

Full Length Research Paper

The role of hostility in the risk of cardiovascular diseases in open population of 25–64-year-old men in Russia/Siberia (WHO MONICA-Psychological Program)

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The purpose of the study was to investigate prevalence of hostility, risk of arterial hypertension (AH), myocardial infarction (MI), and stroke, and genetic traits in open male population in Novosibirsk (Siberia, Russia). Random representative sample of 25–64-year-old men was examined in the WHO MONICA-Psychosocial program in 1994. Hostility level was assessed by Cook-Medley test. Genotyping of VNTR polymorphisms of DRD4 and DAT genes was performed. From 1994 to 2008, all first-time cases of AH, IM, and stroke were registered among individuals without previous CVD. The level of hostility was 76.9%. Compared with control, 5-year MI risk was by 2.57 times higher (95%CI 1–6.1; $p < 0.05$) in men with hostility; hostility led to 3.2-fold increase of IM risk in older age group (95%CI 1–10; $p < 0.05$). Hostility did not increase AH and stroke risks. Dopamine receptor subtype D4 (DRD4) genotypes 4/6 and 4/7 were associated with high hostility levels; genotype 4/4 was associated with moderate and low hostility levels. No associations with DAT genotypes and alleles were found. Open population of 25–64-year-old men of Novosibirsk showed high hostility prevalence predictive of IM risk. Hostility did not affect AH and stroke risks and was associated with certain VNTR polymorphisms of DRD4 gene.

Key words: Hostility, risk, arterial hypertension, myocardial infarction, stroke, DRD4 gene, DAT gene.

INTRODUCTION

Hostility was the most intensely studied in 1980s when its association with physical health was found [Ironson *et al.*, 1992; Munakata *et al.*, 1999; James and Schluskel, 1993; Barefoot *et al.*, 1989; Kawachi *et al.*, 1996; Dembroski *et al.*, 1989; Schneider *et al.*, 1986; Smith, 1992; Linden *et al.*, 1993; Larkin, 1982; Suarez *et al.*, 1998; Brosschot and Thayer, 1998; Suarez *et al.*, 1997; Christensen and Smith, 1993; Markovitz, 1998; Scherwitz *et al.*, 1992; Musante *et al.*, 1992; Vögele, 1998; Suarez *et al.*, 1998; Lipkus *et al.*, 1994; Miller *et al.*, 1998; Barefoot *et al.*, 1995; Berkman and Syme, 1979; Blazer, 1982; House *et al.*, 1982; Orth-Gomér and Johnson, 1987; Kaplan *et al.*, 1988; Seeman *et al.*, 1993; Kawachi *et al.*, 1996]. While studying hostility, Barefoot JC *et al.* [Barefoot *et al.*, 1983]

confirmed that this particular personality trait was stable in time and contributed to prediction of cardiovascular and total mortality [Barefoot *et al.*, 1983]. These data can be interpreted as evidence that the individuals with hostility (hostile attitude to surrounding people) exert stronger and more frequent stress reactions in the everyday life. These people more often perceive different situations as threatening which leads to conflict and negative interactions [Suarez *et al.*, 1997].

Different biological mechanisms of hostile behavior have been proposed [Rozanski *et al.*, 1999]. In this context, hostility, aggressiveness, and other traits leading to cruel and abusive behavior including impulsiveness were studied. About 50% of interpersonal differences in the aggressiveness are explained by the genetic factors [Miles and Carey, 1997] perhaps related to the impact of temperament on manifestation of aggressiveness and antisocial behavior. In particular, emotional sensibility and

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Table 1. Random represented sample of 25-64-year-old men in Oktyabrsky District of Novosibirsk: screening 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

activity are considered as predictors of aggressiveness [Gjone and Stevenson, 1997] whereas antisocial personality disorder develops when there is a combination of low level of harm avoidance, high level of novelty search, and low level of reward dependence [Cloninger and Svrakic, 1997]. Biochemistry-based data reveal the presence of steady negative correlation between hostility and indicators of the dopamine system activity [36]. However, no studies in this particular area of research were performed in Russia.

Considering all above said, the aim of the study was to investigate the prevalence of hostility and its effects on 14-year risks of cardiovascular diseases (CVD) such as arterial hypertension (AH), myocardial infarction (MI), and stroke and to elucidate the genetic traits in open population of 25–64-year-old men in Russia/Siberia (West Siberian metropolis, Novosibirsk city).

MATERIALS AND METHODS

The random representative sample of 25–64-year-old men, residents in Oktyabrsky district of Novosibirsk ($n = 657$; mean age: 44.3 ± 0.4 years), was studied in a framework of the WHO MONICA-Psychosocial subprogram (MOPSY) screening III [World Health Organization, 1985; 1988] (Table 1). The response rate was 82.1%. The sample was formed according to the requirements of the WHO MONICA protocol based on the electoral lists with the use of random number method. The program of screening examination included:

1) Registration of social and demographic data. The social-demographic indicators were registered according to the requirements of the program and included identification 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, and widowed), education level (college, high school, and partially completed high school), profession (senior manager, middle manager, manager, engineering personnel, specialists, highly physically demanding job, moderately physically demanding job, physically undemanding job, student, retired, and disabled).

