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Metabolic Syndrome in an Island Population of the Eastern Adriatic Coast of Croatia

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ABSTRACT

The metabolic syndrome, an assemblage of risk factors, viz., obesity, dyslipidemia, carbohydrate intolerance, and hypertension, associated with development of cardiovascular diseases and Type 2 diabetes, has become a major public health problem in the developed countries. However, data on its prevalence in worldwide populations, particularly in non-industrialized societies is sparse. We report the prevalence of metabolic syndrome in an island population of the eastern Adriatic coast of Croatia, a distinctly homogenous population living in relative isolation with a traditional way of life style pattern. The participants consist of 381 unrelated individuals (136 males, 245 females) from the island of Hvar, age 19 and above. Hvar is among the most populated Croatian islands with a total population of 11,459 individuals according to the 1991 census. Metabolic syndrome was assessed following the National Cholesterol Education Program (NCEP) criteria, with the exception of using body mass index and waist hip ratio as the predictors of obesity. Overall age-adjusted prevalence of metabolic syndrome is 26% (32% in males and 24% in females) with body mass index, and 42% (57% in males and 36% in females) with waist hip ratio as the measures of obesity. Pairwise correlations of the age and sex-adjusted individual components show that with the exception of fasting plasma glucose, the other components of metabolic syndrome are significantly associated with each other, suggesting their co-morbidity. In spite of adherence to a relatively traditional life-style pattern together with a »Mediterranean diet« and rural habitat, the prevalence of metabolic syndrome is substantially high in the population of Hvar. It is likely that factors other than nutritional practices, that might include genetic susceptibility, could potentially be important in predisposition to metabolic syndrome.

***Key words**: metabolic syndrome, Adriatic island, body mass index, waist hip ratio, carbohydrate intolerance, dyslipidemia, cardiovascular disease, Mediterranean diet*

Introduction

Metabolic syndrome, an assemblage of risk factors associated with development of cardiovascular diseases and Type 2 diabetes, has reached epidemic proportions in western societies and has emerged as a major public health problem. The hallmark of the syndrome is a co-occurrence of obesity, dyslipidemia, carbohydrate intolerance and hypertension. Although the notion of metabolic syndrome has gained popularity relatively recently in clinical, epidemiological and genetic literature, clustering of common metabolic risk factors was recognized much earlier[1,2]. A tangible concept of the syndrome was, however, first provided in the Banting lecture by Reaven[3], which he called the »syndrome X«, and suggested that insulin resistance is associated with a series of metabolic risk factors for cardiovascular diseases. With insulin resistance as the common denominator, it is also referred to as the »insulin resistance syndrome«[4,6]. However, the role of insulin resistance as the central feature of the

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syndrome, particularly of its association with cardiovascular diseases remains uncertain, and in 1998, a broader and collective term, »metabolic syndrome«, was adopted by the World Health Organization (WHO)[7]. The syndrome, however, has been, and continues to be defined differently because of uncertainties of the interrelationships of its individual components and their relative burdens to the composite trait with respect to clinical outcomes, morbidity, or mortality[8–11]. Notwithstanding the differences in the definitions adopted across studies, there is indication for an overwhelmingly increased prevalence of the syndrome in industrialized countries. Recent data shows a significant increase in metabolic syndrome in U.S. adults, the age adjusted prevalence rose from 24% in adults aged ≥20 years in NHANES III[12] to 27% in NHANES 1990–2000[13]. These rates are comparable in European populations[14–17]. A recent study among Croatian islanders reported that a third of the study inhabitants have metabolic syndrome[18]. Yet, population-specific data on the prevalence of the syndrome is relatively sparse, and there is a need for understanding whether the relative burden of each component to the composite trait is comparable among populations.

