF definitions. We calculated Pearson's correlation coefficients (point biserial correlation between a continuous and dichotomous trait) between the quantitative traits (adjusted for age, gender and their interaction term) and metabolic syndrome. To test if metabolic components cluster together more than expected by chance, we compared the observed co-prevalence of the individual metabolic syndrome components to the expected distribution following the procedures introduced by Vaidya et al. (2007). Briefly, the observed co-prevalence of metabolic components was calculated as the proportion of the samples with 0–5 co-existing components, which was compared to the expected co-prevalence of 0–5 components based on the marginal prevalence of each individual component under the assumption of independence. The two distributions were compared using a chi-square statistic. Data on self-reported coronary heart disease, gout, diabetes and hypertension including self-reported medication for any of these were collected from the subjects. In addition, subjects with FPG $\geq$ 7.0 mmol/L or HbA1c $\geq$ 6.5% were considered diabetic and those with SBP $\geq$ 140mmHg or DBP $\geq$ 90 mmHg were considered hypertensive. Odds ratios using age-adjusted values were calculated for these diseases with ATPIII and IDF diagnosed metabolic syndrome.

Table I. Descriptive statistics (mean ± SD) of phenotypic traits in men, women and total subjects.

	Men ($n = 598$)	Women ($n = 805$)	p	Total ($n = 1403$)
Age (years)	56.3 ± 15.8	54.6 ± 15.7	n.s.	55.3 ± 15.8
Ht (m)	1.78 ± 0.07	1.64 ± 0.07	$<$0.0001	1.70 ± 0.10
Wt (kg)	87.8 ± 13.0	72.7 ± 12.5	$<$0.0001	79.1 ± 14.7
WC (cm)	99.7 ± 9.8	90.6 ± 12.5	$<$0.0001	94.5 ± 12.3
HC (cm)	103.4 ± 7.5	104.7 ± 10.3	$<$0.001	104.2 ± 9.2
BMI (kg/m^2)	27.8 ± 3.5	27.0 ± 4.6	$<$0.001	27.3 ± 4.2
WHR	0.96 ± 0.06	0.86 ± 0.07	$<$0.0001	0.91 ± 0.08
FPG (mmol/L)	6.2 ± 1.4	5.8 ± 1.3	$<$0.0001	6.0 ± 1.3
HDL (mmol/L)	1.30 ± 0.33	1.53 ± 0.41	$<$0.0001	1.43 ± 0.39
LDL (mmol/L)	3.60 ± 1.01	3.80 ± 1.05	$<$0.001	3.71 ± 1.03
TC (mmol/L)	5.7 ± 1.2	6.0 ± 1.2	$<$0.0001	5.8 ± 1.2
TG (mmol/L)	1.72 ± 1.33	1.37 ± 0.81	$<$0.0001	1.52 ± 1.08
SBP (mmHg)	136 ± 20	130 ± 24	$<$0.0001	133 ± 23
DBP (mmHg)	84 ± 9	80 ± 10	$<$0.0001	82 ± 10
Ins (μIU/mL)	10.73 ± 7.51	10.88 ± 7.55	n.s.	10.82 ± 7.53
Cre (μmol/L)	98 ± 19	79 ± 13	$<$0.0001	87 ± 19
UA (μmol/L)	360 ± 79	265 ± 77	$<$0.0001	306 ± 91
Fib (g/L)	3.6 ± 1.3	4.0 ± 1.4	$<$0.0001	3.8 ± 1.4
Ca (mmol/L)	2.38 ± 0.13	2.38 ± 0.12	n.s.	2.38 ± 0.13
HbA (%)	5.7 ± 0.9	5.8 ± 0.9	n.s.	5.8 ± 0.9

Ht, height; Wt, weight; WC, waist circumference; HC, hip circumference; BMI, body mass index (Wt in kg/Ht in m^2); WHR, waist-to-hip ratio (WC/HC); FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; Ins, insulin; Cre, creatinine; UA, uric acid; Fib, fibrinogen; Cal, calcium; HbA, glycosylated haemoglobin.

Table II. Age-adjusted prevalence (% ± SE) of metabolic syndrome and its components by ATPIII and IDF criteria.

