

## Life Psychosocial Stresses and Coronary Artery Disease

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### ABSTRACT

**Background:** It is hypothesized that the impacts of life events accumulate and can trigger and promote atherosclerosis in susceptible individuals. In the current study, the correlation of total life stressors during 1 year was investigated relative to coronary artery disease (CAD).

**Methods:** The study population consisted of 148 males and 152 females aged 35–76 years. The subjects were classified as CAD cases and controls according to the results of coronary angiography. The severity of CAD was scored on the basis of the number and the extent of lesions at coronary arteries. The stressful events of life were assessed using Holmes-Rahe Questionnaire and was presented as total psychological stress scores per year (TPSS).

**Results:** The frequency of cigarette smoking, diabetes mellitus, and hypertension was more prevalent in CAD cases than control subjects. The levels of TPSS were increased in patients with CAD compared to the controls ( $160.3 \pm 71.3$  vs.  $139.8 \pm 66.5$ ,  $P = 0.020$ ). TPSS was also associated positively with the levels of uric acid, erythrocytes counts, erythrocyte sedimentation rate, aspirin consumption, and negatively with high-density lipoprotein-cholesterol and apo-AI. In logistic regression analysis, TPSS correlated with the occurrence of CAD by the odds ratio of 1.773 (1.073–2.930),  $P = 0.025$ , but the association was weakened after adjustment for classical risk factors, especially hypertension. TPSS exhibited significant association with the severity of CAD [ $F(3,274) = 2.6$ ,  $P = 0.051$ ].

**Conclusions:** The results suggest that TPSS are associated with the occurrence and severity of CAD significantly, but the association is not independent.

**Keywords:** Coronary artery disease, life events, psychosocial, stress

## INTRODUCTION

Coronary artery disease (CAD) is a multifactor disease with more than 250 various psychosocial, genetic,

nutritional, and metabolic risk factors.<sup>[1]</sup> Atherosclerosis is a chronic inflammatory process that begins several decades before its symptoms become clinically evident.<sup>[2]</sup> It is hypothesized that life acute and chronic psychological stresses in susceptible individuals, can trigger and promote atherosclerosis.<sup>[2]</sup>

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There is evidence that shows long-term life negative circumstances have a role in the pathogenesis of cardiovascular events. Abbasi *et al.*, in 6246 hospitalized subjects, found that patients with low socioeconomic status were at a higher risk of in-hospital mortality due to the acute coronary syndromes.<sup>[3]</sup> Subjects who had experienced adversity or traumas during childhood had increased the risk of subsequent cardiovascular events.<sup>[4]</sup> Women who had severe physical or sexual abuse also have higher risk for cardiovascular events.<sup>[4]</sup> Men with certain personality profiles such as Type A are more at risk for the development of cardiovascular disease.<sup>[5]</sup> Kawachi *et al.* studied the relationship of self-report Type A behavior and the incidence of CAD in 1300 community-dwelling men during 7 years.<sup>[6]</sup> Their results show that a high level of expressed anger predicts cardiovascular events. It has been reported that anger, both as an emotional state and as a personality trait, is significantly associated with the propensity to develop myocardial ischemia.<sup>[7]</sup> It has been shown that chest pain is more frequent in patients with Type D personality.<sup>[8]</sup>

The strain of chronic job is also associated with an increased risk of CVD.<sup>[9-11]</sup> A survey among 2355 workers in Japan revealed that working overtime (more than 50 h/week) has a significant association with sleep deprivation (<5 h/day) and high psychological stress.<sup>[9]</sup> A similar study among 1700 people in the USA showed that working overtime relative to fulltime and part-time working was characterized by higher job stress.<sup>[10]</sup>

The causal relationship has been studied between the psychosocial factors and risk development of hypertension in 3300 young adults in the USA for 14 years.<sup>[11]</sup> The results showed that time urgency/impatience and hostility but not achievement striving/competitiveness, depression, and anxiety were associated with the high risk of hypertension. Negative emotions, such as depression and anxiety after adjusting for potential covariates predicted significantly the incidence of CAD in 498 men over a 3-year follow-up period in Minnesota.<sup>[12]</sup>