2) Hostility was evaluated by using the Cook-Medley

hostility questionnaire [Cook and Medley, 1954] adapted for the MONICA-MOPSY program [The WHO MONICA Project, 1989]. Respondents were asked to self-administer the questionnaire. The values of the risk factors in the initial study were taken for analysis without adjusting time series. The methods were strictly standardized and complied with the requirements of protocol of the WHO MONICA project. Processing of data was performed in the MONICA Data Centre (Helsinki, Finland). Quality control was carried out by the MONICA Quality Control Center (Dundee, Scotland; Prague, Check Republic; Budapest, Hungary). The submitted results were found acceptable [WHO MONICA Project, 1990; Tunstall-Pedoe, 2003; WHO MONICA Project, 1999].

Cardiovascular risks were studied in the representative population sample. All men with ischemic heart disease (IHD) ($n = 53$), AH ($n = 328$), MI ($n = 14$), stroke ($n = 17$), diabetes mellitus ($n = 7$), and unidentified disease ($n = 48$) were excluded from the study. The study cohort included 190 men whose initial age ranging from 25 to 64 years. The period of prospective examination of participants lasted 14 years from January 1, 1995 to December 31, 2008. The study included the following end points: first-time cases of AH, MI, and stroke. Registration of all MI cases was performed based on the WHO program: Register of Acute Myocardial Infarction [Gafarov and Gafarova, 2012]. First-time AH and stroke events were registered during the period of observation. Arterial hypertension and MI cases were identified based on the results of the annual examinations of the population cohort, medical charts, hospital discharge reports, outpatient clinic reports, interviews with relatives, autopsy reports, and medical forensic reports.

During annual examinations, the standardized measurements of arterial blood pressure (ABP) were taken according to the study protocol. Group of AH also included men whose ABP was normal at the moment of examination: these men were taking hypotensive drugs or had discontinued them less than two weeks prior the study [O'Brien et al., 2001]. During the observation period, 46 cases of first-time AH, 30 cases of MI, and 22 cases of stroke were identified.

Genotyping of the VNTR polymorphisms of the DRD4 and DAT genes was performed in the Laboratory of Mole-

Table 2. Frequencies of hostility and new cases of cardiovascular disease among 25-64-year-old men in dependence on age.

Age	First-time hypertension		arterial First-time myocardial infarction		First-time stroke		
	n	%	n	%	n	%	
1. H	25-34	3	6.5	2	9.1	-	-
	35-44	5	10.9	3	13.6	-	-
	45-54	7	15.2	5	22.7	3	25
	55-64	10	21.7	12	54.6	9	75
	25-64	25	54.3	22	73.3	12	54.6
2. NH	25-34	3	6.5	1	12.5	-	-
	35-44	4	8.7	1	12.5	-	-
	45-54	5	10.9	3	37.5	4	40
	55-64	9	19.6	3	37.5	6	60
	25-64	21	45.7	8	26.7	10	45.4
Total	46	100	30	100	22	100	
	$\chi^2 = 0.997, u = 3, p = 1$		$\chi^2 = 0.895, u = 3, p = 0.554$		$\chi^2 = 0.086, u = 3, p = 0.195$		

H: Hostility

NH: No hostility.

Table 3. Prevalence of hostility in open population of 25-64-year-old men in dependence on age.

Age groups	III (1994)									
	NH		LHL		MHL		HHL		Tota	
	n	%	n	%	n	%	n	%	n	%
25-34	47	28.7	40	24.4	25	15.2	52	31.7	164	100
35-44	32	20.4	35	22.3	37	23.6	53	33.8	157	100
45-54	29	23.8	32	26.2	24	19.7	37	30.3	122	100
55-64	29	19.5	43	28.9	27	18.1	50	33.6	149	100
25-64	137	23.1	150	25.3	113	19.1	192	32.4	592	100
	$\chi^2 = 8.316, u = 9, p > 0.05$									

NH: No hostility

LHL: Low hostility level

MHL: Moderate hostility level

HHL: High hostility level

cular Genetic Studies of the FSBI "Research Institute of Therapy" SB RAMS according to the methods described elsewhere [Lichter et al., 1993; Sambrook et al., 1984; Smith et al., 1990; Nanko et al., 1993].

