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Psychosocial Stress and Risk of Myocardial Infarction: A Case-Control Study in Belgrade (Serbia)

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Background: The purpose of this study was to investigate which psychosocial risk factors show the strongest association with occurrence of myocardial infarction (MI) in the population of Belgrade in peacetime, after the big political changes in Serbia.

Methods: A case-control study was conducted involving 154 consecutive newly diagnosed patients with MI, and 308 controls matched by gender, age, and place of residence.

Results: According to conditional logistic regression analysis, after adjustment for conventional coronary risk factors, the odds ratios (95% confidence intervals) for work-related stressful events, financial stress, deaths and diseases, and general stress were 3.78 (1.83-7.81), 3.80 (1.96-7.38), 1.69 (1.03-2.78), and 3.54 (2.01-6.22), respectively. Among individual stressful life events, the following were independently related to MI: death of a close family member, 2.21 (1.01-4.84); death of a close friend, 42.20 (3.70-481.29); major financial problems, 8.94 (1.83-43.63); minor financial problems, 4.74 (2.02-11.14); changes in working hours, 4.99 (1.64-15.22); and changes in working conditions, 30.94 (5.43-176.31).

Conclusions: During this political transition period , stress at work, financial stress, and stress in general as they impacted the population of Belgrade, Serbia were strongly associated with occurence of MI.

Key Words: Case-control study • Myocardial infarction • Psychosocial stress

INTRODUCTION

There is growing evidence from many epidemiological and clinical studies that psychosocial factors contribute independently to the risk of coronary heart diseases (CHD) even after statistical control for the effects of classic cardiovascular risk factors.[1,2] Chronic psychosocial stressors, such as stress at work and in family life, lack of social support, negative emotions, including depression and hostility, the burden of family care-giving, and low socioeconomic status have been shown to be independent factors predictive of CHD.[3] Psychosocial risk factors do not occur in isolation from one another; they show a tendency to cluster in the same individuals and groups, such as those with low socioeconomic status.[4] Stress may affect CHD directly through neuroendocrine and platelet activation, or indirectly through higher frequency of adverse health behaviors such as smoking, poor diet, and sedentary lifestyle, which increase the risk of CHD.[5]

Acute psychological stress also is associated with increased risk for CHD, and it has been reported that intense grief in the days after death of a significant person may trigger the onset of myocardial infarction (MI).[6] The pathophysiological mechanism of acute emotional stress remains unclear, but it is assumed to be related to

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hemodynamic stress in the coronary arteries and rupture of an atherosclerotic plaque, with consequent thrombosis.[7]

Cardiovascular diseases (CVDs) are the leading cause of death in the Serbian population, and in 2010 they accounted for 54.7% of all causes of death.[8] In addition, during the past two decades, Serbia has experienced significant political and economic changes which may have affected the health of the population and the occurence of CVDs.

The role of psychosocial risk factors in occurence of MI in the Serbian population was investigated in an earlier study,[9] but that study covered the period 1998-2000, when Serbia was being bombarded by NATO forces (1999), and when the country faced the political and economic problems conected with the civil war in the early 1990s. That study found that patients who reported that a son or other family member had been mobilized in the military before the onset of illness had 138 times the risk of acute myocardial infarction (AMI), and patients who had been mobilized themselves had 84 times the risk.[9]

Another Serbian study investigated mortality trends from MI in the population of Belgrade from 1990-2010. That study found an increase in mortality from MI in both genders until the mid-1990s, and then a significant decrease in the subsequent period.[10] Despite that, CVDs, including cerebrovascular and ischemic heart diseases, are still the leading cause of death in the country. After events such as the civil war, NATO bombardment, and hyperinflation, people were faced with other kinds of stressful life events.

Therefore, the aim of this study was to investigate which possible psychosocial risk factor shows the strongest association with the occurence of MI in the Belgrade population in peacetime, after termination of big political changes in Serbia. The hypothesis was that these factors were similar to those seen in other populations, and that work-related stressful events and financial problems would be the most important.

