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Long-term cardiovascular damage in Leningrad Siege survivors

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Abstract

Objective. To assess the prevalence of markers of preclinical vascular, kidney and brain damage in the survivors of the Leningrad Siege (SLS) in the long-term period of life, as well as to determine a possible connection with starvation in the prenatal period and early childhood. **Design and methods.** A prospective cohort study of 305 SLS was initiated in 2009–2011. In a control sex- and age-matched group we recruited people born in the same time period in other regions of the Soviet Union and permanently residing in Leningrad after the World War II (n = 51). At the second visit in 2013–2014, 252 residents of besieged Leningrad were examined (the response rate was 82,6%). Blood pressure measurement and anthropometry were performed according to standard methods. The laboratory examination included the assessment of fasting glucose, lipids, and creatinine with the calculation of the glomerular filtration rate (GFR) according to the CKD-EPI formula. The concentration of albumin and creatinine was determined, and the albumin-creatinine ratio was calculated. All patients underwent assessment of the pulse wave velocity by the applanation tonometry (SphygmoCor, AtCor, Australia), cardio-ankle vascular index (CAVI) and ankle-brachial index (VaSera VS 1500, FukudaDenshi, Japan). For cognitive assessment, the Mini-Mental State Examination (MMSE) scale was used. **Results.** The analysis included data of 184 residents of besieged Leningrad (52 males (28,3%) and 132 females (71,7%), average age 74,7 years old) divided into three groups depending on the age period during the Siege: 132 people in the first group (late childhood and adolescents), 28 people in the early childhood group, 24 people in the third "intrauterine" group. The control group included 44 people: 13 males (29,5%) and 31 females (70,5%), average age 75,5 years old. The survivors of the besieged Leningrad showed lower anthropometric characteristics — lower weight (p = 0,005) and body mass index (p = 0,004) compared with the control group. There were no differences in the prevalence of vascular, renal and cerebral lesions. The lowest arterial stiffness according to the CAVI index was detected in the "intrauterine" group compared to early, late childhood and adolescent groups (p = 0,015). Renal dysfunction was detected only in the first group (late childhood and adolescents). **Conclusions.** The residents of the besieged Leningrad demonstrate low prevalence of renal dysfunction and arteriosclerosis of the large arteries and atherosclerosis of the peripheral arteries, as well as preserved cognitive function. The increased arterial stiffness and decreased

GFR in SLS who experienced the siege in late childhood and adolescence are most likely due to the older age.

Key words: arteriosclerosis, starvation, survivors of the Leningrad siege, aging, atherosclerosis, cognitive dysfunction, arterial stiffness, renal dysfunction, subclinical arterial lesion

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Распространенность поражения сердечно-сосудистой системы в отдаленном периоде жизни у жителей блокадного Ленинграда

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Резюме

Цель исследования — оценить распространенность маркеров доклинического поражения сосудов, почек, головного мозга у жителей блокадного Ленинграда (ЖБЛ) в отдаленном периоде жизни, а также определить возможную связь с голоданием во внутриутробном периоде и раннем детском возрасте. **Материалы и методы.** Проспективное когортное исследование 305 ЖБЛ было инициировано в 2009–2011 годах. Также была сформирована контрольная группа, сопоставимая по полу и возрасту, из людей, родившихся в тот же временной промежуток в других регионах Советского Союза и после Великой Отечественной войны, постоянно проживающих в Ленинграде (51 человек). На втором визите в 2013–2014 годах обследовано 252 ЖБЛ (отклик составил 82,6%). Были проведены измерение артериального давления и антропометрия согласно стандартным методикам. Лабораторное обследование включало определение липидного спектра, глюкозы, креатинина с расчетом скорости клубочковой фильтрации (СКФ) по формуле CKD-EPI. Проводилось определение концентрации альбумина и креатинина в разовой порции мочи с последующим расчетом альбумин-креатининового соотношения. Всем пациентам выполнена оценка скорости распространения пульсовой волны на приборе SphygmoCor (AtCor, Австралия) методом аппланационной тонометрии, определение сердечно-лодыжечного сосудистого индекса (СЛСИ) и лодыжечно-плечевого индекса на аппарате VaSera VS-1500 (Fukuda Denshi, Япония). Для оценки когнитивной функции пациента использовалась краткая шкала оценки психического статуса (Mini-Mental State Examination, MMSE). **Результаты.** В анализ включено

