Rational Pharmacotherapy in Cardiology 2024;20(5):496-505
DOI:10.20996/1819-6446-2024-3101
ISSN 1819-6446 (Print)
ISSN 2225-3653 (Online)

РОССИЙСКОЕ КАРДИОЛОГИЧЕСКОЕ ОБЩЕСТВО

ORIGINAL STUDIES

Impact of non–high–density lipoprotein cholesterol in mortality and cardiovascular events among middle–aged Russian men: 40 years ago and now

Shalnova S. A.[1], Imaeva A. E.[1]*, Balanova Y. A.[1], Kutsenko V. A.[1], Kapustina A. V.[1], Metelskaya V. A.[1], Imaeva N. A.[1], Nazarov B. M.[2], Ivlev O. E.[1], Yarovaya E. B.[1,3], Drapkina O. M.[1]

[1]National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia
[2]LLC «Healthy Family», Moscow, Russia
[3]M. V. Lomonosov Moscow State University, Moscow, Russia

Aim. To evaluate the non-high density lipoprotein cholesterol (non-HDL-C) predictive ability in relation to cardiovascular events, all-cause and cause-specific mortality and among middle-aged Russian men now and 40- years ago.
Material and methods. For analysis data from 9507 men aged 35-64 without cardiovascular disease (CVD) who did not receive lipid-lowering therapy, participants of two independent population prospective cohort studies – 40-year retrospective (Russian-LRC) and conducted at the present time (ESSE-RF) – were used. In the analysis, all-cause mortality, cancer and CVD mortality, and non-fatal CVD (myocardial infarction and STEMI stroke) were assessed. The follow-up period for the LRC study was 10 years, and for the ESSE-RF study, it was 7.8 years.
Results. The mean value of non-HDL-C was 0.3 mmol/L higher among participants from the Russian-LRC cohort than among men from the ESSE-RF cohort. Low non-HDL-C levels were associated with an increased risk of all-cause mortality. A strong link between high levels of non-HDL-C and the development of fatal and non-fatal CVD events was also found in both cohorts. Men with non-HDL-C levels ⩾4.5 mmol/L in the LRC study and ⩾4.2 mmol/L in the ESSE-RF study had a significantly increased risk of fatal and non-fatal CVDs (63% and 27%, respectively) and decreased risk of cancer mortality (28% and 50%, respectively).
Conclusion. Downwards trends in non-HDL-C levels over the past 40 years were indicated. The study identified a decline of non-HDL-C in the general population level since the 1970s of the 20th century. Up to the present time, there is still a non-linear relationship between the level of non-HDL-C and total mortality, that could be explained by the presence of differently directed associations between this parameter, cancer mortality and the development of fatal and non-fatal CVDs.

Keywords: non-high-density lipoprotein cholesterol, men, dyslipidemia, all-cause mortality, cancer mortality, cardiovascular mortality, cardiovascular diseases, cardiovascular events

For citation: Shalnova S. A., Imaeva A. E., Balanova Y. A., Kutsenko V. A., Kapustina A. V., Metelskaya V. A., Imaeva N. A., Nazarov B. M., Ivlev O. E., Yarovaya E. B., Drapkina O. M. Impact of non-high-density lipoprotein cholesterol in mortality and cardiovascular events among middle-aged Russian men: 40 years ago and now. *Rational Pharmacotherapy in Cardiology.* 2024;20(5):496-505. DOI: 10.20996/1819-6446-2024-3101. EDN CHBBGM

*Corresponding Author: imaevaasiia@yandex.ru

Received: 27.08.2024
Review received: 12.09.2024
Accepted: 30.10.2024

Background

Dyslipidemia is one of the leading risk factors for atherosclerosis-related cardiovascular diseases (ACVDs). Until recently, low-density lipoprotein cholesterol (LDL-C) was considered to be one of the main parameters of the lipoprotein spectrum, which is used as a target in evaluating the effectiveness of therapeutic and preventive measures [1]. However, studies assessing exclusively LDL-C did not consider other potentially atherogenic lipoproteins, such as LDL metabolic remnants, intermediate-density lipoproteins, lipoprotein(a), and very low-density lipoproteins. As a result, non-high density lipoprotein cholesterol (non-HDL-C), representing the sum of all potentially atherogenic lipoproteins, was proposed as a new indicator of risk of CVD [2].

