Original Article

The Role of Different Domains of Perceived Stress in the Development of Cardiovascular Events: A Cohort Study

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Abstract

Background: Long-term distress plays a crucial role in the development and prognosis of cardiovascular events (CVEs). The current study aims to evaluate the role of distress and its domains in the pathogenesis of CVE.

Materials and Methods: This study is part of the Isfahan Cohort Study conducted on 3283 healthy individuals in 2007–2015 to assess the distress level, domains of perceived stressors, and their correlation with CVE development. The demographic and lifestyle characteristics of the studied population were recorded. General Health Questionnaire-12 (GHQ-12) and the Stressful Life Event questionnaire (SLE) were applied to investigate the stress level and its domains, respectively. Kaplan–Meier plots were depicted to show the correlation of CVE incidence with both stress statuses at study entry and the perceived stress level within the 8-year follow-up.

Results: The logistic regression assessments showed that the stress score was an independent predictor for CVEs incidence in both crude model (P value = 0.001; OR: 1.08; 95%CI: 1.03-1.13) and by controlling the sociodemographic (P value = 0.004; OR: 1.08; 95%CI: 1.02-1.12) and lifestyle factors (P value = 0.001; OR: 1.07; 95%CI: 1.01-1.13). Domains, including home life, financial problems, personal conflicts, loss and separation, and health concerns, were independently associated with CVEs incidence regardless of sociodemographic and lifestyle factors (P value < 0.05).

Conclusions: The current study represented an independent role for long-term distress in the development of CVEs. Besides, home life, financial problems, personal conflicts, loss and separation, and health concerns were the major long-term perceived stressors responsible for CVE development.

Keywords: Cardiovascular disease, cohort studies, psychological stress

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Introduction

Cardiovascular diseases (CVD) contribute to the most frequent cause of morbidity and mortality in developed and low-to-moderate income countries since decades ago.[1] Despite the notable decline in mortality due to cardiovascular events (CVE), these disorders remained a serious public health issue and a significant burden for the healthcare systems.[2]

There is substantial evidence regarding the critical role of psychosocial distresses as the risk factors for developing

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CVD in the general population.[3] These stressors can affect the incidence and the outcomes of CVDs, to the extent of up to two-folds elevated CVE-related mortality.[4]

Distress is one of the inevitable elements, along with the human being's life, representing in many forms and may lead to a maladaptive psychological response.[5] Despite the evident documents regarding the link between acute emotional distress and the incidence of acute CVEs,[6,7] the information about the long-term influence of chronic distresses on physical well-being, CVD, in particular, has not been well-established.[8,9] In other words, a human being may perceive various types of stress sources, such as financial problems, social support, personal and occupational conflicts, chronic illnesses or separation, and loss, but the pathophysiology of each domain of perceived stress in CVE development is not well-known.

Contrary to the rapidly rising trend in the prevalence of chronic distress and stressful conditions,[10] limited protocols have recommended controlling the perceived stress in patients at high risks for developing CVD and even, there is no practical guideline for primary prevention in the general population.[11,12] Therefore, a concise model is critical to achieving a thorough insight into the association of perceived stressors with CVE and, eventually, to design practical guidelines for the management of perceived stress and diminish the risk of CVE incidence. The current study is aimed to investigate the role of perceived stresses in the development of CVEs.

Materials and Methods

Study population

The current study is derived from the Isfahan Cohort Study (ICS), a population-based study conducted on 6323 healthy individuals aged 35 years old and greater at baseline who were residents of urban and rural areas in the center of Iran in 2001.[13]

Pregnancy, mental retardation, and a history of hemorrhagic disorders were the unmet criteria. Over 20% of the medical records' defects or the filled questionnaires were determined as the exclusion criteria.

The evaluated population was followed through calls to refer to the nearest health center where a skilled nurse and a physician performed the physical examinations, and the study questionnaires were provided every 6 years (2001, 2007, and 2013). However, any incidence of CVE was questioned biannually.