184 ЖБЛ: 52 мужчины (28,3 %) и 132 женщины (71,7 %), средний возраст — 74,7 года. В зависимости от возраста исследуемого на момент блокады Ленинграда 132 человека были отнесены к группе «старший детский и подростковый возраст», 28 человек к группе «раннего детского возраста» и 24 человека к «внутриутробной» группе. Группу контроля составили 44 человека: 13 мужчин (29,5 %) и 31 женщина (70,5 %), средний возраст — 75,5 года. У ЖБЛ регистрировались только более низкие антропометрические показатели — массы тела (p = 0,005) и индекса массы тела (ИМТ) (p = 0,004), по сравнению с контрольной группой. Различий в распространенности поражения сосудов, почек и головного мозга выявлено не было. Наименьшая ригидность артерий согласно показателю СЛСИ была выявлена во «внутриутробной» группе по сравнению с группами младшего, старшего детского и подросткового возраста (p = 0,015). При оценке функции почек была выявлена почечная дисфункция только в первой группе — старшего детского и подросткового возраста. **Выводы.** Анализ состояния сердечно-сосудистой системы у ЖБЛ выявил низкую распространенность почечной дисфункции, артериосклероза крупных артерий и атеросклероза периферических артерий, а также сохранную когнитивную функцию. Повышенная жесткость артерий и снижение СКФ, выявленные у лиц, переживших блокаду в старшем детском и подростковом возрасте, вероятнее всего, являются следствием более преклонного возраста этой группы.

Ключевые слова: артериосклероз, голодание, жители блокадного Ленинграда, старение, атеросклероз, когнитивная дисфункция, жесткость артерий, почечная дисфункция, субклиническое поражение артерий

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Background

In the scientific literature there is more and more evidence that the state of the cardiovascular system is determined not only by traditional risk factors that are important in the adult life, but also depends on the conditions of intrauterine development and the early period of life [1]. Adverse developmental conditions, restriction of nutrient intake in the early stages of life, can lead to an increased risk of cardiovascular complications in adulthood [2]. The most valuable information on the effects of nutrition during pregnancy on the health of children and adults can be obtained from the study of people born during periods of war and natural disasters. One of the most interesting historically developed population for studying the effect of starvation on the development of cardiovascular complications in adulthood is the group of survivors of the Leningrad Siege (SLS). Studies have been conducted that demonstrate the association of the fasting in the prenatal, childhood and adolescent periods with an increased risk of developing cardiovascular diseases in adulthood. Thus, SLS had a high prevalence of arterial hypertension, in addition, they had excessive compensation of nutrition in later adult life, leading to obesity [3]. There is also evidence of a higher prevalence of myocardial infarction, acute cerebrovascular accident and diabetes mellitus in elderly people who survived the Leningrad siege in childhood. An increase in complicated forms of atherosclerosis of the aorta, coronary and cerebral arteries has been described in men, who survived the Leningrad siege at the age of 11 years [4].However, data on arterial stiffness, cognitive function, and the initial forms of renal dysfunction in this unique population are not described in the literature. Objective. To assess the prevalence of markers of preclinical vascular, kidney and brain damage in the survivors of the Leningrad siege (SLS) in the long-term period of life, as well as to determine a possible connection with starvation in the prenatal period and early childhood.

Materials and methods

A prospective cohort study was carried out by forming a random sample of 2200 survivors. The

list was provided by the SLS society of the Primorsky district of the Saint- Petersburg. The first visit of 305 SLS was initiated in 2009–2011 to assess the prevalence of risk factors and cardiovascular diseases, markers of cardiovascular aging. The results were presented earlier [5]. The control group, comparable in gender and age, was formed from people born in the same time period in other regions of the Soviet Union and after the Great Patriotic War, permanently residing in Leningrad (St. Petersburg). The exclusion criteria was an indication of significant starvation during the Great Patriotic War. The second visit took place in 2013–2014. 252 of 305 participants were examined: 25 people died, 26 people withdraw from the study, two people did not get through. The response was 82.6 %. From the control group 51 people were examined at the first visit. 45 participants came to the second visit (response 88.2 %).

SLS were divided into groups depending on the year of the birth and age period of the child's development, in which they underwent the Leningrad Siege:

- 1st group (late childhood and adolescents): persons born from 1930 to January 1, 1941;
- 2nd group (early childhood): participants born in the period from 1 January 1 to 31 October 31, 1941;
- group 3 ("intrauterine"): participants with a birth date from November 1, 1941 to January 27, January 27,1943.