MATERIALS AND METHODS

A case-control study was conducted from January 2006 to October 2009, involving 154 consecutive patients newly diagnosed with MI and hospitalized in the coronary care unit at the Clinic of Cardiovascular Diseases, Belgrade. Diagnoses were made by cardiologists and involved typical chest pain symptoms plus either elevations in cardiac enzyme concentrations or diagnostic changes as measured by an electrocardiogram according to criteria of the World Health Organization (WHO).[11] Cases were excluded from the study if they had a personal history of MI or a chronic illness that could affect risk factors for CVD (malignant tumors, systemic connective tissue diseases) or were physically or mentally unable to answer questions. For each patient, two controls were selected from among those treated during the same period for rheumatic and gastrointestinal diseases and light injuries at either the Institute of Rheumatology, the Institute of Gastroenterology, or the Clinic of Orthopedics in Belgrade. The first two patients who met matching criteria were chosen as controls. Cases and controls were individually matched by gender, age (± 2 years), and place of residence. Although no major differences have been seen between the genders in event exposure, women have a broadly higher risk for most or all categories of stressful life events and are at greater risk for a subset of events.[12]

Two physicians used a questionnaire to interview patients face-to-face during the first five days after their diagnosis with disease. We used a standard questionnaire for life events.[13,14] Cases and controls were interviewed about stressful life events during the previous 12 months. They were asked whether they experienced any of the listed life events as stressful ("have you, during 12 month before the present disease, experienced any of the following life events as stressful?"). Interviewers were instructed to ask the questions strictly as they were written and to record the months when stressful life events occured.

Stressful life events were analysed in two ways: as individual life events and, because the majority of stressful events were rare, as grouped life events. Questions regarding education were excluded from analysis because our study sample consisted of middle-aged and elderly participants, none of whom reported stressful life events regarding education. In addition, only two participants reported criminality problems and we did not code them as a separate category but they were included it in the general stress category. Work stress and

financial stress are very common in the Serbian population, and each was coded as a separate category. Because family relationships are very strong in the Serbian population family, social and marital stress were coded as family stress, as were pregnancy, childbirth, migration, and cohabitation. Death and diseases were separated into a distinct category because we consider them to be extreme negative stressors (child's death, spouse's death, death of close family member, death of close friend, hospitalization of a family member because of serious illnes, serious disease od participant). Coders were blind to case vs. control status.

Beside stressful life events, patients were interviewed about the presence of classical cardiovascular risk factors, such as current smoking, drinking alcohol, sedentary occupational physical activity, obesity, hypertension, diabetes, hyperlipidemia, and family history of cadiovascular disease.

Degree of obesity was estimated based on body mass index (BMI) and waist to hip ratio (WHR). According to WHO classifications, subjects with BMI $\geq$ 30.00 were obese.[15] Data on participants' personal histories were obtained from medical documentation. Current smokers were defined as those who had smoked at least one cigarette per day during the previous 12 months. Subjects who had a sedentary job or were unemployed were classified as group with sedentary occupational physical activity. A sedentary job was defined as one that involved sitting, with walking and standing for two hours or less out of an eight-hour day and lifting of no more than 5 kg.

Laboratory data were obtained from medical records. Hyperlipidemia was identified if a subject was on hypolipidemic medication or had a serum total cholesterol level of 5.2 mmol/L or greater. During the study period, in Belgrade, every patient hospitalized, regardless of department, had blood tests and cholesterol levels taken routinely. All institutions where research was conducted are teaching units of the Clinical Centre of Serbia and have the same methods for laboratory testing. Hypertension and diabetes mellitus were identified if subjects were undergoing treatment for these diseases, not by testing upon admission or during hospitalization. The Ethics Committee of the University of Belgrade Medical Faculty approved the study, and oral informed consent was obtained from all participants before participating in the study.

Continuous variables were described as means $\pm$ standard deviation (SD), and categorical variables were presented by counts and percentages. In data analysis, Cox proportional hazard regression model was used for unadjusted and multivariable analysis. All variables significantly associated with MI by unadjusted analysis at a level of $p \leq 0.10$ were included in multivariable analysis. Conditional logistic regression models were used to estimate the odds ratios (ORs) and to test for trend. The two-sample t test was used to compare the average numbers of stressful events between cases and control groups. All p-values are based on two-tailed tests, and $p < 0.05$ was considered as significant. Statistical analysis was performed using SPSS software version 15.0 (SPSS, Inc., Chicago, Illinois, USA).