Statistical analysis was carried out by using SPSS 11.5 version software. To check statistical significance of the intergroup differences, Pearson's chi-squared test was used [Glants, 1998]. Cox proportional-hazards regression model was used to assess risk coefficient, hazard ratio (HR), taking into account time series-adjusted control [Cox, 1972; Nasledov, 2004]. Associations between vital

exhaustion and VNTR polymorphisms of the DRD4 and DAT genes were assessed by calculating odds ratio (OR) and 95 % confidence interval (95% CI min-max). Values were considered statistically significant when p was < 0.05.

RESULTS

The level of hostility among 25-64-year-old men was 76.9% (Table 3). The prevalence rate of hostility in cohort

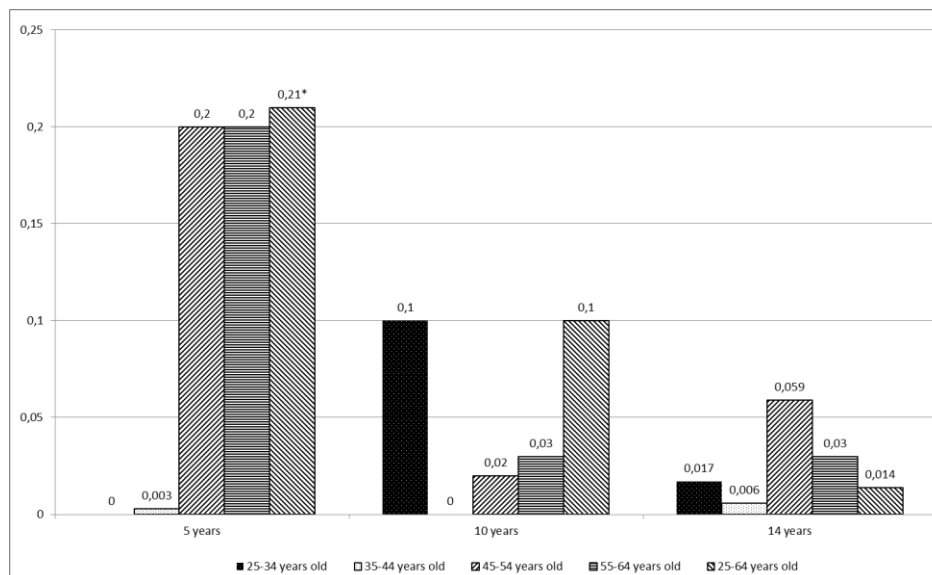


Figure 1. Comparative analysis of age-adjusted odds ratios of arterial hypertension development in individuals with hostility.

of men with first-time AH was 54.3% (Table 2).

Cox proportional-hazards regression analysis showed that hostility exerted protective effect against AH development among 25–64-year-old men for 5-year period (HR = 0.21; 95%CI 0.01–0.09). Protective tendency of hostility on the risk of AH development was documented in 25–64-year-old men for 10-year and 14-year periods: HR = 0.1 and HR = 0.014, respectively ($p > 0.05$) (Figure 1).

Among men with first-time MI, the individuals with the presence of hostility accounted for 73.7% (Table 2). Distribution of marital statuses among men with hostility was as follows: never married (11.1%); married (59.3%); divorced (18.5%); widowed (11.1%) ($\chi^2 = 4.856$, $\nu = 3$, $p > 0.05$).

Statistically significant differences in the frequency of MI occurrence were found when we compared (i) group of married hostile men with groups of divorced hostile men and widowed men with and without hostility ($\chi^2 = 8.981$, $\nu = 1$, $p > 0.01$; $\chi^2 = 15.332$, $\nu = 1$, $p < 0.0001$; $\chi^2 = 5.142$, $\nu = 1$, $p < 0.05$, respectively); (ii) groups of divorced and widowed hostile men with groups of married men with and without hostility ($\chi^2 = 4.005$, $\nu = 1$, $p < 0.05$; $\chi^2 = 8.727$, $\nu = 1$, $p < 0.01$, respectively).

The educational levels of hostile individuals with MI were distributed as follows: university diploma (17.9%); incomplete higher education/college degree (14.3%); high school diploma (17.9%); and incomplete secondary school/elementary education (50%) ($\chi^2 = 10.119$, $\nu = 3$, $p < 0.01$).

Statistically significant differences in the frequencies of MI occurrence were found when we compared (i) hostile group of incomplete secondary/elementary education with hostile groups of higher education, incomplete higher

education/college degree, and high school diploma as well as with hostility-free groups of higher education and incomplete higher education/college degree ($\chi^2 = 8.355$; $\chi^2 = 9.891$; $\chi^2 = 6.026$, $\nu = 1$, $p < 0.01$; $\chi^2 = 5.157$; $\chi^2 = 3.571$, $\nu = 1$, $p < 0.05$, respectively); (ii) hostile groups of higher education and incomplete higher education/college degree with hostility-free group of incomplete secondary education ($\chi^2 = 6.021$; $\chi^2 = 7.381$, $\nu = 1$, $p < 0.01$; $\chi^2 = 4.497$, $\nu = 1$, $p < 0.05$, respectively).

