

Non-High Density Lipoprotein Cholesterol: A Modern Benchmark for Assessing Lipid Metabolism Disorders

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Aim. To perform a population analysis of Non-High Density Lipoprotein Cholesterol level (non-HDL-C) in Russian population and to evaluate its association with cardiovascular events.

Material and Methods. The material consisted of results obtained from 11 regions of the ESSE-RF1 Study and from 4 regions of the ESSE-RF2 Study. Study protocols were identical. The studies were performed in 2012-2014 and 2017, respectively. Endpoints were assessed in 19041 people aged 35-64 years. The median follow-up was 6.5 years in ESSE RF (1) and 3.8 years in ESSE RF(2). Analysis was performed for three lipid variables: total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C in two samples: the general population sample and the same sample without individuals with coronary heart disease (CHD), myocardial infarction (MI) and/or stroke history and not taking statins (the population sample of "without a history of cardiovascular diseases [CVD]"). The analysis of nonlinear associations was performed using the generalized additive Cox model. The combined cardiovascular endpoint was represented by cardiovascular death and nonfatal MI and stroke. Traditional and laboratory FRs, socio-demographic parameters were analyzed. The significance level for all tested hypotheses was set to be 0.05.

Results. The prevalence of elevated non-HDL-C level (≥ 3.7 mmol/L) was found to be 74.6%. No gender differences were found: there was 74.6% for men and 74.5% for women. Both mean values and prevalence of elevated non-HDL-C were increased with age in women, and its level was slightly decreased in men after 55 years old. Almost all analyzed RFs were significantly associated with elevated non-HDL-C in these two population samples. In both samples elevated TC and elevated LDL-C were associated with all-cause mortality after correction for all RFs. On the contrary, the non-HDL-C was associated with CVD combined end points. It has been shown that the risk of these end points increases uniformly with increase in levels of non-HDL-C, no nonlinear associations were found.

Conclusion. The results of a population-based analysis of non-HDL-C performed in the Russian population for the first time confirmed that elevated non-HDL-C levels contribute significantly to determining the risk of cardiovascular events in the medium term. It can be assumed that the new risk scales (SCORE2 and SCORE OP) proposed by the European Society of Cardiology and the European Society of Preventive Cardiology, which include non-HDL C instead of TC, will allow adequate assessment of 10-year cardiovascular risk for Russians. However, continued monitoring of endpoints in order to obtain stable associations is required.

Keywords: population-based study, non-high-density lipoprotein cholesterol, cardiovascular risk, ESSE-RF Study.

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Introduction

The cholesterol theory of atherosclerosis has been leading since the time of N.N. Anichkov and S.S. Khalatov. Numerous studies have established a stable relationship between elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and atherosclerotic cardiovascular diseases (ACVD), as well as mortality [1-3]. Thus, lipid-lowering therapy is considered an important strategy in the primary and secondary CVD prevention. [4-6].

For many years, an elevated LDL-C level has been considered as a major risk factor for CVD, and the success of drug therapy was due to the achievement of its target levels, determined depending on the patient's cardiovascular risk [7,8]. The work of P.H. Frost and R.J. Havel is among the first publications to introduce cholesterol that is non high-density lipoproteins cholesterol (non-HDL-C) as a tool for screening and risk assessment [9]. In 2001, the ATP III (Adult Treatment Panel III) guidelines introduced non-HDL-C as an alternative target for patients with hypertriglyceridemia [10]. And only in recent decades, a paradigm shift has taken place: the level of non-HDL-C was proposed to be considered as the main risk factor for CVD. It was found that the concentration of non-HDL-C is associated with the characteristics of the metabolic syndrome [11], and its high level correlates with the severity of coronary heart disease (CHD), especially in the presence of hypertriglyceridemia [12,13]. The question of the relationship between the level of non-HDL-C and vascular stiffness is also discussed [14]. A Brazilian study showed that the new parameter could be a useful tool for assessing the risk of arterial stiffness in postmenopausal women [14].

