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Original Article

Comparative analysis of the variability of carotid intima-media thickness in primary prevention populations of Moscow and Paris

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Abstract: *Background*: It is well-known that the distribution of traditional cardiovascular risk factors (CVRFs) of atherosclerosis, including hypertension, dyslipidemia, smoking, obesity, and diabetes is considerably variable between different countries, however, with some important geographical trends. Thus, CVRFs contribute differently to atherosclerosis development in different countries. Common carotid artery intima-media thickness (CCA IMT) is a validated biomarker of subclinical atherosclerosis that is used in clinical and epidemiological studies to evaluate the impact of CVRFs on atherosclerosis development. *Material and methods:* This comparative cohort study included a random sample of 1200 participants (n = 600 men and n = 600 women) from Moscow, Russia and Paris, France, aged between 55 and 79 years, and free of clinical symptoms of atherosclerosis. The study was conducted to determine the interpopulation variability of CCA IMT. CCA IMT was measured by ultrasonic scanning at the high-resolution regimen. Statistical analysis was performed using Stata 9.1. For comparison of mean values of continuous variables, Mann-Whitney U-test was used; Chi-square, Pearson's test was used for comparison of categorical variables. To determine to what extent presented differences can be explained by differences in traditional CVRFs, the regression model was applied. Path analysis (plug Passport Litigation Decision Analysis & Optimization Module, Datacert, USA) was used to assess the impact of traditional CVRFs on the CCA IMT in both Moscow and Paris study populations. *Results:* There was a significant difference in the distribution of most of the traditional CVRFs between the study populations, including blood pressure, lipid profile, statin treatment, hormone replacement therapy in women, and CVD history. The remarkably high level of difference in the mean values of the CCA IMT was found between Moscow and Paris study populations. In women of both Moscow and Paris study populations, the mean value of CCA IMT was 0.78 and 0.63, respectively. In men of both Moscow and Paris study populations, the mean CCA IMT value was 0.84 and 0.67, respectively. In the Moscow study population, the effects (direct and indirect) of traditional CVRs can explain 42% of the CCA IMT variance in women and 30% - in men. In the Paris study population, direct and indirect effects of traditional CVRFs can explain 27% of the CCA IMT variance in men and 14% - in women. *Conclusion*: The Paris study population significantly differed from the Moscow study population in the distribution and impact of traditional CVRFs. Traditional CVRFs can explain only a small proportion of the interpopulation differences in CCA IMT suggesting the presence of other factors, such as longitude, which can possibly influence these differences. Therefore, this study provided an additional piece of evidence towards the existence of a geographic gradient of carotid IMT.

Keywords: Cardiovascular risk factors, atherosclerosis, intima-media thickness, common carotid arteries

Introduction

According to the World Health Organization (World Heart Day 2017), cardiovascular diseases (CVDs) are a major cause of morbidity and mortality worldwide. Atherosclerosis is accepted underlying cause for most CVDs. The formation of an atherosclerotic lesion can start at

young age [1] undergoing a long (up to several decades) asymptomatic phase in its course of development. It is well-known that increasingly progressive atherosclerosis ultimately leads to major cardiovascular events. Therefore, there is a great need in identifying asymptomatic patients at high risk, who would benefit from intensive and more precise therapeutic interventions. Some authors discussed the utility of different methods of risk stratification, biomarkers, and imaging techniques of subclinical atherosclerosis [2]. Furthermore, non-invasive ultrasound measurement of the intima-medial thickness (IMT) of common carotid arteries (CCA), in association with the presence of most traditional cardiovascular risk factors (CVRFs), was developed as a sensitive and reproducible technique for identifying and quantifying of subclinical atherosclerotic disease and CVD risk prediction [3, 4]. Moreover, the recent meta-analysis of 119 clinical trials including a large number of patients revealed that the extent of intervention effects on CCA IMT progression can predict the degree of reduction in CVD risk [5].

