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Predictive Impact of Coronary Risk Factors in Southern Croatia: A Case Control Study

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A B S T R A C T

The aim of study was to compare the impact of coronary risk factors on the incidence of acute myocardial infarction (MI) between Croatia, Central and Eastern Europe, and the rest of the world. As a part of the large international INTERHEART case-control study of acute MI in 52 countries (15,152 cases and 14,820 controls) we have investigated the relationship between several known risk factors (smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors) and MI among patients without previously known coronary heart disease in Southern Croatia. The main identified MI risk factors in Southern Croatia were heavy smoking (>20 cig/day; OR 3.86; 95% CI 2.31–6.46), diabetes mellitus (OR 2.83; 95% CI 1.58–5.23), abnormal ratio of B-100 and A-1 apolipoproteins (OR 2.23; 95% CI 1.28–3.89), elevated waist to hip ratio (OR 1.96; 95% CI 1.21–3.18), and arterial hypertension (OR 1.68; 95% CI 1.15–2.45). Protective was moderate alcohol consumption (OR 0.63; 95% CI 0.40–0.99). The prevalence of major MI risk factors in Croatia is similar to that in the surrounding countries and in the world, accounting for over 90% of the population attributable risk. However, physical activity, dietary and psychosocial factors are seemingly less important in this country, while moderate alcohol consumption is more protective than regionally or globally.

Key words: *risk factors, myocardial infarction, Croatia, INTERHEART, family medicine*

Introduction

In the past 30 years or so cardiovascular disease (CVD) morbidity and mortality in developed countries has visibly decreased and now is apparently stagnant, while in developing and transitional countries it is steadily increasing. These countries, such as Croatia, are considered to be in third stage of epidemiological transition, having 35–65% of total mortality attributable to CVD, predominantly due to coronary heart disease (CHD) and stroke[1]. The CVD epidemic in transitional countries is following the increasing rates of hypertension, obesity, smoking, diabetes and sedentary lifestyle[1]. Among the CVD components the most important is CHD[2]. Between 1971 and 2000 the share of CVD mortality in Croatia increased from 37.9% to 53.2%[3]. The main diagnoses were CHD (35.0%) and stroke (31.4%)[3]. In order to improve the population levels of coronary risk, instead of sophisticated technology, invasive procedures and expensive medications, a lot of education, human understanding, persuasion, and common sense is desperately needed, which can be delivered only in personalized family practice. Globally, it is estimated that nine potentially modifiable risk factors contribute to more than 90% of myocardial infarctions (MI)[4,5]. Approximately 80–90% of patients with symptomatic CHD, and more than 95% patients who died from CHD, had at least one of the four traditional risk factors (smoking, hypertension, dyslipidemia, and diabetes)[6,7]. Little research has been done to quantify the relationship between the prevalence of CHD risk factors and MI in Croatia. According to the available data, the most prevalent coronary risk factor in Southern

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Croatia is arterial hypertension, followed by physical inactivity, smoking, obesity, and inadequate dietary habits; there is seemingly no noticeable difference in risk factors' distribution between the Croatian provinces[8,9]. In order to gain more relevant evidence and to compare our results with other countries in the region and worldwide we eagerly participated in INTERHEART, a case-control study designed to examine the relationship between several CHD risk factors and MI[4,5,10–12].