All subjects signed an informed consent and were interviewed according to the questionnaire, which includes information about concomitant diseases and therapy. The prevalence of cardiovascular diseases was recorded on the basis of the data collected during the examination and the doctor's conclusion based on the results of laboratory and instrumental examinations.

All subjects underwent anthropometry: measurement of height (medical stadiometer, (Russia)) and body weight (medical scales VEM-150 — "Massa-K", (Russia)) with the calculation of BMI according to the Quetelet formula. Blood pressure (BP) and pulse rate were measured by the OMRON device (Japan) on the right hand after 5 minutes of rest in a sitting position three times with the calculation of the average value from the last two measurements.

A fasting blood sample was taken with the determination of the lipid profile (total cholesterol, high density lipoproteins, low density lipoproteins, triglycerides), glucose levels, creatinine with the calculation of the glomerular filtration rate (GFR) according to the CKD-EPI formula [6]. Morning urine sample was collected to determine the concentration of albumin and creatinine, followed by the calculation of the albumin-creatinine ratio.

The analysis of blood and urine parameters was performed on Abbot Architect c8000 biochemical analyzer (USA). Instrumental methods were used to assess the condition of the arteries.

1. The assessment of the pulse wave velocity (PWV) was carried out using the SphygmoCor device (AtCor, Australia) by the applanation tonometry [7]. The pulse wave was recorded sequentially in the proximal (carotid) and distal (femoral) arteries, while an electrocardiogram (ECG) was recorded simultaneously. Carotid-femoral PWV was calculated taking into account the travel time of the wave between the registration points, determined using

Table 1

VASCULAR, KIDNEY AND BRAIN DAMAGE CRITERION

Target organ	Parameters	Deviation criterion
Kidney	GFR	< 60 ml/min/1.73 m^2
	ACR	> 3.4 mg/mmol
Vessels	PWV	> 10 m/s
	CAVI	> 9.0
	ABI	< 0.9
	PP	≥ 60 mm. Hg.
Brain	MMSE	< 25 points

Note: GFR — glomerular filtration rate (CKD-EPI); ACR — albumin-creatinine ratio; PWV — pulse wave velocity; CAVI — cardio-ankle vascular index; ABI — ankle-brachial index; PP — pulse pressure; MMSE — Mini-Mental State Examination.

the R wave on the ECG. The distance between the carotid artery and the jugular notch was subtracted from the distance between the jugular notch and the registration point above the femoral artery.

2. Determination of the cardio-ankle vascular index (CAVI, Cardio-AnkleVascularIndex) and ankle-brachial index (ABI) was carried out using the VaSera VS-1500 device (FukudaDenshi, Japan) [8]. CAVI was measured automatically on the right and on the left, CAVI was calculated between the heart valve and the malleolar artery, using a phonocardiographic signal (II tone) and plethysmograms obtained by applying cuffs to the brachium and lower leg. ABI measurement was also performed automatically on the right and left and was calculated as the ratio of the systolic blood pressure in the lower leg arteries to the systolic blood pressure in the brachial artery.

A short scale for assessing mental status (Mini-Mental State Examination, MMSE) was used to determine the patient's cognitive function. Test include an assessment of orientation in time and space, sensation, memory, concentration and speech. It is a 30-item questionnaire. The test result is obtained by summing the answers for each of the items, and is estimated in points [96].

To assess the target organ damage were taken the criteria, presented in the table 1 [9, 10, 8].

Data analysis was performed using the following mathematical and statistical methods: quantitative variables were assessed for normality of distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests (with normal distribution- average, standard deviations, confidence interval. With nonnormal distribution -median and interquartile range. Ratings were described with absolute values and percentages. Student's t-test was calculated by comparing the mean values with a normal distribution of data. Variance analysis was carried out when comparing several groups in two stages (at the first stage- the Fisher's F-test was calculated, at the second stage- post hoc analysis). The Mann-Whitney U test was used to compare independent populations in the nonnormal distribution of the data. Comparison of nominal data was carried out using the Pearson χ^2 test.