The professional statuses of men with hostility and MI were distributed as follows: middle managers (10.7%); managers (3.6%); technical engineering personnel (3.6%); highly physically demanding jobs (17.9%); moderately physically demanding jobs (7.1%); physically undemanding jobs (10.7%); and retired (46.4%) ($\chi^2 = 4.586$, $\nu = 1$, $p > 0.05$). Statistically significant differences in the frequencies of MI occurrence were found (i) between the group of retired men with hostility and the groups of managers, physically demanding jobs, and moderately physically demanding jobs with hostility ($\chi^2 = 5.814$; $\chi^2 = 6.171$, $\nu = 1$, $p < 0.01$; $\chi^2 = 18.147$; $\nu = 1$, $p < 0.0001$, respectively); (ii) between the group of physically undemanding jobs with hostility and the groups of technical engineering personnel and moderately physically demanding jobs with hostility ($\chi^2 = 5.883$; $\chi^2 = 9.483$, $\nu = 1$, $p < 0.01$, respectively); (iii) between the group of moderately physically demanding jobs with hostility and the group of highly physically demanding jobs without hostility ($\chi^2 = 6.243$, $\nu = 1$, $p < 0.01$).

In the model of Cox proportional-hazards regression, the 5-year risk of MI in 25–64-year-old men with hostility was 2.57 times higher (95%CI 1–6.1; $p < 0.05$) compared with individuals without hostility; the risk was 3.2 times higher (95%CI 1–10; $p < 0.05$) in the older age

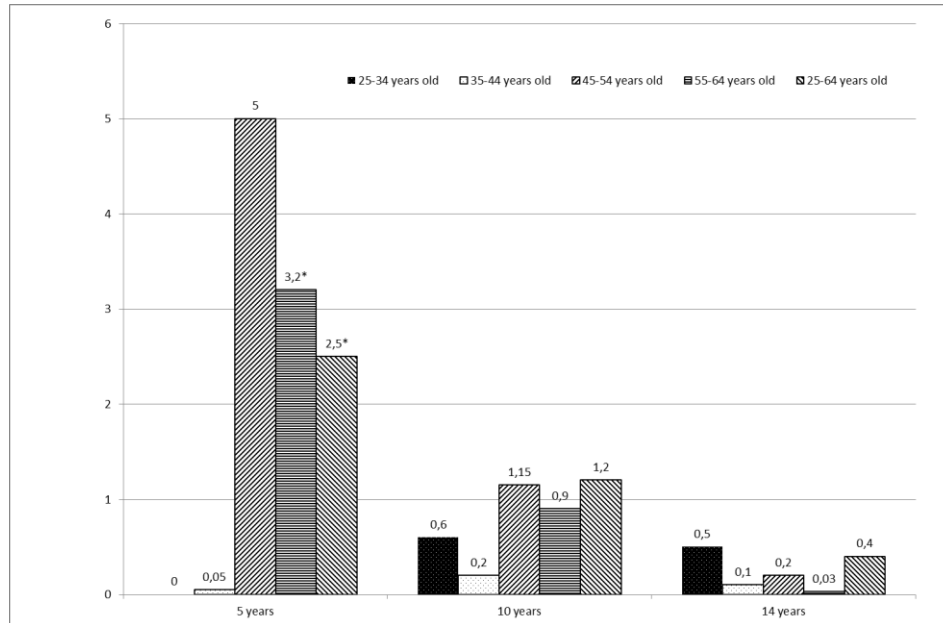


Figure 2. Comparative analysis of age-adjusted odds ratios of myocardial infarction development in individuals with hostility.