In this study, we report the prevalence of metabolic syndrome in an island population of the eastern Adriatic coast of Croatia. Previous reports had shown high prevalence of obesity and hypertension in these island communities[19–22] indicating that metabolic syndrome could be high in them. The Croatian islands are inhabited by a unique group of populations, who are predominantly of Slavic origins, founded by two major waves of immigration from the mainland. The first influx of Croats had occurred between 6th and 8th century AD and the second took place between 15th and 18th century during the Turkish wars[23]. Since the time of their founding, the island populations have remained relatively isolated largely due to confinement to geographic isolation. In spite of sharing a common European descent, these island populations are distinct from those of the mainland Europeans practicing a more traditional life-style pattern, that includes an agricultural subsistence in a rural setting and living on a typical »Mediterranean diet« of fish, potatoes, vegetables, olive oil and red wine.

Materials and Methods

Study participants and measurements

The study was conducted in the island of Hvar, one of the most populated among the Middle Dalmatian islands (Figure 1). According to the 1991 census, the total population of Hvar was 11,459 individuals living in 24 settlements consisting of 21 villages and 3 small townships. In 1995, anthropometric measurements, blood pressure data and blood samples were collected from 381 unrelated individuals, 136 males and 245 females, aged 19 to 65 years from various settlements.

Anthropometric measurements of height, weight, waist and hip circumference were obtained by following techniques as described previously (24). Data on stature and weight were combined into a body mass index (BMI = weight in kg/height in m^2) and waist and hip circumference into a waist hip ratio (WHR = waist circumference/hip circumference) score for defining two alternate measures for assessing obesity. Blood pressure was measured three times. The second and the third measurements were used to calculate the mean systolic (SPB) and diastolic blood pressure (DBP). Blood samples were drawn after a 12-hour fast and serum was separated and kept frozen until shipped to the biochemical laboratory in Zagreb, where biochemical tests were performed using standard, previously described methods[25,26] to measure fasting glucose (FPG), cholesterol (LDL, HDL and total), and triglycerides (TG).

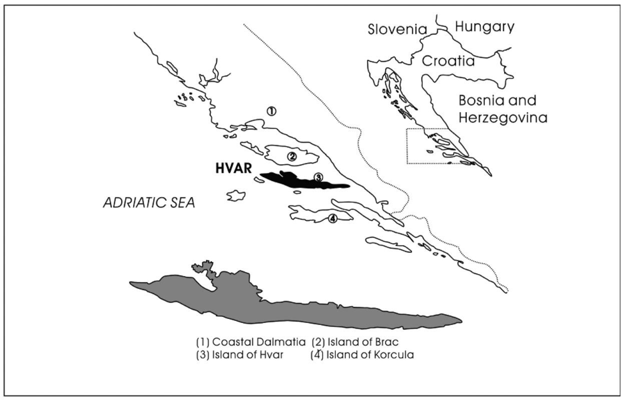


Fig. 1. Map of the eastern Adriatic coast showing the location of the island of Hvar.

Definition of metabolic syndrome

Two definitions of metabolic syndrome, one proposed by the World Health Organization (WHO)[7], and the second as defined in the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)[8], have been adopted in most studies.

The WHO definition requires that individuals with metabolic syndrome have hyperinsulinemia or fasting plasma glucose ≥110 mg/dL (6.1 mmol/L) and at least two of the following following: 1) abdominal or general obesity – WHR >0.90 and >0.85 in women, or BMI ≥30 kg/m^2; 2) dyslipidemia – TG ≥150 mg/dL (1.69 mmol/L) or HDL (high-density lipoprotein) cholesterol <35 mg/dL (0.90 mmol/L) in men and <40 mg/dL (1.0 mmol/L) in women; 3) high blood pressure ≥140/90 mm Hg, or treated with medication; 4) microalbumineria – urinary albumin excretion rate >20 μg/min or albumin:creatinine ratio >30 mg/g.

The NCEP definition does not explicitly include insulin resistance or glucose intolerance as required criteria, rather defines the syndrome as the co-occurrence of three or more of the following five criteria: 1) abdominal obesity – waist circumference >102 cm in men and >88 cm in women; 2) triglycerides ≥150 mg/dL (1.69 mmol/L);

3) HDL cholesterol <40 mg/dL in men (1.04 mmol/L) and <50 mg/dL in women (1.29 mmol/L); 4) high blood pressure ≥130/85 mm Hg; 5) fasting plasma glucose ≥110 mg/dL (6.1 mmol/L).

