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Association of high-sensitivity C-reactive protein with fatal and non-fatal cardiovascular events in working-age people: data from the ESSE-RF study

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Aim. To study the relationship of different levels of high-sensitivity C-reactive protein (hs-CRP) with cardiovascular events and assess its contribution to the development of outcomes in Russian regions.

Material and methods. The work used the data from the multicenter study ESSE-RF — a representative sample of male and female population aged 25-64 years. All participants signed informed consent. The study included 10421 people (women, 6399 (61,4%)). The cohort was followed up from 2012 to 2019 (median follow-up period, 5,5 years). A hard endpoint (cardiovascular mortality and nonfatal myocardial infarction (MI)) was determined in 187 people, while a soft endpoint (nonfatal MI, stroke, revascularization, heart failure progression and cardiovascular mortality) — in 319 people.

Results. The results showed that hs-CRP is significantly associated with the main risk factors (with the exception of low-density lipoproteins). At the same time, it was found that optimal hs-CRP level for predicting the risk of cardiovascular events (CVE) in Russian population is significantly lower than 3 mg/L, but higher than 1 mg/L (1,54/1,89 mg/dL for men and women, respectively). Adding hs-CRP to sex and age significantly improved risk prediction (AUC, 79,7; 95% CI, 77,8-81,7). At the same time, adding a wide list of confounders to hs-CRP, sex and age does not improve the model's predictive value (AUC, 79,7; 78,2-82,1).

Conclusion. This study for the first time showed a significant independent contribution of hs-CRP to CVEs development in the Russian population, and the addition of hs-CRP to sex and age significantly increased the predictive value of model.

Keywords: high-sensitivity C-reactive protein, cardiovascular events, risk factors.

Relationships and Activities. The ESSE-RF prospective study was carried out within the state assignment № AAAA-A17-117070760036-6.

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Based on numerous studies, now there is a concept of additional or novel risk factors (RFs), which, together with the classical factors, increase the predictive power. In recent years, the researchers actively searched for novel biomarkers.

One of these biomarkers is C-reactive protein (CRP), which is a marker of inflammation. This unusual, "bifacial" biomarker brings us more and more surprises. Dozens of years have passed since the CRP discovery by Tilet W and Francis T (1930) [1], but a new CRP role was identified after the discovery of a high-sensitivity technique for measuring CRP (1994-1997), which allowed researchers to look at the problems of nonspecific inflammation from a different angle.

Subsequently, it became known that high-sensitivity CRP (hs-CRP) level increases sharply during the inflammatory response, causing coronary artery damage due to the direct activation of endothelial cells. Factors causing artery spasm contribute to the formation of microthrombi and impaired microcirculation, which has a strong effect on plaque development. In an experimental study, it was shown that this process requires a transition from pentameric CRP to its monomeric conformation (mCRP) [2].

Given the discovery of vesicular transport system, we now know that exosomes can carry different cell components, including proteins and lipids [3]. The study by Melnikov I.S. et al. (2019) suggested that in patients with coronary artery disease (CAD), blood increase in circulating exosomes carrying mCRP and leukocyte markers on their surface, as well as the mCRP in atherosclerotic areas, may indicate the participation of mCRP in the pathogenesis of coronary atherosclerosis [4].

In 2001, the American Heart Association published guidelines for determining hs-CRP to stratify the risk of cardiovascular diseases (CVD), in particular CAD, in the moderate risk group [5].

Finally, the Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER study) showed that statins, regardless of total cholesterol (TC) levels, reduced hs-CRP concentration, which decreased the risk of cardiovascular events (CVE) [6].

However, despite the evidence from numerous studies, the data are contradictory, especially when it comes to the relationship between hs-CRP and the death risk among population.

The aim was to study the relationship of different levels of high-sensitivity C-reactive protein (hs-CRP) with cardiovascular events and assess its contribution to the development of outcomes in Russian regions.