RESULTS

Table 1 shows the characteristics of MI cases and controls. Cases and controls were matched by age and gender. Education, marital status, and WHR did not differ significantly between the two groups. Presence of diabetes, hypertension, and hyperlipidemia in personal history and cardiovascular disease in family history were significantly higher in cases than in controls. Smoking, alcohol consumption, BMI, and sedentary occupational physical activity also were significantly more frequent in cases than in controls.

Table 2 shows the ORs of primary, nonfatal MI in relation to psychosocial stress after adjustments for traditional coronary risk factors. Compared to controls, cases more frequently reported general stress, stress at work, financial problems, and deaths and diseases during the past 12 months. Cases reported work-related stressful events at a rate almost three times higher than did controls (24% vs. 7%, respectively), and cases reported financial stress at four times the rate of controls (29% vs. 7%, respectively). Family-related stressful events did not differ significantly between the two groups.

As Table 3 shows, when stressful life events were analyzed separately, according to multivariate conditional logistic regression analysis, MI was significantly associated with the death of a close family member, death of close friend, major and minor financial prob-

Table 1. Characteristics of myocardial infarction cases and controls

Characteristics	Cases (n = 154) mean ± SD or no. (%)	Controls (n = 308) mean ± SD or no. (%)	p value*
Age (years)	57.5 ± 10.9	57.7 ± 11.0	matched
Gender (women)	38 (24.7)	76 (24.7)	matched
Education > 12 years	54 (35.1)	92 (29.9)	0.27
Occupation			0.96
Farmers	5 (3.2)	5 (1.6)	
Mannual workers	46 (29.9)	96 (31.2)	
Lower administrators and professionals	29 (18.8)	68 (22.1)	
Higher administrators and professionals	69 (44.8)	124 (40.3)	
Unemployed	5 (3.2)	15 (4.9)	
Marital status (married)	119 (77.3)	244 (79.2)	0.60
Current smoking habit	91 (59.1)	105 (34.1)	< 0.001
Current alcohol drinking	74 (48.0)	107 (34.7)	0.005
Sedentary occupational physical activity	76 (49.3)	112 (36.4)	0.007
Leisure time activity	70 (45.5)	144 (46.8)	0.80
BMI ≥ 30 kg/m^2	43 (27.9)	54 (17.5)	0.008
WHR	0.94 ± 0.08	0.93 ± 0.07	0.51
Hyperlipidemia	60 (39.0)	60 (19.5)	< 0.001
Hypertension	85 (55.2)	107 (34.7)	< 0.001
Diabetes	29 (18.8)	26 (8.4)	0.002
Family history of cardiovascular disease	99 (64.3)	160 (51.9)	0.01

BMI, body mass index; SD, standard deviation; WHR, waist to hip ratio.
* According to unadjusted logistic regression analysis.

Table 2. Psychosocial stress in myocardial infarction cases and controls according to multivariable conditional logistic regression analysis

Groups of stressful events	Cases (n = 154) no. (%)	Controls (n = 308) no. (%)	Adjusted OR* (95%CI)	p value#
Deaths and diseases	55 (35.7)	70 (22.7)	1.69 (1.03-2.78)	0.04
Family related stressful events	18 (11.7)	50 (16.2)	0.77 (0.40-1.48)	0.43
Work related stressful events	37 (24.0)	28 (9.1)	3.78 (1.83-7.81)	< 0.001
Financial problems	45 (29.2)	22 (7.1)	3.80 (1.96-7.38)	< 0.001
General stress	120 (77.9)	161 (52.3)	3.54 (2.01-6.22)	< 0.001

OR, odds ratio; 95% CI, 95% confidence interval.
* ORs were adjusted for current smoking, alcohol drinking, sedentary occupational physical activity, BMI, hypertension, diabetes, hyperlipidemia, and family history of cadiovascular disease. # According to multivariable conditional regression analysis.

lems, change of working hours (prolonged working-hours or change in working-hours schedule), and change in working conditions (new boss, new department, reorganisation of work activities).

The risk of MI increased with the number of stressful life events (p for trend < 0.001) and was highest in those who had four or more events (OR = 6.2). The average number of stressful life events was significantly greater in patients than in controls (1.29 vs. 0.68, *t*-test = 6.56, p < 0.001) (Table 4).