The baseline data were recruited in 2007 because we did not assess the distress level and perceived stress at baseline (2001); therefore, the follow-up information was gathered from 2007–13 and 2013–15. By the distress assessment initiation, one-hundred-fifty subjects who experienced any CVEs from 2001 to 2007 were excluded.

Assessments

Cardiovascular events

The cardiovascular events were defined based on the International Classification of Disease diagnosis and procedure codes (ICD-10) and included fatal and nonfatal myocardial infarction (MI), fatal and nonfatal stroke, unstable angina (UA), and sudden cardiac death.

A trained nurse telephoned the participants and asked about the incidence of any CVE biannually; therefore, cases who experienced any CVE were requested to refer and provide their medical records, if they were alive; otherwise, the medical data were retrieved from hospital archives or verbal autopsies. A single physician filled the checklists, and the data regarding the incidence of various types of cardiovascular outcomes were confirmed by a panel consisting of four cardiologists and a neurologist.

Sociodemographic and lifestyle risk factors

The obtained sociodemographic factors included age, gender, marital status (married vs. unmarried defined as single, divorced, or widow), and educational level (classified as 0–5 years, 6–12 years, and >12 years).

Assessed lifestyle factors included physical activity, smoking, dietary score, and body mass index (BMI). Leisure time physical activity was determined by matching the frequency of most familiar leisure time physical activities of Iranian people (number of sessions per day) and average period (hours and minutes per session). The intensity of leisure time physical activity was stated in metabolic units (MET). One MET is equal to 3.5 mL/kg/min O2 consumption.[14]

Smoking was defined as the current use of the least of a cigarette per day.

The dietary score was defined using a 48-item validated food frequency questionnaire[15] and measured considering 12 groups of foods regarding both healthy and unhealthy dietary intake.[16] Weight in kilograms divided by height in meters.[17]

Distress and perceived stress assessments

To assess the distress level of the participants, General Health Questionnaire-12 (GHQ-12) was applied. This consists of 12 questions regarding the recent experience of a particular symptom or behavior. Each item is scored on a bimodal scale of zero, zero, 1, and 1 as less than usual, no more than usual, rather more than usual, or much more than usual, respectively. Therefore, the maximum score of the questionnaire, which represents worse conditions, equals 12. The cut-point of the study was considered as four or above. The Persian version of this questionnaire has been validated by Montazeri *et al*. in 2003[18] and used in the current study.

The latter means to recruit the perceived stress domains was the stressful life event questionnaire (SLE) proposed by Roohafza and colleagues in 2011. This questionnaire consists of 83 items assessing the self-perceived frequency and intensity of stressful life events within the previous 6 months, answered

by 6-point Likert scales (0 = never, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe). A higher score represents a worse condition. The assessed events evaluate eleven domains, including home life, financial problems, social relation, personal conflict, job conflict, educational concerns, job security, loss and separation, sexual life, daily life, and health concerns. This Persian questionnaire has been validated with Cronbach's alpha of 0.92.[19] In the current study, in order for a qualitative assessment of the perceived stress and its quantitative measurements, a median of 22 was defined as the cutoff level, and the scores above it were determined as the high level of stress.

Statistical analysis

As the distress-related data were recruited since 2007, the patients who experienced CVEs from 2001 to 2007 were excluded from the analysis. The obtained data were entered into the Statistical Package for Social Sciences (version 22, IBM Corporation, Armonk, NY, USA). The descriptive data were presented in mean, standard deviation, absolute numbers, and percentages. The Chi-square test was used to compare categorical variables, and the quantitative variables were compared using the independent *t*-test or Mann–Whitney. The outcome variables classified with ICD-10 were fatal and nonfatal myocardial infarction (MI), fatal and nonfatal stroke, unstable angina (UA), and sudden cardiac death are all considered as a single CVE variable. Binary logistic regression analysis was applied to find the association between CVE and distress/perceived stressors in crude (model 1) and adjusted models, including sociodemographic factors (age, gender, marital status, and educational level) (model 1) and sociodemographic factors (age, gender, marital status, and educational level) plus lifestyle ones (physical activity, dietary status, smoking status, and BMI) (model 2). Odds ratios (ORs) were reported with the corresponding 95% confidence intervals (95% CIs). Kaplan–Meier plots were depicted to show the correlation of CVE incidence with both stress statuses at study entry and the perceived stress level within the 8-year follow-up. The *P* value of less than 0.05 was considered as a significant level.