Non-HDL-C is the sum of all apolipoprotein (apo) B-containing lipoproteins, and its elevated levels could be regarded as a «new atherogenic dyslipidemia» [15] and consider as a first-line predictor for detecting dyslipidemia. This position is based on numerous studies comparing non-HDL-C levels with blood levels of LDL-C or apo B [16-18]. The BARI (Bypass Angioplasty Revascularization Investigation) study showed that elevated non-HDL-C level is a significant and independent predictor of non-fatal myocardial infarction (MI) [19]. In 2020, Kathariya G. et al found that non-HDL-C is a much more specific and sensitive parameter for assessing the risk of elevated systolic blood pressure than LDL-C calculated using the Friedwald formula [20].

X. Su et al. and R. Puri et al. reviewed in detail the significance of the benefits of determining the level of non-HDL-C [21,22]. First, there is no additional cost to assessing non-HDL-C, as it can be easily calculated by subtracting the level of HDL-C from the level of TC. Second, TC and HDL-C quantitation methods are standardized, so calculation of non-HDL-C is considered to be a preferred approach than direct determination of LDL-C or apo B levels, because methods for determining apo B have not been rigorously standardized. Third, fasting blood sampling is not required to determine non-HDL-C levels because its level is not affected by diet. Furthermore, the calculation of LDL-C using the Friedwald formula is invalid when triglyceride (TG) levels are >400 mg/dL. Fourth, determination of non-HDL-C levels allows to assess the content of all potentially atherogenic lipoproteins, including very low density lipoproteins cholesterol, and remnants of lipoproteins with a high content of triglycerides. Moreover, the contribution of these lipoproteins to atherogenic risk is taken into account only when determining non-HDL-C, but not LDL-C. And fifthly, LDL-C is currently considered the main target for reducing the risk of ACVD. This also applies to non-HDL-C, because LDL-C is included in the latter as the main component. Finally, an elevated level of non-HDL-C, associated with a high risk of ACVD, is largely due to the presence in the lipid spectrum of highly atherogenic small, dense LDL particles, the accumulation of which is a reflection of an increased level of triglycerides [12,23,24].

It is known that patients remain at significant residual risk of major adverse cardiovascular events when using LDL-C as the primary target of drug therapy despite aggressive treatment. There is also ample evidence to support an association between lower non-HDL-C levels and reduced CVD risk. Non-HDL-C is a more integral characteristic of atherogenic particles than LDL-C, and surpasses it in ability to predict major cardiovascular events, so the residual risk becomes significantly lower [12,21]. At present, the significance of non-HDL-C in predicting the risk of (CHD) is well studied: apparently, non-HDL-C is superior to LDL-C in terms of prognostic capabilities [13].

The 2021 guidelines for CVD prevention in clinical practice include non-HDL-C in the definition of total CVD risk instead of TC, highlighting the importance of non-HDL-C in determining CVD prevention strate-

gies and predicting the risk of major complications. Thus, reducing the level of non-HDL-C is defined as one of the main therapeutic goals [25].

Interesting data are presented in the work of K.M. Pencina et al. [26]. This study determined the extent to which non-HDL-C levels in people aged 25-40 years predict future lipid trajectories. Elevated levels of non-HDL-C detected early in life persist in most young adults during later life, leading to a significant increase of population CVD risk. The results obtained suggest that early monitoring of lipid levels in individuals aged under 40 years will identify the majority of people with a high probability of dyslipidemia throughout their life, and therefore with a high long-term risk of developing CVD [26].

At the same time some researchers believe that an elevated level of non-HDL-C is not an optimal indicator of CVD risk, and suggest considering other indicators, for example, the ratio of TC to HDL-C [27].

In Russia, the level of LDL-C is currently used as the leading risk factor for diseases associated with atherosclerosis, and the achievement of target levels for this parameter is the most important indicator of the success of lipid-lowering drugs in the treatment of dyslipidemia.

The aim of this analysis was to study the population characteristics of non-HDL-C and assess its association with cardiovascular events.