Table 2

COMPARATIVE ANALYSIS OF PARAMETERS IN SURVIVORS OF THE LENINGRAD SIEGE AND THE CONTROL GROUP

Parameters	SLS (n = 184)		Controls (n = 44)		p-value
	M ± SD	95 % CI	M ± SD	95 % CI	
Age, years	74.7 ± 2.6	74.4–75.0	75.5 ± 2.8	74.6–76.3	0.08
Height, sm	159.4 ± 9.0	158.3–160.5	162.0 ± 9.6	159.1–164.9	0.08
Weight, kg	73.2 ± 14.5	71.4–75.0	80.1 ± 18.7	74.5–85.7	0.005
BMI, kg/m2	28.8 ± 5.3	28.1–29.4	30.5 ± 6.5	28.5–32.4	0.004
SBP, mm.Hg.	149.6 ± 23.5	146.7–152.6	150.1 ± 21.6	143.6–156.7	0.84
DBP, mm.Hg.	80.7 ± 11.4	79.3–82.1	83.1 ± 11.5	79.6–86.6	0.19
	Me	Q1–Q3	Me	Q1–Q3	
TC, mmol/l	5.5	[4.6–6.4]	5.4	[4.8–6.4]	0.87
HDL, mmol/l	1.3	[1.1–1.6]	1.2	[1.0–1.5]	0.21
LDL, mmol/l	3.4	[2.6–4.1]	3.52	[3.0–4.3]	0.37
TG, mmol/l	1.2	[0.9–1.6]	1.1	[0.8–1.69]	0.77
Glucose, mmol/l	5.4	[5.0–6.0]	5.6	[5.2–6.0]	0.15
PWV, m/s	10.3	[8.9–11.8]	10.4	[9.5–13.0]	0.42
PP, mm.Hg.	66.2	[57.5–79.0]	63.0	[57.5–76.0]	0.46
ABI	1.05	[0.98–1.1]	1.03	[0.97–1.08]	0.36
CAVI	9.35	[8.5–9.9]	9.25	[8.6–10.0]	0.92
MMSE, points	28	[27–29]	28	[27–29]	0.84
GFR, ml/min/1,73 m^2	76.4	[66.0–83.9]	77.6	[66.5–88.9]	0.48
ACR, mg/mmol	0.91	[0.51–1.48]	0.89	[0.63–1.66]	0.61

Note: SLS — survivors of the Leningrad siege; CI — confidence interval; BMI — body mass index; SBP — systolic blood pressure; DBP — dyastolic blood pressure; TC — total cholesterol; HDL— high density lipoproteins; LDL— low density lipoproteins; TG — triglycerides; PWV — pulse wave velocity; PP— pulse pressure; ABI — ankle-brachial index; CAVI — cardio-ankle vascular index; MMSE — Mini-Mental State Examination; GFR — glomerular filtration rate (CKD-EPI); ACR — albumin-creatinine ratio.

Table 3

PREVALENCE OF VASCULAR, KIDNEY AND BRAIN DAMAGE IN SURVIVORS OF THE LENINGRAD SIEGE IN COMPARISON WITH THE CONTROL GROUP

Parameters	SLS (n = 184)	Controls (n = 44)	p-value
Hypertension, n (%)	165 (89.6 %)	38 (86.4 %)	0.42
DM, n (%)	36 (19.5 %)	7 (15.9 %)	0.67
ACE/TIA, n (%)	19 (10.3 %)	5 (11.4 %)	0.55
MI, n (%)	19 (10.4 %)	8 (18.2 %)	0.19
Stable CHD, n (%)	69 (37.7 %)	20 (45.5 %)	0.34
CHF, n (%)	81 (44.3 %)	25 (56.8 %)	0.13
PWV > 10 m/s, n (%)	100 (57.1 %)	23 (59.0 %)	0.83
PP ≥ 60 mm.Hg., n (%)	168 (67.2 %)	28 (62.2 %)	0.6
ABI < 0.9, n (%)	26 (14.1 %)	6 (13.6 %)	1.0
CAVI > 9.0, n (%)	126 (68.5 %)	31 (70.5 %)	0.79
MMSE < 25 баллов, n (%)	11 (6.1 %)	4 (9.3 %)	0.49
GFR < 60 ml/min/1.73 m^2, n (%)	22 (12.0 %)	4 (9.1 %)	0.79
ACR > 3.4 mg/mmol, n (%)	17 (9.3 %)	8 (18.2 %)	0.10

Note: SLS — survivors of the Leningrad siege; DM — diabetes mellitus; ACE — acute cerebrovascular event; TIA — transitory ischaemic attack; MI— miocardial infarction; CHD — coronary heart disease; CHF — chronic heart failure; PWV— pulse wave velocity; PP — pulse pressure; ABI — ankle-brachial index; CAVI — cardio-ankle vascular index; MMSE — Mini-Mental State Examination; GFR— glomerular filtration rate; ACR — albumin-creatinine ratio.