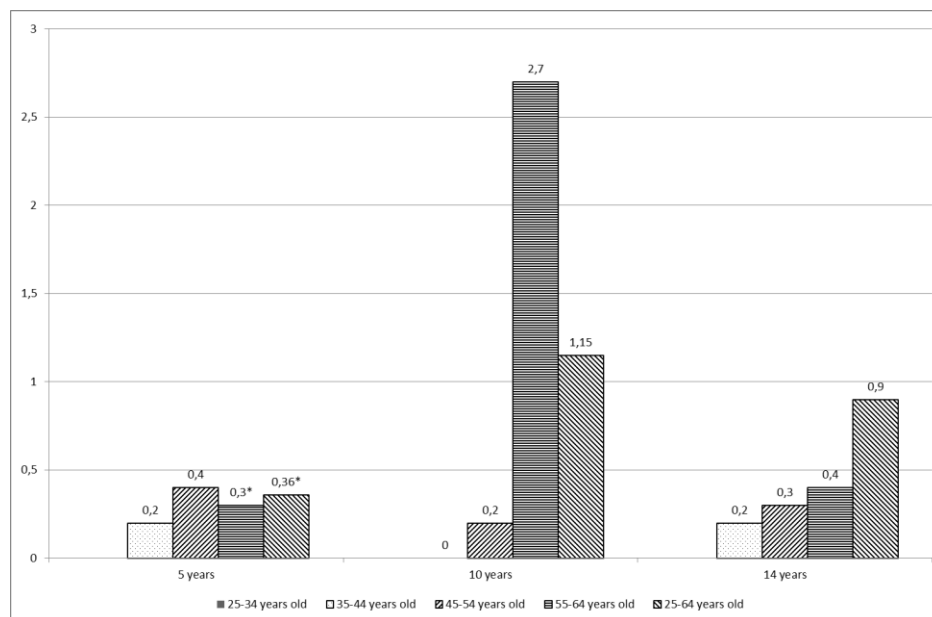


Figure 3. Comparative analysis of age-adjusted odds ratios of stroke development in individuals with hostility.

group compared with men without hostile pattern. For 10 years, the tendency of increasing MI risk in men with hostile behavior remained and the risk was 1.2 (95%CI 0.5–2.7; $p > 0.05$). For 14 years, MI risk in men with hostility was 0.4 ($p > 0.05$) (Figure 2). The rate of men with hostility among individuals with stroke was 54.6% (Table 2).

Cox proportional-hazards regression model showed the protective effect of hostility on the risk of stroke for the

first five years of the study: HR = 0.36 (95%CI 0.13–0.93; $p < 0.05$). During the next 10 years of observation, there was an insignificant tendency to increasing risk of stroke in individuals with hostility: HR = 1.2 (95%CI 0.1–10; $p > 0.05$). Fourteen years after beginning of the screening, the protective tendency of the effects of hostility on the risk of stroke was observed: HR = 0.3 (95%CI 0.1–0.9; $p > 0.05$) (Figure 3). Table 4 presents distribution of the carriers of various VBTR polymorphisms of the DRD4

Table 4. Frequencies of genotypes and alleles of VBTR polymorphisms of the DRD4 gene in population and their associations with hostility.

Genotypes	Population		Hostility							
	n	%	No		Low		Moderate		High	
			n	%	n	%	n	%	n	%
2/2	26	6.1	10	9.2	5	4.5	4	4.3	7	6.6
2/3	1	0.2	0	0	0	0	0	0	1	0.9
2/4	53	12.5	18	16.5	14	12.5	7	7.6	14	12.5
2/5	2	0.5	0	0	1	0.9	0	0	1	0.9
2/6	10	2.4	1	0.9	4	3.6	1	1.1	4	3.6
2/7	1	0.2	0	0	0	0	0	0	1	0.9
3/3	8	1.9	2	1.8	2	1.8	3	3.3	1	0.9
3/4	24	5.6	8	7.3	6	5.4	4	4.3	6	5.4
3/6	3	0.7	0	0	0	0	0	0	3	2.7
3/7	2	0.5	0	0	0	0	0	0	2	1.8
4/4	246	57.9	61	56	72	64.3*	68	73.9	45	40.2*
4/5	4	0.9	1	0.9	1	0.9	0	0	2	1.8
4/6	18	4.2	2	1.8	3	2.7	5	5.4	8	7.1
4/7	9	2.1	1	0.9	0	0	0	0	8	7.1*
4/8	1	0.2	0	0	0	0	0	0	1	0.9
5/5	3	0.7	2	1.8	1	0.9	0	0	0	0
5/6	2	0.5	1	0.9	0	0	0	0	1	0.9
6/6	9	2.1	2	1.8	3	2.7	0	0	4	3.6
7/7	3	0.7	0	0	0	0	0	0	3	2.7
$\chi^2 = 88.126, df = 54, p = 0.002$										
Alleles	n	%	n	%	n	%	n	%	n	%
2	26	6.1	39	17.9	29	12.9	16	8.7	35	15.6
3	9	2.1	12	5.5	10	4.5	10	5.4	14	6.3
4	323	76.0	152	69.7	168	75.0	152	82.6	129	57.6
5	9	2.1	6	2.8	4	1.8	0	0	4	1.8
6	42	9.9	8	3.7	13	5.8	6	3.3	24	10.7
7	15	3.5	1	0.5	0	0	0	0	17	7.6
8	1	0.2	0	0	0	0	0	0	1	0.4
$\chi^2 = 80.293, df = 18, p = 0.0001$										

gene in dependence on the level of hostility.