At present, the link with cancer is still poorly understood, while a series of studies have demonstrated significant associations between non-HDL-C and ACVDs [3, 4]. Some evidence suggests that this parameter is a somewhat better predictor of CVD mortality than LDL-C level and might be a more precise predictor for recurrent ischemic stroke and all-cause death within 1 year in patients with acute ischemic stroke [5, 6]. Liao P et al. reported that non-HDL-C levels might be a practical predictor of long-term death in patients with CHD [7]. According to the European Society of Cardiology (ESC) Guidelines on cardiovascular disease prevention in clinical practice, non-HDL-C is used as an input in the Systemic Coronary Risk Estimation 2 (SCORE2) and SCORE2-Older Persons risk algorithms [1].

However, the results of not all studies were straightforward. The meta-analysis evaluating the prognostic ability of LDL-C, non-HDL-C, and apo-B demonstrated no significant differences in the predictive accuracy of these three markers [8]. In a study of people living in the Mediterranean region, non-HDL-C levels had no effect on all-cause mortality [9]. According to other data, not only increased but also decreased levels of non-HDL-C predict the occurrence of adverse events. Hu H et al. demonstrated that high and low non-HDL-C levels were associated with a high risk of stroke and its subtypes [10]. Another study reported a U-shaped association between non-HDL-C levels and mortality in the adult population [11]. In other words, most researchers considered that additional studies devoted to detailed evaluation of non-HDL-C are necessary.

Gender is an important risk factor affecting the incidence and outcomes of CVDs. The risk factor profile and its impact on fatal and non-fatal events differ between men and women. Dyslipidemia is an important cardiovascular risk factor for both sexes, but elevated LDL-C is more likely to increase the risk of ACVD in men than in women of middle age [12]. Generally, CHD among men occurred at a younger age, and the risk of developing CHD was higher than that in women of the same age. Moreover, the mortality rate from stroke and CHD in middle-aged men was usually higher than that in middle-aged women, and these differences might remain for most of their lifetimes [13]. Similar results were obtained for cancer morbidity and mortality. According to data from various meta-analyses, the morbidity and mortality rates among men were higher than those among women [14]. In the Russian Federation, the mortality rate of middle-aged men is more than 4 times higher than that of women; therefore, the survey of the factors affecting male mortality and CVD incidence is highly relevant.

Health is often seen as an individual characteristic that changes over time due to other factors, such as habits, social and environmental factors and medical care [15]. The health status of men today and 40 years ago is assumed to differ significantly, including due to a higher prevalence of various risk factors and worse diagnosis and treatment of CVDs. The aim of the present study was to evaluate the predictive ability of non-HDL-C levels in relation to all-cause and cause-specific mortality and cardiovascular events among middle-aged men. The main advantage of this study was that the analysis concerning non-HDL-C was conducted on two representative male cohorts living in RF 40 years ago and currently.

Material and Methods

The design and methods of each study have been described in previous publications [16, 17]. The study was approved by the independent ethical committee of FGBU "NMIC TPM" of the Ministry of Health of the Russian Federation (Protocol 04-08/20 of 02.07.2020). Before participation in the study, the participants signed informed consent. The present analysis was based on data from two independent population prospective cohort studies, namely, Russian Lipid Research Clinics (Russian-LRC) and Epidemiology of Cardiovascular Diseases in the Russian Federation (ESSE-RF-1, ESSE-RF-2).

The Russian LRC was a prospective cohort study conducted from 1975-1977 that included 3,809 men aged 40 to 59 from the Moscow region of the RF. The ESSE-RF study enrolled 20,232 subjects aged 35 to 64 from 2013 (ESSE-RF-1) to 2017 (ESSE-RF-2) from 15 regions of RF. In each region, trained medical personnel, using standardized protocols, completed questionnaires, conducted physical tests, and collected and prepared blood samples for laboratory analysis in the National Medical Research Center for Therapy and Preventive Medicine (NMRC TPM).

After excluding all women, participants with a history of CVD, receiving lipid-lowering medications at baseline and with missing data on total cholesterol, HDL-C or follow-up data, a total of 9,507 men aged 35-64 were enrolled in the analysis.

All participants were interviewed using similar standard questionnaires, containing sociodemographic

data, information on smoking status, disease history (self-reported), and others. Physical tests included blood pressure (BP) measurement according to a standardized procedure on the right arm. In the Russian LRC study, BP was measured four times, first using a standard mercury sphygmomanometer and then a random zero device, with repeats of both. The BP level used for this study represented the average of two BP measurements. In ESSE-RF, the measurement was conducted three times with at least a two-minute interval between measurements using a calibrated digital electronic device (Omron M4), and the average value was taken into account.