DISCUSSION

In the population of Belgrade during peacetime, stressful life events associated with the occurence of MI were similar to those events seen in other populations. Because of problems related to the post-civil war transi-

Table 3. Individual stressful life events as risk factors for myocardial infarction according to multivariable conditional logistic regression analysis

Individual stressful events	Cases (n = 154) no. (%)	Controls (n = 308) no. (%)	Adjusted OR* (95% CI)	p value[#]
Death of close family member	26 (16.9)	30 (9.7)	2.21 (1.01-4.84)	0.05
Death of close friend	12 (7.8)	1 (0.3)	42.20 (3.70-481.29)	0.003
Major financial problems	16 (10.4)	4 (1.3)	8.94 (1.83-43.63)	0.007
Minor financial problems	30 (19.5)	17 (5.5)	4.74 (2.02-11.14)	< 0.001
Change of working-hours[†]	16 (10.4)	8 (2.6)	4.99 (1.64-15.22)	0.005
Change of working conditions[‡]	12 (7.8)	3 (1.9)	30.94 (5.43-176.31)	< 0.001

OR, odds ratio; 95% CI, 95% confidence interval.

* ORs were adjusted for current smoking, alcohol drinking, sedentary occupational physical activity, BMI, hypertension, diabetes, hyperlipidemia, and family history of cardiovascular disease. [#] According to multivariable conditional regression analysis.

[†] Prolonged working-hours and change in working-hours schedule. [‡] New boss, new department, reorganisation of work activities.

Table 4. Number of individual stressful life events in patients and controls

Stressful event	Cases (n = 154) no. (%)	Controls (n = 308) no. (%)	OR (95%CI)
0	34 (22.1)	147 (47.7)	1
1	71 (46.1)	122 (39.6)	1.30 (0.88-1.93)
2-3	43 (27.9)	37 (12.0)	2.84 (1.74-4.64)
4 or more	6 (3.9)	2 (0.7)	6.20 (1.24-31.10)

OR, odds ratio; 95% CI, 95% confidence interval.

tion, stress at work and financial problems were found to be most strongly associated with MI. Cases also reported deaths and/or diseases more frequently than did controls in the year preceding the MI.

Many studies have investigated the relationship between CVDs and adverse working conditions (physical workload, noise, long working hours, shift work) and social job characteristics (occupational position).[16-19] Stress at work has been associated with an increased risk of CHD,[16,17] but this relationship has not been found in all studies.[18] According to the meta-analyses of seven cohort studies, the risk of coronary artery diseases was highest among participants who reported job stress and unhealthy lifestyles.[20] The INTERHEART study found a positive correlation between stress at work and MI.[21] According to a Danish cohort study, high psychological demands at work were found to be a risk factor for CHD.[22] A Japanese study reported that MI patients worked significantly longer hours per week prior to their disease in comparison to healthy workers.[23] According to this study, AMI patients who reported acute stressful events at work during the month prior to AMI were 6.88 times more likely to believe that job stress/overwork caused their AMI after controlling for working hours per week and age. Persons with longer working hours were more likely to be exposed to high job demands and to have less time for recreational leisure time activities.[24] However, a group of experts in Australia, after reviewing the evidence relating to major psychosocial risk factors, concluded that there was no strong, consistent evidence for a causal association between work-related stressors (job control, demands, and strain) and CHD.[18] In our study, a change in working hours (actually prolonged-working hours and modification of working-hours schedule) and a change in working conditions (new boss, new department, reorganisation of work activities) had the largest impact on the occurrence of MI.

In Serbia, many companies, govermment and administrative bodies now have Western working hours, from 9 AM to 5 PM, instead of the previous working hours of from 7 or 8 AM to 3 or 4 PM.[25] In addition, working after regular hours is commonplace. A process of Westernization was initiated in the 1990s, which now has resulted in changes to the work environment and work schedules, higher job demands, and changes in the relationships between workers and their superiors.

Financial stress also has been associated with risk of MI. In a study by Shah et al.,[26] financial stress was shown to affect long-term outcomes after the onset of MI, such as general and disease-specific health status, hospital readmission, and all-cause mortality. According to the INTERHEART study, severe financial stress was more frequent in cases than in controls, with a population-attributable risk of 11%.[21] In addition, major and

minor financial problems were associated with occurrence of MI, independently of other variables. In the present study, both major and minor financial problems were significantly related to MI, independent of other risk factors.