Materials and Methods

The setting of our study was Coronary Care Unit, Split University Hospital Center, which is the second largest hospital in Croatia and a tertiary health center for Southern Croatia. It covers an area of more than 500,000 people. We took part in the INTERHEART study from February 1999 to November 2003, representing Croatia, while other countries from the region of Central and Eastern Europe were Greece, Hungary, Poland, Czech Republic, and Russia[4,12]. According to INTERHEART publication policy here we present data for Southern Croatia, compared to those from the rest of Central and Eastern Europe region. Cases were all eligible patients with first MI aged over 18 years, admitted to the Coronary Care Unit with characteristic symptoms, ECG and laboratory changes indicative of a new MI[4]. Within one month of admission, at least one control subject was recruited and matched to every MI case by age (±5 years) and sex. Eligible controls were community-based (e.g. unrelated visitors of the MI patient) or hospital-based (e.g. check-up visit, minor surgery). Structured questionnaires were administered and physical examinations undertaken in the same manner in cases and controls. Information about demographic factors, lifestyle (smoking, physical activity, and dietary patterns), personal and family history of cardiovascular disease, risk factors (hypertension, diabetes mellitus), and psychosocial factors (depression, permanent stress) was obtained[4,12]. Height, weight, waist and hip circumferences were determined by a standardized protocol. Only self-reported history of hypertension and diabetes was used in this analysis. Non-fasting blood samples (20 ml) were drawn from every individual. It was centrifuged within 2 h, and frozen immediately at –20°C or –70°C. Samples were shipped in nitrogen vapor tanks by courier to a blood storage site (Hamilton, Canada) and analyzed. Current smokers were defined as individuals smoking any tobacco in the previous 12 months and included those who had quit within the past year. Former smokers were defined as those who had quit more than a year earlier. Waist-to-hip ratio was calculated as the waist circumference divided by the hip circumference. Cutoffs for waist-to-hip ratio tertiles were 0.90 and 0.95 in men and 0.83 and 0.90 in women. Body mass index (BMI) was calculated as body weight divided by squared body height. Cutoffs used for BMI tertiles were 20 kg/m^2 and 25 kg/m^2. Cutoffs for ApoB/ApoA1 tertiles were derived from all controls. Individuals were judged to be physically active if they were regularly involved in moderate (walking, cycling, or gardening) or strenuous exercise (jogging, football, and vigorous swimming) for 4 h or more a week. Regular alcohol intake was defined as consumption three or more times per week, and only daily consumption of both fruits and vegetables was considered protective. After matching of pairs, the results were presented in frequency tables, and frequency differences were assessed by Pearson's χ^2-test. Continuous variables were presented as means with standard deviations and compared using the t-test. The findings presented are for models fitted with unconditional logistic regression, adjusted for the matching criteria. When data were categorized by tertiles, used were the mentioned cutoff points. Estimates of odds ratios and accompanying 95% confidence intervals were presented for every risk factor. Statistical analyses were done in Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Canada.

Results

During the study period in Split were enrolled 263 cases and 264 controls, while in the whole region there were 1727 cases and 1927 controls (15,152 cases and 14,820 controls across the globe). The median age of cases with first MI in Southern Croatia was about 6 years lower in men than in women (58.2±12.2 years vs. 64.5±10.8 years; t=3.75; p<0.001). Similar was the median age of males in whole region; they were some 7.5 years younger than women (58.9±11.8 vs. 66.4±11.3 years; t=12.5; p<0.001). Croatian male MI patients were three times more prevalent than female (74.6% *vs.* 25.4%) while this proportion was just two times higher in whole region (67.9% *vs.* 32.1%; χ^2=8.38; p=0.004). Table 1 shows the distribution of participants by gender and prevalence of risk factors. The frequency of Croatian female cases was significantly less than in the region (by 30.6%; 25.4% *vs.* 33.3%; χ^2=6.21; p=0.013). Among the Croatian MI cases a higher prevalence of former (22.1% *vs.* 20%; χ^2=0.57; p=0.452) and current smokers (45.4% *vs.* 44.2%; χ^2=0.12; P=0.734) was noted, with less non-smokers (32.5% *vs.* 35.8%; χ^2=0.97; p=0.324). Ever smoking (67.5%) was also higher in Croatia, accounting

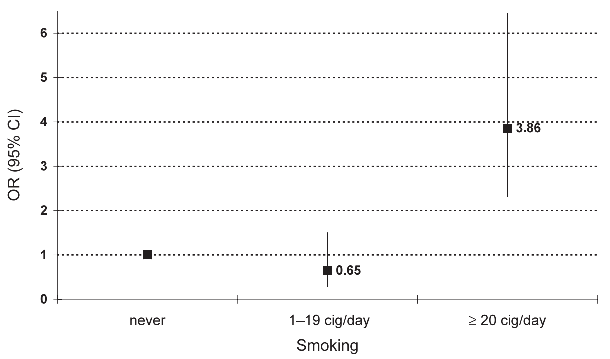

Fig. 1. Increasing risk of myocardial infarction in Southern Croatia based on smoking status. OR – odds ratio; cig/day – smoked cigarettes per *day.*

TABLE 1
CHARACTERISTICS OF CROATIAN SUBJECTS INCLUDED IN THE STUDY, COMPARED TO THOSE IN FIVE COUNTRIES FROM THE REGION OF CENTRAL AND EASTERN EUROPE