Comparative analysis showed that the carriers of 4/4 genotype were found more often in the group of men with moderate level of hostility (73.9%) than in the group with high level of hostility (40.2%) among the carriers of all other genotypes of the DRD4 gene ($\chi^2 = 23.263, u = 1, p < 0.0001$) and compared with the carriers of 2/4 genotype: OR = 3 (95%CI 1.1–8); ($\chi^2 = 5.178, u = 1, p = 0.023$); than in the group where hostility was completely absent (56%) compared with the carriers of all other genotypes of the DRD4 gene: OR = 2.2 (95%CI 1.2–4); ($\chi^2 = 6.990, u = 1, p < 0.01$) and compared with the carriers of 2/4 genotype 2/4 ($\chi^2 = 5.119, u = 1, p < 0.05$). The carriers of 4/4 genotype were also found more often in the group with low level of hostility (64.3%) ($\chi^2 = 13.044, u = 1, p < 0.0001$) or without hostility (56%) ($\chi^2 = 5.515, u = 1, p < 0.01$) than in the group with high level

of hostility (40.2%) compared with the carriers of all other genotypes.

On the contrary, the carriers of longer alleles of the DRD4 gene (4/6 genotype) more often had high level of hostility (7.1%) than low level of hostility (2.7%) compared with the carriers of genotype 4/4 ($\chi^2 = 4.866, u = 1, p < 0.05$); than without hostility (1.8%) compared with the carriers of 2/2 genotype ($\chi^2 = 3.844, u = 1, p < 0.05$), 2/4 genotype ($\chi^2 = 4.014, u = 1, p = 0.045$), and 4/4 genotype ($\chi^2 = 5.192, u = 1, p < 0.05$). On the contrary to the carriers of 2/4 genotype, the carriers of 4/6 genotype were found more often in the group with moderate level of hostility (5.4%) than in the group without hostility (1.8%) ($\chi^2 = 4.401, u = 1, p = 0.05$).

The carriers of 4/7 genotype of the DRD4 gene were found more often in the group with high level of hostility (7.1%) than in the group without hostility (0.9%) compared

Table 5. Frequencies of genotypes and alleles of VNTR polymorphisms of the DAT gene in population and their associations with hostility.

Genotypes	Population		Hostility							
	n	%	No		Low		Moderate		High	
			n	%	n	%	n	%	n	%
8/8	4	1	1	1	2	1.9	0	0	1	0.9
9/9	15	3.7	4	4	4	3.8	3	3.5	4	3.4
6/10	3	0.7	1	1	1	1.0	1	1.2	0	0
8/10	1	0.2	1	1	0	0	0	0	0	0
9/10	149	36.6	31	31	37	35.6	37	43	44	37.6
10/10	223	54.8	60	60	55	52.9	45	52.3	63	53.8
10/11	4	1.0	0	0	3	2.9	0	0	1	0.9
10/12	1	0.2	0	0	0	0	0	0	1	0.9
11/11	7	1.7	2	2	2	1.9	0	0	3	2.6
			$\chi^2 = 18.930, u = 24, p = 0.756$							
Alleles	n	%	n	%	n	%	n	%	n	%
6	3	0.4	1	0.5	1	0.5	1	0.6	0	0
8	9	1.1	3	1.5	4	1.9	0	0	2	0.9
9	179	22	39	19.5	45	21.6	43	25	52	22.2
10	604	74.2	153	76.5	151	72.6	128	74.4	172	73.5
11	18	2.2	4	2	7	3.4	0	0	7	3
12	1	0.1	4	2	7	3.4	0	0	7	3
			$\chi^2 = 14.553, u = 15, p = 0.484$							

with the carriers of all genotypes of the DRD4 gene (OR = 8.3, 95%CI 1.02–67.5); ($\chi^2 = 5.480, u = 1, p < 0.01$), 2/4 genotype ($\chi^2 = 5.756, u = 1, p < 0.01$), 3/3 genotype ($\chi^2 = 3.704, u = 1, p < 0.05$), 3/4 genotype ($\chi^2 = 4.874, u = 1, p < 0.05$); and 4/4 genotype ($\chi^2 = 7.199, u = 1, p < 0.001$). Hostility was absent more often in the carriers of 2/2 genotype (9.2%), 2/4 genotype (16.5%), and 3/4 genotype (7.3%). High level of hostility in the carriers of 2/6 genotype and 6/6 genotype of the DRD4 gene was found equally frequently (3.6%). The carriers of 3/3 genotype of the DRD4 gene more often had moderate level of hostility (3.3%). Carriership of other genotypes of the DRD4 gene in men with different levels of hostility did not exceed 3% ($\chi^2 = 88.126, u = 54, p < 0.01$).