According to the current knowledge, the distribution of traditional CVRFs of atherosclerosis, including hypertension, dyslipidemia, smoking, obesity, and diabetes varies widely between countries, however, with some important geographical trends. Remarkably, the study showed a different association between traditional CVRFs and the presence of atherosclerotic disease in ethnic groups [6]. Moreover, the IMPROVE study suggested that there is a geographical gradient of carotid IMT, which was not fully explained by between-country differences in CVRFs [7]. In this study, we aimed to explore interpopulation CCA IMT variability, in association with traditional CVRFs, as well as to assess the predictive power of traditional CVRFs in two study populations of Moscow, Russia and Paris, France. In this way, we will provide an additional piece of evidence towards the existence of a geographic gradient of carotid IMT.

Material and methods

Subjects

Totally 1200 participants (n = 600 men and n = 600 women) from Moscow, Russia and Paris, France were included in this epidemiological study. Written informed consent was obtained from each participant. Inclusion criteria were applied as following: age 55-79 years; the absence of clinical manifestations of diseases of atherosclerotic origin; women to be at least five years after menopause (spontaneous or surgical). Exclusion criteria were applied as following: age under 55 or over 79 years; abnormal anatomical configuration of the neck and muscles; severe tortuosity and/or depth of the carotid arteries and/or unusual locations of twigs; history of myocardial infarction, cardiac angina, stroke, and acute transient ischemic attacks; presence of an aortic aneurysm, revascularization of carotid, coronary, and/or peripheral arteries; congestive heart failure (III-IV class, according to the New York Heart Association (NYHA)) functional classification; presence of serious chronic diseases; refusal to sign an informed consent.

High-frequency ultrasound

CCA IMT was used as a quantitative marker of carotid atherosclerosis. CCA IMT was measured by ultrasonic scanning at high-resolution regimen. The distal portions of the right and left carotid arteries were scanned in the lateral angle of interrogation. CCA IMT was measured on the far wall of the distal segment under the area of the carotid bifurcation. The measurements of CCA IMT were taken with M'Ath computer software (Metris, SRL France). The average of two measurements (from the right and left sides in lateral position) was considered as an integral indicator of mean CCA IMT.

Statistical analysis

Statistical analysis was performed using Stata 9.1. For comparison of mean values of continuous variables, Mann-Whitney U-test was used. Chi-square, Pearson's test was used for comparison of categorical variables. Results were presented as mean ± standard deviation (SD) or as the number (percentage) of subjects. The significance of differences was estimated with 0.05 level of confidence.

Path analysis

Path analysis (plug Passport Litigation Decision Analysis & Optimization Module, Datacert, USA) was used to assess the impact of traditional CVRFs on the CCA IMT in both Moscow and Paris study populations. The model suggested

was used for the assessment of both direct and indirect effects of independent phenotypic traits on the dependent variable (CCA IMT). This analysis involved the specification of the path model that can approximate the effect of a set of phenotypic factors on the CCA IMT attribute. In contrast to the traditional regression analysis, path analysis was applied to evaluate complex relationships between a dependent variable and independent variables. The specified path model aimed to determine high predictive power rather than the exact causal connections of CVRFs involved. Thus, the model effects were considered primarily, in terms of their predictive power, rather than as causal connections. For each variable used in the model as a dependent, regression coefficient was estimated demonstrating the degree of the influence of other variables involved as predictors. The analysis was performed in the Mplus statistical software, which allowed to specify the path and structural covariance models. Path analysis model assumptions, identical to the basic assumptions of regression, identified the need to verify the normal distribution of the dependent variables and the absence of multicollinearity of predictors. These tests were performed for each data set, which was used for the estimation of model parameters. For the analysis, the whole data set was divided into four subgroups, according to sex and territory. In each subgroup, pre-analysis was performed to test the basic assumptions of the model. The distribution was assessed using the Kolmogorov-Smirnov normality test. Testing the multicollinearity presence was performed through the evaluation of the nonparametric Spearman correlation matrix since many predictors were measured on an ordinal and dichotomous scale, which does not allow for parametric methods of estimation. A general path model was estimated for each subgroup independently using the Maximum Likelihood Robastified estimator.

Results

In total, 1200 participants were included in this study (n = 600 (50%) of participants were recruited from Paris, France, and n = 600 (50%) of participants were recruited from Moscow, Russia). Both Paris and Moscow study populations were equally divided by sex (n = 300 (50%) of women and n = 300 (50%) of men). The mean age of the overall sample was 60.6 years (SD 11.1). Clinical characteristics of the study participants were presented in **Table 1**.

