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Research article

DEVELOPING THE METHODOLOGY FOR HEALTH RISK ASSESSMENT WITHIN PUBLIC MANAGEMENT OF SANITARY-EPIDEMIOLOGICAL WELFARE OF THE POPULATION

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The article focuses on generalizing Russian scientific and methodical developments aimed at updating and supplementing the health risk assessment methodology. This methodology is a key component in tackling tasks related to providing sanitary-epidemiological welfare of the population. Russian approaches to risk assessment are shown to have a significant peculiarity, which is a wide use of methods of multidimensional statistical analysis, mathematical modeling, fuzzy logic, and their combinations. The most significant Russian scientific innovations include development of qualitative risk assessment, non-carcinogenic health risks included; severity of health disorders taken into account in risk assessment; methodical support for assessing integral risks under exposure to heterogeneous environmental factors. Russian experts suggested and developed an idea that it was possible to model evolution of risks and their growth under changing exposures. Approaches to assessing risks evolution under long-term exposure to variable factors made it possible to solve a whole set of applied hygienic tasks. In addition to establishing qualitative characteristics of non-carcinogenic risks under exposure to chemicals, methods for assessing risks under exposure to environmental noise, certain lifestyle factors and factors related to work process have also been substantiated and implemented.

Progressive development of the health risk assessment methodology ensured operative, smooth and effective transitions of control and surveillance activities performed by Rospotrebnadzor onto a fundamentally new control platform that relies on the risk-based model.

Obviously, analytical opportunities offered by the health risk assessment methodology are extensive. Development of methodical grounds in hygiene and epidemiology as well as design of applied algorithms and approaches to risk assessment and management based on the fundamental methodology should involve several trends. We should extend our knowledge on mechanisms of health disorders under exposure to heterogeneous environmental factors and work-related ones; hygienic standardization needs improvement; we should apply situational modeling and prediction of sanitary-epidemiological welfare under changing or preset conditions; we should provide substantiation for the strategic and tactical regulatory actions aimed at managing threats and risks. The experience accumulated in developing the health risk assessment methodology in variable spheres should be considered a starting point for creating new risk assessment and risk management technologies. They should give an opportunity to solve any tasks related to providing sanitary-epidemiological welfare of the population in the Russian Federation.

Keywords: public health, risk assessment, sanitary-epidemiological welfare.

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The Order by the RF President "On the National Security Strategy of the Russian Federation" issued on July 02, 2021 No. 400[1] declares the preservation of the country population and development of its human potential to be the top priority and the most vital task. In both the nearest and remote future, efforts taken by public authorities at any level should be focused on finding solutions to the issue. Accordingly, it is necessary to build and implement new public administration models based on the best available world practices and scientific developments [1, 2]. A key component in public health preservation and development of human potential is sanitary-epidemiological welfare of the population. Providing it makes it necessary to rethink certain managerial criteria and mechanisms [3].

At the contemporary stage of the society development, it is hardly possible to make the environment absolutely harmless for public health since this requires extremely high economic costs. Awareness of the fact predetermined creation of a new paradigm for safety of environmental factors for people. Key postulates in this new system of ideas and views are human health as the top priority among other elements in everyday life and the non-zero risk concept [4].

At the end of the 20th and the beginning of the 21st century, the world expert society formulated fundamental postulates of health risk analysis (such as the necessity to separate risk assessment and risk management) [5–8], determined principles and key stages in risk assessment [9] with a system of indicators for such assessment [7], and established approaches to informing about risks [10].

Russia was quick to get involved into mastering this new methodology for assessing and managing public health risks under exposure to environmental factors. Model studies were accomplished in cooperation with American colleagues in the Moscow region, Perm, Samara, the Sverdlovsk region, Angarsk, and some other cities and regions in the country [11, 12]. Risk assessment practices were expanded and generalized. New approaches were considered vital and significant and this was confirmed by an interdepartmental document signed by the RF Chief Sanitary Inspector and the RF Chief State Inspector on Environmental Protection. The document was entitled "On application of the health risk assessment methodology to manage environmental quality and public health in the Russian Federation"[2].

Initially, health risk assessment was in the highest demand within the system of social-hygienic monitoring when it came down to management of sanitary-epidemiological welfare in the country. Application of the new methodology became the most significant and even revolutionary change in the system of social-hygienic monitoring since its creation. The aforementioned document was truly strategic in its essence and its implementation led to several effective practical decisions. They expanded the sphere where the methodology for health risk assessment could be applied and reinforced analytical capabilities of monitoring quite substantially [13–16].