Material and methods

The material of the multicenter study «Epidemiology of Cardiovascular Diseases in the Regions of the Russian Federation (ESSE-RF)» was representative samples of free living male and female population aged 35-64 years [median age was 52 (44; 58)] from 11 regions of the Russian Federation. The study was approved by the Independent Ethics Committee of the Federal State Budgetary Institution «National Medical Research Center for Therapy and Preventive Medicine» of the Ministry of Health of Russian Federation? Federal State Budgetary Institution «National Medical Research Center for Cardiology» of the Ministry of Health of Russian Federation, and Federal State Budgetary Institution «National Medical Research Center named after V.A. Almazov» of the Ministry of Health of Russian Federation and co-executing centers. All participants signed an informed consent. Overall study response rate was about 80%. To in-

crease the power of the study, the results of the ESSE-RF2, whose protocol is identical to the protocol of the ESSE-RF1, were included into analysis. The studies were carried out in 2012-2014 and 2017, respectively.

A systematic stratified multi-stage random sample was used, formed according to the territorial principle on the basis of medical institutions.

Sample members were interviewed using a standard questionnaire developed on the basis of adapted international methods. The modular questionnaire contains socio-demographic data (gender, age, education, income level); data on smoking and alcohol consumption status; health data; disease history. This analysis included education, age, place of residence (urban/rural) and family income level.

In addition, blood pressure levels, heart rate (HR), anthropometric parameters, and the biochemical laboratory tests were measured. The following risk factors for CVD: hypertension (blood pressure, $BP \geq 140/90$ mmHg or $BP < 140/90$ mmHg with antihypertensive therapy); elevated HRR ≥ 80 beats per minute; TC ≥ 5.0 mmol/L; LDL-C > 3.0 mmol/L; HDL-C < 1.0 mmol/L for men and < 1.2 mmol/L for women; non-HDL-C > 3.7 mmol/L; elevated lipoprotein (a) (Lp(a) > 9 mg/dl); hyperuricemia (serum uric acid > 400 μ mol/l for men and > 360 μ mol/L for women); hyperglycemia (fasting plasma glucose ≥ 6.1 mmol/L); increased highly sensitive C-reactive protein ≥ 3 mg/L; reduced glomerular filtration rate < 90 mL/min/1.73 m²; obesity (body mass index ≥ 30 kg/m²); abdominal obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women); current smoking.

The prevalence of elevated non-HDL-C was estimated in 22,373 people, including 8,417 men and 13,956 women aged 35-64 years. In a biennial prospective cohort study, endpoints were determined using direct and indirect contact. We first established the participant's vital status, then the causes of death and new non-fatal CVD cases. We obtained mortality data from a regional register with ICD-10 coded causes of death. Morbidity was checked and specified according to the case histories and in the Compulsory Medical Insurance Fund.

The median follow-up was 6.5 (5.3; 6.8) years in ESSE-RF1 and 3.8 (3.6; 3.9) years in ESSE-RF2. A total of 465 all-causes deaths were included in the analysis, 174 out of them were deaths from CVD.

The combined endpoint (CEP) was CVD death plus non-fatal MI and stroke. A total of 608 CEPs were registered. 19,041 people were included in the survival analysis.

Statistical analysis was carried out using the R3.6.1 environment. Pearson's nonparametric skewness coefficient was used to estimate the deviation of the distribution from the normal one. It was calculated as the difference between the mean and median, normalized to the standard deviation. Mean and standard deviation ($M \pm SD$) were given for unimodal parameters with non-parametric skewness < 0.2 , median and interquartile range [Me (Q25; Q75)] were given for other quantitative parameters. Qualitative indicators were described by relative frequencies in percent.

Differences between two independent samples were assessed using the Mann-Whitney's test for continuous parameters, and Fisher's exact test for discrete parameters. Linear regression models were used to «adjust» for covariates. Region indicators were introduced into all regression models as covariates to exclude the effect of regions. The Kaplan-Meier's method was used to construct survival curves. Survival curves were compared by log-rank test with Holm's correction for multiple comparisons. The contribution of risk factors to mortality was assessed using univariate and multivariate Cox proportional hazards models.

