Conventional Risk Factors and Acute Coronary Syndrome during a Period of Socioeconomic Transition: Population-based Case-control Study in Tirana, Albania

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Aim To assess the association between conventional risk factors and acute coronary syndrome in Albania, a transitional country in Southeast Europe.

Methods A population-based case-control study was conducted in Tirana in 2003-2006. A total of 467 consecutive patients with nonfatal acute coronary syndrome were recruited. There were 370 men with mean ± standard deviation (SD) age of 59.1 ± 8.7 years and 97 women with mean±SD age of 63.3 ± 7.1 years. The control group comprised a population-representative sample of Tirana residents. In the control group, there were 469 men with mean±SD age of 53.1 ± 10.4 years and 268 women aged 54.0 ± 10.9 years. A structured questionnaire on demographic, socioeconomic, psychosocial factors, and health behaviors was administered. Physical measurements included anthropometrics and blood pressure. Venous blood and adipose tissue aspirations from the gluteal region were frozen-stored for future analysis. Multivariable-adjusted logistic regression was used to assess the independent associations of conventional risk factors with acute coronary syndrome.

Results Upon adjustment for covariates, family history of coronary heart disease was found to be a strong predictor of acute coronary syndrome in both men (odds ratio [OR], 3.70; 95% confidence interval [CI], 2.58-5.30) and women (OR, 4.53; 2.40-8.57). Waist-to-hip ratio in men (OR, 4.03; 2.83-5.73) and obesity in women (OR, 3.31; 1.54-7.14) were strongly associated with acute coronary syndrome. In men, but not in women, there was a significant association with hypertension and current smoking ($P = 0.011$ and $P<0.001$, respectively). Diabetes was not significantly independently associated in either sex.

Conclusion Classical risk factors predicted coronary heart disease in Albania, similarly as in the rest of the world, although associations with family history and anthropometric indices were stronger. These findings are resulting largely from the heterogeneous adoption of lifestyles conducive to increased coronary risk in transitional countries, and they point to the urgent need for targeted public health interventions.

The relationship between coronary heart disease and risk factors such as smoking, high blood pressure, diabetes, obesity, and distribution of body fat is well established in developed countries (1-4). However, data on conventional risk factors, their patterns, determinants, and associations with coronary heart disease are scarce for the transitional countries of South East Europe. Unique among former communist countries in Southeast Europe, Albania was under Stalinist communist regime, and following the breakdown of this rigid government in 1990, it experienced a major social, cultural, and economic upheaval (5). Over the past 15 years changes in life-style (diet, tobacco, alcohol consumption, and physical exercise) have taken place, particularly in urban settings (6-8). The available evidence suggests an increase in alcohol intake, particularly among men (6). Smoking appears to have increased too, although smuggling makes it very difficult to validly estimate cigarette consumption in Albania (7). In 2001, the lifetime prevalence of smoking in Tirana was 61% in men and 24% in women (8). Furthermore, in 2001, 49% of men and 58% of women in Tirana reported largely sedentary leisure time activities such as reading and watching television (9). Although there is little information about cardiovascular disease occurrence in Albania, available data suggest that cardiovascular disease mortality may have increased over the past few years (10,11), and that cardiovascular disease morbidity (based on hospital admission counts) in both Tirana and the whole country has been increasing continually in the last decade (10).

In this context, we undertook a population-based case-control study of coronary heart disease in Tirana between June 2003 and January 2006. Here, we report on the association of selected conventional risk factors such as smoking, anthropometric indices, hypertension, diabetes, and family history of coronary heart disease with acute coronary syndrome.

Methods

Study population

Cases. Acute coronary syndrome includes Q-wave and non-Q-wave acute myocardial infarction, and unstable angina (12,13). The definition of myocardial infarction and/or unstable angina in our study was based on: 1) electrocardiogram (ECG) findings; 2) patients' clinical signs and symptoms; 3) echocardiography as a complementary examination for assessment of disorders of segmental kinesis and left ventricular function, and 4) elevated cardiac enzymes. The latter procedure was performed only in selected patients because it is not a routine test at the University Hospital Center in Tirana.