	Men ($n = 595$)	Women ($n = 799$)	p	Total ($n = 1394$)
Abdominal obesity, WC (ATPIII)[a]	31.1 ± 2.0	45.7 ± 2.2	$<$0.001	39.5 ± 1.5
Abdominal obesity, WC (IDF)[b]	61.7 ± 3.0	69.3 ± 2.8	n.s.	66.1 ± 2.0
Elevated fasting glucose (ATPIII)[c]	29.4 ± 1.9	16.6 ± 1.2	$<$0.0001	21.7 ± 1.1
Elevated fasting glucose (IDF)[d]	58.8 ± 2.9	38.6 ± 2.0	$<$0.0001	46.6 ± 1.7
Low HDL cholesterol (ATPIII)[e]	20.2 ± 1.9	28.0 ± 1.9	$<$0.05	24.8 ± 1.4
Low HDL cholesterol (IDF)[f]	20.4 ± 1.9	28.1 ± 1.9	$<$0.05	24.9 ± 1.4
Elevated triglycerides (ATPIII)[g]	37.9 ± 2.6	18.2 ± 1.3	$<$0.0001	25.8 ± 1.3
Elevated triglycerides (IDF)[h]	41.3 ± 2.6	22.4 ± 1.4	$<$0.0001	29.7 ± 1.3
Hypertension (ATPIII)[i]	52.5 ± 2.7	37.8 ± 1.8	$<$0.01	43.6 ± 1.5
Hypertension (IDF)[j]	54.3 ± 2.7	38.5 ± 1.9	$<$0.001	44.6 ± 1.5
Metabolic syndrome (ATPIII)[k]	28.3 ± 2.0	23.2 ± 1.4	n.s.	25.0 ± 1.2
Metabolic syndrome (IDF)[l]	42.9 ± 2.4	35.9 ± 1.8	n.s.	38.5 ± 1.4

[a] men, $>$102 cm; women, $>$88 cm; [b] men, $\geq$94 cm; women, $\geq$80 cm; [c] $\geq$6.1 mmol/L; [d] $\geq$5.6 mmol/L or previously diagnosed type 2 diabetes; [e] men, $<$1.04 mmol/L; women, $<$1.29 mmol/L; [f] as [e] or specific treatment for hypoalphalipoproteinemia; [g] $\geq$1.69 mmol/L; [h] as [g] or specific treatment for hypertriglyceridemia; [i] systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mmHg; [j] as [i] or treatment of previously diagnosed hypertension; [k] any three of [a], [c], [e], [g], and [i]; [l] is [b] plus any two of [d], [f], [g] and [j]. n.s.: not significant.

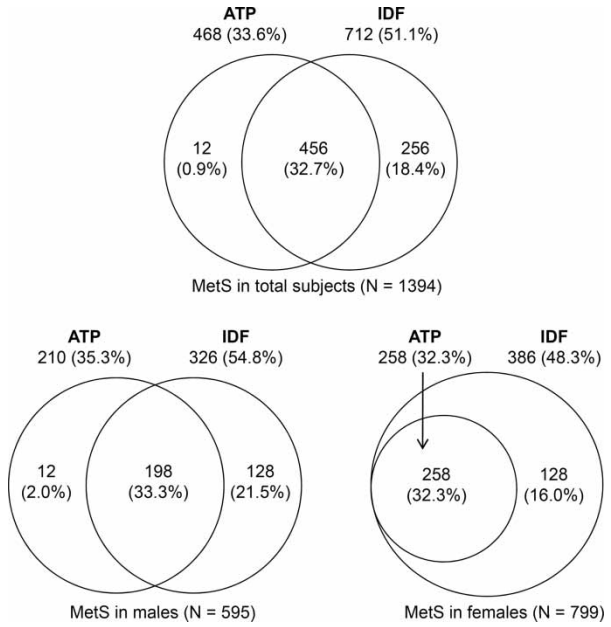

Figure 2. Venn diagrams of crude prevalence of metabolic syndrome by ATPIII and IDF definitions.

RESULTS

Descriptive statistics of the 19 phenotypic traits are summarized in Table I. The mean age was similar in men and women (56.3 and 54.6 years, respectively). Mean values of the majority of traits, however, differed significantly between the genders with the exceptions of insulin, calcium and HbA1c. Men had significantly higher mean values of Ht, Wt, WC, BMI, WHR, FPG, TG, SBP, DBP, creatinine and uric acid. Average HC, HDL, LDL, TC and fibrinogen levels were significantly higher in women. The mean WC in women was above the normal ATPIII and IDF cut-off values, while in men it exceeded only the IDF cut-off. Although mean BMI in both genders did not exceed the obesity threshold ($\geq 30\,kg/m^2$), it fell in the overweight range ($25-29.9\,kg/m^2$). In both genders, mean FPG, HDL and TG levels were within the normal ranges (see legend of Table II for threshold values). With respect to blood pressure, only mean SBP was higher than normal ($\leq 130\,mmHg$) in men.