We have followed a working definition as proposed in ATP III with the exception that we have used BMI (≥30 kg/m^2) and/or WHR (≥0.90) as predictors of obesity.

Statistical analysis

Descriptive statistics (i.e., mean and standard error) of the component traits (BMI, WHR, systolic and diastolic blood pressure, TG, FPG, and HDL cholesterol) and age for the total sample, in males and females, separately, were computed using the SPSS software version 11.5. Age-adjusted and gender-specific prevalence of the component traits, using cut-offs of the NCEP definition were computed, which were used for age-gender standardized rate computations, using the age-structure of the US population as standard[12] for which the sampling weight data was kindly provided by Dr. E.S. Ford. Pearson correlation coefficient was used as the measure of pairwise relationship of the component scores. The principal component analysis employed the varimax rotation routine of the SPSS 11.5 software, with two principal components selected on the basis of the two largest eigen values.

Results

Descriptive statistics of the relevant traits are presented in Table 1. The mean age of the study participants was 47.5 years (49.2 years for males and 46.6 years for females). Taken together, with the exception of TG in females and fasting glucose in both sexes, the mean values of all other traits are outside the range of normal cut-off values. Although by definition, BMI in both sexes does not fall in the »obese« category (BMI ≥ 30 kg/m^2), the averages are well within the overweight group (BMI = 25–29.9 kg/m^2).

The age-adjusted prevalence of the individual metabolic traits (Table 2) shows that in general, the abnormalities are more prevalent in males (7.0 to 87.8%) than in females (5.7 to 60.8%) except for HDL cholesterol (65.0% in males as opposed to 74.9% in females). When obesity is measured by BMI, the prevalence of obesity is relatively lower (20.5% in males and 17.9% in females). However, when obesity is measured by WHR, the prevalence becomes significantly higher (87.8 and 60.8% in

TABLE 1
DESCRIPTIVE STATISTICS OF THE EXAMINED TRAITS IN THE POPULATIONS OF THE ISLAND HVAR, AGE 19 TO 69 YEARS

Trait*	Male		Female		Total	
	N	Mean±SE	N	Mean±SE	N	Mean±SE
Age (yrs)	136	49.15±10.19	245	46.58±10.53	381	47.49±10.47
BMI (kg/m^2)	136	27.54±3.20	243	26.42±4.19	379	26.82±3.90
WHR	133	0.997±0.07	243	0.926±0.07	376	0.951±0.08
SBP (mm Hg)	134	141.8±2.38	242	136.3±31.0	376	138.3±28.3
DBP (mm Hg)	135	91.48±14.66	242	87.95±17.28	376	89.19±16.45
TG (mmol/L)	134	2.28±1.68	238	1.56±1.14	372	1.82±1.40
FPG (mmol/L)	131	4.75±1.95	236	4.30±1.68	367	4.46±1.79
HDL (mmol/L)	126	0.95±0.28	220	1.08±0.30	346	1.03±0.30

*BMI – body-mass index; WHR – waist-hip ratio; SBP – systolic blood pressure; DBP – diastolic blood pressure; TG – triglycerides; FPG – fasting plasma glucose; HDL – high-density lipoprotein cholesterol

TABLE 2
AGE-ADJUSTED PREVALENCE (%) OF INDIVIDUAL METABOLIC ABNORMALITIES ASSOCIATED WITH METABOLIC SYNDROME IN HVAR

Trait	Male		Female		Total	
	N	%±SE	N	%±SE	N	%±SE
BMI ≥ 30 kg/m^2	136	20.5±4.0	243	17.9±2.6	379	18.2±2.2
WHR ≥ 0.90	133	87.8±3.7	243	60.8±3.1	376	69.2±2.7
SBP ≥ 130 mm Hg and DBP ≥ 85 mm Hg	134	64.6±5.0	242	45.3±2.3	376	50.9±2.6
TG ≥ 1.69 mmol/L	134	52.7±4.6	238	29.9±3.1	372	37.3±2.6
FPG ≥ 6.1 mmol/L	131	7.0±2.4	236	5.7±1.8	367	6.2±1.5
Low HDL < 1.04 mmol/L in male and < 1.29 mmol/L in female	126	65.0±5.1	220	74.9±3.6	346	71.1±3.0