Sesso *et al.* studied the correlation of symptomatic depression assessed by five different depression scales and the risk of CAD in 1300 men for 7 years.<sup>[13]</sup> Their results show that depression may be positively associated with the risk of CAD. York *et al.* investigated the relationship between the symptoms of depression and cardiovascular reactivity in 128 patients with CAD.<sup>[14]</sup> Their findings showed that patients with more depressive symptoms have lower cardiovascular reactivity. Fleet *et al.* reviewed the effect of panic disorder among patients consulting for chest pain.<sup>[15]</sup> They found that panic disorder is present in more than 30% of chest pain patients with or without CAD and suggested if it has not been recognized and left untreated, the risk for disease progression may be augmented. Kermott *et al.* assessed stress using a

“self-rated stress” (SRS) instrument in relation with coronary artery calcification in 325 patients undergoing a comprehensive health assessment.<sup>[16]</sup> Their findings show that SRS do not add predictive value beyond the classical risk factors calculated by Framingham equation.

Holmes-Rahe proposed the hypothesis that, stresses as created by life events were a cause of illness.<sup>[17]</sup> These researches developed the Social Readjustment Rating Scales (SRRS) and deduced life change units (LCUs).<sup>[18]</sup> The effects of various types of life psychosocial stressors are additive. Therefore, it is informative to study the additive impact of different psychological stressors for 1 year before the patients recruit for angiography. As our knowledge, there is not any data regarding total psychological stress scores (TPSS) value in normal and CAD patients in the Iranian population. The current study was performed to investigate the association of total long-term life psychosocial stress with CAD.

## METHODS

### Study design and participants

The research project was approved as the name of “life psychosocial stresses and CAD,” number of 1393–1998 by the Ethical and Research Committee of the Mazandaran University. There is informed consent for all patients. The assessment of angiography and measurements of anthropometrics were as described previously.<sup>[1]</sup> The study population was 148 men and 152 women aged 35–76 years who had positive “sport test” and were potentially susceptible to CAD and were consequently referred to coronary angiography at Zahra Hospital of University of Mazandaran. The subjects with a recent history of acute myocardial infarction, percutaneous transluminal coronary angioplasty, infectious or inflammatory disease, severe liver or renal disease, neoplasm, and hematologic disorders were excluded from the study. The subjects who had one or more significant narrowed ( $\geq 70\%$ ) coronary artery were considered to be CAD cases, whereas those without any narrowing (<10%) were taken as controls. The severity of coronary occlusion was scored on the basis of the number and the extent of lesions as 1 (normal), 2 (mild), 3 (moderate), and 4 (severe).<sup>[19]</sup>

### Procedures and variables assessments

The procedure is described for the collection of blood samples, preparations of plasma, and the measurements of lipids.<sup>[1]</sup> The measurements were done on fresh samples. All parameters of biochemistry and hematology were measured by routine laboratory methods.

The stressful life events were assessed using Holmes-Rahe Questionnaire.<sup>[18]</sup> The questionnaire is a 43-item self-report survey that lists common life events including the death of close companions, long joblessness, family and spouse disputes, serious financial, occupational, and

social problems. Some questions of the questionnaire were revised, and the validation has been confirmed.<sup>[18]</sup>

### Statistical analysis

The results are presented as the mean  $\pm$  standard deviation and median (25–75% quartiles) for normal and skewed distributed variables, respectively. The significant differences of categorical variables were assessed by Chi-square and continuous variables by Student's *t*-test. Mann–Whitney U-test was applied if a continuous variable showed skewed distribution. The difference of TPSS in the levels of CAD severity was evaluated using the analysis of variance. Bivariate correlation analysis was performed to show the association of TPSS scores

with other risk factors. Multivariate logistic regression analysis was carried out to find the independency of correlation (SPSS, IBM, version 21, US). All *P* values are two-tailed, and differences were considered statistically significant if  $P \leq 0.05$ .

## RESULTS

### Demographic and clinical parameters of the subjects

The frequency of cigarette smoking, diabetes mellitus, and hypertension was more prevalent in CAD cases than control subjects [Table 1]. There were significant differences in the consuming antilipidemics, nitrates,