Age-adjusted prevalence of metabolic syndrome and the individual components defined by ATPIII and IDF are shown in Table II. Abdominal obesity measured by WC was highly prevalent, 39.5% by ATPIII and 66.1% by IDF in the total sample; women had higher rates than men. Prevalence of elevated FPG was over 2-fold higher by the IDF standard (46.6%) compared to the ATP-III standard (21.7%) with the rates being significantly higher in men. Women had a significantly higher prevalence of low HDL than men by both definitions (28% vs 20%); whereas elevated TG and hypertension were significantly higher in men than in women according to both definitions. Overall 43.6% and 44.6% of the subjects were hypertensive based on ATPIII and IDF criteria, respectively. The prevalence of metabolic syndrome was 25% and 38.5% by ATPIII and IDF definitions, respectively. Although men had somewhat higher prevalence of metabolic syndrome, the difference between genders was not significant.

In the total sample ($n = 1394$), 32.7% ($n = 456$) of the participants had metabolic syndrome by both ATPIII and IDF criteria, with similar rates of 33.3% and 32.3% among men and women, respectively (Figure 2). Only 12 men (2% among men and 0.9% overall) met the ATPIII criteria alone (not showing the syndrome by IDF criteria); while a larger fraction (21.5% of men and 16.0% of women, 18.4% of the total sample) showed the syndrome only by the IDF definition.

We calculated the expected co-prevalence (a multinomial distribution ranging from 0–5) of the metabolic syndrome traits for both IDF and ATPIII (Figure 3); in the IDF analysis WC was considered as an independent component trait instead of it being a core requirement. The observed distribution of trait co-prevalence under the assumption of independence was significantly different from the expected prevalence ($p < 0.0001$ for all comparisons). For both IDF and ATPIII, co-prevalence of four and five traits was observed more frequently than expected in both men and women. A higher-than-expected frequency of zero components was observed in both definitions.

In addition to the defined metabolic syndrome components, we collected data on three anthropometric measurements (Ht, Wt and HC) and eight biochemical

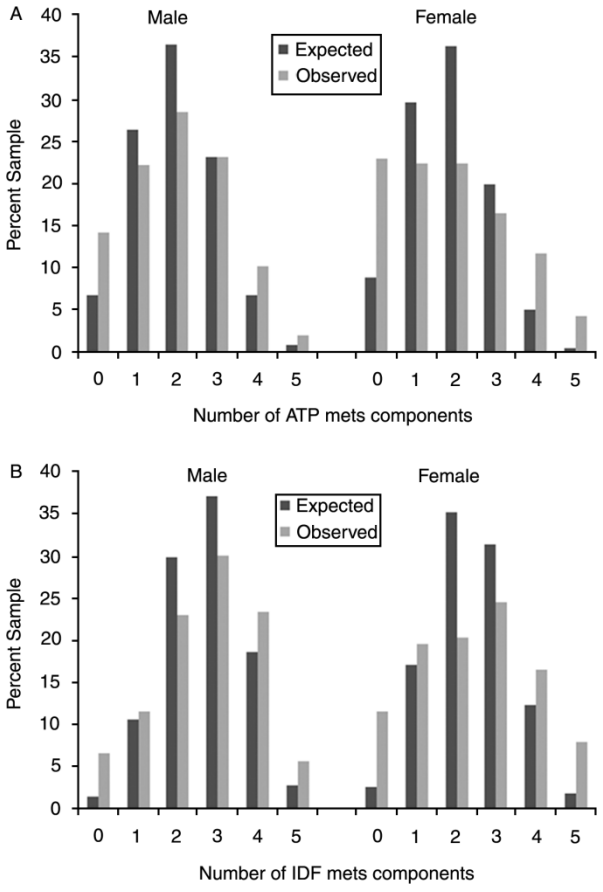

Figure 3. Expected and observed co-prevalence of the components of metabolic syndrome by ATPIII (*a*) and IDF (*b*) definitions.

Table III. Age-adjusted prevalence (% ± SE) of metabolic abnormalities not included in the definitions of metabolic syndrome.

	Men ($n = 598$)	Women ($n = 805$)	P	Total ($n = 1403$)
BMI (kg/m^2): ≥ 25.0	74.3 ± 3.4	54.1 ± 2.4	< 0.001	62.1 ± 2.0
BMI (kg/m^2): > 30.0	21.1 ± 1.8	18.7 ± 1.4	n.s.	19.5 ± 1.1
WHR: > 0.90 (M); > 0.85 (W)	78.6 ± 3.5	54.2 ± 2.5	< 0.0001	64.0 ± 2.0
LDL (mmol/L): > 3.00	72.2 ± 3.5	71.2 ± 2.8	n.s.	71.3 ± 2.2
Cholesterol (mmol/L): > 5.00	71.4 ± 3.4	70.9 ± 2.8	n.s.	70.8 ± 2.2
Insulin (μIU/mL): > 24.90	4.0 ± 0.8	4.1 ± 0.7	n.s.	4.0 ± 0.5
Creatinine (μmol/L): > 125 (M); > 107 (W)	3.6 ± 0.6	2.2 ± 0.4	n.s.	2.8 ± 0.4
Uric acid (μmol/L): > 403 (M); > 337 (W)	23.7 ± 1.9	10.3 ± 0.9	< 0.0001	15.6 ± 0.9
Fibrinogen (g/L): > 3.5	38.5 ± 2.4	51.7 ± 2.4	< 0.01	46.3 ± 1.7
Calcium (mmol/L): > 2.53	10.1 ± 1.5	7.2 ± 0.9	n.s.	8.3 ± 0.8
HbA1c (%): > 6.0	14.1 ± 1.3	15.4 ± 1.2	n.s.	14.9 ± 0.9