	Croatia		Rest of the region	
	Cases	Controls	Cases	Controls
Characteristic	Percentage (%) of the examinees			
Males	74.6	75.5	67.7	61.6
Former smokers	22.1	27.3	20.0	22.5
Current smokers	45.4	28.8	44.2	29.4
Heavy smokers	41.8	20.8	30.2	16.1
Diabetes mellitus	17.3	6.82	15.0	7.47
Arterial hypertension	46.1	37.1	49.2	34.1
BMI (3. tertile)	48.4	52.5	45.2	41.0
ApoB/ApoA-1 (3. tertile)	52.3	43.1	45.9	31.9
WHR (3. tertile)	59.4	40.9	47.4	41.0
Depression	19.2	21.7	16.4	15.0
Permanent stress	9.02	8.17	6.59	5.36
Alcohol consumption	73.3	79.5	22.5	24.3
Fruit and vegetables (daily)	45.9	49.2	27.4	35.2
Physical activity	30.4	31.1	19.6	23.7

BMI – body mass index; ApoB/ApoA-1 – apolipoprotein B-100 *vs.* apolipoprotein A-1 ratio; WHR – waist to hip ratio

for 75% higher MI risk than non-smoking (Table 2). Current smoking was liable for 2.5 times higher risk in comparison to non-smoking, while quitting decreased the risk to levels similar to non-smoking (Figures 1 and 2). Heavy smoking (≥20 cigarettes/day) was the most important single risk factor in Southern Croatia, increasing MI risk four times. Although diabetes mellitus accounted for only 17.3% of Croatian cases, it was nevertheless by 15.3% more prevalent than in the region (17.3% *vs.* 15%; χ^2=0.83; p=0.364), and it increased the MI risk three times compared to controls. About half of the Croatian cases had self-reported hypertension, which was marginally less than in the region (46.1% *vs.* 49.2%; χ^2=0.85; p=0.358), increasing the MI risk by two thirds (Table 2). The prevalence Croatian overweight cases (BMI>25 kg/m^2) was 7.08% higher than in the region (48.4% *vs.* 45.2%; χ^2=0.83; p=0.362), while normal BMI distribution was almost equal (32.5% *vs.* 32.7%; χ^2=0.83; p=0.362). MI risk did not differ significantly between the BMI tertiles (Table 2). In Southern Croatia there were 25.3% more cases with abdominal obesity (WHR 3rd tertile 59.4% *vs.* 47.4%; χ^2=11.98; p<0.001), and 30% less cases in the 2nd tertile of WHR distribution (23.3% *vs.* 30.3%; χ^2=10.11; p=0.002), than in the region. As shown in Figure 3, abdominal obesity (WHR >0.95 for males, >0.9 for females) doubled the MI risk in comparison to lean persons (cf. Table 2 as well). Unfavorable ApoB/ApoA1 ratio increased the risk of MI more than two times (Figure 4). Significantly less Croatian cases (by 69.5%) were in the first tertile of ApoB/Apo-A1 distribution than in the region (13.1% *vs.* 22.2%; χ^2=9.22; p=0.002), while higher prevalence in the other two tertiles was marginal: higher

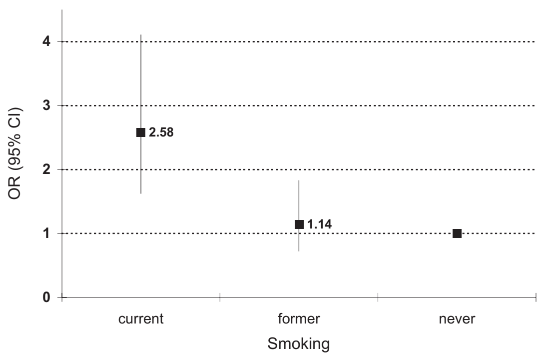

Fig. 2. Decreasing risk of myocardial infarction in Southern Croatia based on abstinence from smoking.

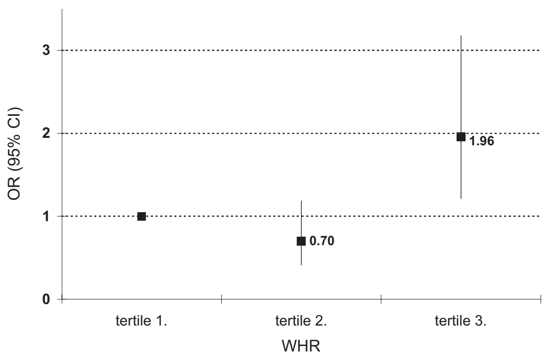

Fig. 3. Increasing risk of myocardial infarction in Southern Croatia based on WHR. WHR – waist to hip ratio.

