CARDIOVASCULAR DISEASES AND VITAL EXHAUSTION: LONGITUDINAL STUDY IN RUSSIA/SIBERIA (WHO MONICA — PSYCHOSOCIAL PROGRAM)

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Aim. To study prevalence rates of vital exhaustion and its effects on 14-year risk of cardiovascular disease (CVD) (arterial hypertension (AH), myocardial infarction (MI), and stroke) development and genetic traits in open population of 25–64-year-old men in Russia/Siberia (West Siberia metropolis, Novosibirsk).

Material and methods. Random representative sample of 25–64-year-old men was studied in a framework of WHO MONICA-Psychosocial Program (MOPSY) in 1994. Maastricht Questionnaire (MQ) was used to assess vital exhaustion. Genotyping for variable number of tandem repeats (VNTR) polymorphisms in DRD4 and DAT genes was performed. All new cases of AH, MI, and stroke were registered among people without CVD for 14 years (from 1994 to 2008). Statistical analysis was done by using software package SPSS 11.5. Cox proportional hazards regression model was used for evaluation of risk coefficient (hazard ratio (HR) taking into account time-adjusted control. X^2 test was used to assess statistical significance of differences between the groups.

Results. In the study population, the vital exhaustion rate was 66,8%. Hazard ration was significantly increased (AH: HR=3,2; MI: HR=2,7; stroke: HR=3,2) in men with vital exhaustion compared with vital exhaustion-free individuals in open population during the first five years of observation. Multifactorial modeling showed that vital exhaustion together with concomitant social gradient determined development of AH, MI, and stroke in open population of 25–64-year-old men. Allele 7 of DRD4 and genotype 9/9 of DAT gene were associated with high level of vital exhaustion.

Conclusion: Open population of 25–64-year-old men (Russia/Siberia, Novosibirsk) showed high level of vital exhaustion, a predictor for risk of developing CVD. Vital exhaustion is significantly associated with certain VNTR polymorphisms of DRD4 and DAT gens.

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Key words: arterial hypertension, myocardial infarction, stroke, vital exhaustion, hazard ratio, DRD4, DAT.

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AH — arterial hypertension, DAT — the dopamine transporter, DRD4 — the dopamine D4 receptor, MI — myocardial infarction, MONICA — Multinational Monitoring of Trends and Determinants in Cardiovascular Disease program, VE — vital exhaustion, VNTR — variable number of tandem repeat.

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СЕРДЕЧНО-СОСУДИСТЫЕ ЗАБОЛЕВАНИЯ И ЖИЗНЕННОЕ ИСТОЩЕНИЕ: ПРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ В РОССИИ/СИБИРИ (ПРОГРАММА ВОЗ МОНИКА — ПСИХОСОЦИАЛЬНАЯ)

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Цель. Исследовать распространенность жизненного истощения, его влияния на 14-летний риск развития сердечно-сосудистых заболеваний (ССЗ) (артериальной гипертонии (АГ), инфаркта миокарда (ИМ) и инсульта), а так же генетических особенностей жизненного истощения в открытой популяции среди мужчин 25-64 лет в России/Сибири (г.Новосибирск, мегаполис Западной Сибири).

Материал и методы. Была обследована случайная репрезентативная выборка мужчин 25-64 лет в рамках программы ВОЗ "MONICA-психосоциальная (MOPSY)" в 1994г. Маастрихтский опросник (ОМ) использовался для оценки жизненного истощения. Генотипирование было выполнено для переменного числа тандемных повторов (VNTR) полиморфизмов генов DRD4 и DAT. Все новые случаи АГ, ИМ и инсульта были зарегистрированы у лиц без ССЗ в течение 14 лет (с 1994 по 2008гг). Статистический анализ проводился с помощью пакета программ SPSS 11.5. Кокс-пропорциональная регрессионная модель была использована для оценки риска развития (Hazard ratio — HR) с учетом временного интервала. Тест X2 был использован для оценки статистической значимости различий между группами.

Результаты. В исследованной популяции уровень жизненного истощения составил 66,8%. HR был значительно увеличен (АГ: HR=3,2; ИМ: HR=2,7; инсульт: HR=3,2) у мужчин с жизненным истощением, по сравнению с лицами без жизненного истощения в открытой популяции в течение первых пяти лет наблюдения. Многофакторное моделирование показало, что жизненное истощение вместе с сопутствующим социальным градиентом определяет развитие АГ, ИМ и инсульта в открытой популяции среди мужчин 25-64 лет. 7 аллель DRD4 и генотип 9/9 гена DAT были связаны с высоким уровнем жизненного истощения.

Заключение. В открытой популяции среди мужчин 25-64 лет (Россия/Сибирь, г.Новосибирск) определен высокий уровень жизненного истощения, как предиктор риска развития ССЗ. Жизненное истощение существенно связано с определенными VNTRr-полиморфизмами генов DRD4 и DAT.

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Ключевые слова: артериальная гипертония, инфаркт миокарда, инсульт, жизненное истощение, отношение рисков, DRD4, DAT.

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Over 30 years ago, Appels A. described a syndrome of vital exhaustion (VE) [1]. Several studies have been conducted afterwards showing that VE is associated with coronary events [2, 3, 4], however, the term of VE was not widely recognized. Earlier definition of VE was based on empirical approach aimed at prevention of myocardial infarction (MI) symptoms rather than on the use of existing psychological indicators in ischemic heart disease (IHD) complex [1-6].

Currently, psychosocial factors and, in particular, VE are considered as independent risk factors for developing cardiovascular diseases (CVD) [7-11]. Likelihood of

Table 1

Random representative sample of 25–64-year-old men in the Oktyabrsky District of the city of Novosibirsk: screening study III (1994)

Age groups	n	%
25-34	169	25,7
35-44	136	20,7
45-54	177	27
55-64	175	26,6
25-64	657	100

development of CVD and atherosclerosis is higher in individuals with high level of VE [12-14]. There is still no agreement regarding the effect of VE on stroke development [15, 16]. Some authors believe that the condition of VE develops in population due to long-standing psychosocial problems that are impossible to solve [17, 18]. Dopamine is involved in certain response reactions to surrounding events [19] whereas some dopamine reuptake inhibitors exert antidepressant effect [20]. Therefore, the study of genetic traits in VE is of high demand. It is essential to mention that such studies are absent in Russia.