Besides stress at work and financial problems, the present study found that deaths and/or diseases of anyone close or associated with the subjects to be associated with MI. Grief over the death of a significant person has been associated with an acutely increased risk of MI in the days after such an event occurs, the greatest being in the first 24 hours and progressively declining over time.[6] In addition, increased risk of AMI has been reported in parents who lost a child, but only after six years of follow-up.[27] There is evidence that grief is associated with a proinflammatory state. Cankaya et al.[28] found that women with a history of sudden, unexpected loss of a friend or loved one had higher levels of the proinflammatory cytokine IL-6 and lower levels of anti-inflammatory IGF-1 compared with those who did not report such events. This proinflammatory state is considered related to the instability of atherosclerotic plaque and subsequent MI. In the present study, risk for MI was increased in those who had lost a close family member or close friend. Apparently, it seems that death of a close friend has an even higher risk occurrence of MI than death of a close family member. When we analyzed deaths of close family members, most participants in both groups reported the death of a parent. Our study focused on an adult population, one in which the death of parents is a typical life course transition.[29] In contrast, the death of a close friend reminds subjects of their own mortality, and when that death comes earlier than expected in the lifecycle, it is an even more profound shock.[30] From 2003-2012, Serbia experienced a 2.4% increase in overall mortality due to higher mortality from non-communicable diseases.[31] The highest mortality increase was associated with malignant diseases (17.2%), diabetes (17.1%), and obstructive lung diseases (15.0%). Compared to all European sub-regions, Serbia had a major increase of premature mortality from neoplasms and diabetes mellitus.[32]

Stress at home, including major intra-family conflicts, divorce, and violence, also can be associated with occurrence of MI.[21,33] However, in the present study, family-related stressful events did not show a significant correlation with occurrence of MI. One reason may be that we did not separate possitive events, such as childbirth and weddings, from negative events, such as divorce, and stress caused by deaths and diseases which are also related to stress at home.

The risk of acute MI was correlated with the number of stressful life events that subjects had experienced. In the present study, the average number of stressful life events was higher in cases than in controls, suggesting the significance of stress duration. Some investigators have analyzed the effect of accumulated stressful life events on the development of MI but have not found an association.[34,35]

The present study had several limitations, including the possibility that recall bias was present. Data were collected retrospectively, so the quality of this information was determined to a large extent by the patients' abilities to recall past exposures accurately. A substantial duration of time may be involved between the occurrence of an event and its recall, and when that period is long, reliability for total scores and individual events drops precipitously.[36] Studies have shown that many more events are reported longitudinally than retrospectively. Raphael et al. investigated the occurrence of life events by conducting 10 monthly interviews, using an event category checklist, with persons with temporomandibular pain disorder.[37] Participants reported retrospectively and in detail about life events over the previous month, and only one-quarter of the event categories appeared in both monthly interviews and in retrospective reports for the same period.

A greater limitation might be that recall of past events differed between cases and controls. Reporting bias might affect the study, as life-threatening events influence responses. Collecting data from MI patients during the first five days after diagnosis might affect responses due to their emotional state in these life threatening situations. However, even though responses to life-threatening events may be negative psychological reactions, such as fear, anxiety, depression, and post-traumatic stress disorder, they also may result in positive changes, reflecting resilience or post-traumatic growth and which can contribute to well-being and adaptation to illness.[38]

People are inclined to relate occurrence of disease to stressful events, especially if it is generally accepted

that stress could be related to the disease. At the same time, there is no possibile way to check with veracity an individual's personal reaction to some events. In addition, there is the possibility that CVD might cause stressful life events in several ways; for example, underlying CVD in the months before MI could cause financial problems because of decreased capacity to work, or patients may feel depressed because CVD forced them to give up activities they enjoy.[39] Psychopathological response to the disease is highly variable and depends on personal characteristics and the patient's psychosocial environment. Additionally, we did not collect data on depression, which could be associated with MI and which could have led subjects to cite more critical life events.