Distribution of the levels of hostility among the carriers of alleles of the DRD4 gene ($\chi^2 = 80.293, u = 18, p < 0.0001$) is presented in Table 4. Allele 4 of the DRD4 gene was found more often in the group with moderate level of hostility (82.6%) than in the group with high level of hostility (57.6%) both among the carriers of all other alleles ($\chi^2 = 29.496, u = 1, p < 0.0001$) and compared with the carriers of allele 2 (OR = 2.5, 95%CI 1.3–4.8); ($\chi^2 = 8.914, u = 1, p < 0.01$); than in the group with complete absence of hostility (69.7%) both among the carriers of all other alleles of the DRD4 gene (OR=2, 95%CI 1.2–3.3); ($\chi^2 = 8.985, u = 1, p < 0.01$) and among the carriers of allele 2 ($\chi^2 = 8.178, u = 1, p < 0.01$). The carriers of allele 4 were also more often found in the group with either low hostility level (75%) ($\chi^2 = 15.194, u = 1, p < 0.0001$) or without hostility (69.7%) ($\chi^2 = 7.026, u = 1, p < 0.01$) than

in the group with high hostility level (57.6%) compared with the carriers of all other alleles.

The carriers of short allele 2 were found more often in the group where hostility was absent (17.6%) than in the group with moderate hostility level (8.7%) compared with the carriers of all alleles ($\chi^2 = 7.142, u = 1, p < 0.01$). The carriers of long allele 8 were found more often in the group with high hostility level (10.7%) than in the group with moderate hostility level (3.3%) both compared with the carriers of all other alleles (OR = 3.5 95%CI 1.4–8.9); ($\chi^2 = 8.238, u = 1, p < 0.01$) and with the carriers of allele 4 ($\chi^2 = 12.605, u = 1, p < 0.0001$); than in the group with absent hostility among the carriers of all alleles ($\chi^2 = 8.164, u = 1, p < 0.01$); and than in the group of low hostility level (3.7%) ($\chi^2 = 6.087, u = 1, p < 0.01$) compared with the carriers of allele 4. The carriers of allele 7 were found more often in the group with high hostility level (7.6%) than in the group with absent hostility (0.5%) OR = 17 (95%CI 2.3–135); ($\chi^2 = 14.379, u = 1, p < 0.0001$) in comparison with the carriers of all other alleles of the DRD4 gene.

Comparative analysis of separate genotypes and alleles of the DAT gene with different levels of hostility did not reveal any associations (Table 5).

DISCUSSION

In our population, the prevalence rate of hostility was high (76.9%). High hostility level was found in 32.5% of men and

the highest level of hostility was found in the group of 35–44-year-old men (33.8%). The high rate of high hostility level can be explained by the work of Barefoot *et al.* [Barefoot *et al.*, 1998]. People with hostile attitude more often consider stressful situations as threatening [Barefoot *et al.*, 1983; Boyko, 2004] e.i. chronic stress leads to social disadaptation of the personality and to development of negative attitude to life. According to Boyko VV [Boyko., 2004], hostility develops in the situations of stress and conflict. An increase in the hostility level in middle-aged people is caused by the so called midlife crisis which occurs from 35 to 44 years of age. The course and the outcome of the midlife crisis determine further social-psychological adaptation of an individual and the degree of adaptation success [Erikson, 1996].

In our study, hostility did not increase the risk of AH development. On the contrary, we observed the protective effects. After incorporation of social characteristics into the analysis, hostility still exerted its protective effects in regard to AH. However, some social factors increased the risk of AH development in the presence of hostility, for example: elementary education level, divorce, and widowhood [Sallis *et al.*, 1987; Thomas *et al.*, 2004; Yan *et al.*, 2003]. The population-based observational prospective study CARDIA showed that the presence of hostility increased AH risk by 1.84 times ($p < 0.001$) [Yan *et al.*, 2003]. It should be noted that researchers did not observe significant increases in ABP in individuals with hostility during solving the tasks requiring strain of memory such as the arithmetic or color-word tests [Sallis *et al.*, 1987].

In our study, hostility increased 5-year risk of MI among 25–64-year-old men by more than 2 times compared with individuals without hostility. Moreover, MI risk in the older age group of men with hostility was 3.2 times higher. The tendency to increase MI risk remained in men with hostile behavior for 10- and 14-year periods. This phenomenon may be explained by the fact that the hostile behavior represents the competitive survival or defense mechanisms against stress in the modern society [van Staaden *et al.*, 2011]. On the other hand, the cause of an increase in MI risk in men with hostile pattern can be explained by the unfavorable social component. Myocardial infarction risk is higher in hostile men with elementary educational level, among managers, and middle managers. The unfavorable marital status increased risk of MI in men with hostile behavior, namely, in those who were single, divorced, and widowed. This explains why hostility did not to increase MI risk after removal of social gradient.