Blood was drawn after 12-14 h of fasting. In ESSE-RF, all samples were collected according to the study protocol and prepared for shipping to NMRC TPM. The analyses were performed in the central standardized laboratory on fresh blood or serum aliquots immediately frozen after blood drawing and stored at 80°C. Total cholesterol (TC), LDL-C, HDL-C, and triglyceride levels were measured using standard methods on autoanalysers Technicon AAII (in Russian-LRC) and Abbott Architect c8000 with «Abbott Diagnostic» (USA) kits (in ESSE-RF). The level of serum non-HDL-C was calculated as TC minus HDL-C.

Follow-up was conducted in each study. In the LRC, the first contact with participants or their relatives for collecting endpoints was one year after enrollment in the study. For those who had changed their place of residence, address bureau data were used. For participants who died, death certificates were obtained. If cancer or CVDs were indicated as the cause of death or myocardial infarction (MI) and stroke as non-fatal events, the documented information was collected from the hospital or relatives. Data on non-fatal events were collected only for the first 10 years of follow-up. Thus, we included in the analysis only death records for the first 10 years of observation. In ESSE-RF, the life status of each participant was verified every 2 years. Data were collected by each region and forwarded to the NMRC TPM. Information on non-fatal events was collected through outpatient clinics, hospitals or personal (telephone) contact. Causes of death were identified through official agencies, medical centers and personal (telephone) contact with participant relatives. The median follow-up of the ESSE-RF study was 7.8 years.

In this study, all-cause mortality, cause-specific death (cancer and CVD), and non-fatal CVD (MI and stroke) were analysed as separate endpoints, and CVD mortality added to non-fatal CVDs was considered a combined endpoint.

Statistical analysis was performed using R software (version 3.5.1). Continuous variables close to symmetric are presented as the mean and standard deviation (M±sd). Skewed continuous variables are presented as medians and interquartile ranges (Me [Q1; Q3]). Categorical variables are presented as n (%). The Mann–Whitney U test was used to compare the distributions of continuous variables, and the two-sided Fisher's exact test was used to compare the distributions of categorical variables.

Associations between levels of non-HDL-C and all endpoints were estimated by Cox proportional hazards regression models with 95% confidence intervals. The analysis was carried out in accordance with the non-HDL-C percentiles. The 1st cut-off point corresponded to the target non-HDL-C value (3.4 mmol/l) according to the ESC guidelines [8] and the 2nd, 3rd, 4th, and 5th to 20%, 40%, 60%, and 80% percentiles, respectively.

Multivariable Cox regression was adjusted for age, sex, current smoking, systolic BP and region of residence. Analysis of non-fatal-only endpoints was performed on a sample from which patients with fatal endpoints were excluded.

Associations between levels of non-HDL-C and all endpoints were additionally assessed with generalized additive Cox regression with thin-plate splines using the R package mgcv [18]. Models were adjusted for age, sex, current smoking, systolic BP and region of residence. We considered outcomes statistically significant if the p value was <0.05.

Results

Baseline characteristics of participants in the Russian–LRC and ESSE–RF studies

During the 10-year follow-up period for the LRC study, 418 men died, including 184 from CVD and 156 from cancer; there were 225 cases of MI and stroke. A combined endpoint consisting of CVD death, MI or stroke was registered in 409 participants. During the follow-up period of the ESSE-RF study (7.8 years), 278 participants died from all causes, 106 from CVD, and 80 from cancer; 217 men suffered MI and stroke. The combined endpoint was registered in 623 cases. The baseline characteristics of the participants by cohort and non-HDL-C levels are presented in Table 1. The mean age of the participants in both cohorts was 49 years. At the time of the survey, more than half of the enrolled men from the Russian-LRC study were smokers. In contrast, the mean value of SBP was higher in the ESSE-RF study participants.

The mean value of non-HDL-C among participants from the Russian-LRC cohort was 0.3 mmol/L higher than that among men from the ESSE-RF cohort ($p<0.001$).