Compared to women of the Paris cohort, women of the Moscow cohort had a significantly higher BMI, values of systolic and diastolic BP, total and HDL cholesterol levels, mean CCA IMT values, and incidence of CVD_H. Nonetheless, they exhibited a lower incidence in Diabetes_H.

In men of the Moscow cohort, significantly higher values of systolic and diastolic BP, levels of HDL, LDL, total cholesterol, and mean CCA IMT values were registered, in comparison to men of the Paris cohort. In men of the Moscow cohort, triglyceride levels were lower. Besides, men of this cohort had a lower incidence in diabetes.

In both Moscow and Paris populations, 38.7% and 34.0% of women had treatment for arterial hypertension, respectively. In both Moscow and Paris study populations, 43.7% and 35.3% of men had treatment for arterial hypertension, respectively. Statin therapy had 3.8% and 60.5% of subjects of both Moscow and Paris study populations, respectively. The overall mean value of CCA IMT was 0.73 (SD 0.14) ranging between a minimum of 0.5 and a maximum of 1.8. The average estimated value of CCA IMT was 0.65 (SD 0.13) in the Paris study population and 0.81 (SD 0.15) - in Moscow.

Path analysis

Path analysis was used to assess the impact of traditional CVRFs on the CCA IMT attribute in both Moscow and Paris study populations. Parameters of the specified path model were estimated for each subgroup. The estimated values of standardized regression coefficients, standard error of the estimates, and the corresponding *p*-value were presented in **Tables 2** and **3**.

Moscow population: male subgroup: In the male study subgroup of Moscow population, the following variables (CVRFs) had a statistically significant impact on the CCA IMT, the primary dependent variable, demonstrating a direct cause/effect relationship: age (β = 0.455, *p*-value <0.001), systolic BP (β = 0.249, *p*-value <0.001), BMI (β = 0.100, *p*-value = 0.007), diabetes (β = 0.090, *p*-value = 0.012), and LDL (β = 0.089, *p*-value = 0.010). Analysis

Table 1. Clinical characteristics of the study participants

Variable	Women (n = 600)			Men (n = 600)		
	Moscow	Paris	*P*-value	Moscow	Paris	*P*-value
Age (years)	60.6 ± 11.3	60.2 ± 11.5	0.968	60.7 ± 10.8	60.8 ± 10.7	0.988
Weight (kg)	72.0 ± 3.1	65.8 ± 13.8	<0.001	82.3 ± 14.1	80.0 ± 13.2	0.047
Height (m)	163.0 ± 5.6	159.4 ± 6.1	<0.001	175.6 ± 6.1	172.7 ± 7.1	<0.001
BMI (kg/m^2)	27.1 ± 4.8	25.9 ± 5.4	<0.001	26.7 ± 4	26.8 ± 4.1	0.611
Systolic BP (mm Hg)	133.0 ± 18.7	125.0 ± 6.4	<0.001	139.3 ± 16.5	130.2 ± 17.4	<0.001
Diastolic BP (mm Hg)	81.2 ± 9.6	71.7 ± 10.7	<0.001	85.2 ± 10.5	75.6 ± 10.4	<0.001
Menopause, women (%)	77.7	73.7	0.295	-	-	-
Total Cholesterol (g/L)	5.44 ± 0.4	2.43 ± 0.5	<0.001	5.25 ± 0.4	2.12 ± 0.5	<0.001
Triglycerides (g/L)	1.13 ± 0.5	1.10 ± 0.7	0.234	1.32 ± 0.7	1.48 ± 0.9	<0.001
HDL-Cholesterol (g/L)	1.71 ± 0.2	0.67 ± 0.2	<0.001	1.57 ± 0.2	0.51 ± 0.1	<0.001
LDL-Cholesterol (g/L)	2.48 ± 0.4	1.43 ± 0.6	0.007	2.44 ± 0.4	1.27 ± 0.5	<0.001
Smoking status, smokers (%)	7.3	12.0	0.072	12.7	16.0	0.294
Alcohol (%)	0	0	-	4.7	8.3	0.097
Hypertension (%)	47.3	26.7	<0.001	54.3	29.3	<0.001
Diabetes (%)	4.0	6.3	0.268	5.7	18.3	<0.001
Treatment of arterial hypertension (%)	38.7	34.0	0.270	43.7	35.3	0.022
Treatment of hyperlipidemia (%)	4.0	55.3	<0.001	3.7	65.7	<0.001
Hormone replacement therapy, women (%)	8.3	38.3	<0.001	-	-	-
CVD_H (%)	27.7	13.7	<0.001	26.7	11.7	<0.001
Hypertension_H (%)	48.7	26.7	<0.001	35.3	21.3	<0.001
Diabetes_H (%)	9.3	17.4	0.004	9.4	16.0	0.019
Mean CCA IMT (mm)	0.78 ± 0.15	0.63 ± 0.13	<0.001	0.84 ± 0.15	0.67 ± 0.14	<0.001