Material and methods

The object of the ESSE-RF multicenter study was representative samples of male and female population aged 25-64 years from 6 Russian regions (Vladivostok, Vologda, Ivanovo, St. Petersburg, Tomsk, Tyumen). A multistage stratified sample was selected using the Kish grid [7]. The study was approved by the local ethics committee. All subjects signed informed consent. In general, the response rate was 80,0%. A detailed protocol for the ESSE-RF study was published earlier [8].

A total of 10421 people were studied, including 4022 (38,6%) men and 6399 (61,4%) women. Socio-demographic parameters included sex, age, region, income.

The presence of a prior disease was considered with a positive answer to the question: "Have a doctor ever told you that you have/had the following diseases?: hypertension (HTN), CAD (angina), myocardial infarction (MI), stroke (cerebral vessel thrombosis or hemorrhage), rheumatoid arthritis (RA), cancer, chronic bronchitis, Parkinson's disease (PD)". Smoking status was assessed: never smoked, former smoking, current smoking.

Instrumental diagnostic tests. Blood pressure (BP) was measured twice on the right arm in a sitting posture with a brief in between break (2 min) using an automatic BP monitor OMRON M3 Expert (Japan).

All anthropometric measurements were performed routinely, as in most studies. In the study, the body mass index (BMI) was calculated using the Quetelet's equation (BMI = Height (m) / Weight (kg^2)). Abdominal obesity (AO) was considered as a waist circumference ⩾102/88 cm for men and women.

Laboratory diagnostic tests. In all centers, blood was drawn from the cubital vein after 12 hours of fasting. Blood serum was obtained by low-speed centrifugation at 900g for 20 min at a temperature of +4° C. Biological material samples were frozen and stored at a temperature not exceeding -20° C until they were sent to the federal center. The transportation of biomaterials was carried out by specialized services. The lipid profile parameters, including the levels of triglycerides (TG), glucose and hs-CRP, were determined using an Abbott Architect c8000 analyzer using diagnostic kits from Abbott Diagnostic (USA). Standardization and quality control of the analysis was carried out in accordance with the requirements of the Federal system for external quality control of clinical laboratory procedures.

Hs-CRP was studied in grades of low, moderate and high cardiovascular risk. The hs-CRP values of 3-10 mg/L were taken as the increased level [9].

Prospective follow-up of the cohort from 2012 to 2019 (median follow-up, 5,5 years) revealed hard endpoint (CVD mortality and nonfatal MI) in 187

Table 1

Multivariate regression analysis of the association of hs-CRP with risk factors, adjusted for regions

Parameter	Level of hs-CRP increase depending on the increase in the parameter*	CI	p
+10 years	1,06	(1,04-1,09)	0,0001
Male	0,81	(0,77-0,85)	0,0001
Current smoker	1,12	(1,06-1,17)	0,0001
+10 mm Hg SBP	1,02	(1,01-1,03)	0,001
AHT	1,08	(1,02-1,14)	0,006
+1 logTG	1,32	(1,26-1,39)	0,0001
+1 mmol/L HDL-C	0,81	(0,75-0,87)	0,0001
+1 mmol/L LDL_C	1,02	(1,00-1,04)	0,124
+1 logGlu	1,40	(1,24-1,58)	0,0001
+1 BMI kg/m^2	1,07	(1,06-1,07)	0,0001
+1 logLp(a)	1,02	(1,00-1,04)	0,046
Prior diseases			
Parkinson's disease	1,11	(0,60-2,04)	0,740
Rheumatoid arthritis	1,11	(1,02-1,21)	0,017
Chronical bronchitis	1,07	(1,00-1,14)	0,055
MI	1,05	(0,89-1,24)	0,577
Stroke	1,01	(0,87-1,19)	0,872
CAD	0,96	(0,88-1,04)	0,330
Arrhythmias	1,03	(0,97-1,09)	0,389
Cancer	1,06	(0,93-1,20)	0,383

Note: * — how many times higher is the level of hs-CRP in the risk group or when the continuous parameter is increased by the specified value.