TABLE 2
RISK FACTORS FOR MYOCARDIAL INFARCTION AMONG 263 HOSPITALIZED CASES IN SPLIT

Risk factor	OR	95% CI	p†
Heavy smoking (≥20 cig/day *vs.* never)	3.86	2.31–6.46	<0.0001
Current smoking (*vs.* never)	2.58	1.62–4.11	<0.0001
Ever smoking (*vs.* never)	1.74	1.17–2.59	0.0056
Diabetes mellitus	2.87	1.58–5.23	0.0006
BMI (2nd *vs.* 1st tertile)	1.04	0.61–1.76	0.8861
BMI (3rd *vs.* 1st tertile)	0.93	0.57–1.51	0.7710
WHR (2nd *vs.* 1st tertile)	0.70	0.42–1.19	0.1882
WHR (3rd *vs.* 1st tertile)	1.96	1.21–3.18	0.0065
ApoB/ApoA1 (2nd *vs.*1st tertile)	1.67	0.94–2.97	0.0816
ApoB/ApoA1 (3rd *vs.* 1st tertile)	2.23	1.28–3.89	0.0046
Arterial hypertension	1.68	1.15–2.45	0.0071
Depression	0.83	1.31–0.53	0.4246
Permanent psychosocial stress	0.92	1.94–0.44	0.8286
Alcohol consumption	0.63	0.40–0.99	0.0437
Fruits and vegetables (daily)	0.92	1.94–0.44	0.8287

OR – odds ratio
CI – confidence interval; cig/day – smoked cigarettes *per* day
BMI – body mass index; ApoB/ApoA-1 – apolipoprotein B-100 vs. apolipoprotein A-1 ratio; WHR – waist to hip ratio
†Logistic regression

by 8.78% in the second (34.7% *vs.* 31.9%; χ^2=0.65; p=0.420), and by 13.9% in the third (52.3% *vs.* 45.9%; χ^2=2.89; p=0.089). Moderate and strenuous physical activity did not improve the coronary risk in Southern Croatia despite a markedly higher proportion of such cases than in the region (by 55.1%; 30.4% vs. 19.6; χ^2=14.78; p<0.001). Alcohol consumption deflated the MI risk by one third (Table 2). Three times higher regular consumption of alcohol among Croatians than in the region (73.3% *vs.* 22.5%; χ^2=259.48; p<0.001) did not induce a proportional reduction in MI incidence. Daily intake of fruits and vegetables was much higher in Croatia as well (by 67.5%; 45.9% *vs.* 27.4%; χ^2=34.17; p<0.001), but did not exert noticeable risk reduction (OR 0.93; 95% CI

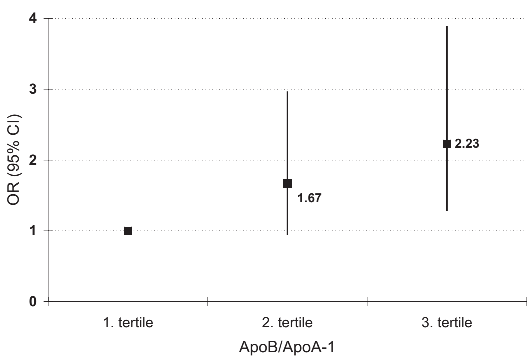

Fig. 4. Increasing risk of myocardial infarction in Southern Croatia based on ApoB/ApoA1 ratio. ApoB – apolipoprotein B-100; ApoA-1 – apolipoprotein A-1.

0.48–1.80; p=0.835). One fifth of the Croatian cases reported some depression, which was by 17.1% higher than in region (19.2% *vs.* 16.4%; χ^2=0.16; p=0.692). Permanent exposure to psychosocial stress did not increase appreciably the MI risk either (Table 2), although it was higher than in the region (9.02% *vs.* 6.59%; χ^2=0.01; p=0.954).

Discussion and Conclusion

Our study has shown that the most important risk factor for MI in Southern Croatia is heavy smoking (≥20 cigarettes/day), followed by current and former smoking.