TABLE 3
AGE-ADJUSTED PREVALENCE OF 1 OR MORE ABNORMALITIES OF METABOLIC SYNDROME IN THE POPULATION OF HVAR

	No. of abnormalities in % ± SE				
	≥ 1	≥ 2	≥ 3	≥ 4	5
BMI as the measure of obesity					
Male	84.4±3.9	64.4±4.7	32.3±4.5	17.4±4.0	1.4±1.3
Female	78.8±3.1	45.3±3.4	23.8±2.8	5.5±1.5	1.7±1.0
Total	80.2±2.5	51.2±2.8	25.9±2.4	9.3±1.7	1.5±0.8
WHR as the measure of obesity					
Male	86.1±3.7	78.3±4.5	56.9±4.9	28.7±4.4	2.5±1.5
Female	82.6±3.0	59.6±3.3	35.8±3.0	14.7±2.4	1.7±1.0
Total	83.5±2.4	65.0±2.8	42.2±2.7	19.0±2.2	2.0±0.8

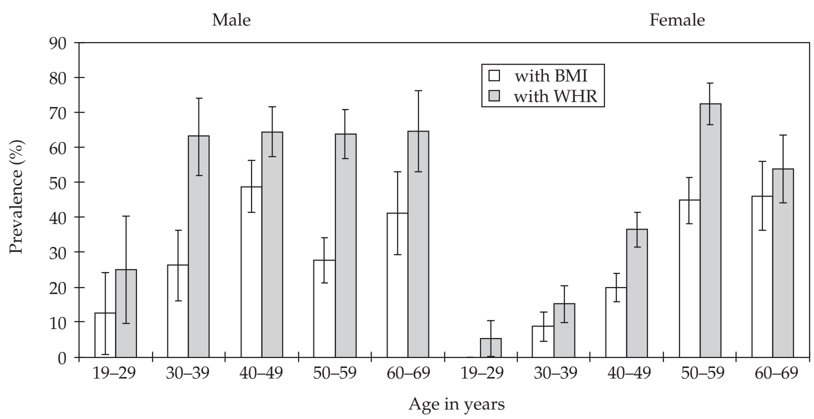
TABLE 4
PEARSON CORRELATION BETWEEN AGE- AND SEX-ADJUSTED COMPONENTS OF METABOLIC SYNDROME IN THE HVAR ISLAND POPULATION

	WHR	SBP	DBP	TG	FPG	HDL
BMI	0.554**	0.260**	0.290**	0.300**	0.119*	–0.313**
WHR		0.533**	0.499*	0.263**	0.047	–0.113*
SBP			0.836**	0.245**	0.132*	–0.118*
DBP				0.254**	0.029	–0.103
TG					0.200**	–0.446**
FPG						–0.076

** p <0.01; * p < 0.05

males and females, respectively). This demonstrates that abdominal obesity is disproportionately high in this population.

The age-adjusted prevalence of one or more of the metabolic abnormalities and co-occurrence of three or more of the components show that metabolic syndrome is substantially high in the population of Hvar, overall 26% with BMI and 42% with WHR as the measures of obesity, respectively (Table 3). The age-specific data (Figure 2) show that with BMI, the prevalence among males increases from 11% in the age group 19–29 years to 47% in 40–49 years, and then drops (though not significantly) to 28% in the age group 50–59 years followed by an increase to 42% in 60–69 years of age. With WHR, however, the trend in males is different, from its lowest prevalence of 24% in the group 19–29 years, the prevalence increases to over 60% in the age group 30–39 years and then it stabilizes with a similar rate in the older age