The operational definition of unstable angina in our study was as follows: a) clinical presentation: 1) a crescendo pattern in frequency, duration and/or intensity of ischemic episodes, or 2) angina occurring at rest, without provocation, or 3) new onset of angina described as severe in patients without previous symptoms of coronary heart disease; b) ECG changes: 1) ST depressions (horizontal or down-slopping at least 1 mm from the J point) in at least two consecutive leads, and/or 2) symmetrical inverted T-waves (≥2mm) in the same leads. In patients classified as unstable angina cases, in the following days after the onset of unstable angina, ECG returned to normality and echocardiography did not reveal wall motion abnormalities.

The operational definition of non-Q-wave myocardial infarction in our study included the following: a) clinical presentation: prolonged crushing chest pain usually lasting more than 30 minutes with more severe and wider radiation than angina and not being relieved by sublingual nitroglycerine; b) ECG changes: same as unstable angina; c) cardiac enzymes: elevated levels of CK-MB measured within 12 hours from the onset of pain; d) echocardiography: abnormal wall motion (hypokinesis, akinesis, or dyskinesis).

The operational definition of Q-wave myocardial infarction in our study included the following: a) clinical presentation, cardiac enzymes and echocardiography: the same as non-Q-wave myocardial infarction; b) ECG changes: ST elevation progressing to pathologic Q-waves (>25% of the R-amplitude in the same lead and/or Q-width >0.04 ms in at least two consecutive leads) (14).

The inclusion criteria for cases in our study were the following: consecutive patients, male or female, aged 35-74 years, residents of the municipality of Tirana, with a diagnosis of acute coronary syndrome (either a first or repeated event), admitted to the University Hospital Center within 48 hours of symptom onset. A total of 467 non-fatal acute coronary syndrome eligible cases were recruited. Mean age ± standard deviation (SD) of male patients was 59.1 ± 8.7 years, and of female patients, 63.3 ± 7.1 years. During the period of recruitment there were 66 additional acute coronary syndrome cases from the city of Tirana who either refused to participate (n = 46), or were advised to do so by their physicians (overall response rate: 467/533 = 87.6%).

Controls. The control group consisted of a population-based sample of Tirana residents. The sampling frame consisted of the entire population of the municipality of Tirana, as registered in the Albanian census of April 2001. This population was, therefore, considered representative of the source population that generated the acute coronary syndrome cases. Based on a population list received from the National Institute of Statistics, we drew an age-and sex-stratified sample of the adult population (1200 individuals: 720 men and 480 women aged 35-74 years). Age-stratification consisted of four groups: 35-44, 45-54, 55-64, and 65-74 years. Each age-group of men had 180 individuals and each group of women had 120 individuals.

Of the 1200 controls targeted for recruitment, 135 were found ineligible: 11 were dead, 14 had self-reported past myocardial infarction, 12 women were pregnant or had delivered in the past 6 months, 17 were bed-bound, 28 emigrated before the start of the study, and 53 had moved from Tirana to other cities in Albania before the start of the study.

Of 1065 eligible controls (655 men and 410 women), 689 individuals fully participated in the study, with a response rate of 64.7% (689/1065). There were 452 men with mean age ± standard deviation (SD) of 52.5 ± 10.2 years and 237 women with mean age±SD of 52.6 ± 10.6 years. Further 48 individuals (17 men, 31 women) underwent a partial interview but refused to be examined giving an overall response rate of 69.2% (737/1065).

Sample size calculation. Calculations of the sample size were made by use of PEPI, version 4 (15) for a number of behavioral and psychosocial hypotheses. The significance level (two-tailed) was taken as 5%, and the power was set at 80%. Based on the most conservative calculations and a control to case ratio of 1.5, the required minimal number of cases and controls to be recruited was 400 and 600, respectively.