The analysis was conducted in two samples: the total sample from the ESSE-RF1 and ESSE-RF2 studies, and the same sample excluding individuals with CHD, a history of MI and stroke, or those taking statins («sample without a history of CVD»).

The analysis of non-linear associations was carried out using the generalized additive Cox model. The

significance level for all tested hypotheses was taken equal to 0.05.

Results

Table 1 shows age and gender indicators of non-HDL-C in the total sample of ESSE-RF1 and ESSE-RF2 studies.

The median level of non-HDL-C doesn't differ significantly from the mean level, that is, the distribution of non-HDL-C levels is close to normal. In the Russian population, a high prevalence of elevated levels of non-HDL-C was found (≥ 3.7 mmol/L) – 74.6%. No gender differences were found: 74.6% for men and 74.5% for women. The mean values and prevalence of elevated levels of non-HDL-C increase in a gradient in women with age; a slight decrease in this parameter was noted only in men over 55 years of age. Notably, the prevalence of elevated non-HDL-C in men is higher at younger ages than in women, and conversely, the prevalence of elevated non-HDL-C in older women is higher than in men. In other words, the steepness of the age-related rise in the level of non-HDL-C in women was more pronounced.

Table 2 shows associations between social and demographic variables, risk factors, and non-HDL-C levels, demonstrating how age-adjusted non-HDL-C levels change in the presence of one or another risk factor. The data in the table show how much non-HDL-C will increase (in mmol/L; age-adjusted) with each of the risk factors. For example, in the general population, the presence of obesity (body mass index ≥ 30 kg/m²) in men was associated with an increase in non-HDL-C by 0.058 mmol/L ($p < 0.001$); hypertension will lead to a significant increase in the level of non-HDL-C by 0.047 and 0.044 mmol/L in men and women, and in a sample

Table 1. Distribution of non-high-density lipoprotein cholesterol and the prevalence of its elevated levels in the total sample of ESSE-RF 1 and ESSE-RF2 Studies

Age group, years	n	M±SD (mmol/L)	≥3.7 mmol/L (%)	≥5.7 mmol/L (%)	n	M±SD (mmol/L)	≥3.7 mmol/L (%)	≥5.7 mmol/L (%)	n	M±SD (mmol/L)	≥3.7 mmol/L (%)	≥5.7 mmol/L (%)	p*
	Overall				Men				Women				
35-44	6029	3,80±1,03	63,3	4,6	2551	4,06±1,10	72,0	7,4	3478	3,61±0,93	57,1	2,5	<0,001
45-54	7811	4,21±1,1	78,2	9,3	2914	4,26±1,14	78,9	10,4	4897	4,18±1,08	77,8	8,7	0,006
55-64	8533	4,37±1,14	81,9	11,4	2952	4,15±1,11	76,2	7,8	5581	4,49±1,13	84,8	13,2	<0,001
Total	22373	4,16±1,12	75,6	8,8	8417	4,16±1,12	75,9	8,6	13956	4,16±1,12	75,4	8,9	0,840
* - difference in the average level of non-high-density lipoprotein cholesterol in men and women (Mann-Whitney test)													

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Table 2. Average increase of non high density lipoprotein cholesterol levels under risk factor (in mmol/L, according to the ESSE-RF1 and ESSE-RF2 Studies)