Associations between percentiles of non–HDL–C levels and mortality

In the LRC population, the occurrence of CVD, such as MI and stroke, was directly related to the level of non-HDL-C (table 2). Cardiovascular risk increased with increasing levels of non-HDL-C. A similar result was obtained for the combined point, which included fatal and non-fatal CVD events, whereas non-HDL-C was not associated with CVD mortality. On the other hand, the analysis of the relationship between non-HDL-C and all-

Table 1. Baseline characteristics of participants in Russian-LRC and ESSE-RF studies by percentiles of non-HDL-C levels

Non–HDL–C	< 3.4 mmol/L	3.4–4.1 mmol/L	4.2–4.7 mmol/L	4.8–5.4 mmol/L	> 5.4 mmol/L	All
Russian–LRC						
n (%)	527 (16)	798 (24)	669 (20)	657 (20)	663 (20)	3314 (100)
Age, years	48,4±5,2	48,9±5,1	49,0±5,1	49,3±5,2	48,9±5,1	48,9±5,1
Current smoking, n (%)	321 (60,9)	437 (54,8)	320 (47,8)	311 (47,3)	305 (46,0)	1694 (51,1)
SBP, mm Hg	133,7±20,8	131,9±20,0	133,0±20,0	133,7±21,4	135,2±21,2	133,4±20,7
Non-HDL-C, mmol/L	2,9±0,4	3,8±0,2	4,4±0,2	5,0±0,2	6,1±0,7	4,5±1,1
TC, mmol/L	4,5±0,6	5,2±0,5	5,7±0,4	6,2±0,4	7,3±0,7	5,8±1,1
HDL-C, mmol/L	1,6±0,5	1,4±0,4	1,3±0,3	1,3±0,3	1,2±0,3	1,3±0,4
LDL-C, mmol/L	2,5±0,5	3,3±0,3	3,8±0,3	4.3±0.4	5.2±0.8	3.8±1.0
Triglycerides,mmol/L	0,8 [0,6; 1,1]	1,0 [0,8; 1,3]	1,1 [0,9; 1,5]	1,4 [1,0; 1,8]	1,65 [1,3; 2,3]	0,80 [0,6; 1,1]
ESSE–RF						
n (%)	1430 (23)	1047 (17)	1239 (20)	1251 (20)	1226 (20)	6193 (100)
Age, years	47,9±8,9	49,1±8,4	49,6±8,4	49,8±8,2	49.9±8.0	49,2±8,4
Current smoking, n (%)	560 (39,2)	337 (32,2)	436 (35,2)	441 (35,3)	450 (36,7)	2224 (35,9)
SBP, mm Hg	134,5±18,5	137,2±18,8	138,6±19,2	138,8±18,9	141,2±19,4	138,0±19,1
Non-HDL-C, mmol/L	2,8±0,4	3,6±0,1	4,1±0,2	4,7±0,2	5,8±0,7	4,2±1,1
TC, mmol/L	4,2±0,6	4,9±0,3	5,4±0,4	6,0±0,3	7,1±0,8	5,5±1,1
HDL-C, mmol/L	1,3±0,4	1,3±0,3	1,3±0,3	1,3±0,3	1,3±0,3	1,3±0,3
LDL-C, mmol/L	2,4±0,5	3,1±0,4	3,5±0,4	4,0±0,4	4,8±0,8	3,5±1,0
Triglycerides,mmol/L	1,1 [0,8; 1,6]	0,9 [0,7; 1,1]	1,1 [0,8; 1,5]	1,3 [1,0; 1,8]	1,6 [1,2; 2,1]	2,0 [1,4; 3,0]

Values are presented as number (%), mean ± standard deviation, or median [Q1; Q3]; SBP – systolic blood pressure, TC – total cholesterol, HDL-C – high-density lipo-protein cholesterol, LDL-C – low-density lipoprotein cholesterol, Non-HDL-C – non-high-density lipoprotein cholesterol

cause mortality showed the opposite result. The highest values of the parameter were associated with the reduced risk of all-cause and cancer mortality by 32% and 60%, respectively. Similar results were obtained for the ESSE-RF population, although the hazard ratio (HR) values were slightly different.

Multivariable adjusted HR for mortality, CVD incidence and combined point according to levels of non-HDL-C on a continuous scale are presented in Figure 1. The association between non-HDL-C levels and the risk of all-cause mortality appeared to be L-shaped. Therefore, in both cohorts, only low levels of lipids were associated with an increased risk of all-cause mortality. There were no significant associations between non-HDL-C and CVD mortality in either cohort. The risk of cancer mortality increased in the presence of low levels of non-HDL-C, while high levels were associated with low risk. High levels of non-HDL-C predicted the incidence of MI and stroke among men in both cohorts. A strong link between high levels of non-HDL-C and the development of fatal and non-fatal CVD events was also found in both cohorts.