Data collection

The examination and interview included a structured questionnaire which included socio-demographic factors, behavioral/life-style factors, self-reported conditions that are risk factors for coronary heart disease and psychosocial factors, measurement of anthropometrics and blood pressure in the control group, and subcutaneous adipose tissue aspirations from the gluteal region to assess fatty acid composition. Venous blood drawn from acute coronary syndrome patients within 3 hours of admission to the emergency department (on average) and fasting blood samples (collected in the controls) were banked at -80°C for future analysis.

Participants who reported that they smoked cigarettes regularly or occasionally were grouped in the analysis as current smokers. Participants

were also asked for life-time smoking. Definitions of hypertension and diabetes were based on a positive response to the question: "Has a doctor ever told you that you have high blood pressure/diabetes?" Family history of coronary heart disease was assessed by a series of questions recording the history of coronary heart disease among participants' family members (mother, father, and siblings). In the analyses, family history of coronary heart disease was treated as a dichotomous variable (none vs at least one family member with a positive history of coronary heart disease).

Weight was measured on a calibrated beam balance (with the precision of 100 g). Measurement was performed in light clothing and without shoes. Height was measured using a tape attached to the wall; subjects were barefoot (with the precision of 1 mm). Measurements of height and weight were equally done in cases and controls by the same examiners using the same scales and tape measure. Body mass index was calculated as weight/height^2 (kg/m^2). Waist circumference was measured at the height of the umbilicus with the subject standing. Hip circumference was measured at the widest point of the buttock or trochanters. Waist-to-hip ratio was individually calculated and dichotomized in the analysis as follows: ≤0.95 vs >0.95 in men and ≤0.86 (median in controls) vs >0.86 in women. We did not use the accepted cutoff point of 0.80 in women, because of its limited discriminatory power in our female population (91% of controls and 96% of cases had waist-to-hip ratio >0.85).

The study was approved by the Albanian Committee of Medical Ethics in June 2003. All participants who agreed to take part in the study gave written consent after being informed about the aims and procedures of the study, as well as the risks involved with blood drawing and/or adipose tissue aspiration.

Statistical analysis

We excluded from the analysis 54 of the 737 control respondents who had preexisting coronary heart disease.

The General Linear Model was used to compare the mean values of numerical variables between acute coronary syndrome cases and controls, separately in men and women. Binary logistic regression was used to assess the unconditional associations of covariates with acute coronary syndrome, separately in men and women. Age-adjusted odds ratios (OR) with 95% confidence intervals (CI) and *P* values were calculated. A *P* value of ≤0.05 was considered as statistically significant. Subsequently, all covariates were entered into the logistic models and removed in a backward stepwise procedure if their *P* value exceeded 0.10. Multivariable-adjusted odds ratios and 95% confidence intervals and *P* values were calculated. The Hosmer-Lemeshow test was used to assess goodness-of-fit; all analyses fitted the criterion (16). All statistical analyses were done with Statistical Package for the Social Sciences, version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

Socio-demographic and risk factor characteristics of Tirana residents admitted with first or repeated acute coronary syndrome events and population-representative controls are presented in Table 1. In 35-74 years control group, current smoking was more frequent in men than women (34% vs 14%), and men were more obese than women (body mass index ≥30 kg/m^2: 18% vs 13%). The prevalence of reported diabetes was similar between the sexes (7% in men and 9% in women) as was the prevalence of self-reported hypertension (15% and 19%). A family history of coronary heart disease was relatively frequent in this population (26% in men and 33% in women. Cases were considerably older than controls (mean age ±SD in men was 59.1±8.7 years vs