Note: BP, blood pressure; BMI, body mass index; CCA IMT, common carotid artery intima-media thickness; CVD_H, family history of cardiovascular disease; Diabetes_H, family history of diabetes; HDL, high-density lipoprotein; Hypertension_H, family history of hypertension; LDL, low-density lipoprotein.

Table 2. CCA IMT predictors in male subgroups of both Moscow and Paris (direct effects)

Variable	Moscow		Paris	
	Std. coefficient, B (S.E.)	*P*-value	Std. coefficient, B (S.E.)	*P*-value
Age	0.455 (0.034)	0.000	0.492 (0.028)	<0.001
BMI	0.100 (0.037)	0.007	0.157 (0.030)	<0.001
Systolic BP	0.249 (0.035)	0.000	0.097 (0.025)	<0.001
Triglycerides	0.010 (0.011)	0.853	0.057 (0.018)	0.303
HDL-Cholesterol	0.033 (0.018)	0.531	-0.086 (0.034)	0.011
LDL-Cholesterol	0.089 (0.035)	0.010	0.206 (0.007)	0.837
Smoking status	0.012 (0.023)	0.824	0.050 (0.002)	0.340
Alcohol	0.071 (0.001)	0.294	0.022 (0.009)	0.763
Diabetes	0.090 (0.036)	0.012	0.030 (0.001)	0.686
CVD_H	0.029 (0.019)	0.600	0.009 (0.022)	0.868
Diabetes_H	0.073 (0.026)	0.158	0.056 (0.026)	0.031
Hypertension_H	0.071 (0.017)	0.204	0.072 (0.018)	0.181

Note: BP, blood pressure; BMI, body mass index; CCA IMT, common carotid artery intima-media thickness; CVD_H, family history of cardiovascular disease; Diabetes_H, family history of diabetes; HDL, high-density lipoproteins; Hypertension_H, family history of hypertension; LDL, low-density lipoproteins; non-sig., non-significant; S.E., standard error; Std. coefficient, standardized coefficient.

of indirect effects of traditional CVRFs on CCA IMT in this subgroup revealed a statistically significant effect of CVD_H (β = 0.194, *p*-value <0.001) through the direct influence on the systolic BP, the significant predictor of IMT. The lack of statistical significance of hyperlipidemia treatment effects on the lipid profile (direct effects) and CCA IMT (indirect effects) was most likely due to a small number of individuals (only 3.7%) taking the statins in the male subgroup of the Moscow study population. In this subgroup, R^2 (coefficient of determination for the specified path model) was equal to 30.1%. Therefore, all determined effects (direct and indirect) of traditional CVRFs can explain 30.1% of the CCA IMT variance in this cohort of subjects.