*	1/8	5/19	22/45	13/47	7/17	0/19	4/46	19/96	26/58	12/26
**	2/8	12/19	19/45	30/47	11/17	1/19	7/46	35/96	42/58	14/26

Fig. 2. Age-specific prevalence of metabolic syndrome (and ** denote the number of individuals within each group with metabolic syndrome measured by obesity BMI and WHR, respectively).*

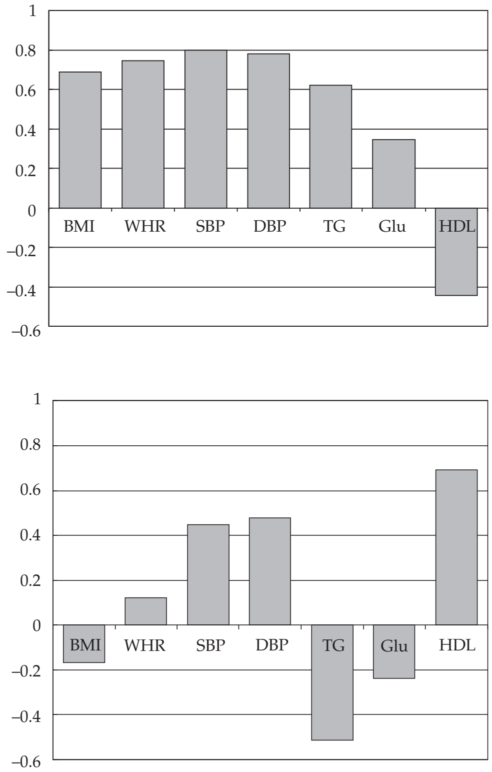


Fig. 3. Factor loadings of individual components of metabolic syndrome for the first two principal components (PC1 above and PC2 below).

groups. In females, using both BMI and WHR, the age-specific prevalence shows a gradual increase from younger to the oldest group with the exception of a somewhat lower prevalence among women of 60–69 years compared to that in the age group 50–59 when WHR is considered.

Pairwise correlations of the age and sex-adjusted individual phenotypes (Table 4) suggest that with three exceptions (WHR-FPG, DBP-FPG, DBP-HDL, and FPG-HDL) all other components are significantly associated with each other, suggesting their co-morbidity in individuals. Fasting glucose appears to be somewhat poorly associated with the other components (with correlations ranging from –0.076 to 0.200, three of the six values are non-significant). With the exception of TG, the association of HDL with the other components is also comparatively weaker (from –0.446 to –0.076, two of which are non-significant). These trends of correlations are also reflected in the factor loadings of the first two principal components (PC1 and PC2) of these variables, shown in Figure 3. The first principal component, which explains 42.7% of the total variance, is nearly a sum-total of all components (a negative coefficient for HDL, as expected) with almost equal weights (0.62 to 0.80), with lower contribution of FPG (weight 0.35) and HDL (weight –0.45). The second principal component (explaining 18.1% of the total variance) shows substantial positive weights of systolic (0.45) and diastolic (0.48) blood pressures, and HDL (0.69), and a negative weight of triglycerides (–0.51).