traits (LDL, TC, insulin, creatinine, uric acid, fibrinogen, calcium and HbA1c). The mean values of these traits are given in Table I and their age-adjusted prevalence rates above normal cut points (reference ranges for the biochemical traits used in the biochemistry laboratory are based on clinical standards for Croatian populations) and are shown in Table III. Markedly high prevalence of elevated levels of HDL (71.3%), total cholesterol (70.8%) and fibrinogen (46.3%) were observed.

Since the studied traits are known to be involved in cardiovascular disease risks and insulin resistance, we calculated Pearson's correlation coefficients (equivalent to point biserial correlation between a binary outcome and continuous trait) to indicate the strength of association between each of the quantitative measures and metabolic syndrome diagnosed as a binary trait by ATPIII and IDF (Table IV). Both definitions of metabolic syndrome correlated strongly with each other ($r = 0.66$, $p < 2.2 \times 10^{-16}$), corroborating the substantial overlap between the definitions as noted above (Figure 2).

Table IV. Correlation of quantitative metabolic traits with metabolic syndrome defined by ATPIII and IDF criteria.

	Men		Women		Total	
	ATPIII	IDF	ATPIII	IDF	ATPIII	IDF
WC	0.472	0.479	0.451	0.427	0.456***	0.443***
TG	0.429	0.292	0.460	0.364	0.429***	0.312***
HDL	−0.319	−0.236	−0.324	−0.245	−0.319***	−0.240***
SBP	0.170	0.146	0.279	0.304	0.233***	0.238***
DBP	0.242	0.187	0.245	0.290	0.244***	0.246***
FPG	0.238	0.193	0.367	0.302	0.309***	0.253***
Ht	0.095	0.083	0.075	0.094	0.084*	0.089*
Wt	0.427	0.408	0.381	0.348	0.401***	0.373***
BMI	0.454	0.437	0.379	0.336	0.404***	0.370***
HC	0.363	0.354	0.341	0.327	0.345***	0.333***
WHR	0.293	0.328	0.304	0.290	0.298***	0.303***
HbA	0.140	0.111	0.249	0.166	0.201***	0.142***
Ins	0.376	0.296	0.339	0.291	0.355***	0.292***
LDL	0.031	0.069	0.077	0.083	0.057	0.076*
TC	0.158	0.156	0.101	0.098	0.126**	0.123**
Ca	0.031	0.056	0.089	0.119	0.064	0.092*
Cre	0.078	0.037	0.056	0.053	0.067	0.044
UA	0.227	0.200	0.289	0.243	0.261***	0.223***
Fib	0.086	0.053	0.073	0.098	0.078*	0.079*
ATPIII	1.000	0.585	1.000	0.716	1.000	0.659***

* Correlation is significant at the 0.01 level (2-tailed); ** Correlation is significant at the 0.0001 level (2-tailed); *** Correlation is significant at the 0.000001 level (2-tailed).

As expected, the measures included in the definitions (WC, TG, HDL, SBP/DBP, FPG) and the related metabolic parameters (i.e. other fatness measures, HbA1c) were significantly associated with metabolic syndrome defined by both ATPIII and IDF. Correlations of the traits not included in the definitions could be accounted for by the corresponding metabolic syndrome measures. For example, the association between HbA1c and metabolic syndrome could be explained by using FPG as a covariate; and the association between body fatness measures could be explained by including WC in the model. Insulin and uric acid also showed strong associations with the syndrome; their signals, however, could not be completely explained by other metabolic syndrome measures, which suggest that insulin and uric acid are likely independently involved in the development of the syndrome. TC, LDL, Ht, calcium and fibrinogen also showed correlations with one or both definitions. There was no observable trend of gender-specific associations of the traits with the syndrome defined by either ATPIII or IDF criteria.