**Table 1: Demographic and clinical characteristics**

|                                      | Without CAD (64)   | With CAD (174)      | <i>P</i> |
|--------------------------------------|--------------------|---------------------|----------|
| <b>Clinical characteristics</b>      |                    |                     |          |
| Age (year)                           | 52.6 $\pm$ 10.5    | 58.9 $\pm$ 9.5      | 0.001    |
| <b>Gender</b>                        |                    |                     |          |
| Male, <i>n</i> (%)                   | 23 (35.9)          | 105 (60.3)          | 0.001    |
| BMI (kg/m <sup>2</sup> )             | 27.3 $\pm$ 4.2     | 26.93 $\pm$ 4.2     | 0.537    |
| Physical inactivity, <i>n</i> (%)    | 36 (56.3)          | 91 (52.3)           | 0.363    |
| Smoking, <i>n</i> (%)                | 5 (7.8)            | 36 (20.7)           | 0.030    |
| Diabetes mellitus, <i>n</i> (%)      | 10 (16.4)          | 59 (34.3)           | 0.009    |
| Hypertension, <i>n</i> (%)           | 28 (43.8)          | 120 (69.0)          | 0.001    |
| Total psychological stress score     | 139.8 $\pm$ 66.5   | 160.3 $\pm$ 71.3    | 0.020    |
| <b>Drugs, <i>n</i> (%)</b>           |                    |                     |          |
| Hypoglycemic                         | 9 (17.3)           | 30 (19.9)           | 0.839    |
| Antilipidemic                        | 22 (37.3)          | 87 (54.4)           | 0.033    |
| Diuretics                            | 8 (15.7)           | 20 (13.2)           | 0.645    |
| Nitrates                             | 15 (29.4)          | 92 (60.9)           | 0.001    |
| Beta-blockers                        | 26 (51.0)          | 101 (66.9)          | 0.046    |
| Calcium antagonists                  | 1 (2.0)            | 25 (16.6)           | 0.006    |
| ACE-inhibitors                       | 6 (11.8)           | 28 (18.7)           | 0.289    |
| Aspirin                              | 30 (58.8)          | 122 (80.8)          | 0.003    |
| <b>Classical biochemical (mg/dL)</b> |                    |                     |          |
| Glucose                              | 104.5 $\pm$ 28.5   | 123.1 $\pm$ 56.6    | 0.001    |
| Triglycerides                        | 141.7 (93.0-194.9) | 157.3 (116.8–231.5) | 0.051*   |
| Total cholesterol                    | 190.7 $\pm$ 47.1   | 185.8 $\pm$ 49.2    | 0.402    |
| LDL-C                                | 113.4 $\pm$ 38.7   | 110.1 $\pm$ 43.     | 0.582    |
| HDL-C                                | 44.9 $\pm$ 11.8    | 39.5 $\pm$ 10.5     | 0.002    |
| Bilirubin                            | 0.04 $\pm$ 0.02    | 0.04 $\pm$ 0.02     | 0.741    |
| Uric acid                            | 4.3 $\pm$ 0.9      | 4.9 $\pm$ 1.1       | 0.001    |
| <b>Hematologic factors</b>           |                    |                     |          |
| Hemoglobin (g/dL)                    | 13.3 $\pm$ 1.6     | 13.4 $\pm$ 1.6      | 0.313    |
| Erythrocytes counts (cells/nL)       | 4.6 $\pm$ 0.5      | 4.6 $\pm$ 0.7       | 0.775    |
| Leukocyte counts (cells/nL)          | 8.4 $\pm$ 1.8      | 8.7 $\pm$ 2.2       | 0.089    |
| ESR (mm/h)                           | 12 (1-61)          | 14 (1-90)           | 0.059*   |
| Platelet counts (cells/nL)           | 264.1 $\pm$ 70.1   | 255.6 $\pm$ 74.2    | 0.032    |
| PTT(s)                               | 27.8 $\pm$ 4.5     | 28.4 $\pm$ 9.8      | 0.506    |

The continuous and categorical variables were compared by *t*- and Chi-square tests respectively. \*Mann–Whitney U-test was applied. The 48 subjects with mild CAD were not included in the analysis. The number in each group has shown in parentheses. The results are presented as the mean $\pm$ SD and median (IQR). ACE=Angiotensin-converting enzyme, BMI=Body mass index, CAD=Coronary artery disease, SD=Standard deviation, LDL-C=Low-density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, ESR=Erythrocyte sedimentation rate, PTT=Partial thromboplastin time, IQR=Interquartile range

beta-blockers, calcium antagonists, and aspirin between two groups. Patients with CAD compared to the controls had higher levels of TPSS and serum glucose, triglycerides, creatinine, uric acid, and lower levels of high-density lipoprotein cholesterol (HDL-C). Erythrocyte sedimentation rate (ESR) and platelets counts also differed significantly between the two groups.