Risk factor	Average increase of the non-HDL-C, level (mmol/L)*			
	Overall		Sample/population without CVD history	
	Males	Females	Males	Females
Smoking currently	+0,001 p=0,828	+0,024 p<0,001	-0,003 p=0,637	+0,023 p=0,003
Obesity	+0,058 p<0,001	+0,040 p<0,001	+0,071 p<0,001	+0,043 p<0,001
Abdominal obesity	+0,046 p<0,001	+0,058 p<0,001	+0,063 p<0,001	+0,065 p<0,001
Arterial hypertension	+0,047 p<0,001	+0,044 p<0,001	+0,060 p<0,001	+0,046 p<0,001
Elevated HR	+0,027 p<0,001	+0,028 p<0,001	+0,029 p<0,001	+0,025 p<0,001
Hyperuricemia	+0,105 p<0,001	+0,095 p<0,001	+0,118 p<0,001	+0,101 p<0,001
Elevated hsCRP	+0,056 p<0,001	+0,052 p<0,001	+0,043 p<0,001	+0,042 p<0,001
Hyperglycemia	+0,070 p<0,001	+0,069 p<0,001	+0,075 p<0,001	+0,079 p<0,001
Elevated (Lp(a)	+0,037 p<0,001	+0,074 p<0,001	+0,038 p<0,001	+0,074 p<0,001
Reduced glomerular filtration rate	+0,058 p<0,001	+0,052 p<0,001	+0,065 p<0,001	+0,057 p<0,001
Higher education	+0,020 p=0,002	-0,005 p=0,313	+0,019 p=0,005	-0,005 p=0,357
Rural	+0,004 p=0,603	+0,021 p<0,001	+0,002 p=0,821	+0,023 p<0,001
High family income	+0,026 p<0,001	-0,001 p=0,859	+0,034 p<0,001	+0,002 p=0,789
Statin intake	-0,133 p<0,001	-0,071 p<0,001	-	-
CVD history†	-0,055 p<0,001	-0,001 p=0,879	-	-
Increasing of the age by 5 years	0,006 p=0,002	0,053 p<0,001	0,012 p<0,001	0,057 p<0,001

* The calculation of the average increase of non-high-density lipoprotein cholesterol in the presence of a risk factor is adjusted by age;
† CVD history – CVD includes coronary heart disease, myocardial infarction, stroke.
CVD – cardiovascular diseases, HR – heart rate, Lp(a) – lipoprotein (a), non-HDL-C – non high-density lipoprotein cholesterol,
hsCRP – high sensitive C-reactive protein

without a history of CVD, hypertension will lead to a significant increase in the level of non-HDL-C by 0.060 and 0.046 mmol/L, respectively. The greatest increase in the level of non-HDL-C in both men and women was noted in the presence of hyperuricemia. Close, although somewhat more pronounced, associations between the level of non-HDL-C and risk factors were obtained in the sample without a history of CVD. Gender differences were no more than 0.01 mmol/L excepting smoking, while associations were found only in women. It's noteworthy that in the

population (general) sample, the presence of a history of CVD was significantly associated with a decrease in non-HDL-C level in men, but not in women.

Thus, almost all included into analysis risk factors were significantly associated with elevated levels of non-HDL-C, both in the general population and in the sample without a CVD and taking lipid-lowering drugs (Table 2). Under these conditions, it was important to analyze the relationship of non-HDL-C levels, as well as LDL-C and TC levels, with mortality and CEP.

The level of TC was negatively associated in a multivariate model with total mortality in the general sample and in the sample without a history of CVD. We didn't find significant associations between TC and CVD mortality in the general sample, while associations with CEP were found in the sample without a history of CVD. An elevated level of LDL-C only affects overall mortality in both samples and only negatively. Elevated levels of non-HDL-C increase CVD mortality in general population, and the frequency of CEP increased significantly in both samples. Figure 1 presents the association estimates for the studied lipids and all endpoints in both samples, adjusted for gender, age, body mass index, smoking, statins, and history of CVD. An increase in the level of TC by 1 mmol/L in the sample without a history of CVD statistically significantly increased the CEP by 10% ($p=0.04$). In the general sample, no relationship

was found between the level of TC and CEP. In both samples, there was no relationship between the level of LDL-C and CEP, while associations between non-HDL-C and CEP were statistically significant.