Abbreviations: AHT — antihypertensive therapy, hs-CRP — high-sensitivity C-reactive protein, CI — confidence interval, CAD — coronary artery disease, BMI — body mass index, MI — myocardial infarction, LP(a) — lipoprotein (a), SBP — systolic blood pressure, TG — triglycerides, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, log — logarithm.

(1,79%) people and soft endpoint (nonfatal MI and stroke, revascularization, heart failure (HF) progression and CVD mortality) in 319 (3,06%) people. The HF progression was considered as the hospitalization due to the disease severity (increase in stage and/or decrease in functional class).

The analysis of the following models (M) was carried out: M1 — hs-CRP; M2 — M1+sex, age; M3 — M2+TC, HTN, PD, RA, bronchitis; M4 — M3+TG, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), glucose, AO.

The central results of descriptive analysis were presented earlier [10].

Statistical data analysis. Statistical analysis was carried out using the R 3.6.1 environment. To assess the associations of hs-CRP and RFs, a linear regression model was used, where the logarithm of hs-CRP was used as a dependent variable. The Kaplan-Meier survival curves were used to estimate the probability of survival at a certain point in time. Comparison of two survival curves was carried out using the log-rank test. When comparing three or more survival curves, the Holm correction for multiple comparisons was applied. The Cox proportional hazards model

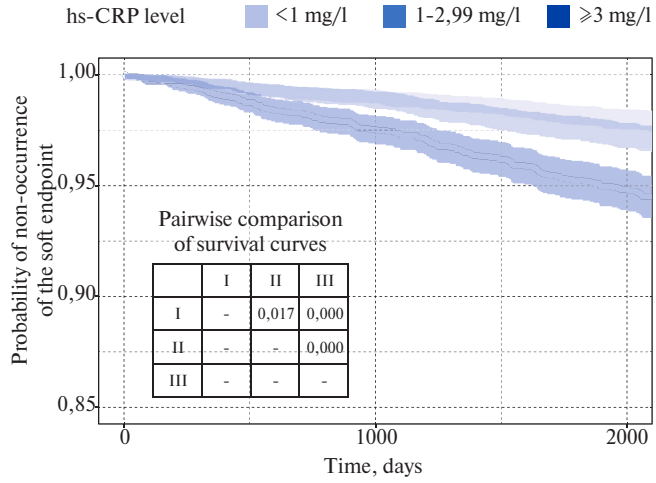

Figure 1. Kaplan-Meier curves of study participants depending on hs-CRP level for the soft endpoint.

Abbreviation: hs-CRP — highly sensitive C-reactive protein.

Table 2

Associations of hard endpoint with hs-CRP in models

Variables in the model	Q4 sex-specific Hs-CRP (1,54/1,89)	Q5 sex-specific Hs-CRP (3,16/3,88)	Hs-CRP >1 mg/L	Hs-CRP >3 mg/L
	RR [95% CI]			
M1	2,59 [1,93-3,48]*	2,4 [1,79-3,22]*	2,01 [1,45-2,77]*	2,32 [1,74-3,11]*
M2	2,00 [1,48-2,02]*	1,77 [1,31-2,38]*	1,52 [1,09-2,11]*	2,76 [1,39-2,5]*
M3	1,91 [1,42-2,59]*	1,67 [1,24-2,26]*	1,4 [1,01-1,95]*	1,8 [1,34-2,42]*
M4	1,78 [1,31-2,43]*	1,55 [1,13-2,12]*	1,28 [0,91-1,8]	1,67 [1,22-2,27]*

Note: * — p<0,05; ** — -region-adjusted models (M). M1 — hs-CRP; M2 — M1+sex, age; M3 — M2+TC, HTN, PD, RA, bronchitis; M4 — M3+TG, HDL-C, LDL-C, glucose, AO; Q — sex-specific quintiles, LDL-C — low density lipoprotein cholesterol ⩾3 mmol/l, HDL-C — high-density lipoprotein cholesterol ⩽1,0/1,2 mmol/L for men and women, respectively, TG — triglycerides ⩾1,7 mmol/L, AO — abdominal obesity (waist circumference — WC ⩾102/88 cm for men and women, respectively), glucose ⩾5,6 mmol/L.