Taking all the above mentioned arguments into account, the objective of our study was to investigate the prevalence rates of VE, the effects of VE on 14-year risk of developing CVD (AH, MI, and stroke), and the genetic traits in open population of 25–64-year-old men in Russia/Siberia (West Siberia metropolis, Novosibirsk).

Material and method

The random representative sample of 25–64-year-old men (n=657; mean age: 44,3±0,4 years), all residents of the Oktyabrsky district of the city of Novosibirsk, was examined in a framework of the screening III of WHO MONICA Program, MONICA-Psychosocial Subprogram (Multinational Monitoring of Trends and Determinants of Cardiovascular Disease & Optional Study (MOPSY) [21, 22] in 1994 (Table 1). Response rate was 82,1%. Sample was formed according to the requirements of the protocol of WHO MONICA based on electoral lists with the use of random number table. The program of screening examination included:

1) Registration of socio-demographic data. The following socio-demographic indicators were registered according to the requirements of the program protocol: number; place of residence; last name; first name; patronymic name; date of birth; date of registration; gender (male: 1; female: 2); marital status (never married; married; divorced; widowed); education level (university degree; undergraduate/college degree; high-school diploma; elementary school/partially completed high school); professional status (higher manager; middle manager; manager; technical/engineering employee; specialist; heavy-labor worker; moderate-labor worker; light-labor worker; student; retired; disabled worker).

2) The study of VE was carried out based on the short 14-item version of the Maastricht Vital Exhaustion Questionnaire (MQ) adapted to MONICA-MOPSY Program [23-25]. Respondents were requested to answer the questions of MQ test by themselves.

The risk factor levels in the initial examination were analyzed without taking into account temporal dynamics. Methods were strictly standardized and corresponded to the requirements of WHO MONICA program protocols. Processing of data was performed in MONICA Data Center (Helsinki, Finland). Quality control was carried out at MONICA quality control centers (Dundee, Scotland; Prague, Czech Republic; Budapest, Hungary). Presented data were considered satisfactory [26-28].

The formed population sample was used for assessment of the risk of developing CVD. All men with cardiovascular pathologies, documented before or during the screening, were excluded from the study (IHD: n=53; AH: n=328; MI: n=14; stroke: n=17; medical history of diabetes mellitus: n=7; first-time diabetes mellitus diagnosed in the screening: n=20; not found: n=28). Study cohort included 190 men with initial age ranging from 25 to 64 years. Duration of the prospective study was 14 years starting from January 1, 1995 through December 31, 2008. The following end-points were established: first-time cases of AH, MI, and stroke. Registration of all MI cases was based on the program of WHO Acute Myocardial Infarction Register [29]. First-time cases of AH and stroke were registered throughout the period of observation. The following sources for identification of AH and stroke cases were used: reports of annual medical checkups of individuals from the population cohort; clinical charts; hospital discharge reports; district polyclinic reports; death certificates; interrogations with relatives; and autopsy and forensic reports.

As a part of annual medical checkup procedure, standardized measurements of arterial blood pressure (ABP) were performed according to the study protocol. The group of AH included both men with high ABP and those with normal ABP who were taking hypotensive drugs at moment of medical examination or stopped hypotensive therapy less than two weeks prior to the examination [30]. During the period of the study, new cases of AH (n=46), MI (n=30), and stroke (n=22) were documented in the study cohort (Table 2).

Genotyping of variable number of tandem repeats (VNTR) polymorphisms in DRD4 and DAT genes was performed in the Laboratory of Molecular and Genetic Studies at the FSBI "Research Institute of Internal Medicine" SB RAMS (Head of Laboratory: Maksimov V. N.) in accordance with methods described elsewhere [31-34].

Statistical analysis was carried out by using the software package SPSS 11.5. Pearson's chi-squared test (χ^2) was used to determine whether there is a significant difference

Table 2

Vital exhaustion prevalence rates and association with new cases of cardiovascular diseases among 25–64-year-old men

№		Screening III (1994)							
		First-time arterial hypertension		First-time myocardial infarction		First-time stroke		Total	
		n	%	n	%	n	%	n	%
1.VE	25-34	5	14,8	1	5	-	-	27	21,3
	35-44	8	23,5	3	15	-	-	29	22,8
	45-54	8	23,5	3	15	3	23	32	25,2
	55-64	13	38,2	13	65	10	76	39	30,7
	25-64	34	73,9%	20	66,7	13	59	127	66,8
2.NVE	25-34	1	8,3	1	10	1	11,1	8	12,7
	35-44	2	16,7	1	10	1	11,1	10	15,8
	45-54	3	25	4	40	4	44,5	20	31,8
	55-64	6	50	4	40	3	33,3	25	39,7
	25-64	12	26,1	10	33,3	9	41	63	33,2
	Total	46	100	30	100	22	100	190	100

Abbreviations: E — vital exhaustion, NVE — no vital exhaustion.

Table 3

Prevalence rates of vital exhaustion in different age-groups of 25–64-year-old men in open population

Age groups	Screening III (1994)							
	NVE		MVE		HVE		Total	
	n	%	n	%	n	%	n	%
25-34	77	46.7**	80	48.5	8	4.8**	165	100
35-44	64	38.8	78	47.3	23	13.9	165	100
45-54	35	27.1	65	50.4	29	22.5*	129	100
55-64	26	17.3***	95	63.3	29	19.3	150	100
25-64	202	33.2	318	52.2	89	14.6	609	100
	χ^2=46.804 υ=6. p<0.0001							

Annotation: * — p<0,05. ** — p < 0,01, *** — p < 0,001.

Abbreviations: E — vital exhaustion, NVE — no vital exhaustion, MVE — moderate vital exhaustion, HVE — high vital exhaustion.

between the groups [35]. Unifactorial and multifactorial Cox proportional hazards regression models were used for evaluation of risk coefficients (hazard ratio (HR)) taking into account time-adjusted control. [36, 37]. Associations between VE and VNTR polymorphisms of DRD4 and DAT genes were assessed by calculating the odds ratios (OR) and their 95% confidence interval (CI) (min-max). Values were considered statistically significant when P was ≤0,05 for all analyses [38].