**Correlation of total psychological stress scores with other risk factors**

Both analyses of parametric and nonparametric partial correlation were used to show the relationship of TPSS with other risk factors [Table 2]. TPSS significantly correlated with the occurrence and severity of CAD. TPSS also associated positively with the levels of uric acid, erythrocytes counts, ESR, aspirin consumption and negatively with HDL-C and apo-AI. No any other significant correlation was observed (results not shown).

**Association of total psychological stress scores with the severity of coronary artery disease**

TPSS exhibited significant association with the severity of CAD [ $F(3,274) = 2.6, P = 0.051$ , Figure 1]. Serum glucose, creatinine, potassium, and HDL-C also showed significant association with the severity of CAD. There was not sex difference in the correlation of TPSS with the severity of CAD (results not shown). No other biochemical parameters had a significant association with the severity of CAD.

**The independency of associations with coronary artery disease**

TPSS alone correlated with CAD by the odds ratio of 1.773 (1.073–2.930),  $P = 0.025$ . The association of TPSS with CAD was adjusted by demographic factors (age, sex), behavioral risk factors (smoking, physical inactivity), plasma lipids (total-C and HDL-C), and metabolic factors (diabetes and hypertension) [Table 3]. TPSS was excluded from the regression equation after adjustment for hypertension. Finally, age, male sex, hypertension, diabetes, total-C and HDL-C were kept in the model significantly. The study participants were also classified into four groups according to the quartiles of

TPSS [Figure 2]. The cutoff points of the quartiles for TPSS were 101, 148, and 198. The relative odds for CAD in the top relative to the bottom quartile of TPSS was 2.35 (1.14–4.85),  $P = 0.020$ .

**DISCUSSION**

The findings of the current study indicate that the TPSS are significantly associated with the prevalence and severity of CAD. However, the correlation was not independent so that it will be less marked if the results are adjusted for the classical risk factors.

**Life chronic psychological stresses and coronary artery disease**

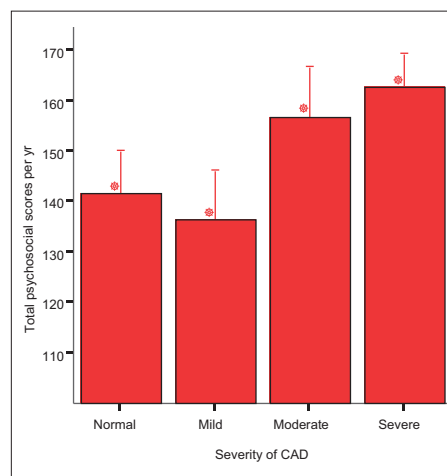
Holmes and Rahe hypothesized that the impacts of different life stressors are additive and if they are collectively significant can lead to several psychosomatic illness.<sup>[18]</sup> The researchers developed the SRRSs and deduced LCUs as the degree of stress caused by an event. According to their hypothesis, any change whether desirable or undesirable has potential to be stressful. Desirable as well as undesirable events require a considerable degree of individual adaptation.<sup>[19]</sup> The optimal levels of stress are associated with health so that both low and high degree of stress can be destructive and impair performance.<sup>[20]</sup> The several studies show that people who experienced more LCUs during a period of 1 year are at more risk for a wide range of physical and mental illness.<sup>[18-21]</sup>

In the present study, the mean of TPSS was  $139.8 \pm 66.5$ /year in control group and increased significantly to  $160.3 \pm 71.3$  in CAD patients [Table 1]. The mean TPSS value observed in the present research was comparable to that reported by other studies.<sup>[18,21,22]</sup> Since the difference of TPSS between two groups was slight, it was excluded from the regression equation