With self-reported disease history, medical review and clinical diagnostic data on the prevalence of four metabolic diseases in our study population (Table V), we performed a preliminary analysis of their risks associated with the syndrome (Table VI). In the total population of 1,403 individuals, the overall prevalence of coronary heart disease, diabetes, gout and hypertension were 9.3%, 17.2%, 5.1% and 53.2%, respectively. The odds ratios for each of these four diseases with metabolic syndrome defined by both ATPIII and IDF criteria were significant, which indicated increased risk of cardiovascular-related diseases associated with the syndrome.

DISCUSSION

Although there is consensus that metabolic syndrome is a co-occurrence of abdominal obesity, carbohydrate intolerance, dyslipidemia and hypertension, the syndrome's definition has varied in the specific requirements of component traits and their cut-off values (World Health Organization 1999; National Institutes of Health 2001; Grundy et al. 2005). In this study we have provided an empirical comparison of data on metabolic syndrome and its components derived from a relatively isolated homogeneous population based on the ATPIII and IDF

Table V. Crude prevalence (% ± SE) of metabolic syndrome related diseases in men, women, and total subjects.

Metabolic disease	Men ($n = 598$)	Women ($n = 805$)	p	Total ($n = 1403$)
Coronary heart disease[a]	9.0 ± 1.2	9.6 ± 1.0	0.7326	9.3 ± 0.8
Diabetes[b]	19.6 ± 1.6	15.4 ± 1.3	0.0439	17.2 ± 1.0
Gout[c]	8.7 ± 1.2	2.4 ± 0.5	< 0.0001	5.1 ± 0.6
Hypertension[d]	58.0 ± 2.0	49.7 ± 1.8	0.0019	53.2 ± 1.3

[a] Self-reported coronary heart disease (answered 'yes' to question 'do you have coronary heart disease' or provided information for year diagnosed and/or medication for this disease). [b] Self-reported diabetes (answered 'yes' to question 'do you have diabetes' or provided information for year diagnosed and/or medication for this disease), or measured FPG ≥ 7.0 mmol/L, or measured HbA1c ≥ 6.5%. [c] Self-reported gout (answered 'yes' to question 'do you have gout' or provided information for year diagnosed and/or medication for this disease). [d] Self-reported hypertension (answered 'yes' to question 'do you have hypertension' or provided information for year diagnosed and/or medication for this disease), or measured SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg.

guidelines and evaluated the association between additional metabolic traits, cardiovascular diseases and metabolic syndrome. Our study population is comprised of volunteers from the island of Hvar; therefore the sample may differ from the general, non-volunteer population. The overall population, however, experiences a relatively homogeneous lifestyle and environmental exposures, reducing the potential bias introduced by our sampling strategy.

Approximately 33% of the subjects could be classified as metabolic syndrome cases by both definitions (Figure 2). Of the subjects whose metabolic syndrome status was discrete by these two definitions, an overwhelming majority belonged to the IDF defined category (95.5%, 256 out of 268 subjects meeting either 'ATPIII only' or 'IDF only' criteria), which was a consistent finding in both genders. This discordance could be explained by (1) the core requirement of abdominal obesity and (2) lower cut-offs for WC and elevated FPG in the IDF definition. Together these resulted in a substantially higher proportion of subjects with obesity and elevated FPG in the IDF category compared to ATPIII (66.1% vs 39.5% for abdominal obesity and 46.6% vs 21.7% for elevated FPG). Further, ATPIII takes into consideration only the measured clinical chemistry values, whereas IDF includes both observed trait measures and treatment history. These observations are in agreement with previously published reports indicating that IDF is a more inclusive definition of the syndrome compared to ATPIII (Ford 2005; Nilsson et al. 2007; Boronat et al. 2009). Therefore, while IDF diagnosis captures more individuals with metabolic syndrome, ATPIII diagnosis detects individuals with more severe metabolic abnormalities.

Under the assumption of trait independence, we found the expected distribution of co-prevalence of the metabolic syndrome components in our study population is significantly different from the predicted distribution (Figure 3). In general, the tails of distributions (0–1 and 4–5 traits) were heavier than the mid-range (2–3 traits). The observed non-random deviation from the expected distributions, which were significant in both genders according to both criteria, indicated mutual dependence and clustering of the components. Vaidya et al. (2007) also reported similar non-random clustering of metabolic traits (higher-than-expected frequency of 0–1 and 4–5 co-prevalent traits) according to ATPIII. This non-independence indicates that, once an individual has developed any of the traits involved in metabolic syndrome, a domino effect ensues and the syndrome progresses to greater severity, involving four-to-five of the diagnostic traits.