Results

In open population of 25–64-year-old men, VE rate was 66,8% (rate of moderate level of VE: 52,2%; rate of high level of VE: 14,6%) (Table 3).

Prevalence rate of VE in cohort of men with first-time AH was 73,9% (rate of moderate level of VE: 58,2%; rate of high level of VE: 15.7%) (χ^2=22,494; ν=2, p<0,0001) (Table 2).

Structure of marital status in men with AH and VE was as follows: never married (3,2%); married (86,7%); divorced (6,9%); widowed (1,6%) (χ^2=6,781; ν=4, p>0,05). Statistically significant results showing higher frequency of AH were found in group of married men with VE compared with those without VE (χ^2=6,771; ν=1, p<0,01).

Pattern of education levels in men with AH and VE was as follows: university degree (29,3%); undergraduate/college degree (25,5%); high-school diploma (18,1%); elementary school/partially completed high school (27,1%) (χ^2=5,31; ν=3, p>0,05).

Statistically significant results showing differences in the frequency of AH development were acquired in group of men with VE who finished elementary school or partially completed high school compared with groups of VE-free men who had university degree, undergraduate degree/college degree, or high-school diploma (χ^2=7,966, ν=1, p<0,01; χ^2=12,166, ν=1, p<0,0001; χ^2=4,292, ν=1, p<0,05; χ^2=4,860, ν=1, p<0,05; χ^2=9,898; ν=1, p<0,01, respectively). Statistically significant results were also found in group of men with VE who had university

diploma compared with group of men with VE who had undergraduate/college degree and VE-free group of men who had high-school diploma (χ^2=9,374; χ^2=6,987, ν=1, p<0,01, respectively).

Professional status of men with VE and AH was as follows: higher managers (5,3%); middle managers (8%); managers (8%); technical/engineering employees (11,2%); heavy-labor workers (15,5%); moderate-labor workers (21.9%); light-labor workers (3,7%); students (0,5%); retired (17,6%) (χ^2=7,75, ν=10, p>0,05).

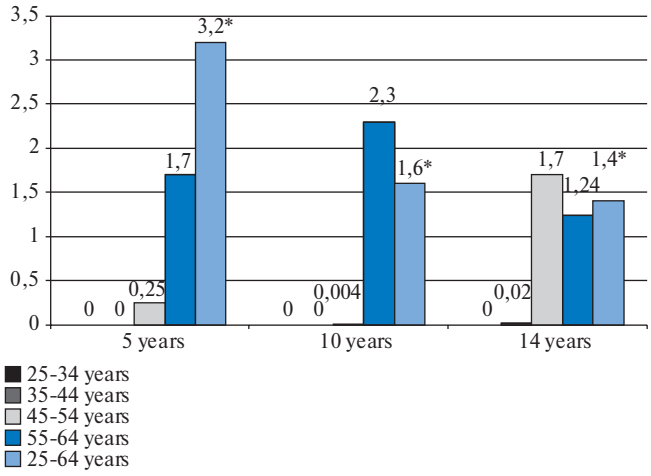

Figure 1. Comparative analysis of relative risk of arterial hypertension development in men with vital exhaustion in different age groups (unifactorial Cox model).
Annotation: * — p<0,05.

Significant differences in frequency of AH were found in VE groups of higher and middle managers, technical/engineering employees; moderate- and light-labor workers, and retired men in comparison with VE-free group of technical/engineering employees (χ^2=6,647, ν=1, p<0,01; χ^2=5,214, ν=1, p<0,05; χ^2=7,462, ν=1, p<0,01; χ^2=4,263, ν=1, p<0,05; χ^2=9,016, ν=1, p<0,01; χ^2=13,523; ν=1, p<0,0001, respectively). Significant differences were also found in VE group of heavy-labor workers compared with groups of technical/engineering employees, light-labor workers, and retired men with VE (χ^2=3,811, ν=1, p<0,05; χ^2=5,370, ν=1, p<0,05; χ^2=10,720; ν=1, p<0,001, respectively). Group of light-labor workers with VE significantly differed from groups of VE-free middle managers and heavy-labor workers (χ^2=4,871; χ^2=5,341, ν=1, p<0,05, respectively).

Unifactorial Cox proportional hazards regression model showed that AH risk among men with VE was 3,2-times higher during the first five years (95% CI 1–7,3; p<0,05) and 1,6-times higher during the first 10 years (95% CI 1–3,4 ; p<0,05) compared to VE-free men. During 14 years, AH risk among men with VE was 1,4-times higher (95% CI 1–3,1; p<0,05) (Figure 1).

Multifactorial Cox proportional hazards regression model included social parameters (educational, professional, and marital statuses) and age. It showed that VE increased AH risk by 2,9 times (95% CI 1–7,9; p<0,05) (Table 4).

Prevalence rate of VE in cohort of 25–64-year-old men with first-time MI was 66,7% (rate of moderate level

Table 4

Risk of cardiovascular diseases in open population of 25–64-year-old men depending on the level of negative vital exhaustion (multifactorial Cox model)

Social factors	Reference group	Group of risk	HR (AH)	HR (MI)	HR (Stroke)
	NVE	HVE	2,9 (1-7,9)*	1,16 (0,6-2)*	2,6 (1-6,8)*
Education	University diploma	Undergraduate/college degree	1,3 (0,2-6)	0,7 (0,3-1,8)	1,8 (0,4-7,6)
		High school	1,8 (0,1-9,7)	1,4 (0,6-3,1)	1,4 (0,3-6,6)
		Elementary school/partially completed high school	2,1 (0,2-41)	2,2 (1,1-4,5)*	4,8 (1,3-17,3)**
Professional status	Higher managers[1]	Middle managers	1,1 (0,5-12)	8,2 (0,9-28)*	-
		Managers	1,6 (0,9-23)	7,3 (0,8-23)*	-
		Technical/engineering employees	0,1-3,09	-	-
		Heavy-labor workers	1,6 (0,6-4,7)	8,3 (1-27)*	5,4 (0,5-57)
		Moderate-labor workers	2,2 (0,9-5,4)	3,2 (0,3-27)	3,1 (0,3-34)
		Light-labor workers	1 (0,04-19)	1,5 (0,1-12)	-
		Retired	7,2 (2,9-17)***	7,2 (0,9-18)	15 (1,6-37)*
Marital status	Married	Never married	2,8 (0,3-23)	3,7 (1,2-11)**	1,9 (0,2-15)
		Divorced	3,3 (1-10,4)*	4,7 (2,3-9,8)***	3,8 (1,2-12,2)**
		Widowed	4,1 (0,8-19)	7 (2,4-20)***	3,6 (0,7-16,7)**
Age groups	25–34 years	35–44 years	0,7 (0,2-2,4)	2,3 (0,6-7,8)	-
		45–54 years	2,8 (1-7,6)	3,8 (1,2-12)*	-
		55-64 years	5,7(2,2-14,5)	5,9 (1,8-19)**	2,4(0,9-6,2)*