Table 4

COMPARATIVE CHARACTERISTIC OF THE STATE OF VESSELS, KIDNEYS AND BRAIN IN DIFFERENT AGE GROUPS OF THE SURVIVORS OF THE LENINGRAD SIEGE

Parameters	1st group (n = 132)		2nd group (n = 28)		3rd group (n = 24)		p-value
	Me	Q1–Q3	Me	Q1–Q3	Me	Q1–Q3	
PWV, m/s	10.1	(8.8–11.9)	10.4	(9.5–11.6)	10.6	(9.4–12.2)	0.73
ABI	1.07	(0.96–1.1)	1.07	(1.04–1.09)	1.05	(1.00–1.09)	0.56
CAVI	9.3	(8.6–9.9)	9.4	(8.95–9.8)	8.8	(8.1–9.75)	0.12
MMSE, points	28	(27–29)	28	(27.5–29)	28.5	(27.5–30)	0.71
GFR, ml/min/1,73 m^2	75.1	(65.4–83.7)	77.4	(65.9–85)	78.0	(71.0–85.4)	0.23
ACR, mg/mol	0.91	(0.55–1.47)	0.87	(0.54–1.68)	1.01	(0.41–1.45)	0.94

Note: PWV — pulse wave velocity; ABI — ankle-brachial index; CAVI — cardio-ankle vascular index; MMSE — Mini-Mental State Examination; GFR— glomerular filtration rate; ACR — albumin-creatinine ratio.

Constraint force (V Cramer) was also evaluated. Mathematical and statistical analysis of the data was carried out using the SPSS Statistics 26. The level of significance when testing statistical hypotheses was taken as $p < 0.05$.

Results

The analysis included data of 184 residents of besieged Leningrad with a full range of laboratory and instrumental examinations: 52 men (28.3 %) and 132 females (71.7 %). In the control group there were 44 people: 13 men (29.5 %) and 31 females (70.5 %). Only significantly lower anthropometric parameters (body weight and BMI) were recorded in the SLS compared to the control group (Table 2). There were no differences in the prevalence of both clinical and preclinical vascular, kidney, and brain damage (Table 3). Comparative analysis of these patients depending on the period of birth did not show statistically significant differences in BMI, blood pressure, glucose and lipid profile. Table 4 present the data of the comparative analysis the average values of markers of target organ damage; no significant differences were found. When assessing

Table 5

PREVALENCE OF THE VASCULAR, KIDNEYS AND BRAIN DAMAGE IN DIFFERENT AGE GROUPS OF SURVIVORS IN THE LENINGRAD SIEGE.

Parameters	survivors group			p-value
	1	2	3	
PWV > 10 m/s, n (%)	68 (54.8%)	17 (63.0%)	15 (62.5%)	0.65
PP ≥ 60 mm.Hg., n (%)	118 (69%)	30 (68.2%)	20 (57.1%)	0.4
ABI < 0.9, n (%)	23 (17.4%)	2 (7.1%)	1 (4.2%)	0.12
CAVI > 9.0, n (%)	92 (69.7%)	23 (82.1%)	11 (45.8%)	0.015 p_{1-3} = 0.035 p_{2-3} = 0.018
MMSE < 25 points, n (%)	8 (6.3%)	2 (7.4%)	1 (4.2%)	1.0
GFR < 60 ml/min/1.73m² n (%)	22 (16.8%)	0	0	0.008
ACR> 3 mg/mmol, n (%)	14 (10.7%)	2 (7.1%)	1 (4.2%)	0.61

Note: PWV — pulse wave velocity; PP — pulse pressure; ABI — ankle-brachial index; CAVI — cardio-ankle vascular index; MMSE — Mini-Mental State Examination; GFR— glomerular filtration rate; ACR — albumin-creatinine ratio.

the prevalence of increased arterial stiffness according to the CAVI, depending on the age group (Table 5), statistically significant differences were obtained — the least stiffness of the arteries was found in the "intrauterine" group compared to the groups of early and late childhood and adolescents. Between the compared signs, a relationship of mean force was noted (V = 0.21). Renal dysfunction was detected in the assessment of renal function only in the first group (late childhood and adolescents).