Table 3. CCA IMT predictors in female subgroups of both Moscow and Paris (direct effects)

Variable	Moscow		Paris	
	Std. coefficient, B (S.E.)	*P*-value	Std. coefficient, B (S.E.)	*P*-value
Age	0.525 (0.028)	<0.001	0.300 (0.050)	<0.001
BMI	0.008 (0.002)	0.879	0.052 (0.001)	0.410
Systolic BP	0.171 (0.035)	<0.001	0.126 (0.042)	0.002
Triglycerides	0.004 (0.0013)	0.765	0.024 (0.015)	0.744
HDL-Cholesterol	-0.058 (0.034)	0.028	-0.058 (0.034)	0.028
LDL-Cholesterol	0.037 (0.018)	0.229	0.059 (0.017)	0.378
Smoking status	0.063 (0.031)	0.220	0.047 (0.002)	0.465
Diabetes	0.058 (0.033)	0.034	0.058 (0.033)	0.034
CVD_H	0.029 (0.018)	0.576	0.062 (0.025)	0.335
Diabetes_H	0.004 (0.029)	0.938	0.013 (0.023)	0.837
Hypertension_H	0.052 (0.017)	0.733	0.082 (0.020)	0.208
Menopause	0.052 (0.011)	0.448	0.020 (0.001)	0.810
Hormone replacement therapy	-0.049 (0.028)	0.329	0.026 (0.017)	0.684

Note: BP, blood pressure; BMI, body mass index; CCA IMT, common carotid artery intima-media thickness; CVD_H, family history of cardiovascular disease; Diabetes_H, family history of diabetes; HDL, high-density lipoproteins; Hypertension_H, family history of hypertension; LDL, low-density lipoproteins; non-sig., non-significant; S.E., standard error; Std. coefficient, standardized coefficient.

Paris population: male subgroup: In the male study subgroup of Paris population, both age (β = 0.492, *p*-value <0.001) and BMI (β = 0.157, *p*-value = 0.007) had the most significant impact on the dependent variable (CCA IMT), thus, demonstrating their greatest predictive power. Also, positively associated with BMI, both systolic BP (β = 0.097, *p*-value <0.001) and diabetes (β = 0.056, *p*-value = 0.031) showed the statistically significant impact on the CCA IMT. In this subgroup, HDL (β = -0.086, *p*-value = 0.011) showed the statistically significant negative association with the dependent variable. These factors showed a direct impact on the dependent variable in this cohort of subjects. Specified indirect effects did not show a statistically significant impact on the CCA IMT in this cohort of subjects. The impact caused by the above-mentioned factors was considered to be accountable for R^2 equal to 27% in this subgroup. Therefore, all determined effects (direct and indirect) of traditional CVRFs can explain 27% of the CCA IMT variance in this cohort of subjects.

Moscow population: female subgroup: In the female study subgroup of Moscow population, age (β = 0.525, *p*-value <0.001) and systolic BP (β = 0.171, *p*-value <0.001) demonstrated positively associated and statistically significant effects on CCA IMT. Therefore, these factors were considered to have the greatest predictive power in this cohort of subjects. Two other factors, such as diabetes and HDL, showed a relatively less important but still statistically significant impact on CCA IMT. The direct association was demonstrated by the diabetes presence (β = 0.058, *p*-value = 0.034), and the negative association was found with HDL (β = -0.058, *p*-value = 0.028). Moreover, BMI (β = 0.241, *p*-value <0.001) and CVD_H (β = 0.243, *p*-value <0.001) showed statistically significant effects on CCA IMT through the direct impact on systolic BP. Therefore, these factors were considered as factors with high prediction power in this cohort of subjects. In this subgroup, R^2 was equal to 42%. Therefore, all determined effects (direct and indirect) of traditional CVRFs can explain 42% of the CCA IMT variance in this cohort of subjects.

Paris population: female subgroup: In the female study subgroup of Paris population, two factors, such as age (β = 0.300, *p*-value <0.001) and systolic BP (β = 0.126, *p*-value <0.001), showed the most significant impact on the dependent variable, thus, demonstrating the most significant predictive power. The presence of diabetes with the positive association (β = 0.058, *p*-value = 0.033) and HDL with the inverse association (β = -0.058, *p*-value =

Table 4. Predictors of CCA IMT differences between women of both Moscow and Paris populations