Abbreviations: HTN — hypertension, AO — abdominal obesity, hs-CRP — highly sensitive C-reactive protein, CI — confidence interval, M — model, WC — waist circumference, TC — total cholesterol, RA — rheumatoid arthritis, TG — triglycerides, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, Q — quintiles, RR — relative risk.

Table 3

Associations of the soft endpoint with hs-CRP in models

Variables in the model	Q4 sex-specific Hs-CRP (1,54/1,89)	Q5 sex-specific Hs-CRP (3,16/3,88)	Hs-CRP >1 mg/L	Hs-CRP >3 mg/L
	RR [95% CI]			
M1	2,4 [1,91-3,01]*	2,29 [1,83-2,86]*	1,92 [1,51-2,46]*	2,23 [1,79-2,79]*
M2	1,9 [1,51-2,39]*	1,73 [1,38-2,17]*	1,45 [1,13-1,86]*	1,23 [1,46-2,3]*
M3	1,8 [1,43-2,27]*	1,62 [1,29-2,04]*	1,36 [1,06-1,75]*	1,75 [1,39-2,2]*
M4	1,72 [1,35-2,19]*	1,57 [1,24-2]*	1,3 [1-1,68]*	1,67 [1,32-2,12]*

Примечание: ; Q — sex-specific quintiles, LDL-C — low density lipoprotein cholesterol ⩾3 mmol/l, HDL-C — high-density lipoprotein cholesterol ⩽1,0/1,2 mmol/L for men and women, respectively, TG — triglycerides ⩾1,7 mmol/L, AO — abdominal obesity (waist circumference — WC ⩾102/88 cm for men and women, respectively), glucose ⩾5,6 mmol/L; * — p<0,05; ** — -region-adjusted models (M). M1 — hs-CRP; M2 — M1+sex, age; M3 — M2+TC, HTN, PD, RA, bronchitis; M4 — M3+TG, HDL-C, LDL-C, glucose, AO.

Abbreviations: HTN — hypertension, AO — abdominal obesity, hs-CRP — highly sensitive C-reactive protein, CI — confidence interval, M — model, WC — waist circumference, TC — total cholesterol, RA — rheumatoid arthritis, TG — triglycerides, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, Q — quintiles, RR — relative risk.

(Cox regression) was used to predict the risk of cardiovascular death or adverse event (CAD, including MI, stroke, revascularization, HF) and to assess the effect of predetermined independent variables on this risk. Additionally, age was included as an independent variable in each of the Cox regressions presented. If the results were presented without separating by sex, then the variable "sex" was also added to the independent variables. The relative risk (RR) and 95% confidence interval [95% CI] were calculated. The Receiver Operator Characteristic (ROC) analysis was carried out. For all types of analysis described, the differences were considered significant at p<0,05.

Results

Multivariate regression analysis, adjusted for regions, revealed that hs-CRP level in men is 20% lower than in women, and in current smokers, regardless of sex − 10% higher. The hs-CRP level is significantly positively associated with an increase in age, systolic И3, BMI, TG, glucose (p<0,0001), antihypertensive therapy (p<0,006) and is inversely associated with HDL-C (p<0,0001). No association with LDL-C was found. In the multivariate model, significant associations with prior diseases persisted only for RA (p=0,017) (Table 1).