Discussion

Analysis of the state of the cardiovascular system in SLS revealed a low prevalence of renal dysfunction, markers of arterio- and atherosclerosis of peripheral arteries, as well as safe cognitive function. Despite the fact that age is one of the main predictors of increased stiffness of the arterial wall, and the prevalence of arterial hypertension was 90%, no more than 60% of those examined over the age of 70 had markers of arteriosclerosis of large arteries according to sphygmometry data.

It is expected, that most of the cardiovascular risk factors represent their influence on the development of cardiovascular complications through the effect on the vascular wall. In this regard, markers of subclinical vascular damage- an increase in arterial stiffness, a decrease in ABI, a thickening of the intima-media complex of the carotid arteries and calcification of the coronary arteries — attract special attention [11].

The processes occurring in the vascular wall with aging can be divided into arteriosclerosis and atherosclerosis. Different instrumental methods make it possible to assess the presence of these two processes. ABI is an easily defined and well reproducible method for detecting asymptomatic atherosclerotic vascular disease. According to E. Selvin and T.P. Erlinger (2004), who examined more than 2000 American residents over 40 years old, the prevalence of peripheral atherosclerosis (ABI < 0.9) in the group of people over 70 years old was 14.55%, which was comparable to our findings (14.11%), although our sample consisted of persons of an older age group [12].

The "gold standard" for assessing arteriosclerosis is the carotid-femoral pulse wave velocity, using applanation tonometry [7]. The increase in arterial stiffness according to PWV data among SLS was 57.1%. When compared with the control group, no significant differences were found (59.0%, p = 0.83). Also, there were no significant differences in the prevalence of arterial stiffness between the age groups of SLS.

In recent years, the volumetric sphygmometry method use to assess CAVI, because it is simple and predictively significant. CAVI does not depend on the blood pressure level at the time of the study [13]. A.V. Turusheva et al (2019) assessed the degree of arterial stiffness, the dependence of the value of the CAVI on age and calculated the rate of its growth in different age groups [14]. This study made it possible to detect a formula for calculat-

ing the predicted value of CAVI depending on age and gender. The developed norms were similar to the values of CAVI in elderly patients with existing cardiovascular diseases and diabetes mellitus.

The mean values of CAVI at the age from 70 to 75 were 9.29 ± 1.23, which is comparable with our data (9.35 [8.5–9.9]). However, CAVI in the SLS of both sexes was found lower than the predicted value, calculated by the formula depending on gender and age. CAVI was 9.09 ± 1.07 in females in our study, predicted CAVI 9.62 ± 1.04; in men it was 9.55 ± 1.41, the predicted CAVI was 9.76 ± 1.01.

T. Yukutake et al (2014) assessed the relationship between CAVI and cognitive function in 179 older adults in community-dwelling elderly in Japan [15]. All subjects were divided into two groups: with a high MMSE value (> 26 points) and a low MMSE value (< 26 points). In the first group CAVI value was 9.13 ± 1.16, in the second- 9.61 ± 1.30. Arterial stiffness parameters obtained in our study (9.35 [8.5–9.9]) are consistent with the mean CAVI values (9.37 ± 1.23) in the work of Yukutake T. et al (2014). We did not find differences in CAVI relationship depending on the MMSE values (9.2 ± 1.12 with normal MMSE value (> 25 points) and 9.37 ± 1.93 with low MMSE value (< 25 points), p = 0.65).

In their work Q. Zhang et al (2019), based on the China Longitudinal Healthy Longevity Study (CLHLS), with a total of 2,603 participants aged 64 and over, described cognitive changes in Chinese older adults from 2005 to 2014 and studied the risk factors for cognitive impairment. Thus, the MMSE value in the sample of Chinese 75–76 years old was 27.3–26.4 points. When comparing the results of the study by Q. Zhang and co-authors (2019), SLS had higher MMSE values (28 [27–29] points) [16]. Also, in our sample, a low prevalence of cognitive impairments (6.1 %) and a low incidence of acute cerebrovascular accidents and transient ischemic attacks (10.3–3 %) were recorded.