Discussion

The prevalence of metabolic syndrome is substantially high in the population of Hvar. Using BMI as the indicator of obesity, the age-adjusted prevalence is 26% (32% in men and 24% in women above the age of 19). When WHR is considered as the measure of obesity, there is a dramatic increase in the prevalence – 42% overall (57% in men and 36% in women). These observations also demonstrate significant gender-specific differences, higher prevalence in males and lower in females. While a comparison with other studies would not be accurate owing to the varied definitions adopted across studies, a relative account of the degree of variation in the prevalence with other populations could be in place. In the context of this work, studies using the NCEP definition or some variation of it are more relevant. Ford et al.[13] reported that the age-adjusted prevalence of metabolic syndrome in the general United States population is approximately 27%. The NHANESIII study[12] estimated that the Mexican-Americans have the highest prevalence (32%) compared to non-Hispanic Whites (24%), African Americans (22%) and other ethnic groups (20%). Meigs et al.[27] reported similar prevalence in the Framingham Offspring Study and San Antonio Heart Study, 20–24% among Whites, and over 30% among the Mexican-Americans. Among the Native-Americans, the prevalence is estimated as 35%[28]. Several studies have been reported from Europe. In the Kuopio Ischemic Heart Disease Risk Factor Study, using alternate definitions based on the WHO and NCEP basic criteria, prevalence of metabolic syndrome was found to vary from 9% to 21% in the Finnish cohort[14,16]. In the West of Scotland Coronary Prevention Study, based on a modified NCEP definition, the prevalence of metabolic syndrome is estimated as 26%[15]. Notably, among some other Mediterranean populations, such as Greeks and the Italians, the prevalence of metabolic syndrome is 24% and 25%, respectively[18], which are similar to that observed in Hvar. Some of the variation in the rate of metabolic syndrome across these populations stems from the criteria used in defining the syndrome.

Two recent studies on metabolic syndrome related traits among the islanders of the eastern Adriatic coast are of particular interest in the context of the present study. The results of these two studies[18,29] are comparable as both are based on investigations conducted in four islands (Rab, Vis, Lastovo, and Mljet) as part of the »1001 Dalmatian« research program. Using the NCEP definition Kolčić et al.[18] reported that the prevalence of metabolic syndrome varies from 25% to ~50% in nine villages distributed on these islands, with an average of ~34%. The highest prevalence, 53%, was found in the island of Mljet, where all of the study participants had fasting plasma glucose level >6.1 mmol/L. Pucarin-Cvetković et al.[29] investigated the relationship of BMI and the individual components of metabolic syndrome and dietary patterns. BMI was found to positively correlated with TG, DBP, and SBP. These correlations are also observed among the participants from Hvar. Interestingly, BMI is not correlated with HDL cholesterol in both studies. There are some observable differences in the results reported in this study with those reported in the previous two investigations[18,29]. Overall prevalence of obesity as measured by BMI (26.8%) in the four island populations from Rab, Vis, Lastovo and Mljet is higher than that in Hvar (18.2%). Using BMI as the predictor of obesity as in the study of Kolčić et al.[18], we also observed a somewhat lower prevalence of metabolic syndrome in the island of Hvar. One of the reasons that could be attributed for this observation is a strikingly lower prevalence of fasting plasma glucose (age-adjusted rate of 6%) among the examinees from Hvar. However, in the population of Hvar, when WHR is factored in as the measure of obesity, the prevalence rises significantly to a level of 42% (57% in males and 36% in females). This underscores that visceral obesity is a significant contributing risk factor to metabolic syndrome in this population. Kolčić et al.[18] found a larger number of women with metabolic syndrome compared to men, whereas we found males with a higher prevalence (32%) compared to females (24%). Notwithstanding these differences, the prevalence of the syndrome in the Adriatic island populations is substantially high and qualitatively similar to the rates observed in the Mexican Americans and the Native Americans of the United States. These observations indicate that industrialized societies are not exclusively at risk; rather, metabolic syndrome has become a global phenomenon across societies and communities irrespective of their socio-economic status and ethnicity. At this time, precise estimates of metabolic syndrome in the Croatian population from the mainland are not available. However, as also emphasized in the report of Kolčić et al.[18], among the cardiovascular risk factors in the general Croatian population, prevalence of high blood pressure and obesity are high[20], which underscore the urgent need for thorough and rigorous investigations of cardiovascular disease related traits in the populations of the entire region.