Next on the list went diabetes mellitus, atherogenic dyslipidemia (high B-100/A-1 apolipoprotein ratio), arterial hypertension and abdominal obesity (WHR >0.95), while BMI did not contribute significantly to CHD events. Moderate alcohol consumption was slightly protective, while beneficial influences of physical activity and ingestion of fruits and vegetables were only marginal. This study is subject to several limitations. First, a case-control design is potentially open to confounding if there is differential ascertainment of risk factors between cases and controls. We have minimized this factor using standardized methods for data collection in both cases and controls. Second, whereas some of the risk factors were ascertained or measured with high accuracy, others were based on history only, and therefore ascertained with some inclusion error. Third, our sample was relatively small, particularly concerning the female gender. All traditional risk factors were significantly associated with the development of MI ($p<0.01$), while tutelary elements, including moderate alcohol consumption ($p<0.05$) were not so strong. However, protective behavior, including abstinence from tobacco, regular exercise, moderate alcohol intake and habitual ingestion of fruits and vegetables reduced the average MI risk by some 80%[4]. These data are similar to those obtained in the region and worldwide as well: most of MI risk could be delineated with nine simple, measurable risk factors[4,12]. Women in Southern Croatia experienced their first MI about 6 years later than men, this delay in the region was 7.5 years and globally 9 years[10]. Female/male ratio was however lower in Croatia than in the region (1/3 *vs.* 2/3). Why Croatian women are more resistant to the occurrence of MI than their counterparts in the region, and nevertheless more prone to its earlier manifestation remains currently unclear. Ever smoking was the most prevalent risk factor (67.5%) among MI cases. We have shown that there is no safe level of smoking; even quitting exerts some residual risk (OR 1.15). That residual excess sharply fell 1–3 years after smoking cessation but remained visible for a long period[11]. Heavy smokers had four-fold elevated risk (OR 3.86), and the odds of MI increased by some 5.6% for every additional cigarette smoked per day; the risk could reach nine-fold levels in those smoking ≥40 cigarettes *per* day[11]. Globally there were much less female (9.25%), than male smokers (33%), and the effect of current smoking was much larger in younger (OR 3.53) than in older individuals (OR 2.55; $p<0.0001$ for interaction); especially in younger heavy smokers, as we have shown previously[13,14]. These results underscore the notion that the first, and most cost-effective measure in primordial and primary prevention of CHD is to avoid smoking.

The presence of diabetes mellitus increased MI risk nearly three-fold. It is estimated that good control of diabetes could decrease population attributable risk (PAR) for MI by one tenth (PAR for Central and Eastern Europe was 9.1%, and globally 9.9%)[4]. Since its worldwide increase is anticipated, especially in developing countries, it is particularly important to keep at bay concomitant risk factors due to their high prevalence in diabetics[15,16]. Arterial hypertension is among the leading MI risk factors across populations and regions. It was responsible for one fourth of PAR in the region of Central and Eastern Europe (PAR 24.5%), while globally it contributed less (PAR 9.9%) for unclear reasons[4]. In Croatia it is, after abdominal obesity, the most prevalent risk factor (46.1% among cases), as in the rest of region (49.2%). Adequate detection, life-style modifications and straightforward drug therapy are nowadays achievable even in low-income countries[17], so that motivation and health-care delivery problems actually overwhelm the financial issues. Linearity of risk increment with dyslipidemia (increase in LDL measured as Apo B-100, and decrease in HDL measured as Apo A1) shown in Croatia is constant globally, confirming the highly predictive value of Apo B-100/Apo A1 ratio[4,12,18].

Nearly half of the Croatian MI cases had abdominal obesity (WHR >0.9 for females, >0.95 for males, in 59.4%) or elevated body mass (BMI>25 kg/m^2 in 48.4%); in any sense the prevalence of overweight was higher in this country than in the region. Corpulence is becoming the most important factor in MI risk continuum: BMI increase by 4.15 kg/m^2 augments the risk by 10%; a 12.1 cm gain in waist circumference enhances the risk by 19%, while WHR increment for mere 0.085 raise the risk by 37%[19]. Abdominal obesity is liable for one third of the global PAR (33.7%), with similar results for Central and Eastern Europe (PAR 28.0%); it is ten times more dangerous than BMI>30 kg/m^2 (PAR 2.8%)[19]! In developed countries abdominal obesity is more threatening nowadays than smoking[19]. Psychosocial factors, including depression and permanent stress exposure, did not contribute significantly to global MI risk neither in Southern Croatia nor in the region, presumably due to the fact that in transitional countries all the population is under particular stress, making the difference between cases and controls negligible. Worldwide these factors may explain up to one third of PAR[5]! Alcohol consumption is highly prevalent in Southern Croatia, and was the only protective factor identified in this sample (OR 0.63). The overall PAR without alcohol in the INTERHEART model was 89.7%; adding moderate alcohol consumption it decreased by less than 1% because of wide variations in alcohol intake and substantial overlap in contributions from other risk factors[4]. While the relationship between alcohol and coronary atherosclerosis is still controversial, current advice about its use should be individually customized, depending on local, social, cultural, and religious background. It seems that protective daily consumption must not exceed 15–20 g[20]. Healthy lifestyle markedly reduces the probability of MI: when united, non-smoking, exercise, daily consumption of fruits and vegetables, and moderate alcohol intake may decrease PAR in the region by 49.6%, and by 54.6% worldwide. In other words, simple general measures may halve the coronary risk. Daily consumption of fruits and vegetables with regular exercise conferred an OR of 0.60. Furthermore, avoiding tobacco, OR would decrease to 0.21, suggesting that modification of these aspects of lifestyle could reduce the individual MI risk well below 25%[4].