The assessment of non-HDL-C as a categorical variable with two levels was performed (table 3). The mean population level in each cohort was used as a cut-off point. Men from the ESSE-RF study with non-HDL-C levels 4.2 mmol/L or higher had a significantly decreased risk of death from all-causes and cancer (28% and 50%, respectively). In the LRC study, there was a 28% lower risk of cancer mortality among men with non-HDL-C concentrations ⩾4.5 mmol/L. No association was found between non-HDL-C concentrations and the risk of CVD death in either cohort. The presence of elevated non-HDL-C levels increased the risk of CVDs by 1.96 and 1.41 for Russian-LRC and ESSE-RF participants, respectively (table 3). Men with serum non-HDL-C concentrations ⩾4.5 mmol/L in the LRC study and ⩾4.2 mmol/L in the ESSE-RF study had a significantly increased risk of fatal and non-fatal CVDs.

Discussion

In the present study, the analysis was performed on two male cohorts who lived in the RF with a difference of forty years. The effect of non-HDL-C on mortality and CVD morbidity in the Russian-LRC study, conducted in 1977, had the same associations as in the ESSE-RF study performed forty years later, although mean serum concentrations of this lipid parameter were higher in

Table 2. Associations between percentiles of non-HDL-C levels and mortality

Non–HDL–C	All–cause mortality HR (95% CI)*	Cancer mortality HR (95% CI)*	CVD mortality HR (95% CI)*	MI + stroke incidence HR (95% CI)*	CVD incidence + mortality HR (95% CI)*
Russian–LRC					
<3,4 mmol/L	0,81 (0,6-1,08)	0,75 (0,48-1,18)	1,00 (0,60-1,67)	**2,04 (1,12–3,75)**	1,39 (0,95-2,05)
3,4-4,1 mmol/L	0,78 (0,57-1,06)	0,69 (0,42-1,12)	1,25 (0,75-2,08)	**2,67 (1,46–4,86)**	**1,76 (1,2–2,58)**
4,2-4,7 mmol/L	0,87 (0,65-1,18)	0,73 (0,45-1,17)	1,46 (0,89-2,39)	**3,37 (1,88–6,07)**	**2,18 (1,51–3,16)**
4,8-5,4 mmol/L	**0,68 (0,49–0,93)**	**0,4 (0,23–0,72)**	1,34 (0,81-2,20)	**3,81 (2,14–6,81)**	**2,27 (1,57–3,28)**
ESSE–RF					
3,4-4,1 mmol/L	1,07 (0,75-1,51)	1,36 (0,73-2,52)	1,60 (0,85-2,98)	**1,75 (1,04–2,92)**	**1,73 (1,16–2,57)**
4,2-4,7 mmol/L	**0,50 (0,33–0,74)**	0,51 (0,24-1,08)	0,95 (0,50-1,82)	**1,70 (1,04–2,77)**	1,40 (0,95-2,06)
4,8-5,4 mmol/L	**0,66 (0,46–0,95)**	0,66 (0,34-1,30)	0,95 (0,50-1,82)	**1,66 (1,02–2,70)**	1,37 (0,93-2,02)
>5,4 mmol/L	0,72 (0,50-1,03)	0,53 (0,26-1,09)	1,27 (0,69-2,33)	**2,84 (1,80–4,47)**	**2,19 (1,52–3,14)**

*Models were adjusted for age, sex, current smoking, education, systolic blood pressure and region of residence, HR – hazard ratio, CI – confidence interval, Non-HDL-C – non-high-density lipoprotein cholesterol, CVD – cardiovascular diseases, MI – myocardial infarction

Table 3. Associations of non-HDL-C levels according to mean level with all-cause, cancer mortality and combined endpoint