Results

In the current study, 3283 participated in the first follow-up (2007), among which 434 (13.2%) experienced CVEs. The second follow-up study in 2013 was conducted on 1704 participants, among whom CVEs occurred in 219 (12.9%).

Older age, male gender, unmarried, and lower education levels were the sociodemographic factors and lower physical activity, current smoking, higher dietary score, and higher BMI were the lifestyle factors that had a statistically significant association with an increased rate of CVEs. The patients who experienced CVEs had remarkably higher distress levels based on GHQ-12 (*P* value < 0.05). Detailed information is demonstrated in Table 1.

The logistic regression assessments showed that the distress score based on GHQ-12, and the perceived stress based on the SLE questionnaire was an independent predictor for CVEs incidence in both crude models and by controlling the sociodemographic and lifestyle factors. Further investigations showed that perceived stress domains, including home life, financial problems, personal conflicts, loss and separation, and health concerns, were associated with the incidence of CVEs. Table 2 represents detailed information.

The Kaplan–Meier survival plot has been demonstrated below in which the distress levels at this study entry based on GHQ-12 (*P* value < 0.05) and the perceived stress level (*P* value < 0.05) based on SLE were independent determinants of survival after CVEs incidence [Figures 1 and 2].

Discussion

Although the effects of long-term distress on the body metabolism have been well-studied and surfing the literature provides an evident document in terms of the correlation between the development of CVEs and distress,[20] the paucity of knowledge is available about the role of perceived stress and its different domains in CVEs incidence, a question that has been tried to be responded in this study.

In this study, we found that distress and various perceived stress domains are independent factors for the incidence and survival of CVE over an 8-year follow-up, aligning with previous reports. Stewart and colleagues conducted a similar 12-year follow-up study on patients with stable angina, showing the significant role of persistent distress in cardiovascular diseases, outcomes, and all-cause mortality.[8] A meta-analysis of 10 prospective cohorts with 68,222 subjects from the Health Survey of England also found a dose-dependent relationship between stress levels and the incidence and outcomes of CVE and all-cause mortality over an average of 8.2 years.[21] These studies have categorized the severity of distress based on GHQ-12, while we have represented it both quantitatively and qualitatively.

Our study's strong point is not only to assess the role of distress merely in the pathogenesis of CVEs but also the perceived stress, and its domains have been investigated. Therefore,

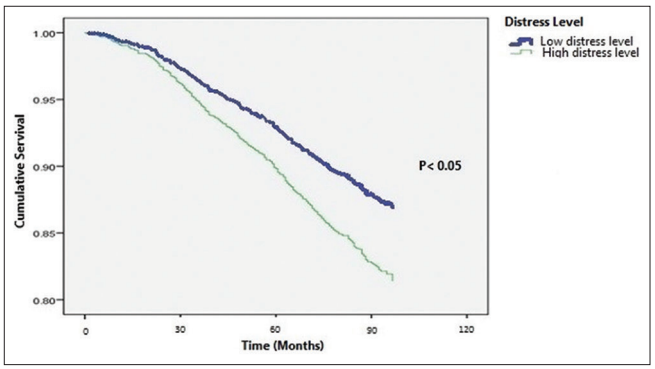


Figure 1: Kaplan–Meier curve representing the role of distress level in the survival following cardiovascular events

Table 1: Sociodemographic, lifestyle, and psychological characteristics in participants with and without cardiovascular events in 2007 and 2013