It may be concluded that we know exactly what the major causes of CHD are: cigarette smoking, overweight and obesity, dyslipidemia, arterial hypertension and diabetes. These risk factors are generally preventable through smoking abstinence or cessation, and appropriate attention to diet, exercise, and avoidance of weight gain and obesity. Indeed, there is extensive evidence that the gains against CHD mortality observed in many countries from 1970 to 2000 were overwhelmingly due to improvements in population levels of risk factors rather than to invasive procedures and new medications. Unfortunately, the recent EUROASPIRE III results show that smoking prevalence among CHD patients although slightly decreasing is stabilized around 20%, that over 60% of them are hypertensive, and that the prevalence of obesity and diabetes is alarmingly rising[21]. Which is the role of general practitioner in this situation? Family medicine has a unique opportunity for behavioral modification at the individual and public health level, using peculiar opportunities of role modeling and personal skills of communication and education[22]. For instance, weight gain has many behavioral components that are not easily addressed by medical therapy alone. The same is true for smoking[23]. It is the person that has to take his/her share of responsibility for his own health and wellbeing, supported by the family doctor. In this perspective we foresee the solution for the actually stagnant or worsening circumstances in preventive cardiology.

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PREDIKTIVNI UTJECAJ KORONARNIH ČIMBENIKA RIZIKA U JUŽNOJ HRVATSKOJ: ISTRAŽIVANJE PAROVA (CASE-CONTROL STUDIJA)

SAŽETAK

Cilj ovog istraživanja bila je usporedba utjecaja koronarnih čimbenika rizika na incidenciju akutnog infarkta miokarda (MI) u Hrvatskoj, središnjoj i istočnoj Europi i svijetu. U sklopu velike međunarodne case-control studije INTERHEART koja se bavi akutnim MI u 52 zemlje (15152 slučaja i 14820 kontrola) istražili smo odnos između više poznatih čimbenika rizika (pušenje, postojeća hipertenzija ili dijabetes, omjer struk/kukovi, obrasci ishrane, tjelesna aktivnost, konzumiranje alkohola, apolipoproteini u krvi i psihosocijalni čimbenici) i MI u pacijenata bez ranije dijagnosticiranog srčanog oboljenja u južnoj Hrvatskoj. Utvrđeni vodeći čimbenici rizika za MI u južnoj Hrvatskoj bili su intenzivno pušenje (≥20 cigareta dnevno; OR 3,86; 95% CI 2,31–6,46), diabetes mellitus (OR 2,83; 95% CI 1,58–5,23), abnormalni omjer B-100 i A-1 apolipoproteina (OR 2,23; 95% CI 1,28–3,89), povišeni omjer struk/kukovi (OR 1,96; 95% CI 1,21–3,18), i arterijska hipertenzija (OR 1.68; 95% CI 1,15–2,45). Umjereno konzumiranje alkohola bilo je zaštitni čimbenik (OR 0,63; 95% CI 0,40–0,99). Prevalencija vodećih čimbenika rizika za MI u Hrvatskoj slična je onoj u susjednim zemljama i drugim zemljama u svijetu i čini preko 90% atributivnog rizika populacije. Tjelesna aktivnost, ishrana i psihosocijalni čimbenici naizgled su manje bitni u ovoj zemlji, dok umjereno konzumiranje alkohola predstavlja značajniji zaštitni čimbenik nego što je to slučaj na regionalnoj ili globalnoj razini.