Discussion

The present study showed that the distribution of the sample from Russian regions by the level of non-HDL-C appeared to be close to the Gaussian curve, and practically didn't differ from it in similar studies [26, 28]. Mean values of non-HDL-C and the prevalence of elevated its levels didn't differ significantly between men (75.9%) and women (75.4%). We compared our results with data from other studies and found that prevalence in our study was lower than in Northern Sweden and higher than in the Greek ATTICA study, which were conducted around the same years as ESSE-RF. The intake of lipid-lowering

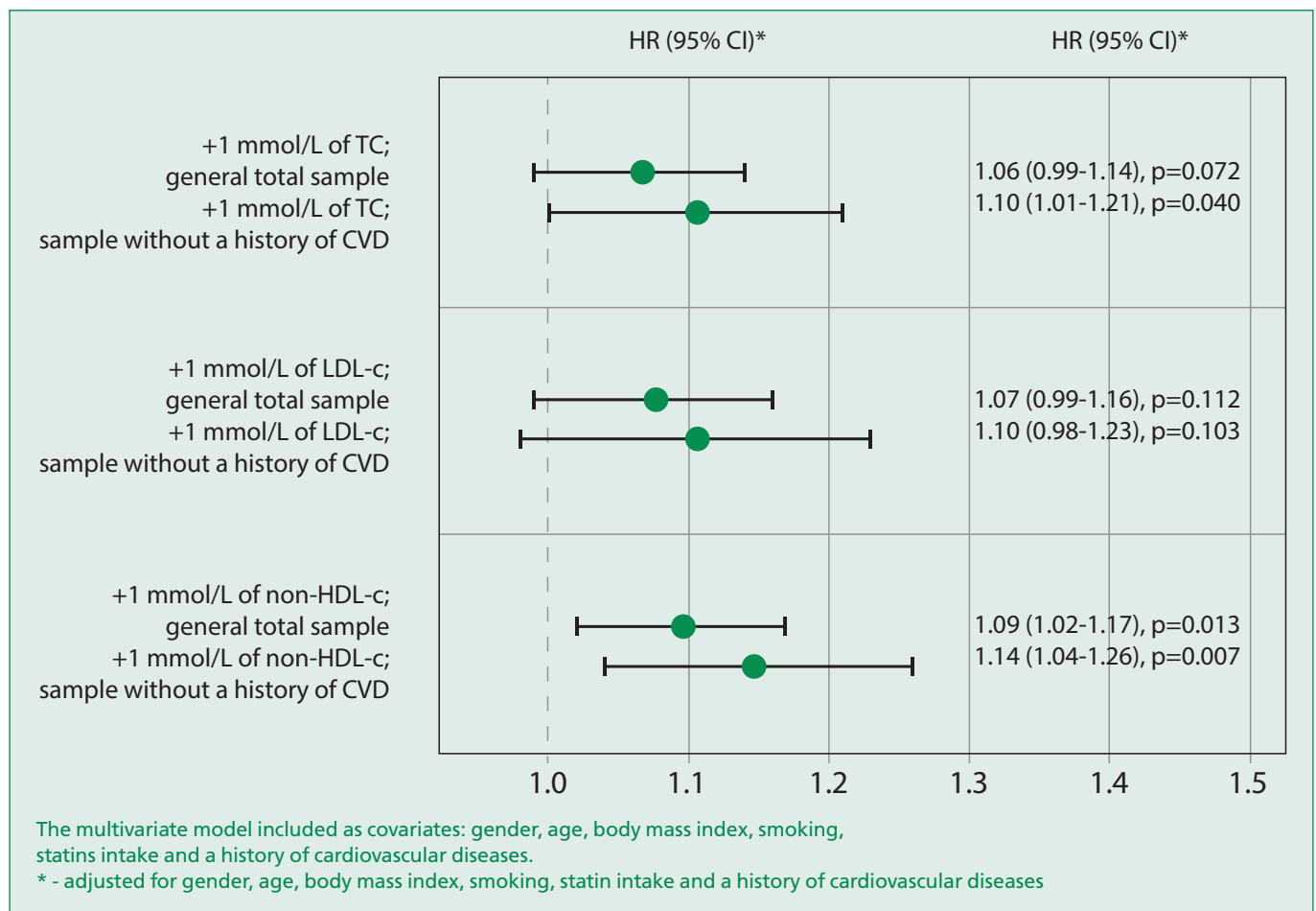


Figure 1. Hazard ratios of total cholesterol, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol for a combined endpoint in a multivariate model in a total sample and a sample without a history of cardiovascular diseases