It should be noted separately that the association of CRP level with age is different for men and women. Dependence of the average CRP logarithm on sex and age: loghs-CRP = -1,09+0,267 (men) + 0,023 (age in years, if a man) + (age in years, if a woman). That is, at 25 years of age, hs-CRP is 10% higher in men than in women. Every ten years, the level of hs-CRP rises by 12% in men and 15% in women. At 39 years old, hs-CRP levels became equal, and by age 65, hs-CRP levels in women are 50% higher than in men.

Survival curves for soft endpoints with Holm correction demonstrate a significant relationship with

the hs-CRP level. The analysis was carried out in three groups of CRP: low risk — up to 1 mg/L, moderate — 1-2,99 mg/L, and high risk — ⩾3 mg/L. Pairwise analysis showed that all curves are pairwise different, and the higher the hs-CRP level, the lower the survival rate (Figure 1).

In order to clarify the hs-CRP risk levels in population, a ROC analysis was performed, which showed that the optimal cut-off point for predicting a soft endpoint is 1,49 mg/L for men and 1,83 mg/L for women, which is close to the fourth quintile (Q4: men — 1,54 mg/L; women — 1,89 mg/L). Therefore, in further analysis, we used the Q4 as a cut-off point.

Cox regression showed significant associations of hs-CRP with hard endpoints regardless of the model (M), with the exception of M4 with hs-CRP >1 mg/L, where no significant association was found (RR, 1,28 [0,91-1,8], p>0,05). The highest risk was already noted in M1 at Q4, which is very slightly inferior to currently accepted point of the increased hs-CRP level (>3 mg/L). Comparison of M1 and M2 did not show the significant RR change, which speaks in favor of a pronounced association of isolated hs-CRP with hard endpoint (Table 2).

A similar data was obtained when analyzing various levels of hs-CRP with soft endpoint, where significant associations were found in all models (Table 3).

The analysis of proportional hazard models showed a rather pronounced and independent role of CRP in the development of both hard and soft endpoints.

ROC analysis for soft endpoints revealed that isolated hs-CRP has an area under the ROC curve equal to 64,2%, which significantly increases to 79,7 when sex and age are added to the model. Further addition of a wide list of confounders did not significantly increase the area under the ROC curve. In other words, it does not significantly increase the predictive power of the model (Figure 2).

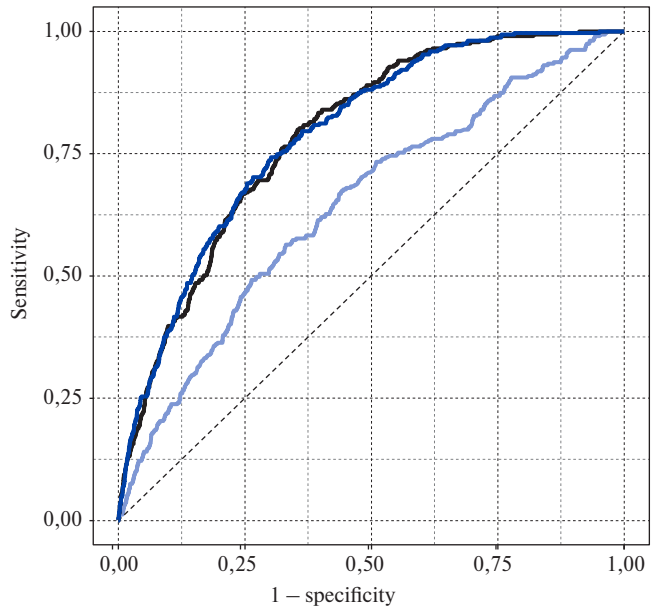

Figure 2. ROC analysis of predictive power of continuous risk factors.
Note: * — adjusted for study regions.
Abbreviations: HTN — hypertension, hs-CRP — highly sensitive C-reactive protein, CI — confidence interval, TG — triglycerides, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, AUC — area under the ROC curve.