Abbreviations: NVE — no vital exhaustion, HVE — high vital exhaustion, HR — hazard ratio, AH — arterial hypertension, MI — myocardial infarction.
Annotations: [1] — Reference group for arterial hypertension: higher managers; reference group for myocardial infarction: technical/engineering employees; reference group for stroke: managers; * — p<0,05. ** — p < 0,01, *** — p < 0,001.

of VE: 44,6%; rate of high level of VE: 22,1% (χ^2=1,597, ν=2, p>0,05) (Table 2).

Marital status of men with VE who suffered from MI was as follows: married (59.1%), never married (75%), divorced (71,4%), and widowed (100%) (χ^2=5,246, ν=6, p>0,05). Statistically significant results showing differences in the frequency of MI development were acquired in group of widowed men with VE compared with groups of never married VE-free men and married men with and without VE (χ^2=4,473, ν=1, p<0,05; χ^2=27,159; χ^2=16,789, ν=1, p<0,0001, respectively). Significant difference was also found in group of divorced men with VE compared with married men with and without VE (χ^2=9,439; χ^2=4,825, ν=1, p<0,05, respectively).

Pattern of education levels in men with MI and VE was as follows: university degree (16%); undergraduate/college degree (16%); high-school diploma (24%); elementary school/partially completed high school (44%) (χ^2=9,271, ν=8, p>0,05).

Significant differences in frequency of MI development were found in VE group of men who completed elementary school or partially completed high school compared with groups of men with and without VE who had university or undergraduate/college degree (χ^2=3,751; χ^2=4,552; χ^2=4,763; χ^2=3,942; ν=1, p<0,05, respectively). Groups of men with VE who had university degree, undergraduate/college degree and high-school diploma significantly differed from group of VE-free men who completed elementary school or partially completed high school (χ^2=12,694, χ^2=14,789, ν=1, p<0,0001; χ^2=8,738, ν=1, p<0,01, respectively).

Professional status of men with VE who suffered from MI was as follows: middle managers (4%); managers (4%); technical/engineering employees (4%); heavy-labor workers (20%); moderate-labor workers (16%); retired (44%) (χ^2=15,795, ν=14, p>0,05).

Statistically significant differences in frequency of MI development were found in group of retired men with VE compared with groups of VE-free middle managers, managers, technical/engineering employees, and moderate-labor workers (χ^2=3,581; χ^2=4,682; χ^2=5,233, ν=1, p<0,05; χ^2=6,174, ν=1, p=0,01; χ^2=5,279, ν=1, p<0,05; χ^2=7,247, ν=1, p<0,01, respectively). Significant differences were found between VE group of moderate-labor workers and VE-free group of light-labor workers (χ^2=3,647, ν=1, p<0,05).

Unifactorial Cox proportional hazards regression model showed that MI risk among men with VE was 2,7-times higher during the first five years (95% CI 1–7; p<0,05) and 2,25-times higher during the first 10 years (95% CI 0,9–5,1; p<0,05) compared to VE-free men. Upon 14 years of the screening study, MI risk among men with VE increased by 2,1 times (95% CI 1,0084–6,472; p<0,05) (Figure 2).

Multifactorial Cox proportional hazards regression model included social parameters (educational, professional, and marital statuses) and age. It showed that effect

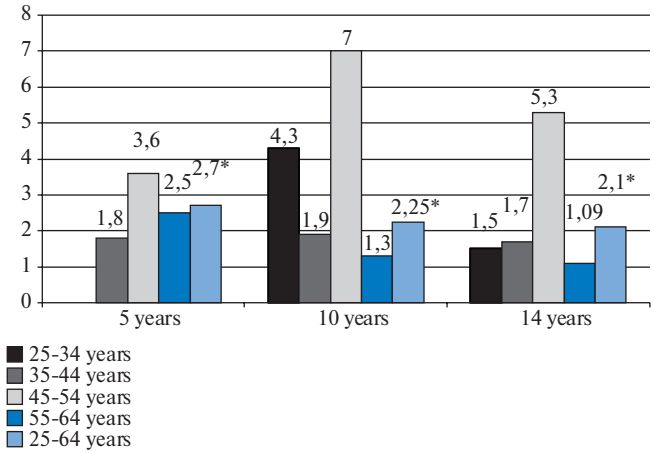

Figure 2. Comparative analysis of relative risk of myocardial infarction development in men with vital exhaustion in different age groups (unifactorial Cox model).
Annotation: * — p<0,05.

of VE on MI risk was less pronounced, but the value was still significant: 1,16 (95% CI 0,6–2; p<0,05) (Table 4).

Prevalence rate of VE in cohort of men with stroke was 59% (rate of moderate level of VE: 41%; rate of high level of VE: 18%) (χ^2=5,219, ν=1, p>0,05) (Table 2).

Marital status of men with VE who suffered from stroke was as follows: never married (5,9%), married (64,7%), divorced (23,5%), and widowed (5,9%) (χ^2=2,579, ν=1, p>0,05).

Statistically significant differences in frequency of stroke were found in group of divorced men with VE compared with groups of married men with and without VE (χ^2=3,696, ν=1, p=0,05; χ^2=6,619, ν=1, p<0,01, respectively). Group of married men with VE significantly differed from group of VE-free widowed men (χ^2=10,825, ν=1, p<0,001).

Pattern of education levels in men with stroke and VE was as follows: university degree (10%); undergraduate/college degree (20%); high-school diploma (10%); elementary school/partially completed high school (60%) (χ^2=1,571, ν=3, p>0,05).