	2007		2013	
	CVE - Mean±SE	CVE + Mean±SE	CVE - Mean±SE	CVE + Mean±SE
Sociodemographic factors				
Age (years)	49.63±0.18	57.37±0.21***	51.47±0.23	46.95±0.55***
Gender (Male) *n* (%)	1361 (47.8%)	243 (56.0%)***	721 (48.6%)	122 (55.7%)***
Marital status (Married) *n* (%)	2558 (90.2%)	371 (86.1%)***	1295 (88.5%)	179 (82.9%)**
Educational level *n* (%)				
0-5 y	1909 (67.5%)	322 (75.4%)***	860 (58.4%)	147 (67.7%)**
6-12 y	695 (24.6%)	79 (18.5%)	452 (30.7%)	51 (23.5%)
>12 y	226 (8.0%)	26 (6.1%)	160 (10.9%)	19 (8.8%)
Lifestyle factors				
Physical activity (Mets/week)	790.59±0.47	637.12±0.43***	786.55±0.49	610.04±0.38***
Current Smoking *n* (%)	494 (17.4%)	85 (19.8%)	292 (19.8%)	49 (22.5%)
Dietary Score	4.69±0.04	5.40±0.09	5.21±0.05	5.63±0.13
Body mass index	27.41±0.05	27.42±0.07	27.87±0.11	28.68±0.09**
Psychological factors				
Distress score	2.93±0.03	3.41±0.10***	3.09±0.05	3.73±0.11***
High distress level (≥4)	789 (27.7%)	148 (34.3%)**	405 (27.4%)	89 (40.6%)***
The severity of perceived stressors				
Homelife	1.43±0.05	1.78±0.08**	2.10±0.08	2.66±0.12**
Financial problems	6.22±0.12	6.20±0.15	6.91±0.16	7.57±0.22
Social relation	2.35±0.07	2.83±0.12**	3.95±0.11	4.10±0.23
Personal conflicts	1.58±0.06	2.03±0.15**	2.85±0.12	3.42±0.24**
Job conflicts	0.77±0.04	0.85±0.10	0.62±0.06	0.81±0.08
Job security	2.40±0.07	2.48±0.11	2.16±0.09	2.23±0.15
Educational concerns	1.28±0.09	1.16±0.05	0.99±0.12	0.90±0.06
loss and separation	1.75±0.05	2.03±0.11	1.89±0.07	2.47±0.17***
Sexual life	0.15±0.06	0.16±0.03	0.39±0.03	0.53±0.09
Daily life	1.03±0.03	1.19±0.09	1.70±0.06	1.98±0.12
Health concerns	0.98±0.03	1.68±0.11***	1.17±0.07	2.20±0.09***
Total perceived stress score	20.82±0.4	22. 51±0.06**	24.64±0.54	28.96±0.74**
High perceived stress level (>22)	971 (34.1%)	166 (38.5%)**	650 (43.8%)	99 (45.2%)

Table 2: Hazard ratio of cardiovascular events according to psychological factors

	Crude	*P*	Model 1	*P*	Model 2	*P*
Distress score	1.08 (1.03-1.13)	0.001	1.08 (1.02-1.12)	0.004	1.07 (1.01-1.13)	0.001
High distress level (≥4)	1.37 (1.13-1.60)	0.007	1.35 (1.11-1.58)	0.01	1.33 (1.07-1.58)	0.03
Severity of Perceived stressors						
Home life	1.01 (0.98-1.04)	0.37	1.04 (1.01-1.07)	0.02	1.04 (1.01-1.07)	0.02
Financial problems	0.99 (0.97-1.01)	0.96	1.02 (1.01-1.04)	0.02	1.02 (1.01-1.04)	0.02
Social relation	1.00 (0.98-1.02)	0.77	1.02 (0.99-1.04)	0.09	1.02 (0.99-1.04)	0.14
Personal conflicts	1.01 (0.98-1.03)	0.28	1.04 (1.01-1.06)	0.01	1.04 (1.01-1.06)	0.02
Job conflicts	0.98 (0.93-1.02)	0.52	1.01 (0.96-1.05)	0.64	1.03 (0.98-1.07)	0.14
Job security	0.99 (0.96-1.01)	0.75	1.01 (0.98-1.04)	0.27	1.02 (0.98-1.05)	0.12
Educational concerns	0.98 (0.94-1.01)	0.33	1.02 (0.96-1.07)	0.41	1.02 (0.97-1.07)	0.14
Loss and separation	1.02 (0.98-1.05)	0.23	1.04 (1.01-1.07)	0.04	1.04 (1.01-1.07)	0.03
Sexual life	1.01 (0.91-1.11)	0.74	1.05 (0.94-1.15)	0.30	1.04 (0.93-1.16)	0.81
Daily life	1.01 (0.96-1.05)	0.6	1.04 (0.98-1.10)	0.09	1.04 (0.98-1.10)	0.24
Health concerns	1.12 (1.07-1.16)	<0.001	1.12 (1.07-1.17)	<0.001	1.13 (1.08-1.19)	<0.001
Total perceived stress score	1.00 (0.99-1.01)	0.36	1.01 (1.003-1.01)	0.0005	1.01 (1.004-1.02)	0.003
High perceived stress level (>22)	1.10 (1.00-1.22)	0.89	1.32 (1.08-1.55)	0.02	1.32 (1.06-1.52)	0.03