51.4±9.7 years, respectively (P<0.001), whereas in women it was 63.3±7.1 years vs 51.7±10.2 years, respectively, P<0.001). In age-adjusted comparisons (Tables 1 and 2), acute coronary syndrome patients had higher body mass index (mean±SD in men was 27.2±3.7 vs 26.6±3.5, respectively, P=0.006, whereas in women it was 27.9±3.8 vs 25.6±3.9, P<0.001) and were more likely to be obese (P=0.113 in men, and P=0.012 in women). Both sexes showed a stepwise association of acute coronary syndrome with body mass index classified as normal, overweight, and obese. However, in women the association was stronger (P=0.001 in women and P=0.145 in men), with odds ratio for obesity in women reaching 4.48 (95% CI, 1.96-10.24), as opposed to 1.57 (95% CI, 1.00-2.47) in men (P for interaction: 0.062). Patients had a higher prevalence of male pattern abdominal obesity (waist-to-hip ratio >0.95 in men and >0.86 in women), more so in men (OR, 3.57; 95% CI, 2.58-4.92) than women (OR, 1.93; 95% CI, 1.09-3.43) (P for interaction 0.025). Self-reported hypertension, smoking, and diabetes were more prevalent in patients than controls, and were of similar magnitude between the sexes. There was evidence of

Table 1. Characteristics of Tirana residents admitted with first or repeated events of acute coronary syndrome (ACS) and population-representative controls without ACS

	Men (n=785)			Women (n=317)		
Variable	cases (n=370)	controls (n=415)	P*	cases (n=97)	controls (n=220)	P*
Age (years, mean±SD)	59.05±8.70	51.44±9.73	<0.001	63.27±7.11†	51.68±10.23	<0.001
Body mass index (kg/m^2, mean±SD)	27.23±3.66	26.60±3.47	0.006	27.86±3.84	25.56±3.88	<0.001
Body mass index ≥30 (kg/m^2)†	19.5	17.6	0.113	25.0	12.7	0.012
Waist-to-hip ratio (mean±SD)	0.97±0.06	0.94±0.04	<0.001	0.88±0.05	0.86±0.04	0.002
Waist-to-hip ratio above cut off‡	56.8	24.9	<0.001	59 (61.5%)	110 (50.0%)	0.026
Hypertension	26.4	15.0	0.067	41.2	18.7	0.100
Diabetes	15.2	6.7	0.018	18.6	8.6	0.064
Family history of coronary heart disease§	51.9	26.2	<0.001	57.7	33.0	<0.001
Current smoking	49.9	34.3	<0.001	17.7	13.7	0.189

*Age-adjusted P values. For numerical variables age adjustment was done by use of the General Linear Model, whereas for categorical variables binary logistic regression was employed.
†Percentages of individuals by variable category.
‡Cut-off point for waist-to-hip ratio: ≤0.95 in men, and ≤0.86 (median in controls) in women.
§At least one parent or sibling.

Table 2. Association of selected risk factors with acute coronary syndrome, age-adjusted odds ratios (OR) and 95% confidence intervals (CI) from binary logistic regression

	Men				Women			
Variable	n	OR	95% CI	P*	n	OR	95% CI	P*
Body mass index	784	1.06	1.02-1.11	0.006	316	1.17	1.08-1.26	<0.001
Body mass index:				0.145 (2)				0.001 (2)
<25	230	1.00	Reference	–	130	1.00	reference	–
25-29.9	409	1.23	0.87-1.75	0.243	134	2.74	1.41-5.31	0.003
≥30	145	1.57	1.00-2.47	0.051	52	4.48	1.96-10.24	<0.001
Waist-to-hip ratio:†								
below cut off	471	1.00	Reference	–	147	1.00	reference	0.026
above cut off	313	3.57	2.58-4.92	<0.001	169	1.93	1.09-3.43	
Hypertension:								
no	623	1.00	Reference	–	235	1.00	reference	–
yes	159	1.44	0.98-2.13	0.067	81	1.65	0.91-3.00	0.100
Diabetes:								
no	691	1.00	Reference	–	280	1.00	reference	–
yes	83	1.88	1.11-3.16	0.018	37	2.14	0.96-4.79	0.064
Family history of coronary heart disease:								
no	478	1.00	Reference	–	183	1.00	reference	–
yes	298	3.52	2.53-4.91	<0.001	126	3.93	2.14-7.23	<0.001
Current smoking:								
no	457	1.00	Reference	–	268	1.00	reference	–
yes	326	2.07	1.51-2.83	<0.001	47	1.70	0.77-3.74	0.189

*Overall P value and degrees of freedom (in parenthesis).
†Cut off point for waist-to-hip ratio: ≤0.95 in men, and ≤0.86 (median in controls) in women.