drugs was approximately the same in these studies, but the level of non-HDL-C didn't always depend on the proportion of people taking lipid-lowering therapy; 4.4% participants in the ESSE-RF 1 and 6.6% in the ESSE-RF were taking statins, and the prevalence of non-HDL-C ≥ 3.7 mmol/L, determined according the criteria of F.J. Brunner [28] was 57.9% and 50.1%, respectively. In Northern Sweden and Greece (ATTICA), the prevalence of high non-HDL-C was 71.7% and 48.9%, and statin use was 6.7% and 5.7%, respectively [29].

In the present study, we found a direct relationship between the level of non-HDL-C and age in men from 35 to 55 years; further, the level of non-HDL-C decreased slightly. A direct relationship with age was observed in women in the range of 35-64 years. Despite the fact that the prevalence of elevated non-HDL-C level in men and women was the same in the sample as a whole, the age trend in women turned out to be steeper: from 57.1% in the group of 35-44 years old to 84.8% in the group of 55-64 years old ($p < 0.001$) compared with men. R. Zhang et al. conducted a large-scale, cross-sectional study of 49,201 men and 35,084 women to study age-related trends in LDL-C and non-HDL-C, where blood lipid levels change with age in the general population have been analyzed. Trends in non-HDL-C and LDL-C levels were plotted by age (from 18 to 85 years, in one-year increments). Positive trends in non-HDL-C levels were identified in women aged 18 to 56 years and negative trends were identified after 57 years of age. An increase in the level of non-HDL-C was observed in men from 18 to 33 years; then the level reached a plateau from 34 to 56 years, and a decrease in non-HDL-C was noted after 57 years, which was confirmed by correcting the effect of confounders [30]. Thus, the ratio between age and the level of non-HDL-C in the sample of men examined in our study turned out to be almost similar to the results of P. Zhang et al. However, these results need further analysis.

Important determinants of health are education and the family prosperity level. Non-HDL-C in men didn't depend on the level of education and family income level; but its lowest level was observed among women with higher education. Similar relationships were obtained in most other studies. Associations with the main risk factors have been described in many publications, and positive associations were

shown in most of them, as in the present study [18-20].

Of considerable interest are the results of comparing the contribution of non-HDL-C, LDL-C, and TC to all-cause and CVD mortality and their contribution to CEP, obtained in this study on the population sample and the sample without a history of CVD. In these samples, the associations of elevated levels of TC and LDL-C with all-cause death adjusted for all risk factors were found. On the contrary, the level of non-HDL-C was associated with CEP. The result of the generalized additive model (not shown) indicates the absence of a non-linear association between the relative risk in the Cox model and the onset of CEP. Thus, the use of the usual linear Cox model is justified and shows all the information about the association of non-HDL-C and CEP. The result obtained will contribute to the study of non-HDL-C as a predictor of high ACVD risk at the population level using the new scale proposed by the European Society of Cardiology and the European Society of Preventive Cardiology and will make it possible to adequately assess the CVD risk in Russia.

Study limitations. The number of endpoints may not be sufficient to conclude that non-HDL-C should be the primary lipid variable in determining ACVD risk.

Conclusion

The results of this population analysis of non-HDL-C level, conducted for the first time in the Russian Federation, generally confirm the data of other studies that the level of non-HDL-C makes a significant contribution to the cardiovascular risk detection. Nevertheless continued observation of the endpoints is required in order to obtain stable associations.

Relationships and Activities. None.

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