When the risk assessment procedure was included into the most vital document of the sanitary service in the country entitled "the Sanitary Rules and Norms SanPiN 2.1.1.1200-03. Sanitary protection zones and sanitary classification of enterprises, constructions and other objects", it became the extremely important step in integrating the risk assessment methodology into the system of public administration tools. The Sanitary rules imperatively demanded "*a reduction in effects produced by pollution on ambient air (chemical, biological, and physical) down to levels established by the existing hygienic standards, and for enterprises belonging to the hazard category I or II, both down to levels established by the existing hygi-*

[1] O Strategii natsional'noi bezopasnosti Rossiiskoi Federatsii: Ukaz Prezidenta RF ot 02.07.2021 № 400 [On the National Security Strategy of the Russian Federation: The RF President Order issued on July 02, 2021 No. 400]. *GARANT: information and legal support*. Available at: https://base.garant.ru/401425792/ (August 30, 2022) (in Russian).

[2] Ob ispol'zovanii metodologii otsenki riska dlya upravleniya kachestvom okruzhayushchei sredy i zdorov'ya naseleniya v Rossiiskoi Federatsii: Postanovlenie Glavnogo gosudarstvennogo sanitarnogo vracha RF № 25 ot 10.11.1997, Glavnogo gosudarstvennogo inspektora RF po okhrane prirody № 03-19/24-3483 ot 10.11.1997 [On application of the health risk assessment methodology to manage environmental quality and public health in the Russian Federation: The Order by the RF Chief Sanitary Inspector No. 25 dated November 10, 1997, The RF Chief State Inspector on Environmental Protection No. 03-19/24-3483 dated November 10, 1997]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/420276120 (August 30, 2022) (in Russian).

enic standards and to levels of acceptable risks for population health" [3]. The document made it possible to involve large business and experts on spatial planning and urban development as stakeholders in risk assessment and analysis of its results [17, 18].

At the same time risk assessment within social-hygienic monitoring and design of sanitary protection zones was accomplished in accordance with approaches and criteria that were mostly developed abroad and fixed in trustworthy international documents.

However, Russian scientific approaches relied on much wider use of certain methods from the very beginning. These methods include multidimensional statistical analysis (multiple regressions, factor analysis, neural networks etc.) and mathematical modeling; the methods and their combinations are quite common for assessing relationships within the "environment – health" system, establishing reasons and conditions for functional disorders of various organs and systems or analyzing the structure of threats and risks for health [19–21]. Russian experts have developed new approaches to application of health risk assessment to prove damage to human health as well as to conjugation of exposure assessments and health risks with vector maps of specific territories and settlements based on geoinformation systems [22–24].

An important trend in the methodology development involves increasing reliability and correctness when assessing population exposure to harmful factors. Thus, there are new approaches to assessing air pollutant exposure based on conjugating calculated and field data suggested in the work [25]. This makes it possible to simultaneously consider specific spatial distribution of pollutions over a given territory and actual contents of chemicals in ambient air that are registered at environmental or social-hygienic monitoring posts. Risk assessment results, combined with such mathematical processing procedures as factor and / or cluster analysis, allow determining specific zones within settlements that have similar risk levels and the same harmful factors, spotting out priority ones among such zones, and then determining reasons and sources of unacceptable health risks at later stages. Figure 1 provides an example map showing spatial distribution of risks over a given territory. Such approaches are extremely vital and interesting especially now when management of industrial emissions is in transition to principles of quoting[4].

It is important that development and practical application of the risk assessment methodology substantially increased the demand for results of social-hygienic monitoring. Thus, for example, according to E.E. Andreeva, A.V. Ivanenko with colleagues [26, 27], several vital managerial actions were taken in Moscow due to the improved system of social-hygienic monitoring and constant and systemic communications with decision-makers about results obtained by assessing health risks for people living in a megacity and exposed to harmful environmental factors. These actions resulted in positive medical and demographic trends, obvious stabilization or even a decrease in population incidence authentically associated with exposure to harmful environmental factors and a decline in frequency of severe diseases (perinatal pathology and congenital malformations, etc.).

S.V. Kuzmin with colleagues [28] show that more extensive use of the risk assessment methodology in the Sverdlovsk region ensured a substantial growth in the number of managerial decisions taken by regional and municipal authorities or by management of specific economic

[3] SanPiN 2.1.1.1200-03. Sanitarno-zashchitnye zony i sanitarnaya klassifikatsiya predpriyatii, sooruzhenii i inykh ob"ektov / utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha RF ot 25 sentyabrya 2007 goda № 74 [Sanitary Rules and Norms SanPiN 2.1.1.1200-03. Sanitary protection zones and sanitary classification of enterprises, constructions and other objects (approved by the Order by the RF Chief Sanitary Inspector No. 74 dated September 25, 2007)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902065388 (August 30, 2022) (in Russian).