Significant differences in frequency of stroke events were documented in group of men with VE who finished only elementary school or partially completed high school compared with groups of men with VE who had university degree, undergraduate/college degree, and high-school diploma (χ^2=4,272; χ^2=4,334; χ^2=3,590, ν=1, p<0,05, respectively).

Professional status of men with VE who suffered from first-time stroke was as follows: managers (10%); heavy-labor workers (20%); moderate-labor workers (20%); retired (50%) (χ^2=0,918, ν=3, p>0,05).

Statistically significant differences in frequencies of stroke were found between VE groups of retired men and moderate-labor workers (χ^2=3,359; ν=1, p<0,05). Groups of managers and heavy- and moderate-labor workers with VE significantly differed from group of VE-free retired

men (χ^2=7,471, ν=1, p<0,01; χ^2=15,182; χ^2=17,683, ν=1, p<0,0001, respectively).

Unifactorial Cox proportional hazards regression model showed that risk of stroke among men with VE was

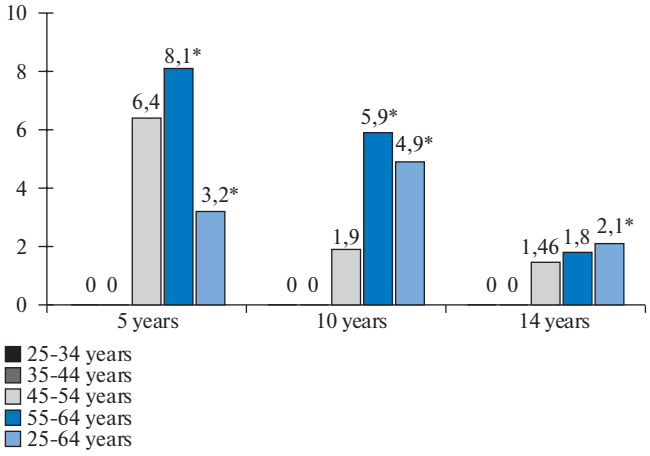

Figure 3. Comparative analysis of relative risk of stroke in men with vital exhaustion in different age groups (unifactorial Cox model).
Annotation: * — p<0,05.

3.2-times higher during the first five years (95% CI 1–9; p<0,05) compared to VE-free men. Presence of VE increased risk of stroke in group of 55–64-year-old men increased by 8,1 times (95% CI 1–63; p<0,046) (Figure 3).

Multifactorial Cox proportional hazards regression model included social gradient and age. It showed that risk of stroke in men with VE was 2,6 (95% CI 1–6,8; p<0,05) (Table 4).

Genotyping data from men with different level of VE showed that carriers of genotype 7/7 were present more often in group of men with high level of VE (2,6%) compared to other groups (χ^2=39,186, ν=36, p>0,05). Carriers of allele 7 were present more often in group with high level of VE (3,3%) compared with VE-free group (1,2%) (Table 5).

Men, carriers of genotype 9/9 in DAT gene, were present significantly more often in high-VE-level group (15,2%) than in moderate-VE-level group (2,3%) with OR=7,4 vs. carriers of other genotypes (95% CI 2,4–22,6) (χ^2=16,238, ν=1, p<0.0001); OR=7,5 vs. carriers of geno-

Table 5

Frequencies of genotypes and alleles of VNTR polymorphisms in DRD4 gene in population and their association with vital exhaustion

Genotypes of DRD4 gene	Population		Vital exhaustion					
			No		Moderate		High	
	n	%	n	%	n	%	n	%
2/2	26	6,1	8	6,3	17	7,7	1	1,3
2/3	1	0,2	0	0	1	0,5	0	0
2/4	53	12,5	20	15,6	23	10,4	10	13,2
2/5	2	0,5	1	0,8	1	0,5	0	0
2/6	10	2,4	4	3,1	6	2,7	0	0
2/7	1	0,2	1	0,8	0	0	0	0
3/3	8	1,9	1	0,8	4	1,8	3	3,9
3/4	24	5,6	8	6,3	9	4,1	7	9,2
3/6	3	0,7	1	0,8	1	0,5	1	1,3
3/7	2	0,5	0	0	2	0,9	0	0
4/4	246	57,9	69	53,9	133	60,2	44	57,9
4/5	4	0,9	1	0,8	1	0,5	2	2,6
4/6	18	4,2	7	5,5	8	3,6	3	3,9
4/7	9	2,1	2	1,6	6	2,7	1	1,3
4/8	1	0,2	0	0	0	0	1	1,3
5/5	3	0,7	1	0,8	2	0,9	0	0
5/6	2	0,5	1	0,8	0	0	1	1,3
6/6	9	2,1	3	2,3	6	2,7	0	0
7/7	3	0,7	0	0	1	0,5	2	2,6
Allele			χ^2=39,186, u=36, p=0,329					
2	26	6,1	42	16,4	65	14,7	12	7,9
3	9	2,1	11	4,3	21	4,8	14	9,2
4	323	76,0	176	68,8	313	70,8	112	73,7
5	9	2,1	5	2	6	1,4	3	2
6	42	9,9	19	7,4	27	6,1	5	3,3
7	15	3,5	3	1,2	10	2,3	5	3,3
8	1	0,2	0	0	0	0	1	0,7
			χ^2=20,495, u=12, p=0,058					

type 9/10 (95% CI 2,3–24,3) (χ^2=13,815, ν=1, p<0,0001), and OR=7,3 vs. carriers of genotype 10/10 (95% CI 2,3–23,11) (χ^2=14,769, ν=1, p=0,0001) (Table 6).

Table 6

Frequencies of genotypes and alleles of VNTR polymorphisms in DAT gene in population and their association with vital exhaustion

Genotype of DAT gene	Population		Vital exhaustion					
			No		Moderate		No	
	n	%	n	%	n	%	n	%
8/8	4	1	2	1,6	2	0,9	0	0
9/9	15	3,7	0	0	5	2,3	10	15,2***
6/10	3	0,7	1	0,8	1	0,5	1	1,5
8/10	1	0,2	1	0,8	0	0	0	0
9/10	149	36,6	49	38,3	79	37,1	21	31,8
10/10	223	54,8	73*	57	118	55,4	32	48,5
10/11	4	1,0	1	0,8	3	1,4	0	0
10/12	1	0,2	1	0,8	0	0	0	0
11/11	7	1,7	0	0	5	2,3	2	3,0
Allele			χ^2=41,076, u=16, p=0,001					
	n	%	n	%	n	%	n	%
6	3	0,4	1	0,4	1	0,2	1	0,8
8	9	1,1	5	2	4	0,9	0	0
9	179	22	49	19,1	89	20,9	41	31,1**
10	604	74,2	199	77,7	319	74,9	86	65,2
11	18	2,2	1	0,4*	13	3,1	4	3
12	1	0,1	1	0,4	0	0	0	0
			χ^2=19,792, u=10, p=0,031					

Annotation: * — p<0,05. ** — p<0,01, *** — p<0,001.