Our results agree well with data obtained by other researchers. For example, the study titled Kuopio Ischemic Heart Disease Risk Factor Study (Finland) showed that, in the highest quartile, men with hostility had 2-fold risk of death from all causes and 3-fold risk of death from CVD compared with men in the lowest quartile. Risk of MI development in men with hostility

increased by 2.18 times [Everson *et al.*, 1997]. The components of hostility have been studied separately and play role as well. Only potential hostility, divided into the low and high hostility categories, as well as the antagonistic interpersonal component of hostility (stylistic hostility) had positive non-regulated association with the cases of IHD. After standardizing the traditional risk factors, only dichotomous potential hostility was found a significant risk factor of IHD [Everson *et al.*, 1999]. Hostile individuals tend to cynical behavior, distrust others, and frequently release anger. It should be mentioned that the anger suppression in individuals with hostile attitudes leads to an increase in the intima-media thickness of coronary arteries compared with those who release anger [Anderson *et al.*, 2006a; 2006b; 2005]. Moreover, high level of cynical hostility was documented as an age-adjusted predictor of non-fatal and fatal CVD [Haukkala *et al.*, 2010; Möller *et al.*, 1999; van Staaden *et al.*, 2011]. Even less is known about the effects of hostility on the risk of stroke and cerebrovascular diseases.

In our study of open population of 25–64-year-old men, hostility did not increase risk of stroke (HR = 0.36). On the contrary, hostility exerted the protective action even after adjustments for social and age-related factors (HR = 0.29). According to data of the internationally-recognized literature, tendency to aggression, cruelty, and hostility is associated with the number of genes involved in the dopamine system functioning [Association of anxiety-related traits, 1996]. For example, Comings D.E. *et al.* [Comings *et al.*, 1996] found that there is an association between certain behavioral problems in school, like an expulsion from the school due to a fight, and polymorphism of the type 2 dopamine receptor DRD2 gene in the war veterans with post-traumatic stress disorder. It should be noted that aggressive behavior is found in many other genetic syndromes. Steyaert J. *et al.* (1997), described three boys with microdeletion in the chromosome 8 whose main symptoms were hyperactivity and aggressiveness whereas boys' IQ was normal though not high. Healthy boys of the early adulthood age showed an association between steady aggressiveness and long allele of the DRD4 gene [Mejia *et al.*, 1997].

Based on these premises, in our study, we analyzed the associations between the candidate dopamine system genes, in particular, the DRD4 and DAT genes, and hostility taking into account the fact that open population of 25–64-year-old men can be characterized as highly hostile.

Among carriers of long 2/6, 4/6, 4/7 and 6/6 genotypes of the DRD4 gene, high level of hostility was found more often. The situation was similar in regard to carrier ships of the long and short alleles of the DRD4 gene in the groups with different hostility levels. Individuals with longer allele variants of the DRD4 gene more often had high hostility level; the carriers of short alleles of the DRD4 gene had either low level of hostility or the absence of hostility. Analysis of the associations showed

that odds ratio of the development of high hostility level was 8 times higher than in the carriers of 4/7 genotype of the DRD4 gene compared with both the carriers of the short allele DRD4 gene genotypes and with the carriers of all other genotypes. Men, the carriers of 4/6 genotype, had high or moderate level of hostility compared with the carriers of 2/4 and 4/4 genotypes of the DRD4 gene.

The highest odds ratio of the development of high hostility level was observed in the carriers of allele 7 (OR = 17.8). The carriers of short allele 4 of the DRD4 gene, on the contrary, had 2.5-fold chance of development of the moderate level of hostility compared with the high level. Low level of hostility or complete absence of hostility were also often present. Therefore, our study showed that certain VNTR polymorphisms of the DRD4 gene were associated with hostility.

The process of dopamine uptake by the neurons plays an important role in the dopamine exchange; dopamine uptake is an active transmembrane transport via the dopamine transporter. In this, mediator reuptake is important not only for the quick termination of the effects on target organs, but also for prevention of an exhaustion of the presynaptic storage of dopamine during the rhythmic activity. Therefore, the studies of the dopamine transporter gene (DAT), localized on the chromosome 5 (5p15.3), is of high interest for researchers in regard to the pathological changes in psychological activity [Gelernter *et al.*, 1994; Sander *et al.*, 1997; Sabol *et al.*, 1999; Lerman *et al.*, 1999; Gerra *et al.*, 2005; Segman *et al.*, 2002]. However, studying the distribution of the carriers of the different DAT gene genotypes and alleles by the level of hostility did not reveal any statistically significant differences in our study. We observed only tendency to the prevalence of moderate level of hostility in the carriers of genotype 9/10 and allele 9; hostility was absent in the carriers of genotypes 10/10 and 9/9 and allele 10. No associations between separate genotypes and alleles of the DAT gene and different levels of hostility were found.

CONCLUSIONS

Data of our study provide the characterization of open 25–64-year-old male population of Novosibirsk with high prevalence rate of hostility (76.9%).

The presence of hostility significantly increased risk of MI development in open population of 25–64-year-old men with the highest values in the oldest age group (55–64 years). At the same time, hostility was not associated with risks of development of AH and stroke.

High level of hostility was significantly associated with genotypes 4/6 and 4/7 of the type 4 dopamine receptor DRD4 gene. No associations between separate genotypes and alleles of the DRD4 genes and different levels of hostility were found.

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