Table 3. Association of selected risk factors with acute coronary syndrome, multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) from binary logistic regression

	Men (n = 767)			Women (n = 307)		
Variable	OR	95% CI	*P**	OR	95% CI	*P**
Age	1.09	1.07-1.11	<0.001	1.16	1.11-1.20	<0.001
Body mass index ≥30				3.31	1.54-7.14	0.002
Waist-to-hip above cut off†	4.03	2.83-5.73	<0.001			
Hypertension	1.76	1.14-2.72	0.011			
Diabetes						
Family history of coronary heart disease	3.70	2.58-5.30	<0.001	4.53	2.40-8.57	<0.001
Current smoking	2.15	1.52-3.06	<0.001			
Nagelkerke R^2	0.381			0.435		

*In both sexes, all the variables presented in the table were included in a backward stepwise elimination procedure with a *P* value to exit set at >0.10. Empty cells refer to the variables excluded from the logistic models in men and women, respectively.
†Cut off point for waist-to-hip ratio: ≤0.95 in men and ≤0.86 (median in controls) in women.

a strong relationship between family history of coronary heart disease and acute coronary syndrome in both sexes: OR, 3.52 for men (95% CI; 2.53-4.91) and OR, 3.93 for women (95% CI, 2.14-7.23).

Upon adjustment for all covariates in a backward stepwise procedure, family history of coronary heart disease remained a particularly strong predictor of acute coronary syndrome in both sexes: OR, 3.70; 95% CI, 2.58-5.30 in men and OR, 4.53; 95% CI, 2.40-8.57 in women (Table 3). The relationship with waist-to-hip ratio persisted in men (OR, 4.03; 95% CI, 2.83-5.73), whereas in women the relationship with overall obesity remained evident (OR, 3.31; 95% CI, 1.54-7.14). In men, but not in women, significant associations persisted for hypertension and current smoking (OR, 1.76; 95% CI, 1.14-2.72 and OR, 2.15; 95% CI, 1.52-3.06, respectively).

Discussion

The main findings of our study were the strong association of acute coronary syndrome with family history of coronary heart disease in both sexes, strong association with the waist-to-hip ratio in men, association with obesity in women, and similar associations with smoking, diabetes, and hypertension in both sexes.

The relationship between family history of coronary heart disease and acute coronary syndrome found in our study was stronger than that reported in an earlier hospital-based case-control study in Tirana, which included patients with a first event of non-fatal myocardial infarction and controls recruited from patients admitted to the departments of Orthopedics and Ear, Nose, and Throat (17). There was evidence of a positive association of family history of coronary heart disease with myocardial infarction, albeit less strong than in our study. It should be noted that the definition of family history of coronary heart disease in this earlier study included only parental history of coronary heart disease, whereas in our analysis it was defined as a positive history of at least one family member, either parent or sibling. Parental history of coronary heart disease has been established as an important life course risk factor for coronary heart disease (18) which appears to be partly mediated through behavioral factors such as smoking, diet, and alcohol consumption and partly through genetic factors (19). Although the possibility of differential reporting on family history of coronary heart disease between cases and controls in our study as an explanation for the strong association cannot be discounted, the fairly high prevalence in the controls and the similarity in rates of parental history among the controls of the two studies (17% vs 19% in men and 22% vs 21% in women) argues against underestimation of family history in the control population.