Discussion

In current medicine, there is a generally accepted view that psyche is the most sophisticated and vulnerable apparatus of human adaptation to social and ecological environment. Therefore, this type of adaption may fail the first in cases when the extreme pressure, especially in a situation of chronic stress, has an effect on the organism [39-42]. According to G. Selie's concept of general adaptation syndrome, the long-lasting uncontrollable physical and psychological distress leads to decompensation stage characterized with increased anxiety, depression, feelings of helplessness and despair, which eventually result in the exhaustion stage [43]. In our population, high level of VE occurred more often in the older age groups.

In Russia, similarly to the rest of the world, cardiovascular diseases (AH, MI, and stroke) remain one the most challenging problems of cardiology [44]. Our data showed that vital exhaustion increased the risk of AH development by over three times during the first five years of the study. The strongest effect of VE on the risk of AH development was found in divorced men. The concept of VE is relatively young; this phenomenon was mainly studied as a condition preceding IHD [1-6]. Population-based studies of the effects of VE on AH risk are absent. There are only indirect indications of the pathophysiological mechanisms that occur, for example, via the development of atherosclerosis in young people with VE [13, 14] which perhaps can explain our results [47-49].

Our data showed that the risk of MI development was almost three times higher during the first five years of the study among men with VE compared with those who were VE-free. Vital exhaustion increased the MI risk by over two times during the first 10 and 14 years of observation. Investigation of social gradient demonstrated that the risk of MI development was higher among those men with VE who had elementary level of education and/or belonged to the categories of heavy-labor workers and middle-managers. This heterogeneity of social status of people in whom VE increased the risk of MI development is essential for the phenomenon of VE defined as "mental condition characterized with excessive fatigue, feelings of demoralization or frustration, and increased irritability" whose contributing factors include conflict situations at workplace which explains such a high MI risk in this category of people [1-6, 9]. Influence of marital status is undeniable: the MI risk is higher in men who are divorced, widowed or never married.

Prerequisite for studying the effects of VE on the risk of stroke was the fact that feeling of fatigue is often diagnosed after stroke though many stroke patients reported fatigue before the disease [10, 11]. In our study, VE increased the risk of stroke development by 3,2 times during the first five years of observation. Notably, maximum risk of stroke was documented in the older age group. During 10-year period, risk of stroke increased in main population and decreased in 55–64-year-old age group. Our results agree well with results of prospective cohort study conducted by G. E. Schuitemaker et al. [10] who showed that the risk of stroke in individuals with VE increased by 13% together with an increase in MQ score derived from every single item on the questionnaire scale. This indicator remained statistically significant after standardization based on other risk factors such as systolic blood pressure, diastolic blood pressure, diabetes mellitus, and smoking suggesting that effect of VE on the risk of stroke development was independent of traditional factors. The risk of stroke was higher in men with VE and elementary education level, which perhaps may be explained by the fact that individuals who suffered from stroke mainly belonged to the older age group with predominance of retired men or to the group of heavy- and moderate-labor workers.

Symptoms of VE occurred equally frequently among both married men and men without family (divorced and widowed). Nevertheless, frequency of stroke was higher in divorced and widowed men with VE.

Coordinated work of brain mediators and modulators underlies emotional state and behavior in humans and animals [50]. This provided rationale for our study whose main objective was to analyze association between VE and DRD4 and DAT genes that belong to dopaminergic system of the brain.

Among men with different levels of VE, our data showed that VE increased together with an increase in number of VNTR polymorphisms in DRD4 gene. The high levels of VE were present significantly more often in carriers of allele 7 of DRD4 gene.

According to our current understanding of the dopamine biosynthesis, this mediator is involved in the process of adaptation. Deficit of dopamine leads to exhaustion of the nervous system whereas its increased level results in bipolar disorder [52-57].

It has been shown that affinity of dopamine to the receptor is decreased in individuals with long form of DRD4 gene (number of tandem repeats of six and more). These people are less sensitive to dopamine. Therefore, they require stronger stimulation to achieve the same reaction compared with carriers of short form of the gene [58-60]. This may likely be a cause of the high prevalence rate of genotypes with long alleles of DRD4 gene in men with VE.

As in the case of the DRD4 gene, VNTR polymorphisms in DAT gene can be associated with some pathological conditions where dopamine metabolism is altered [61]. Carriers of VNTR polymorphism of genotype 9/9 of DAT gene were present more often among men with the high level of VE. Similarly, the carrier ship of allele 9 increased chances for pertaining to the above-mentioned group.

Despite available literature is lacking, the reports of studies on associations between VE and VNTR polymorphisms in the dopamine transporter gene, it is nevertheless known that these polymorphisms can be associated with some human pathological conditions where the abnormalities in brain dopaminergic system play the key pathogenetic role. It is known that individuals with short form of DAT gene in genome more often develop posttraumatic stress disorder [53, 63], which can explain the obtained results. It should be noted that the genetic traits found in open male population can be responsible for pathophysiologic alterations in functions and compensation abilities of dopaminergic system, being the predisposing background for development of psychological and social risk factors of cardiovascular diseases (AH, MI, and stroke).

Conclusion

1. The study revealed high prevalence rate (66,8%) of vital exhaustion in open population of 25–64-year-old men, residents of Novosibirsk.

2. Risks of arterial hypertension, myocardial infarction, and stroke were maximal in the presence of vital exhaustion during the first five years of study. Ten- and 14-year risks of arterial hypertension and myocardial infarction decreased compared with corresponding 5-year risks. Ten-year risk of stroke significantly increased in open population of 25–64-year-old men.

3. Vital exhaustion and components of social gradient (education, professional status, marital status, and age) are predictors of development of arterial hypertension, myocardial infarction, and stroke in open population of 25–64-year-old men.