Model 1: sociodemographic (age, gender, marital status and educational level) adjusted. Model 2: sociodemographic (age, gender, marital status, and educational level) and lifestyle (physical activity, dietary score, smoking status, and body mass index) adjusted (full adjusted)

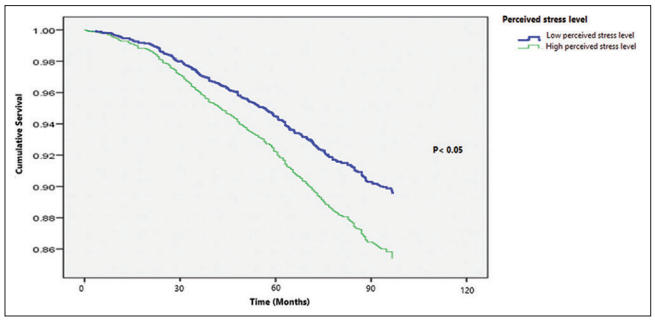


Figure 2: Kaplan–Meier curve representing the role of perceived stress level in the survival following cardiovascular events

further evaluations revealed that the perceived stressors, including home life, financial problems, personal conflicts, loss and separation, and health concerns,[19] could play an independent role in the incidence of CVEs regardless of a person's sociodemographic or lifestyle characteristics.

Based on the SLE questionnaire, home life considers aspects, including addiction, conflicts in familial interactions, and legal problems.[19] These factors contribute to a person's social life, conditions that may lead to violence, social isolation, and lacking social support. Furthermore, legal problems may cause incarceration and, in addition to its adverse impacts on mental health, can pose a financial burden.[22]

Interestingly, Henderson and colleagues evaluated the role of early familial conflicts in adulthood CVE incidence and found a steep correlation, primarily due to its psychosocial effects on facing lifelong stress and secondarily shaping future life interactions.[23]

Financial problems are a well-studied chronic stressor for developing CVEs.[24] According to the SLE questionnaire provided by Roohafza *et al*.,[19] financial issues such as debt, major financial problems, low income, mortgages, and inflation can impact health through various pathways. Poverty primarily leads to inadequate and unhealthy diets, but more complex processes are also involved.[25] Financial problems significantly burden individuals, causing them to work longer hours, neglect personal health, impair their sense of coherence, engage in unhealthy behaviors like smoking and anger, and reduce social activities, leading to isolation.[26-28] These factors, along with other neglected variables, increase the risk of CVE development.

In our investigation, the other domain of perceived stressor was personal conflicts, another determined domain by the SLE questionnaire[19] that involves social interactions, including lacking social supports, cultural alienation, failure to achieve life goals and intimacy, and loneliness.

Intimate relationships, such as marriage or any other type of intimacy, help people better adjust to different life emotions. Close relationships, having someone to feel sympathy and empathy with, and sexual activity as a notifying part of a very intimate relationship are associated with self-esteem, social support, and the ability to face stressful conditions. Gallagher *et al*.,[29] and Smith[30] are two researchers who separately investigated these aspects and represented a significant inverse correlation of intimacy with CVE incidence.