Another potential limitation is that patients in the control group were not from the general population. Instead, they were selected from other clinics, including rheumatology, gastroenterology, and orthopedics. They also may have had specific diseases and psychosocial stresses (probably related to their diseases). Although a population-based control group would have been a better solution, a hospital-based control group is easier to recruit and derives from the same population as the MI patients. In addition, selecting patients from clinics can eliminate the effect of stress due to hospital admission, because this stress will be present in both groups.[40]

Another potential limitation is that our case-control study was matched in age, gender, and place of residence, but not for other risk factors such as diabetes mellitus, hypertension, and hypercholesterolemia where a propensity-score match could solve this problem. There has been increasing interest in methods based on propensity score in order to reduce or eliminate the effects of confounding factors when using observational data. In our study, we used multivariate conditional logistic regression to control for the effects of confounding factors.[41] In a matched case-control study investigating risk factors of congenital hypothyroidism, Rezaeian et al. used and compared two statistical models, a multiple conditional logistic regression model and propensity score analyses, to control for confounding factors and to obtain the net effects of each variable.[42] The overall statistical power of the two methods was nearly the same, and the results of both methods were nearly similar, with no statistically significant difference. Given this observation, we suspect that using propensity-score analysis would not have changed the results of our study significantly.

Lastly, the precision of OR estimates was low (broad confidence limits, especially for individual stressful life events, particularly for the death of a close friend and change of working conditions), indicating the need for a study with a larger number of participants. In addition, reliability and validity of the Paykel Stressful Life Event questionnaire were not tested in the Serbian population.

CONCLUSIONS

In peacetime in Serbia, after the country has completed a transition through substantial political changes, stress at work, financial stress, and stress in general are strongly associated with occurence of MI.

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REFERENCES

1. Rozanski A, Blumenthal JA, Davidson KW, et al. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol* 2005;45:637-51.
2. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol* 2008;51:1237-46.
3. Von Känel R. Psychological distress and cardiovascular risk: what are the links? *J Am Coll Cardiol* 2008;52:2163-5.
4. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2007;28:2375-414.
5. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999; 99:2192-217.
6. Mostofsky E, Maclure M, Sherwood JB, et al. Risk of acute myo-