Geraci G. et al (2017) examined elderly patients with arterial hypertension (126 participants over 65 years old and 350 people under 65 years old) and demonstrated that the group of elderly patients with arterial hypertension had lower GFR, higher parameters of arterial stiffness and prevalence albuminuria compared with middle-aged patients with arterial hypertension [17]. The pulse wave velocity was independently of other factors associated with albuminuria in elderly patients, while in middle-aged people it did not correlate with any indices of kidney damage in middle-aged patients. Age is an important modifier of the relationship between renal function and renal hemodynamics with subclinical vascular damage in elderly people without cardiovascular disease. In our study, renal dysfunction was recorded only in people of the most age group who underwent the Siege in adolescence and late childhood, and the least stiffness of the arteries was noted in the youngest, "intrauterine" group, but the differences were not significant compared to other groups. In her work L. P. Horoshinina et al (2000) showed a tendency to an increase in the frequency of vascular kidney damage in the structure of kidney and urinary system diseases in elderly people who survived the Leningrad Siege in childhood or adolescence (14 %). In patients with renal vascular diseases, there was a statistically significant increase in end-stage renal failure in the main group compared with the control group (3.5 ± 1.1 % in the SLS group and 0.80 ± 0.57 % in the comparison group, p <0, 05) [18].

A. L. Ariev and co-authors also described a more pronounced decrease of renal function in persons with dyscirculatory encephalopathy who survived the Leningrad Siege in childhood: the prevalence of the 3rd stage of chronic kidney disease, lower GFR values. In addition, it was shown that SLS have close direct correlations between the concentration of melatonin in saliva (as an indicator of body homeostasis), age and GFR. The difference in the level of concentration of melatonin in saliva in this population may be due to the influence of the transferred multifactorial stressful situations (hunger, cold, bombing, psychoemotional stress and others), which led to a restructuring of the adaptive processes in the body, an increase in the compensatory capabilities of the kidney, despite lower functional parameters, or it is genetically determined characteristics of persons who survived the Leningrad Siese in childhood [19].

A study of the adult population, who survived the Dutch famine winter of 1944–1945, showed that intrauterine nutritional deficiencies are associated with an increase in the incidence of microalbuminuria (MAU) in adulthood and a decrease in creatinine clearance, which cannot be explained only by cardiovascular risk factors [20]. Fasting in midgestational leads to a decrease in the envolvement

of sufficient glomeruli and thus may increase the risk of MAU and possibly affect kidney function in adulthood. The prevalence of MAU in the SLS was comparable to the Dutch population (9.3 % and 7.2 %, p = 0.77). However, in our study, we did not find a greater occurrence of MAU in individuals who survived starvation during the prenatal period. Perhaps the low prevalence of kidney damage is associated with the low incidence of diabetes mellitus in the population of residents of besieged Leningrad.

In our study, there were no statistically significant differences in the prevalence of arterial lesions, renal and cognitive dysfunctions among the survivors of the Leningrad Siege compared with the control group. SLS had only lower body mass indices, in contrast to the control group, which is similar to our earlier data [5]. This can be explained by the fact that fasting in early childhood can directly lead to a decrease in anthropometric indicators, impaired of compensation abilities. In addition, it is possible that the parents of the overwhelming majority of children who survived the Leningrad Siege were themselves born of malnourished mothers. Therefore, these children may have had a low birth weight. And maternal undernutrition leads to the formation of low body weight at the birth of even her term infant [21].

It is nessasary to discuss possible limitations of our study.We may not have been able to assess the negative effects of fasting due to survival bias. Our study did not include patients who were most vulnerable to starvation and other stress factors and who died in the first decades of a peaceful life. Possibly a protective effect of caloric restriction in survivors diets is a proven anti-aging factor and a possible cause of relative cardiovascular well being [22].

Further study of transgenerational mechanisms of transmission of adaptive mechanisms will reveal protective behavioral patterns that contributed to the longevity of SLS.

Conclusions

The prevalence of confirmed cardiovascular diseases and preclinical markers of arteriosclerotic vascular damage, renal dysfunction and cognitive impairment in SLS was low even in old age.

There were no significant differences in the prevalence of cardiac pathology between SLS and the control group.

The increased arterial stiffness and decreased renal function in SLS who experienced the siege in late childhood and adolescence are most likely due to the older age.

Conflict of interest
The authors declare no conflict of interest.

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