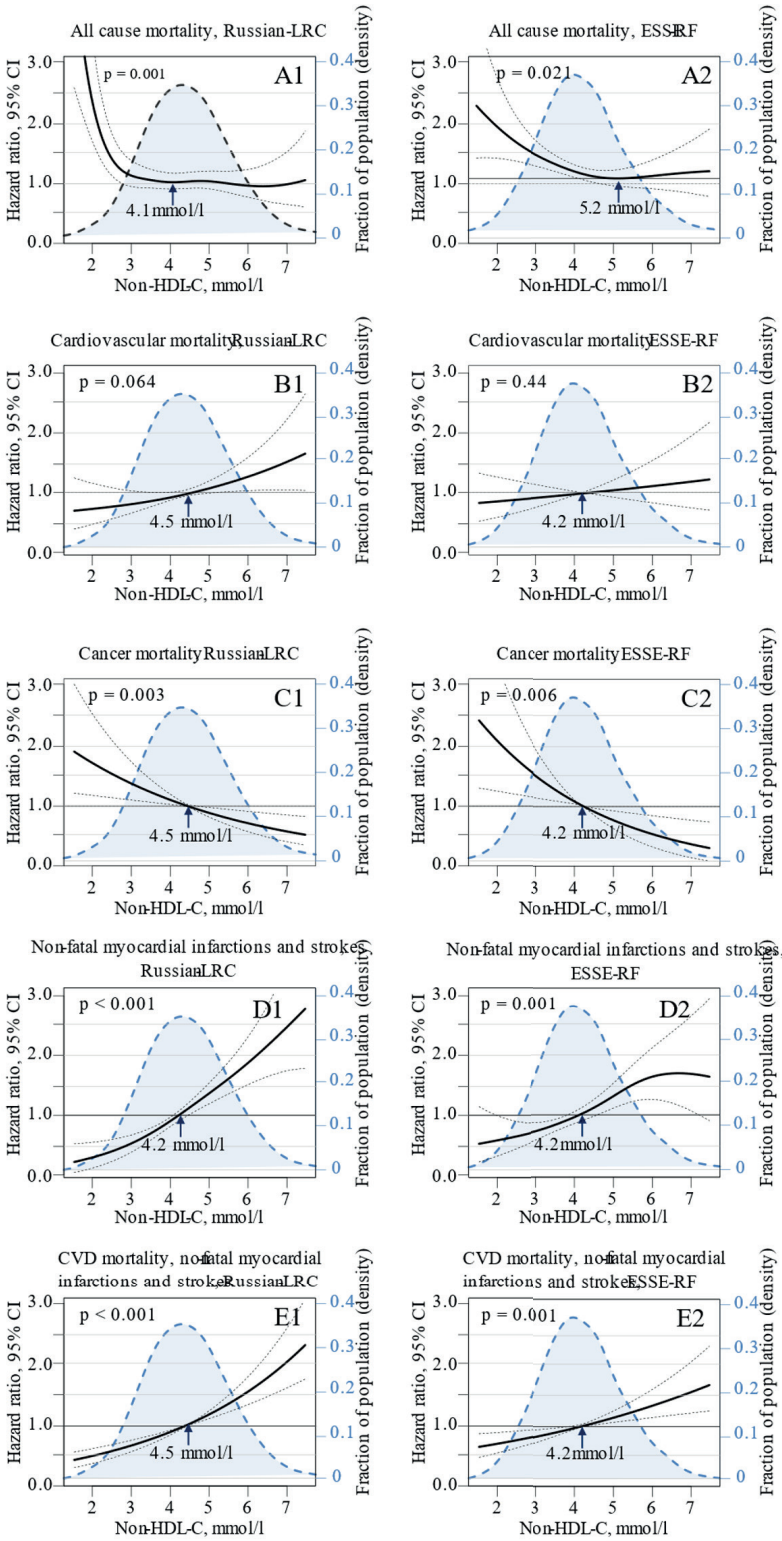
Non–HDL–C	All–cause mortality HR (95% CI)*	Cancer mortality HR (95% CI)*	CVD mortality HR (95% CI)*	MI + stroke incidence HR (95% CI)*	CVD incidence + mortality HR (95% CI)*
Russian–LRC					
<4,5 mmol/L	Reference	Reference	Reference	Reference	Reference
⩾4,5 mmol/L	0,91 (0,75-1,1)	0,72 (0,52-0,99)	1,3 (0,97-1,74)	1,96 (1,49-2,58)	1,63 (1,34-1,99)
ESSE–RF					
<4,2 mmol/L	Reference	Reference	Reference	Reference	Reference
⩾4,2 mmol/L	0,72 (0,56-0,91)	0,50 (0,31-0,79)	1,03 (0,70-1,52)	1,41 (1,07-1,86)	1,27 (1,01-1,58)

*Models were adjusted for age, sex, current smoking, education, systolic blood pressure and region of residence, HR – hazard ratio, CI – confidence interval, Non-HDL-C – non-high-density lipoprotein cholesterol

participants from the Russian-LRC study. In both cohorts, low non-HDL-C levels were significantly associated with an increased risk of all-cause mortality and cancer, whereas high levels were significantly associated with the incidence of CVD and a combination of fatal and non-fatal CVD. In addition, non-HDL-C levels lower than the population mean were shown to be associated with the lowest risk of all-cause mortality and cancer mortality but with the highest risk of CVD incidence.