Although the primary objective of this study was to estimate the prevalence of metabolic syndrome and to provide a comparative analysis of the two prevalent definitions, we also measured a number of additional traits that are involved in the cascade of cardiovascular diseases and insulin resistance. The majority of the quantitative traits were strongly associated with metabolic syndrome diagnosed by either definition. In particular, the body fatness measures (Wt, BMI, WC, HC, WHR) emerged as strong contributors to the state of metabolic syndrome. Abdominal obesity has been recognized as an independent predictor of cardiovascular disease risk and altered metabolic profile (Despres and Lemieux 2006; de Koning et al. 2007). Consequently, WC was incorporated as the essential criterion in IDF definition (Alberti et al. 2005). In our population, WC had by far the strongest correlation with the syndrome; $r = 0.456$ and 0.443 for ATPIII and IDF, respectively. Association between the body fatness measures, not included in the definitions, and metabolic syndrome could be accounted for by including WC as a covariate. These observations corroborate that WC is the most integral measure of obesity in the definitions of the syndrome. Among the biochemical traits, FPG, HbA1c, HDL, TG, insulin and uric acid showed strong associations

Table VI. Odds ratio for metabolic syndrome-related diseases in men and women.

	Men ($n = 598$)		Women ($n = 805$)	
Metabolic disease	ATPIII	IDF	ATPIII	IDF
Coronary heart disease[a]	2.51 (1.43–4.40)	2.52 (1.35–4.70)	4.05 (2.49–6.58)	5.46 (3.03–9.84)
Diabetes[b]	3.45 (2.28–5.23)	3.06 (1.95–4.82)	8.81 (5.70–13.63)	6.73 (4.13–10.97)
Gout[c]	3.00 (1.69–5.34)	3.73 (1.86–7.49)	3.65 (1.46–9.15)	3.83 (1.33–11.05)
Hypertension[d]	3.96 (2.71–5.80)	5.52 (3.88–7.86)	9.34 (6.47–13.50)	11.19 (8.06–15.54)

[a] Self-reported coronary heart disease (answered 'yes' to question 'do you have coronary heart disease' or provided information for year diagnosed and/or medication for this disease). [b] Self-reported diabetes (answered 'yes' to question 'do you have diabetes' or provided information for year diagnosed and/or medication for this disease) or measured FPG ≥ 7.0 mmol/L, or measured HbA1c ≥ 6.5%. [c] Self-reported gout (answered 'yes' to question 'do you have gout' or provided information for year diagnosed and/or medication for this disease). [d] Self-reported hypertension (answered 'yes' to question 'do you have hypertension' or provided information for year diagnosed and/or medication for this disease) or measured SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.

with metabolic syndrome. Although insulin and uric acid are not included in the definitions, their independent associations with metabolic syndrome warrant further investigation. The correlation of uric acid is notable as several studies have shown it to be associated with metabolic syndrome and cardiovascular risk factors (Culleton et al. 1999; Coutinho et al. 2007). Of interest, gout (a consequence elevated uric acid) was recognized as a key component in one of the earliest descriptions of the cluster of CVD risk factors by Eskil Kylin in 1923 (c.f. Eckel et al. 2005). Insulin has repeatedly been associated with risk for atherosclerosis and the components of metabolic syndrome (Hanson et al. 2002; McLaughlin et al. 2003).

According to reference ranges used in the clinical biochemistry laboratory in Zagreb (Table III), a sizeable fraction of the study population were found with elevated levels of LDL (71.3%) and TC (70.8%). These, together with high prevalence of low HDL and elevated TG levels (Table II), indicate significant risk for dyslipidemia. We also found a high prevalence of abnormal fibrinogen levels, a marker of inflammation, above the normal cut point (46.3%). Elevated levels of fibrinogen have been implicated in increased risk for cardiovascular diseases (The Fibrinogen Studies Collaboration 2007; Kressel et al. 2009). Both LDL and fibrinogen, however, were weakly correlated with metabolic syndrome in our study (Table IV).

A substantial body of data confirms metabolic syndrome as a major determinant of CVD and T2D (Hanson et al. 2002; Lakka et al. 2002; Eckel et al. 2005; Galassi et al. 2006), although there is also considerable controversy over the contribution of MetS to cardiovascular disease risk above any of the individual components (Kahn et al. 2005; Reaven 2006; Eddy et al. 2008; Lee et al. 2008). More recently, questions have been raised about the utility of metabolic syndrome in clinical practice and epidemiological studies (Eckel et al. 2010; Simmons et al. 2010). Although we were unable to address the question of causality between metabolic syndrome and the four diseases, we found significant odds ratios for each of them with both ATPIII and IDF definitions, indicating a high co-occurrence of the syndrome and cardiovascular diseases. Due to the cross-sectional nature of this study, morbidity of these diseases was evaluated by prevalence rather than incidence (age of disease onset was unknown). In this study, we have evaluated additional metabolic traits, not included in the definitions, which are otherwise involved in cardiovascular disease risk and insulin resistance.