Variable	Std. coefficient (B)	S.E.	*P*-value
BMI	0.029	0.011	0.672
Systolic BP	0.151	0.061	0.013
Smoking status	0.019	0.007	0.831
Diabetes	0.074	0.024	0.108
Treatment of arterial hypertension	0.111	0.061	0.037
Menopause	0.054	0.031	0.097
Menopause duration	0.120	0.058	0.037
Hormone replacement therapy	-0.023	0.011	0.529
Treatment of hyperlipidemia	0.014	0.002	0.718
CVD_H	0.045	0.024	0.412
Diabetes_H	0.023	0.013	0.629
Hypertension_H	0.031	0.017	0.371
Triglycerides	0.047	0.022	0.118
HDL-Cholesterol	-0.078	0.009	0.101
LDL-Cholesterol	0.013	0.003	0.783

Note: BP, blood pressure; BMI, body mass index; CCA IMT, common carotid artery intima-media thickness; CVD_H, family history of cardiovascular disease; Diabetes_H, family history of diabetes; HDL, high-density lipoproteins; Hypertension_H, family history of hypertension; LDL, low-density lipoproteins; non-sig., non-significant; S.E., standard error; Std. coefficient, standardized coefficient.

0.34) also showed a statistically significant impact on the CCA IMT. Therefore, this set of factors can represent a model of direct effects on the dependent variable in this cohort of subjects. In terms of indirect effects, two factors showed the statistically significant influence on CCA IMT through the influence on systolic BP: BMI (β = 0.221, *p*-value = 0.008) and CVD_H (β = 0.145, *p*-value = 0.028). In this subgroup, R^2 was equal to 14.3%. Therefore, all determined effects (direct and indirect) of traditional CVRFs can explain 14.3% of the CCA IMT variance in this cohort of subjects.

Overall, the remarkably high level of difference in the mean values of the CCA IMT was found between the study populations. In women of both Moscow and Paris study populations, the mean CCA IMT value was 0.78 and 0.63, respectively. The mean CCA IMT estimate was 0.84 and 0.67 in males of Moscow and Paris study populations, respectively.

Regression model

To determine to what extent presented differences can be explained by differences in traditional CVRFs, the regression model was used. In this model, the random variable was considered as the dependent variable representing the absolute difference in CCA IMT values between the two populations of the same age and sex (to neutralize the influence of these factors). The dataset was transformed into a matrix of pairwise distances for all observed characteristics between all possible pairs of both Moscow and Paris study populations. The regression model was constructed and analyzed using the Mplus software package with the estimator, which allowed to include categorical variables as predictors. The results of the regression model evaluation, i.e., standardized coefficient, standard error, and *p*-value obtained separately for men and women of both Paris and Moscow populations, were presented in **Tables 4** and **5**, respectively.

Analyzing regression model, only differences in three factors, such as systolic BP (β = 0.151, *p*-value = 0.013), CVD_H (β = 0.111, *p*-value = 0.037), and menopause duration (β = 0.120, *p*-value = 0.037), significantly influenced the total differences in CCA IMT values in women. This set of factors can explain only 10.1% of the total variance of the dependent variable (the differences in values of CCA IMT between women in Paris and Moscow study populations), while 89.9% of the difference in CCA IMT values between women of these populations cannot be explained by the differences in values attributed to traditional CVRFs. Hence, it is highly likely that these differences were influenced by other factors omitted.

In men, differences in three factors, such as systolic BP (β = 0.207, *p*-value <0.001), BMI (β = 0.140, *p*-value = 0.015), and HDL (β = -0.193, *p*-value = 0.006) significantly influenced the total differences in the CCA IMT values. These factors can explain 13.5% of the total variance of the dependent variable (differences in values of CCA IMT between men in Paris and Moscow study populations), whereas 86.5% of differences in the CCA IMT values between men of these populations cannot be explained by the differences in values attributed to tradi-

Table 5. Predictors of CCA IMT differences between men of both Moscow and Paris populations

Variable	Std. coefficient (B)	S.E.	*P*-value
BMI	0.140	0.058	0.015
Systolic BP	0.207	0.056	<0.001
Smoking status	0.029	0.006	0.562
Alcohol	0.038	0.012	0.231
Diabetes	0.029	0.015	0.311
Treatment of arterial hypertension	0.021	0.010	0.712
Treatment of hyperlipidemia	0.067	0.021	0.681
CVD_H	0.048	0.018	0.473
Diabetes_H	0.037	0.014	0.396
Hypertension_H	0.028	0.011	0.413
Triglycerides	0.041	0.021	0.732
HDL-Cholesterol	-0.193	0.070	0.006
LDL-Cholesterol	0.026	0.007	0.619