While a uniform definition of the metabolic syndrome is deemed necessary, it is clear that the contribution of the individual traits to the syndrome could vary across populations rendering a single definition impractical. In the population of Hvar, the comparatively poorer correlations of HDL cholesterol and fasting glucose with the other components suggest that not all individual traits contribute equally towards the co-occurrence of their morbid conditions and partially explain why the prevalence of the syndrome could vary by the definition employed. In Hvar, if metabolic syndrome were estimated using the WHO definition, which explicitly includes some measure of impaired glucose tolerance or insulin resistance, the prevalence would substantially decrease (to ~3%). This leads to a question with respect to the risks associated with metabolic syndrome. Is metabolic syndrome a uniform determinant of both type 2 diabetes and cardiovascular disease; or, conversely, is it a determinant of one or the other or both in specific populations? While our current data is inadequate to answer these questions, it might be prudent to suggest that based on the incidence of individual traits in a population, the definition of the syndrome would need modification to portray the realistic prevalence and associated risks.

It has been reported that that a »Mediterranean-style diet« significantly reduces the rate of all-cause mortality and metabolic syndrome in Europeans[31,32]. Therefore, it is intriguing that in spite of adherence to a relatively traditional life-style pattern together with a »Mediterranean diet« and rural habitat, the prevalence of the syndrome among the islanders of Hvar is considerably high and comparable to that observed in the industrialized societies. However, there is need for comprehensive studies to assess changes in life style and dietary patterns among the islanders in recent times[29]. We have previously reported differences in nutritional habits between the mainland and coastal Croatian populations, the latter including those of the islands[19,20]. The coastal populations consume significantly higher proportions of fish, olive oil, fresh and boiled vegetables, and 10 fold higher consumption of red wine compared to the mainland Croatians. While, as noted before, the prevalence of metabolic syndrome in the mainland populations has not yet been estimated, the high prevalence of the syndrome among the islanders is likely influenced by factors apart from the nutritional practices, health attitudes and behavior. Among these, genetic factors could potentially be important, which, however, need to be thoroughly explored.

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METABOLIČKI SINDROM OTOČKE POPULACIJE HRVATSKE ISTOČNOJADRANSKE OBALE

S A Ž E T A K

Metabolički sindrom kao skup rizičnih faktora kao što su pretilost, dislipidemija, netolerancija ugljikohidrata i hipertenzija, povezanih sa razvojem kardiovaskularnih bolesti te diabetesa tipa 2, postala je glavvni problem javnog zdrastva u razvijenim zemljama. No, podataka o prevalenciji metaboličkog sindroma među svjetskim populacijama, pogotovo neindustrijaliziranih društava je vrlo malo. U ovom radu iznjeti su podaci o prevalenciji metaboličkog sindroma na otočkoj populaciji hrvatske istočnojadranske obale. Populacija je izrazito homogena te obitava u relativnoj izolaciji i životnim stilom koji je skladu s tradicionalnim obrascima. Ispitanike čine 381 osoba koje nisu u srodstvu (136 muškaraca, 245 žena) sa otoka Hvara, u dobi od 19 godina naviše. Hvar je među najnastanjenijim otocima u Hrvatskoj te broji 11,459 stanovnika prema popisu iz 1991. Metabolički sindrom određivao se prema kriteriju National Cholesterol Education Program (NCEP), uz iznimke da su korišteni indeks tjelesne mase te omjer struk-kuk kao prediktori pretilosti. Ukupna učestalost metaboličkog sindroma podešena prema godinama je 26% (32% kod muškaraca i 24% kod žena) u slučaju kad je indeks tjelesne mase uzet kao mjera pretilosti. U slučaju omjera struk-kuk kao mjere pretilosti ukupna učestalost metaboličkog sindroma je 42% (57% kod muškaraca i 36% kod žena). Korelacije individualnih komponenti podešenih prema godinama i spolu pokazuju kako su, uz iznimku glukoze u plazmi po gladovanju, ostale komponente metaboličkog sindroma značajno povezane jedna s drugom, što ukazuje na komorbiditet. Usprkos života na relativno tradicionalan načina te »Mediteranske« prehrane i ruralnog okruženja, prevalencija metaboličkog sindroma je poprilično visoka na Hvaru. Vjerojatno je kako osim prehrambenih navika, neki drugi čimbenici koji bi mogli uključivati genetsku predodređenost, mogu potencijalno biti predispozicija za metabolički sindrom.