The Croatian islanders are characterized by a high prevalence of obesity and metabolic abnormalities constituting metabolic syndrome. Although the overall prevalence of general obesity (BMI $\geq 30\,kg/m^2$) was modest at 19.5%, overweight (BMI $\geq 25\,kg/m^2$) was highly prevalent at 62.1%. Central obesity measured by both WHR and WC was highly prevalent and strongly correlated with metabolic syndrome diagnosed by both ATPIII and IDF criteria. This indicates that central fat accumulation is integral in the development of metabolic syndrome and the associated cardiovascular risk factors in this Adriatic population. Further, in our study population, men and women with metabolic syndrome were at elevated risk for coronary heart disease, diabetes, gout and hypertension, highlighting the significant morbidity of the metabolic components. Previous studies in the Adriatic islands reported similarly high rates of obesity, hypertension and other metabolic diseases (Smolej-Narancic and Zagar 2000; Rudan et al. 2003; Pukarin-Cvetkovic et al. 2006; Kolcic et al. 2006). In a population adhering to an active and traditional lifestyle and Mediterranean diet, these observations necessitate further studies and longitudinal investigations to determine unique metabolic characteristics that may offer explanations for the markedly high prevalence of metabolic syndrome and its components.

ACKNOWLEDGEMENTS

The study was supported by the following grants: 'Population Structure of Croatia–Anthropogenic Approach (No. 196-1962766-2751)', 'Complex Traits Variation and Health in Children, Adolescents and Centenarians (No. 196-1962766-2747)', 'Aging, Changes of Functions of Internal Organs, Working Ability and Biological Ages (No. 196-0342282-0291) funded by the Croatian Ministry of Science, Education and Sports; 'Genetics of Metabolic Syndrome in an Island Population (NIH-DK069845) funded by the National Institutes of Health, USA; RK was supported by a training grant fellowship from the National Institutes of Environmental Health Sciences, USA (T32 ES010957).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

Alberti KG, Zimmet P, Shaw J. 2005. The metabolic syndrome - a new worldwide definition. Lancet 366:1059–1062.

Boronat M, Saavedra P, Varillas VF, Wagner AM, Lopez-Plasencia Y, Alberiche MP, Novoa FJ. 2009. Differences in traditional and emerging cardiovascular risk factors of subjects discordantly classified by metabolic syndrome definitions of the International Diabetes Federation and the National Cholesterol Education program. Nutr Metab Cardiovasc Dis 19:417–422.

Cameron AJ, Shaw JE, Zimmet PZ. 2004. The metabolic syndrome: prevalence in worldwide populations. Endocrinol Metab Clin North Am 33:351–375.

Coutinho TA, Turner ST, Peyser PA, Bielak LF, Sheedy PF, Kullo IJ. 2007. Associations of serum uric acid with markers of inflammation, metabolic syndrome, and subclinical coronary atherosclerosis. Am J Hypertens 20:83–89.

Culleton BF, Larson MG, Kannel WB, Levy D. 1999. Serum uric acid and risk of cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 131:7–13.

de Koning L, Merchant AT, Pogue J, Anand SS. 2007. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. Eur Heart J 28:850–856.

Deka R, Smolej Narancic N, Xi H, Turek S, Cubrilo-Turek M, Vrhovski-Hebrang D, Janicijevic B, Szirovicza L, Rudan I, Jin L, Chakraborty R, Rudan P. 2008. Metabolic syndrome in an island population of the Eastern Adriatic coast of Croatia. Coll Anthropol 32:85–91.

Despres JP, Lemieux I. 2006. Abdominal obesity and the metabolic syndrome. Nature 444:881–887.

Eckel RH, Alberti KGMM, Grundy SM, Zimmet PZ. 2010. The metabolic syndrome. Lancet 375:181–183.

Eckel RH, Grundy SM, Zimmet PZ. 2005. The metabolic syndrome. Lancet 365:1415–1428.

Eddy DM, Schlessinger L, Heikes K. 2008. The metabolic syndrome and cardiovascular risk: implications for clinical practice. Int J Obes 32(Suppl 2):S5–S10.

Ford ES. 2005. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care 28:2745–2749.

Ford ES, Giles WH, Dietz WH. 2002. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 287:356–359.

Galassi A, Reynolds K, He J. 2006. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 119:812–819.

Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. 2005. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 112:2735–2752.

Gu D, Reynolds K, Wu X, Chen J, Duan X, Reynolds RF, Whelton PK, He J. for the InterASIA Collaborative Group. 2005. Prevalence of the metabolic syndrome and overweight among adults in China. Lancet 365:1398–1405.