Elevated levels of TC are a well-known ACVD risk factor, and until recently, its component, LDL-C, was considered one of the most important targets for lipid-lowering therapy. Therefore, the U-shaped association of LDL-C with mortality from CHD in middle-aged and elderly men, found by the Russian-LRC study in 1988, has raised questions about the causes and consequences of this contribution to mortality that remain unanswered until the present time [19]. However, in recent years, a number of studies have reported that non-HDL-C, as well as other lipid profile parameters, are recommended for calculating the risk of fatal events. Thus, in the present study, the role of non-HDL-C in mortality and the occurrence of CVDs was evaluated.

Since the 1980s, a decrease in the general population level of non-HDL-C in economically developed and developing countries has been observed [20]. The publication of studies showing a link between atherosclerosis and CVDs since the late 1990s contributed to increased prescription of statins and patient awareness of the need to lower cholesterol-affected dietary habits, especially the replacement of saturated fats with unsaturated fats and the reduction of trans-fats. Researchers consider that these therapeutic and preventive actions are the major contributors to



Figures A1-E1 are based on Russian-LRC data (1977-1979), and figures A2-E2 are based on ESSE-RF data (2013-2017). Black lines indicate multivariable adjusted HRs, with dashed black lines showing 95% confidence intervals (CI). Reference lines are indicated by lines at an HR of 1.0. Dashed blue curves show the fraction of the population with different levels of non-HDL-C. HRs were adjusted for age, sex, current smoking, education, systolic BP and region of residence.

Non-HDL-C — non-high-density lipoprotein cholesterol, CVD — cardiovascular diseases

Figure 1. Multivariable adjusted HR or different endpoints according to levels of non-HDL-C on a continuous scale

a decline in cholesterol levels [21, 22]. Our study also noted a decrease in non-HDL-C levels in the group of individuals surveyed in the ESSE-RF in the 2010s compared to participants from the LRC study. Persons receiving statins and those with CVD were excluded from the analysis. In the Russian-LRC, less than 1% of the total cohort had been taking lipid-lowering therapy, whereas in the ESSE-RF study, approximately 5.2%. We can assume that the lower mean non-HDL-C levels in the ESSE-RF are related to the fact that individuals with elevated levels of TC had previously been prescribed lipid-lowering therapy and at the time of the study had quit their treatment, while the effect of therapy remained [23]. Nevertheless, the results of the analysis of the association between non-HDL-C and mortality for the ESSE-RF study are similar to the Russian-LR C.

R-X. Zeng et al., in a recent study, showed a U-shaped association of non-HDL-C levels with all-cause mortality. The authors explain their findings by the fact that high levels of non-HDL-C play a role in the progression of atherosclerosis, which leads to an increased risk of death [24]. Our study found an L-shaped association of this parameter with all-cause mortality, which can be explained by similar results regarding cancer mortality and the absence of an association between non-HDL-C and CVD mortality.

Associations between lipid levels and cancer incidence and mortality have been studied for the past 40 years. Cholesterol, in addition to playing an important role in the formation of cell structure and function, is involved in bile acid synthesis and serves as a precursor of vitamin D synthesis and steroid hormones. Some evidence suggests that low levels of TC may be an indicator for certain cancers, including breast cancer [25]. The researchers suggest that these results may be related to the fact that cholesterol catabolism is increased in malignant cells, as well as a higher consumption of cholesterol for biogenesis of new cell membranes in cancerous tissues [26]. It should be noted that non-HDL-C is a major part of TC and therefore has a similar effect. However, it remains unclear whether low non-HDL-C is an indicator for death from cancer or from its complications. On the one hand, cancer can change cholesterol metabolism, and receptor-expressing tumor cells attract cholesterol metabolites to support the growth of tumors, consequently resulting in a decrease in the circulating levels of cholesterol [27]. Moreover, experimental studies have shown that high serum levels of cholesterol increase the antitumour functions of natural killer cells and reduce the growth of liver tumors in mice [28]. On the other hand, malnutrition has been reported to be responsible for the paradoxical relationship between non-HDL-C levels and all-cause mortality, and malnutrition is known to accompany and greatly influence the outcome in cancer patients [29, 30]. Moreover, the authors, who identified a connection between non-HDL-C and malnutrition among patients with acute CHD, recommend assessing and improving the nutrition status before lipid-lowering therapy [30].