cardial infarction after the death of a significant Person in one's life. *Circulation* 2012;125:491-6.
7. Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. *J Am Coll Cardiol* 1994;23:809-13.
8. Institute of Public Health of Serbia. "Dr Milan Jovanovic Batut". Health statistical yearbook of republic of Serbia 2010. Belgrade: Institute of Public Health of Serbia; 2011.
9. Deljanin Z, Rancic N, Tiodorović B, et al. Association of stressful life events with acute myocardial infarction in population in the city of Nis within the period from 1998-2000. *Vojnosanit Pregl* 2007;64:463-8.
10. Vujcic IS, Sipetic SB, Dubljanin ES, Vlajinac HD. Trends in mortality rates from coronary heart disease in Belgrade (Serbia) during the period 1990-2010: a joinpoint regression analysis. *BMC Cardiovasc Disord* 2013;13:112.
11. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, et al. Myocardial infarction and coronary deaths in the World Health Organisation MONICA projects. Registration procedures, event rates, and case-fatality rates in 38 population from 21 countries in four continents. *Circulation* 1994;90:583-612.
12. Chatterjee R, Arora M. Life events and psychiatric disorders. *Mental Health Reviews 2005*, Accessed from http://www.psyplexus.com/mhr/.html
13. Paykel ES, Prusoff BA, Uhlenhuth EH. Scaling of life events. *Arch Gen Psychiatry* 1971;25:340-7.
14. Paykel ES. Methodological aspects of life events research. *J Psychosom Res* 1983;27:341-52.
15. World Health Organization (WHO). Obesity: preventing and managing the global epidemic: report of a WHO consultation. Geneva: World Health Organization; 2000.
16. Eller NH, Netterstrom B, Gyntelberg F, et al. Work-related psychosocial factors and the development of ischemic heart disease: a systematic review. *Cardiol Rev* 2009;17:83-97.
17. Kivimäki M, Nyberg ST, Batty GD, et al. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet* 2012;380:1491-7.
18. Bunker SJ, Colquhoun DM, Esler MD, et al. "Stress" and coronary heart disease: psychosocial risk factors. *Med J Aust* 2003;178:272-6.
19. Backe EM, Seidler A, Latza U, et al. The role of psychosocial stress at work for the development of cardiovascular diseases: a systematic review. *Int Arch Occup Environ Health* 2012;85:67-79.
20. Kivimäki M, Nyberg ST, Fransson EI, et al. Associations of job strain and lifestyle risk factors with risk of coronary artery disease: a meta-analysis of individual participant data. *CMAJ* 2013;185:763-9.
21. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:953-62.
22. Netterstrøm B, Kristensen TS, Sjøl A. Psychological job demands increase the risk of ischaemic heart disease: a 14-year cohort study of employed Danish men. *Eur J Cardiovasc Prev Rehabil* 2006;13:414-20.
23. Fukuoka Y, Dracup K, Froelicher ES, et al. Do Japanese workers who experience an acute myocardial infarction believe their prolonged working hours are a cause? *Int J Cardiol* 2005;100:29-35.
24. Virtanen M, Heikkilä K, Jokela M, et al. Long working hours and coronary heart disease: a systematic review and meta-analysis. *Am J Epidemiol* 2012;176:586-96.
25. Ognjanov G. Serbian Business Culture. In: Terterov M, Ed. Doing bussines with Serbia. 2nd ed. London: GMB Publishing Ltd, 2006: 31-7.
26. Shah SJ, Krumholz HM, Reid KJ, et al. Financial stress and outcomes after accute myocardial infarction. *PloS One* 2012;7:e47420.
27. Li J, Hansen D, Mortensen PB, Olsen J. Myocardial Infarction in parents who lost a child: a nationwide prospective cohort study in Denmark. *Circulation* 2002;106:1634-9.
28. Cankaya B, Chapman BP, Talbot NL, et al. History of sudden unexpected loss is associated with elevated interleukin-6 and decreased insulin-like growth factor-1 in women in an urban primary care setting. *Psychosom Med* 2009;71:914-9.
29. Marks NF, Jun H, Song J. Death of parents and adult psychological and physical well-being: a prospective U.S. National Study. *J Fam Issues* 2007;28:1611-38.
30. Witkin G. The Female Stress Survival Guide. 3rd ed. New York: Newmarket Press; 2000.
31. Institute of Public Health of Serbia. "Dr Milan Jovanovic Batut". Health statistical yearbook of republic of Serbia 2012. Belgrade: Institute of Public Health of Serbia; 2013.
32. Santric Milicevic M, Bjegovic V, Terzic Z, et al. Serbia within the European context: an analysis of premature mortality. *Popul Health Metr* 2009;7:12.
33. Tao XU, Wei LI, Teo K, et al. Association of psychological risk factors and acute myocardial infarction in China: the INTER-HEART China study. *Chin Med J* 2011;124:2083-8.
34. Kornerup H, Osler M, Boysen G, et al. Major life events increase the risk of stroke but not of myocardial infarction: results from the Copenhagen City Heart Study. *Eur J Cardiovasc Prev Rehabil* 2010;17:113-8.
35. Andersen I, Diderichsen F, Kornerup H, et al. Major life events and the risk of ischaemic heart disease: does accumulation increase the risk? *Int J Epidemiol* 2011;40:904-13.
36. Dohrenwend BP. Inventorying stressful life events as risk factors for psychopathology: toward resolution of the problem of intracategory variability. *Psychol Bull* 2006;132:477-95.
37. Raphael KG, Cloitre M, Dohrenwend BP. Problems of recall and misclassification with checklist methods of measuring stressful life events. *Health Psychol* 1991;10:62-74.
38. Groleau D, Whitley R, Lespérance F, Kirmayer LJ. Spiritual reconfigurations of self after a myocardial infarction: influence of culture and place. *Health Place* 2010;16:853-60.
39. Dragano N, Wege N. Supplement: detailed description of the relations between CVD and mental ill health. Website:

http://www.enwhp.org/fileadmin/downloads.
40. Gupta R, Kishore J, Bansal Y, et al. Relationship of psychosocial risk factors, certain personality traits and myocardial infarction in Indians: a case-control study. *Indian J Community Med* 2011; 36:182-6.
41. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399-424.
42. Rezaeian S, Poorolajal J, Moghimbegi A, Esmailnasab N. Risk factors of congenital hypothyroidism using propensity score: a matched case - control study. *J Res Health Sci* 2013;13:151-6.