Discussion

The results obtained in our study including more than 10 thousand people showed that an increased level of hs-CRP is a reliable and independent predictor of CVE in the Russian population, even with significant relationships with the main RFs and RA, which is one of the most prominent representatives of chronic inflammatory diseases, and its relationship with hs-CRP is not in doubt among most researchers [10]. At the same time, it was found that the hs-CRP level, which is optimal for predicting the CVE risk, in Russian population is significantly lower than 3 mg/L, but higher than 1 mg/L (Q4 — 1,54/1,89 mg/L in men and women, respectively). This shows that above these levels, hs-CRP has a significantly higher risk of CVE than at lower levels, and slightly higher than at an hs-CRP ⩾3 mg/L. Notably, adding hs-CRP to sex and age significantly improves risk prediction. In other words, the negative effect of increased hs-CRP begins at its lower values It is important to emphasize that adding a broad list of confounders to hs-CRP, sex and age does not improve the predictive power of the model. Over the past decade, more than 20 prospective cohort studies have shown that hs-CRP levels are independently associated with future risk of MI, stroke, metabolic syndrome, and type 2 diabetes. Most studies with adequate sample sizes have demonstrated that hs-CRP adds predictive information to the risk stratification.

Some studies have reported conflicting data on the association between hs-CRP and mortality risk in the population. Thus, the meta-analysis of 14 studies (up to October 2016, n=83995), studying the effect of elevated baseline hs-CRP levels on cancer, CVD, or all-cause mortality in the general population, showed that when comparing the highest versus lowest hs-CRP level, RR was 1,25 [95% CI, 1,13-1,38] for cancer mortality, 2,03 [95% CI, 1,65-

2,50] for CVD mortality, and 1,75 [1,55-1,98] for all-cause mortality [11]. Subgroup analyzes showed an effect of elevated hs-CRP levels on cancer mortality in men but not in women [RR, 1,03; 0,83-1,27]. The authors conclude that elevated hs-CRP levels can independently predict the risk of mortality from CVD in a population [11]. The National Health and Nutrition Examination Survey (NHANES III) also found an association of high hs-CRP with all-cause mortality (RR, 1,80 [1,32-2,46], p=0,001) and CVD (RR, 1,54 [1,08-2,18]) in men. However, modelling did not confirm the association of a high hsCRP levels with CVD mortality [12].

In turn, according to recently published meta-analysis of 22 studies, comparison of moderate hs-CRP to low hs-CRP levels showed the RR of 1,30 [1,20-1,41] and 1,43 [1,22-1,68] for all-cause and CVD mortality, respectively. In the group with high hs-CRP, the RR was 1,75 [1,59-1,92], 2,02 [1,70-2,41], 1,32 [1,21-1,45] for all-cause, CVD, and cancer mortality. This meta-analysis demonstrated that the relationship between hs-CRP and mortality was non-linear for all-cause and CVD mortality and linear for cancer and non-cardiovascular mortality [13].

Recently published results of the Brazilian study showed a significant association of hs-CRP with all-cause mortality in a multivariate model [14].

The studies with an Asian population demonstrated that hs-CRP level in Asians is reduced in comparison with white Europeans [15, 16]. Thus, the median hs-CRP level in the Korean population is 0,6 (95% CI, 0,3-1,3) in men and 0,4 (0,1-1,1) in women (p<0,001). Only 8,6% of men and 6,2% of women reached the standard cut-off point for hs-CRP >3 mg/L, which is the upper tertile in the Caucasian population. Moderate-risk hs-CRP models improved the reclassification of CVD mortality risk by 24,9% (p=0,04). Standard cutoff points for CRP in the Asian population may lead to risk underestimation [17]. In addition, both Asian and European studies indicate the need for additional analysis to study the sex contribution at different age periods to unfavorable risk.

Conclusion

This study for the first time showed a significant independent contribution of hs-CRP to CVEs development in the Russian population, and the addition of hs-CRP to sex and age significantly increased the predictive value of model.

Relationships and Activities. The ESSE-RF prospective study was carried out within the state assignment № AAAA-A17-117070760036-6.