4. The high level of vital exhaustion was significantly associated with allele 7 of DRD4 gene and genotype 9/9 of DAT gene.

References

1. Appels A. Psychological prodromata of myocardial infarction and sudden death. Psychother Psychosom. 1980; 34:187–95.
2. Appels A, Otten F. Exhaustion as precursor of cardiac death. Br J Clin Psychol. 1992; 31: 351–6.
3. Appels A, Mulder P. Fatigue and heart disease. The association between 'vital exhaustion' and past, present and future coronary heart disease. J Psychosom Res. 1989; 33: 727–38.
4. Cole WR, Kawachi I, Sesso HD. Sense of exhaustion and coronary heart disease among college alumni. Am J Cardiol. 1999; 84: 1401–5.
5. Pignalberi C, Patti G, Chimenti C, et al. Role of different determinants of psychologival distress an acute coronary syndrome. J. Am. Coil. Cardiol. 1998;32(3): 613-9.
6. Prescott E, Holst C, Grønbaek M, et al. Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study. Int J Epidemiol. 2003; 32: 990–7.
7. Gafarov VV, Gagulin IV. Epidemiological approach to the study of psychosocial factors. Bulletin of Siberian Branch of the USSR Academy of Medical Sciences. 1993; 3: 77-81.
8. Gafarov VV, Pak VA, Gagulin IV, Gafarova AV. Epidemiology and prophylactics of chronic noncommunicable diseases during two decades and in the period of social-economic crisis in Russia (Publishing House of Siberian Branch of the Russian Academy of Sciences, Novosibirsk, 2000) 282 p.
9. Bages N, Appels A, Falger PR. Vital exhaustion as a risk factor of myocardial infarction: a case-control study in Venezuela. Int J Behav Med. 1999; 6: 279-90.
10. Schuitemaker GE, Dinant GJ, van der Pol GA, Appels A. Assessment of vital exhaustion and identification of subjects at increased risk of myocardial infarction in general practice. Psychosomatics. 2004; 45: 414-8.
11. Schwartz SW, Carlucci C, Chambless LE, Rosamond WD. Synergism between smoking and vital exhaustion in the risk of ischemic stroke: evidence from the ARIC study. Ann Epidemiol. 2004; 14: 416-24.
12. Williams JE, Mosley TH Jr, Kop WJ, et al.. Vital exhaustion as a risk factor for adverse cardiac events (from the Atherosclerosis Risk In Communities [ARIC] study). Am J Cardiol. 2010; 15: 1661-5.
13. Chumaeva N, Hintsanen M, Ravaja N, et al. Chronic stress and the development of early atherosclerosis: Moderating effect of endothelial dysfunction and impaired arterial elasticity. Int J Envinron Res Public Health. 2009; 6: 2934–49.
14. Chumaeva N, Hintsanen M, Ravaja N, et al. Interactive effect of long-term mental stress and cardiac stress reactivity on carotid intima-media thickness: The Cardiovascular Risk in Young Finns study. Stress. 2009; 12: 283–93.
15. Schuitemaker GE, Dinant GJ, Van Der Pol GA, et al. Vital exhaustion as a risk indicator for first stroke. Psychosomatics. 2004; 45: 114-8.
16. Kornerup H, Marott JL, Schnohr P, et al. Vital exhaustion increases the risk of ischemic stroke in women but not in men: results from the Copenhagen City Heart Study. J Psychosom Res. 2010; 68: 131-7.
17. Elovainio M, Jokela M, Kivimäki M, et al. Genetic Variants in the DRD2 Gene Moderate the Relationship Between Stressful Life Events and Depressive Symptoms in Adults: Cardiovascular Risk in Young Finns Study. Psychosomatic Medicine. 2007; 69: 391-5.
18. Kivimäki M, Vahtera J, Elovainio M, et al. Death or illness of a family member, violence, interpersonal conflict, and financial difficulties as predictors of sickness absence: longitudinal cohort study on psychological and behavioral links. Psychosom Med. 2002; 64: 817–25.
19. Pani L, Porcella A, Gessa GL The role of stress in the pathophysiology of the dopaminergic system. Mol Psychiatry. 2000; 5: 14–21.
20. Paes de Sousa M, Tropa J. Evaluation of the efficacy of amineptine in a population of 1,229 depressed patients: results of a multicenter study carried out by 135 general practitioners. Clin Neuropharmacol. 1989;12: 77–86.
21. World Health Organization (1985). Proposal for the Multinational Monitoring of Trends in cardiovascular disease. Geneva.
22. World Health Organization (1988). MONICA Psychosocial Optional Study. Suggested Measurement Instruments. Copenhagen: WHO Regional Office for Europe.
23. Appels A, Mulder P. Excess fatigue as a precursor of myocardial infarction. Eur Heart J 1988; 9: 758-64.
24. Appels A, Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. Int J Cardiol. 1988; 17: 15-24.