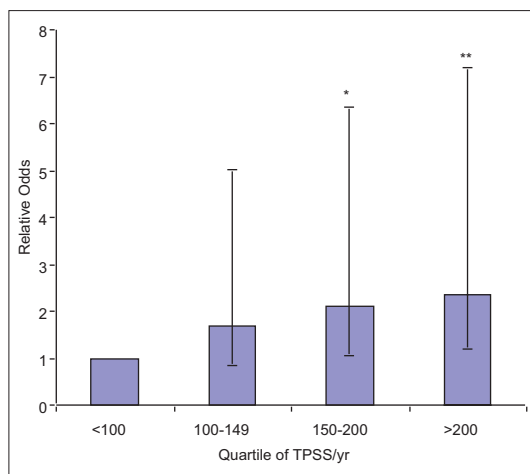
**Table 2: The correlation coefficients**

| Variables           | Correlation coefficients (r) | P      |
|---------------------|------------------------------|--------|
| Incidence of CAD    | 0.157                        | 0.021  |
| Severity of CAD     | 0.164                        | 0.008  |
| HDL-C               | -0.129                       | 0.035  |
| apo-AI              | -0.134                       | 0.049  |
| Uric acid           | 0.176                        | 0.018  |
| Erythrocytes counts | 0.127                        | 0.037  |
| Aspirin             | 0.129                        | 0.047  |
| PT                  | -0.131                       | -0.032 |

CAD=Coronary artery disease, HDL-C=High-density lipoprotein cholesterol, PT=Prothrombin time



**Figure 1: Association of total psychological stress scores with the severity of coronary artery disease**



**Figure 2: Relative odds for coronary artery disease associated with quartiles of total psychological stress scores. Error bars show 95% confidence intervals for risk estimates. \* and \*\* indicate the P values of 0.043 and 0.020 respectively**

**Table 3: Multivariate logistic regression analysis**

| Model | Included variables  | OR    | 95% CI      | P     |
|-------|---------------------|-------|-------------|-------|
| 1     | TPSS, unadjusted    | 1.773 | 1.073-2.930 | 0.025 |
| 2     | TPSS, adjusted      | 1.718 | 1.007-2.929 | 0.047 |
|       | Sex                 | 3.307 | 1.923-5.685 | 0.001 |
|       | Age                 | 1.048 | 1.019-1.077 | 0.001 |
| 3     | TPSS                | 1.669 | 1.003-2.777 | 0.049 |
|       | Smoking             | 1.922 | 0.940-3.929 | 0.073 |
|       | Physical inactivity | 0.794 | 0.480-1.072 | 0.369 |
| 4     | TPSS                | 1.732 | 1.020-2.940 | 0.042 |
|       | Cholesterol         | 1.008 | 1.001-1.015 | 0.028 |
|       | HDL-C               | 0.934 | 0.905-0.964 | 0.001 |
| 5     | TPSS                | 1.654 | 0.996-2.837 | 0.062 |
|       | Diabetes            | 1.810 | 1.020-3.162 | 0.050 |
|       | Hypertension        | 2.157 | 1.274-3.651 | 0.004 |

OR=Odds ratio, CI=Confidence interval, TPSS=Total psychological stress scores, HDL-C=High-density lipoprotein cholesterol

so that it has not recognized as an independent risk factor for CAD. Our data showed that the subjects who experienced TPSS as 100–149, 150–199, and >200 units/year are at more risk for CAD by the relative odds of 1.69, 2.09, and 2.35, respectively. According to Holmes-Rahe Questionnaire, death of relatives, spouse disputes, health and financial problems have more contributions in stress scores, but their prevalence is low. On the other hand, the minor stressors with low scores occur more frequently.

### The molecular mechanisms involved in mental stress

At the molecular level, different mechanisms may be participated to injure the vascular endothelium.<sup>[3]</sup> Psychosocial stresses influence immune system, hemodynamic, and metabolism.<sup>[3,22]</sup> Stress via sympathetic system has chrono- and inotropic effect

on the heart which elevates the heart rate and blood pressure.<sup>[23]</sup> The authors also indicated that CAD patients have significant stress-hemoconcentration which is important in the changes of hemodynamic.<sup>[24]</sup> Psychological stress is associated with increase in plasma-free fatty acids, cholesterol and triglyceride, consistent with atherogenic lipid profile.<sup>[25-27]</sup>

## CONCLUSIONS

The current results showed that TPSS is associated significantly with the prevalence and severity of CAD in Iranian subjects. Although this correlation occurred in TPSS <300 values, but it was in dose-dependent manner. It is suggested to recognize and reduce the factors of psychological stresses for preventing atherosclerosis.

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Dr. Rasouli designed and conducted the study, analyzed the data, interpreted the findings, and wrote the manuscript. Dr. Bagheri performed coronary angiography and analyzed its results. Alikhani, Meshkini, and Dinarvand were MSc students and gathered the data. Mal Haysom proof-read the manuscript.

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## Conflicts of interest

There are no conflicts of interest.

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