References

1. Tillet W, Francis T. Serological reaction in pneumonia with a non protein somatic fraction of Pneumococcus. J Exp Med.1930;52(4):561-71. doi:10.1084/jem.52.4.561.
2. Khreiss T, József L, Potempa LA, Filep JG. Conformational Rearrangement in C-Reactive Protein Is Required for Proinflammatory Actions on Human Endothelial Cells. Circulation. 2004;109:2016-22. doi:10.1161/01.CIR.0000125527.41598.68.
3. The Nobel Prize in Physiology or Medicine 2013 http://www.nobelprize.org/nobel_prizes/medicine/laureates/2013/. (Date 03.03.2021).
4. Melnikov IS, Kozlov SG, Chumachenko PV, et al. Monomeric C-reactive protein and local inflammatory reaction in the wall of the coronary arteries in patients with stable coronary artery disease. Russ J Cardiol. 2019;24(5):56-61. (In Russ.) doi:10.15829/1560-4071-2019-5-56-61.
5. Futterman LG, Lemberg L. High sensitivity C-reactive protein is the most effective prognostic measurement of acute coronary events. J Critical Care. 2002;11(5):482-6.
6. Ridker PM, Danielson E, Fonseca FA. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195-207. doi:10.1056/NEJMoa0807646.
7. Kish L. Survey Sampling. New York: John Wiley and Sons, 1965. ISBN: 0-471-48900 X.
8. Boytsov SA, Chazov EI, Shlyakhto EV, et al. Epidemiology of cardiovascular diseases in different regions of Russia (ESSE-RF). The rationale for and design of the study. Preventive medicine. 2013;6:25-34. (In Russ.)
9. Pearson T, Mensah G, Alexander R, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107:499-511. doi:10.1161/01.cir.0000052939.59093.45.
10. Evstifeeva SE, Shalnova SA, Deev AD, et al., on behalf of the participants of the ESSE-RF study. The prevalence of elevated levels of C-reactive protein and its association with traditional risk factors and morbidity among residents of the Russian Federation (according to the ESSE-RF study). Ration Pharmacother Cardiol. 2014;10(6):597-605. (In Russ.)
11. Li Y, Zhong X, Cheng G, et al. Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. Atherosclerosis. 2017;259:75-82. doi:10.1016/j.atherosclerosis.2017.02.003.
12. Stephen M, Amrock SM, Weitzman M. Effect of increased leptin and C-reactive protein levels on mortality: Results from the National Health and Nutrition Examination Survey. Atherosclerosis. 2014;236(1):1-6. doi:10.1016/j.atherosclerosis.2014.06.009.
13. Ni P, Yu M, Zhang R, et al. Dose-response association between C-reactive protein and risk of all-cause and cause-specific mortality: a systematic review and meta-analysis of cohort studies. Ann Epidemiol. 2020;51:20-7. doi:10.1016/j.annepidem.2020.07.005.
14. Maluf CB, Barreto SM, Giatti L, et al. Association between C reactive protein and all-cause mortality in the ELSA-Brasil cohort. J Epidemiol Community Health. 2020;74(5):421-27. doi:10.1136/jech-2019-213289.
15. Nisa H, Hirata A, Kohno M, et al. High-sensitivity C-reactive protein and Mortality risks of all-cause and cause-specific mortality in a Japanese population. doi:10.7314/APJCP.2016.17.5.2643.
16. Shena Y, Zhanga Y, Xionga S, et al. High-sensitivity C-reactive protein and cystatin C independently and jointly predict all-cause mortality among the middle-aged and elderly Chinese population. Clinical Biochemistry. 2019;65:7-14. doi:10.1016/j.clinbiochem.2018.12.012.
17. Sung Ki-C, Ryu S, Chang Y, et al. C-reactive protein and risk of cardiovascular and all-cause mortality in 268 803 East Asians. Eur Heart J. 2014;35(27):1809-16. doi:10.1093/eurheartj/ehu059.