Migration has become one of the unavoidable events in the present world. Some people migrate by force, and some seek a better life. Regardless of the cause of migration, which in the first group is associated with more unfavorable results, migration confronts one with a new culture. Inability to cope with this new environment leads to isolation and loneliness. Although studies in this area are limited, they indicate a significant effect of this cultural alienation on CVEs incidence.[31]

Loss of or separation from close family members due to death or hospitalization and children's separation from family is another perceived stress that independently played a causative role for CVE development. We assume that loss/separation, along with its short-term consequences due to grief, imposes long-term distress as well, whereas a person may feel lonely, experience a lack of social support, isolate from society, and refrain from interaction with others.[32] In addition to emotional effects, loss and separation may lead to a financial burden.[33]

The last perceived stressor directly associated with increased risk of CVE was a health concern, an aspect defined as a minor illness or major physical disease leading to hospitalization based on the SLE questionnaire,[19] which involves a person's sense of coherence. Numerous studies have shown that a remarkably concerned person about their health has a weaker sense of coherence, in general. This condition impairs their ability to cope with stressful situations, a fact that affects their health-related quality of life negatively.[34,35]

Various causes have been proposed to link distress with CVE, but the mechanisms are not well-understood. Evidence shows increased peripheral vascular resistance and elevated blood pressure in individuals with impaired social interactions who are isolated from society.[36,37] Besides, animal studies have shown that atherosclerosis development was more prominent among socially isolated animals compared to those housed in groups.[38,39] These factors are known precursors of CVE. Molecular assessments have demonstrated that loneliness and social stress are directly associated with CVE risk factors through several pathways, including activation of the hypothalamic–pituitary–adrenocortical axis and the sympathetic nervous system, glucocorticoid resistance, upregulation of proinflammatory cytokines, and overproduction of free radicals and oxidative stress.[31] Chronic anxiety about health in this topic leads to an imbalance in the neuroendocrine secretions, elevated levels of proinflammatory cytokines, and an increase in the oxidative metabolism, factors that lead to atherosclerotic processes.[40-42]

Despite efforts to understand how distress accelerates atherosclerosis, reactions to different perceived stressors vary.

We believe that individual perceptions of specific stressors lead to different responses. Thus, while distress generally increases CVE risk, managing diverse stressors requires personalized medicine. Surprisingly, job insecurity and conflicts did not correlate with CVE incidence, although they were expected to play significant roles. Most literature highlights these factors as increasing CVE risk and related mortality.[43] Job-related stress impacts body metabolism through chronic increases in counter-regulatory and proinflammatory factors.[44,45] Job insecurity affects men, as primary earners, more than women. The mixed gender sample in our study might explain these findings.[46,47]

Despite the large population of this study, a significant limitation in the current report is to have many missed cases because of our inability to follow-up, which may be a bias source. In addition, the sociodemographic and lifestyle-related factors were self-reported in which the participants may have overestimated the physical activity or underestimated the smoking status. The third limitation of this study may be attributed to the adjustments. Despite all of the analyses' adjustments, it is still possible that unmeasured confounders interfere with a part of the associations between distress and CVE-related factor.

Conclusion

In summary, the current study results supported the previous investigations, representing an independent role for long-term perceived stress in the development of CVEs. Nevertheless, we tried to determine the type of perceived stressors responsible for increased risk of CVE incidence and found the independent role of home life, financial problems, personal conflicts, loss and separation, and health concerns in CVE development. Another finding of this study revealed that in addition to the diversity in individuals' ability to cope with life perceived stresses, which is directly associated with CVE incidence, the mechanism by which each stressor leads to the development of CVEs may vary by the others. Therefore, for the long-term management of distress, the domain of perceived stress should be considered.

Ethics approval and consent to participate

The Ethics Committee of Cardiovascular Research Institute approved the study protocol, which met the Helsinki Declaration's criteria. The participants were informed about the study protocol, reassured about their information confidentiality, and signed written consent.

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Consent for publication

The written consent was obtained from patients who tended to participate in the study.

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Conflicts of interest

There are no conflicts of interest.

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