25. The WHO MONICA Project. A worldwide monitoring system for cardiovascular diseases: Cardiovascular mortality and risk factors in selected communities. World Health Stat A 1989; 27-149.
26. WHO MONICA Project prepared by Kuulasmaa K. et al. Baseline population survey data book. MONICA Memo 178 A. Helsinki, 1990
27. Tunstall-Pedoe H, editor. Prepared by Tunstall-Pedoe H, Kuulasmaa K, Tolonen H, Davidson M, Mendis S with 64 other contributors for The WHO MONICA Project. MONICA Monograph and Multimedia Sourcebook. Geneva: World Health Organization; 2003. ISBN 92 4 1562234.
28. WHO MONICA Project prepared by Asplund K., et al. Stroke event registration quality report. MONICA Memo 212 A. — Helsinki. 1999.
29. Gafarov V.V., Gafarova A.V. Long-term trends and determinants of myocardial infarction morbidity, mortality, and lethality in Russian population. Internat.J.Med.and Med.Sci.— 2012; 2(11): 256-62.
30. Brien E. Blood pressure measuring devices: recommendations of the European Society of Hypertension. BMJ. 2001; 322: 531–36.
31. Lichter JB, Barr CL, Kennedy JL, et al. A hypervariable segment in the human dopamine receptor (DRD4) gene. Hum. Mol. Genet. 1993; 2:767-73.
32. Maniatis T, Fritsch EF, Sambrook J, Methods of genetic engineering. Molecular cloning (Trans. in Russian language) (Mir Publishing House, Moscow, 1984) 357 p.
33. Smith CL, Klco SR, Cantor CR. Pulsed Field Gel Electrophoresis and the Technology of Large DNA Molecules. In Davies K, editor. Genome Analysis: A Practical Approach. Translation from English. Moscow. Mir Publishers, 1990: 58-94.34. Nanko S, Hattori M, Ikeda K, Sasaki T, Kazamatsuri H, Kuwata S Dopamine D4 receptor polymorphism and schizophrenia. Lancet. 1993; 341: 689-90.
35. Glants C. Biomedical statistics. Translated from English. Moscow. 1998. Practika.
36. Cox D.R. Regression Models and Life Tables. Journal of the Royal Statistical Society Series B. 1972; 34: 187–220.
37. Nasledov AD, Mathematical approaches of psychological study. Analysis and data interpretation (St. Petersburg, 2004) 388 p.
38. Bühl A, Zöfel P. SPSS Version 11,5. Einführung in die moderne Datenanalyse unter Windows, 2005, 608 p.
39. Gafarov VV, Gromova EA, Kabanov YuN, Gagulin IV. Personality and its interaction with social environment: the road untrodden (Publishing House of Siberian Branch of the Russian Academy of Sciences, Novosibirsk, 2008) 280 p.
40. Gromova H, Gafarov V, Gagulin I. Depression and risk of cardiovascular diseases among male aged 25-64 (WHO MONICA-psychosocial). J. Alaska Medicine. 2007: 2(49): 242-5.
41. Gafarov V, Gromova H, Gagulin I., et al. Arterial hypertension, myocardial infarction and stroke: risk of development and psychosocial factors. J. Alaska Medicine. 2007; 2(49): 114-6.
42. Gagulin IV, Gafarov AV, Gafarov VV, Pak VA. Breathes Vital Exhaustion And Its Relationship With Other Psychosocial Factors And Coronary Heart Disease. World of Science, Culture, Education. 2010; 3 (22): 178-80.
43. Selye H. The stress of life. New York: McGraw-Hill, 1977. 515p.
44. Oganov RG, Kalinina AM, Maslennikova GY, Koltunov IE, Prerequisites of prophylactics of cardiovascular diseases in the Russian Federation. Cardiovascular Therapy and Prophylactics. 2010; 6:4-9.
45. Ayvazyan TA, Psychorelaxation in the treatment of hypertension. Cardiology. 1991; 31: 95-8.
46. Marrkovitz JH, Matthews KA, Kannel WB Psychological predictors of hypertension in the Framingham study. Is there tension in hypertension in the tension in hypertension? J.A.M.A., 1993; 270: 2439-43.
47. Gafarov VV, Gromova EA, Gagulin IV, Pilipenko PI The study of risk for development of myocardial infarction according to WHO MONICA-Psychosocial program. The Journal of Neurology and Psychiatry n.a. S.S. Korsakova. Stroke. Supplement. 2005; 13: 36-41.
48. Gafarov VV, Gromova EA, Gagulin IV, Gafarova AV. Study of myocardial infarction risk factors within the framework of the WHO Monica-psychosocial program. Klin Med (Mosk). 2006; 84(6): 24-6.
49. Gafarov VV, Gromova EA, Gafarova AV, et al. Vital exhaustion in open population of 25–64-year-old men (epidemiological study based on WHO MONICA-Psychosocial program). Bulletin of Siberian Medicine. 2009; 1:(2)(8), 19-22.
50. Alfimova MV, Golimbet VE, Genes and neurophysiological indicators of cognitive processes: overview of the studies. Journal of Higher Nervous Activity n.a. I.P. Pavlov. 2011; 61: 389-401.
51. Korsten P, Mueller JC, Hermannstädter C, et al. Association between DRD4 gene polymorphism and personality variation in great tits: a test across four wild populations. Mol Ecol. 2010; 19: 832-43.
52. Cloninger CR A systematic method for clinical description and classification of personality variants: A proposal. Arch. Gen. Psychiatry. 1987; 44: 573–88.
53. Cloninger CR, Svrakic DM Integrative psychobiological approach to psychiatric assessment and treatment. Psychiatry. 1997. 60: 120–41.
54. Cloninger CR, Zohar AH Personality and the perception of health and happiness. J Affect Disord. 2011; 128: 24-32.
55. Greenwood TA, Schork NJ, Eskin E, Kelsoe JR. Identification of additional variants within the human dopamine transporter gene provides further evidence for an association with bipolar disorder in two independent samples. Mol. Psychiatry. 2006; 11: 125-33.
56. Mazei-Robison MS, Couch RS, Shelton RC, et al. Sequence variation in the human dopamine transporter gene in children with attention deficit hyperactivity disorder Neuropharmacology. 2005.; 49: 724-36.
57. Gafarov V, Voevoda M, Gromova E, et al. Genetic markers for trait anxiety as the risk factors for cardiovascular diseases (WHO-MONICA Program and MONICA-Psychosocial Subprogram). International Journal of Medicine and Medical Sciences. 2012; 2(12): 284-9.
58. Korsten P, Mueller JC, Hermannstädter C, et al. Association between DRD4 gene polymorphism and personality variation in great tits: a test across four wild populations . Mol Ecol. 2010; 19: 832-43.
59. Matthews LJ, Butler PM Novelty-seeking DRD4 polymorphisms are associated with human migration distance out-of-Africa after controlling for neutral population gene structure. Am J Phys Anthropol. 2011; 145: 382-9.
60. Ray LA, Bryan A, Mackillop J, et al. The dopamine D Receptor (DRD4) gene exon III polymorphism, problematic alcohol use and novelty seeking: direct and mediated genetic effects .Addict Biol. 2009; 14: 238-44.
61. Vandenbergh DJ, Persico AM, Hawkins AL, et al. Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. Genomics. 1992:14: 1104-6.
62. Gelernter J, Kranzler HR, Satel SL, Rao PA. Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. Neuropsychopharmacology. 1994; 11: 195-200.
63. Gianaros PJ, Manuck SB. Neurobiological Pathways Linking Socioeconomic Position and Health. Psychosom Med. 2010; 72: 450–61.