Note: BP, blood pressure; BMI, body mass index; CCA IMT, common carotid artery intima-media thickness; CVD_H, family history of cardiovascular disease; Diabetes_H, family history of diabetes; HDL, high-density lipoproteins; Hypertension_H, family history of hypertension; LDL, low-density lipoproteins; non-sig., non-significant; S.E., standard error; Std. coefficient, standardized coefficient.

tional CVRFs. Hence, it is highly likely that these differences were influenced by other factors omitted.

Discussion

The study compared the distribution and impact of traditional CVRFs on CCA IMT, the quantitative estimate of carotid atherosclerosis, in two study populations of Moscow, Russia and Paris, France equally divided by sex. There was a significant difference in most of the traditional CVRFs between the study populations, including BP, lipid profile, statin treatment, hormone replacement therapy in women, and CVD_H. The values of CCA IMT were significantly higher in the Moscow study population, compared to that in the Paris study population.

In our study, significant differences in phenotypic factors among men from both Moscow and Paris populations can define significant differences in the predictive and explanatory power of the specified model. Although, the presence of universal classical CVRFs factors (age, systolic BP, BMI, and diabetes) demonstrated the highest statistically significant effect, as well as the highest predictive power in both male subgroups of Moscow and Paris study populations. The relative importance of these factors was different in these subgroups. Moreover, while the dependent variable in the male subgroup of the Moscow study population was affected by the LDL, it was affected by HDL in the male subgroup of the Paris study population. From the statistical perspective, this difference can be explained primarily by the fact that the higher LDL variance was found in the Moscow study population, as well as both the lower absolute values and the variance of HDL, compared to the Paris study population. Besides, in contrast to the male subgroup of the Paris study population, the presence of statistically significant indirect effects on the dependent variable through the influence of independent factors on the level of systolic BP was found in the Moscow male study subgroup.

In female subgroups, the set of the factors influencing CCIMT variability was found to be identical for both Moscow and Paris study populations and included age, systolic BP, presence of diabetes, HDL, BMI, and CVD_H. The relative importance of these factors was also similar in these subgroups. However, this set of factors can explain 42% of the variance of the dependent variable in the Moscow study population and only 14.3% - in Paris. Thus, the predictive power of some traditional CVRFs differed significantly in these data sets. The estimates of the regression model parameters suggested that traditional CVRFs have relatively low predictive power, which was confirmed by the significant CCA IMT variance observed in all studied subgroups. The analysis revealed that the following factors have the most significant prognostic power: age, systolic BP, diabetes, BMI, and HDL level. However, they cannot be considered as absolutely universal predictors because some CVRFs did not show any statistical significance, for example, in the male subgroup of the Moscow population, HDL level was not statistically significant. The relative importance of these factors varied dramatically between the study subgroups of both Moscow

and Paris study populations (14% and 42% of the explained variance of the dependent variable, respectively).

Results of the model evaluation of the Moscow study population demonstrated the higher predictive power of traditional CVRFs of the model (30% and 42% of the explained variance in men and women, respectively), compared to the Paris population (27% and 14% of the explained variance in men and women, respectively). In this way, we can suggest that compared to the Moscow study population, in the Paris study population, the influence of other factors outweighed the effects of traditional CVRFs and determined the CCA IMT variance to a greater extent. Perhaps, this difference can partly be explained by the treatment of hyperlipidemia, but the problem of a low number of people from the Moscow study population taking statins did not allow to test this assumption. The significant difference in CCA IMT values between Moscow and Paris study populations could not be based solely on the differences in the parameters of the sample, the observed differences in the distribution of traditional CVRFs. The differences in CCA IMT values caused by the differences in samples represented only 10.1% and 13.5% in women and men, respectively.