In our study, low non-HDL-C levels were significantly associated with an increased risk of cancer mortality but decreased risk of CVD incidence. In the study of Guan X-M et al., which was carried out earlier, similar results were obtained: high non-HDL-C levels were negatively associated with the risk of all-site cancer as well as ACVD risk [31]. The obtained results can be explained by the fact that dyslipidemia characterized by high non-HDL-C levels is considered a risk factor for atherosclerosis and CVD, including CHD and stroke [32]. Indeed, non-HDL-C reflects the content of all apolipoprotein B-containing lipoproteins, including potentially atherogenic LDL particles (in many cases small dense ones) and triglyceride-rich remnants, whose elevated levels are associated with ischemic heart disease [33]. Thus, non-HDL-C could be regarded as a good predictor of high CVD mortality. Abdullah SM et al found that high levels of LDL-C and non−HDL-C were independently associated with a 50% to 80% increased risk of CVD mortality. The authors concluded that the obtained results were important for the development of new approaches to lipid profile correction [34]. At the same time, in our study, there was only a tendency for an increased risk of death in the presence of elevated non-HDL-C levels. To explain the data obtained, it is necessary to conduct additional research. According to the ESC Guidelines for the Prevention of Cardiovascular Disease in Clinical Practice, non-HDL-C is a reasonable alternative treatment target for patients with CVD. This recommendation is derived from the fact that an elevated level of non-HDL-C significantly increased the risk of fatal and non-fatal CVDs [1, 32]. The highest permitted level of this parameter as a target for lipid-lowering therapy is 3.4 mmol/l [1].

Although the results obtained in our study are also true for the male cohort as in guidelines, we had to use the target (<3,4 mmol/L) value as the first percentile for the reference in regression for both cohorts. This was because the mean level of non-HDL-C was higher than the data used in the development risk assessment models to estimate the 10-year risk of CVD in Europe [1], and the proportion of participants with values below the target was less than 20% in the Russian-LRC study. In addition, rather than target non-HDL-C levels, the mean levels of the parameter were used as the cut-off points for the categorical analysis, performed on each cohort. The risk of fatal and non-fatal CVDs increased 1.6 times and 1.3 times among men with mean non-HDL-C levels ⩾4.5 mmol/L in the Russian-LRC study and ⩾4.2 mmol/L in the ESSE-RF study, respectively.

Study imitations

First, only men were included in the analysis. Second, the cohorts differed by place of residence: the participants included in the Russian-LRC study lived in Moscow, and the ESSE-RF participants lived in 15 other regions of the Russian Federation. However, it should be noted that the correction for place of residence was included in all analysed regressions.

Conclusion

The results of the study showed a decline in population-wide non-HDL-C levels since the 1970s. Non-HDL-C levels were associated with all-cause mortality. The non-linear association of non-HDL-C with all-cause mortality has been observed up to the present time and may be explained by the presence of differently directed associations between this parameter, cancer mortality and the development of fatal and non-fatal CVDs. Elevated levels of non-HDL-C were associated with increased risk of fatal and non-fatal cardiovascular events, while lower levels of this parameter were associated with cancer mortality.

Relationships and Activities. None.

Funding: The study was performed with the support of National Medical Research Center for Therapy and Preventive Medicine of the Ministry of Healthcare of the Russian Federation.

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About the Authors
Svetlana A. Shalnova, *ORCID 0000-0003-2087-6483*
Asiia E. Imaeva, *ORCID 0000-0002-9332-0622*
Yulia A. Balanova, *ORCID 0000-0001-8011-2798*
Vladimir A. Kutsenko, *ORCID 0000-0001-9844-3122*
Anna V. Kapustina, *ORCID 0000-0002-9624-9374*
Victoria A. Metelskaya, *ORCID 0000-0001-8665-9129*
Natalia A. Imaeva, *ORCID 0000-0002-8058-1081*
Badriddin M. Nazarov, *ORCID 0000-0003-2145-1284*
Oleg E. Ivlev, *ORCID 0000-0002-3663-6305*
Elena B. Yarovaya, *ORCID 0000-0002-6615-4315*
Oxana M. Drapkina, *ORCID 0000-0002-4453-8430*