In our study, there was evidence of positive associations with overall obesity, particular-

ly in women, and abdominal obesity, particularly in men. Overweight, obesity, and distribution of body fat have been shown to have important consequences for coronary heart disease morbidity and mortality (20) and are strongly associated with numerous coronary heart disease risk factors, such as elevated levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, blood pressure, C-reactive protein, and insulin resistance, as well as with lower levels of high-density lipoprotein cholesterol, an important protective factor for coronary heart disease (20). Rates of obesity and overweight are increasing in transitional countries of Southeast Europe (6), including Albania (21). A cross-sectional study conducted in Tirana in 2001 (21) with 1120 adults, aged 25 years and over, reported a higher overall prevalence of obesity (22% in men and 31% in women) than in the current study. It is possible that there might have been an overestimation of obesity in the 2001 survey due to potential selection bias, as participants included in that survey were invited to be examined primarily for problems related to obesity and diabetes. Nevertheless, overweight and obesity pose a serious public health concern in Albania in view of the rapid changes in lifestyle with processed foods increasingly replacing traditional foods (5,6).

In our study, diabetes was associated with an excess risk in both sexes, although it was not retained in multivariable-adjusted models. The prevalence of diabetes has rapidly increased in Albania since 1980. Thus, a study which included 162706 Tirana residents aged 20-69 years, reported a prevalence rate of diabetes of approximately 1% between 1976 and 1980 (22), whereas in 2001 it reported an overall prevalence rate of 6.3% (22). Therefore, as elsewhere, the increase in the prevalence of diabetes, consequent to increased obesity and reduced energy expenditure, is another issue of concern in Albania and bears important health policy implications, similar to the situation in other populations undergoing rapid transition and social change (23).

Hypertension was another predictor of acute coronary syndrome in our study, particularly in men. It is well-documented that hypertension is an important risk factor for coronary heart disease and this has been confirmed by the Global Burden of Disease Study update for 2000 (24). Therefore, the rapid pace of transition and its inherent association with hypertension (25) bear important implications for both health care and health promotion sectors in Albania.

In our study, current smoking status was associated with an excess risk of acute coronary syndrome events in both sexes, but in men it is associated with a greater population burden due to the relatively low prevalence of smoking among Albanian women, as seen in our control group. The lifetime prevalence of smoking in our study was 49% (95% CI, 44-53%) in men and 26% (95% CI, 20-32%) in women, which is comparable with a prior study conducted in Tirana in 2001 which reported rates of 61% and 24%, respectively (8). Standardized death rates for lung cancer among Albanian men appear to be higher than in the European Union (6), suggesting a higher prevalence of smoking. Tobacco consumption has increased in the last few years in Albania (6,8). The increasing rate of smoking in Albania indicates that tobacco will make a substantial contribution to premature morbidity and mortality in the future (6,26). Furthermore, smoking has been blamed for the premature deaths of one in five Albanian males under 70 years. A particular concern is the increasing prevalence rate of smoking in young and middle-aged men (6,26). Therefore, given the increasing smoking rates especially among males, there is an urgent need to implement effective tobacco control legislation in Albania.

The limitation of our population-based case-control study is lying in the participation rates. Although we obtained a satisfactory response rate among cases (88%), the rate in the controls was

65%-69%, allowing for the possibility of selection bias, a recognized weakness of case-control studies. Information bias (in particular, differential misclassification) between cases and controls is unlikely to occur for the anthropometric variables because they were measured identically in both groups. However, data obtained by interview could be affected by case status.

In conclusion, our findings point to the role of the conventional risk factors in the genesis of coronary heart disease in Albania, the most isolated former communist country in the Southeast Europe. The relationship of acute coronary syndrome with anthropometric measures, smoking, hypertension, and diabetes in both men and women in our study indicates that, generally, these classical risk factors operate in transitional countries of Southeast Europe similarly as elsewhere. However, the increasing rates of engagement in unhealthy behaviors such as smoking, sedentary lifestyle, excessive alcohol consumption, and unhealthy diet are not homogenous in the adult populations of such transitional countries as Albania (6,8,9). Therefore, greater heterogeneity in the adopting of a "modern" lifestyle may lead to larger within-population differences in risk factor distributions that may serve to strengthen the relationship of the conventional risk factors with coronary heart disease, as seen for the anthropometric variables.

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