The results obtained in this study were in consistence with other studies. Several papers reported a similar level of association between CCA IMT and the presence of traditional CVRFs [8, 9]. The Multi-Ethnic Study of Atherosclerosis showed associations (model R^2, 19.5%) of IMT with the combination of factors, such as age, sex, systolic BP, total cholesterol, HDL cholesterol, hypertension treatment, diabetes, and smoking [8]. In another study, the proportion of carotid IMT explained by traditional CVRFs was 15%-17% with age and BP being the most important factors [9].

Furthermore, the IMPROVE study showed that the latitude can be an important determinant of CCA IMT [7]. The results obtained in our study can confirm this fact because mean CCA IMT value in the Moscow study population was found to be similar to that obtained in Finnish and Swedish populations in the IMPROVE study. In turn, we can suggest that longitude can be another factor influencing the interpopulation CCA IMT variability since classical CVRFs cannot explain fully the differences in the mean CCA IMT values between the populations of this study. Thus, longitude, which includes genetic, nutritional, or environmental factors, may be an important contributor to the existence of a geographic gradient of the CCA IMT variability. The influence of environmental factors on atherosclerosis and a CVD development was demonstrated [10]. This study showed that a certain amount of solid dust particles of exhaust gases in atmospheric air can be related to the degree of subclinical atherosclerosis and the development of CVDs, including coronary heart disease and myocardial infarction. Genome-wide association study approach has yielded a growing number of genetic markers that potentially can serve as predictors of CVD outcomes [11]. Although, it is required to generalize these markers across different populations. Interestingly, mitochondrial DNA mutations have recently emerged as novel markers of atherosclerosis [12]. Their study demonstrated the association of threshold heteroplasmy levels of mitochondrial DNA mutations with the predisposition to the initiation and development of atherosclerosis in human arteries. Remarkably, the incidence of some variants of the mitochondrial genome was different in samples derived from different populations (Russian and Kazakh populations were studied) [13]. In addition, the differences in the mortality rates of ischemic heart disease between Russia and France were observed suggesting a geographical gradient of atherosclerosis-related cardiovascular mortality [14]. Importantly, the existence of a geographical gradient of carotid IMT, which highly correlated with the known gradient of cardiovascular mortality was confirmed [15].

Of note, CCA IMT variability in Moscow population was also assessed previously indicating the presence of European geographic gradient of CCA IMT [16]. Besides, the interpopulation variability of CCA IMT, as well as the role of CVRFs were determined in selected high-risk population sample recruited in Moscow, Russia and Milan, Italy [17]. This study also provided evidence indicating the presence of West-to-East geographic gradient of CCA IMT.

The limitation of the current study was the fact that we were able to assess only the impact of traditional CVRFs on CCA IMT variability, whereas other parameters measured by carotid ultra-

sound may have a greater degree of association with the CVRFs and greater predictive power. The Tromso study showed that the total plaque area had a stronger association with CVRFs than CCA IMT, and only two factors, such as age and sex were stronger predictors of IMT than total plaque area parameter [18]. The combined analysis of CCA IMT and other plaque parameters, in association with CVRFs, improved cardiovascular risk prediction, compared to CCA IMT alone in the Atherosclerosis Risk In Communities (ARIC) study [19]. Complex assessment of IMT of the internal carotid artery and carotid bulb, as well as different characteristics of a carotid plaque, such as plaque number, plaque thickness, plaque area, and plaque volume, were shown to improve cardiovascular risk stratification [20, 21].

Conclusion

This study showed that the Paris study population significantly differed from the Moscow study population in the distribution and impact of traditional CVRFs. Remarkably, traditional CVRFs factors can explain only a small proportion of the CCA IMT variation between these populations suggesting the presence of other factors, such as longitude, also influencing interpopulation CCA IMT variability. Therefore, this study provided an additional piece of evidence towards the existence of a geographical gradient of carotid IMT.

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Disclosure of conflict of interest

None.

Abbreviations

Hypertension_H, Family history of hypertension; Diabetes_H, Family history of diabetes; BMI, Body mass index; CCA, Common carotid artery; CVD, Cardiovascular disease; CVD_H, Family history of cardiovascular disease; CVRFs, Cardiovascular risk factors; HDL, High-density lipoprotein; IMT, Intima-media thickness; LDL, Low-density lipoprotein; BP, Blood pressure; SD, Standard deviation.

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