Hanson RL, Imperatore G, Bennett PH, Knowler WC. 2002. Components of the "metabolic syndrome" and incidence of type 2 diabetes. Diabetes 51:3120–3127.

Kahn R, Buse J, Ferrannini E, Stern M. 2005. The metabolic syndrome: time for a critical appraisal. Diabetes Care 28:2289–2304.

Keighley ED, McGarvey ST, Turituri P, Viali S. 2006. Farming and adiposity in Samoan adults. Am J Hum Biol 18:112–122.

Kolcić I, Vorko-Jović A, Salzer B, Smoljanović M, Kern J, Vuletić S. 2006. Metabolic syndrome in a metapopulation of Croatian island isolates. Croat Med J 47:585–592.

Kressel G, Trunz B, Bub A, Hulsmann O, Wolters M, Lichtinghagen R, Stichtenoth DO, Hahn A. 2009. Systemic and vascular markers of inflammation in relation to metabolic syndrome and insulin resistance in adults with elevated atherosclerosis risk. Atherosclerosis 202:263–271.

Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. 2002. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 288:2709–2716.

Lee CM, Huxley RR, Woodward M, Zimmet P, Shaw J, Cho NH, et al. 2008. The metabolic syndrome identifies a heterogeneous group of metabolic component combinations in the Asia-Pacific region. Diabetes Res Clin Pract 8:377–380.

Martinovic I, Barac L, Furac I, Janicijevic B, Kubat M, Pericic M, Vidovic B, Rudan P. 1999. STR polymorphisms in the population of the Island of Hvar. Hum Biol 71:341–352.

McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. 2003. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med 139:802–809.

National Institutes of Health. 2001. Third report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). NIH Publication No 01-3670. Bethesda, MD: National Institutes of Health.

Nilsson PM, Engstrom G, Hedbald B. 2007. The metabolic syndrome and incidence of cardiovascular disease in non-diabetic subjects – a population-based study comparing three diffferent definitions. Diabet Med 24:464–472.

Pucarin-Cvetkovic J, Mustajbegovic J, Jelinic JD, Senta A, Nola IA, Ivankovic D, Kaic-Rak A, Milosevic M. 2006. Body mass index and nutrition as determinants of health and disease in population of Croatian Adriatic islands. Croat Med J 47:619–626.

Reaven GM. 1988. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37:1595–1607.

Reaven GM. 2006. The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr 83:1237–1247.

Rudan P, Sujoldzic A, Simic D, Bennett LA, Roberts DF. 1992. Population structure in the eastern Adriatic: the influence of historical processes, migration patterns, isolation and ecological pressures, and their interaction. In: Roberts DF, Fujiki N, Torizuka K, editors. Isolation, migration and health. Cambridge University Press, Cambridge, England. SSHB. p 204–218.

Rudan I, Rudan D, Campbell H, Carothers A, Wright A, Smolej-Narancic N, Janicijevic B, Jin L, Chakraborty R, Deka R, Rudan P. 2003. Inbreeding and risk of late onset complex disease. J Med Genet 40:925–932.

Simmons RK, Alberti KGMM, Gale EAM, Colagiuri S, Tuomilehto J, Qiao Q, Ramachandran A, Tajima N, Brajkovich Mirchov I, Ben-Nakhi A, Reaven G, Hama Sambo B, Mendis S, Roglic G. 2010. The metabolic syndrome: useful concept or clinical tool? Report of WHO Expert Consultation. Diabetologia 53:600–605.

Smolej-Narancic N. 1999. Nutritional Status of the Population in Dalmatia, Croatia. Coll Antropol 23:59–68.

Smolej-Narancic N, Zagar I. 2000. Overweight and fatness in Dalmatia, Croatia: comparison with the U.S. population reference. Coll Antropol 24:411–421.

Song J, Kim E, Shin C, Kim S-S, Lee HK, Jung M, Jung S-C, Jo SA, Jo I. 2004. Prevalence of the metabolic syndrome among South Korean adults: the Ansan study. Diabet Med 21:1154–1155.

The Fibrinogen Studies Collaboration 2007. Association of plasma fibrinogen levels with established cardiovascular disease risk factors, inflammatory markers, and other characteristics: individual participant meta-anlaysis of 154,211 adults in 31 prospective studies. Am J Epidemiol 166:867–879.

Vaidya D, Szklo M, Liu K, Schreiner P, Bertoni A, Ouyang P. 2007. Defining the Metabolic Syndrome Construct: Multi Ethnic Study of Atherosclerosis (MESA) cross-sectional analysis. Diabetes Care 30: 2086–2090.

Weiner JS, Lourie JA. 1981. Practical human biology. London: Academic Press.

World Health Organization. 1999. Report of a WHO consultation, Geneva Definition, diagnosis and classification of diabetes mellitus and its complications