[4] O provedenii eksperimenta po kvotirovaniyu vybrosov zagryaznyayushchikh veshchestv i vnesenii izmenenii v otdel'nye zakonodatel'nye akty Rossiiskoi Federatsii v chasti snizheniya zagryazneniya atmosfernogo vozdukha: Federal'nyi Zakon ot 26.07.2019 № 195-FZ (prinyat Gosudarstvennoi Dumoi 17 iyulya 2019 goda, odobren Sovetom Federatsii 23 iyulya 2019 goda) [On accomplishing the experiment on quoting emissions of pollutants and making alterations into specific legal acts of the Russian Federation regarding reduction of ambient air pollution: The Federal Law issued on July 26, 2019 No. 195-FZ (approved by the State Duma on July 17, 2019, approved by the Federation Council on July 23, 2019)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_329955/ (August 30, 2022) (in Russian).

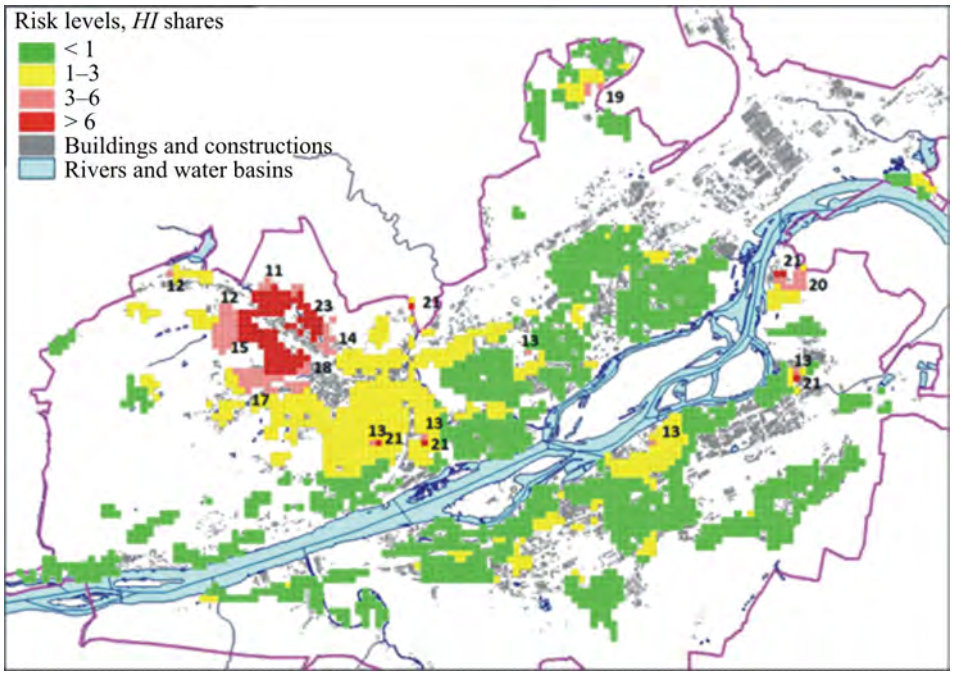


Figure 1. Zoning of a city territory as per levels of public health risks. Identification of zones with unacceptable risks of diseases of the immune system under exposure to ambient air pollution

entities and aimed at providing sanitary-epidemiological welfare of the population. Situations when consumers' rights were violated were settled according to pre-trial procedures by 1.3 times more frequently. A share of claims made by Rospotrebnadzor to defend unidentified individuals and satisfied by courts grew by 1.2 times.

Still, the most significant issues in public administration[5], including those related to sanitary-epidemiological welfare of the population, required substantial development of approaches stipulated by foreign methodical documents:

– declining quality of human potential in the country and insufficient human resources;

– ineffective public administration as regards reducing loads on businesses together with preserving proper protection of guarded social values;

– global climate change that poses potential threats for public health and living environment;

– growing variable environmental threats and hazards for public health due to wide use of harmful (including highly toxic) chemicals, their accumulation in the environment; new chemicals, biological agents and drugs being developed and implemented though their effects on people and the environment have not been studied enough; growing prevalence of antimicrobial resistance;

– growing intensity of physical environmental factors, noise, and electromagnetic radiation, especially on urbanized territories;

– many objects of accumulated environmental damage being located in close proximity to settlements, recreation zones, or agri-

[5] Edinyi plan po dostizheniyu natsional'nykh tselei razvitiya Rossiiskoi Federatsii na period do 2024 goda i na planovyi period do 2030 goda (utv. rasporyazheniem Pravitel'stva RF ot 01.10.2021 № 2765-r) [The Unified Plan on achieving national goals of the Russian Federation development for the period up to 2024 and for the planned period up to 2030 (approved by the RF Government Order dated October 01, 2021 No. 2765-r)]. *GARANT: information and legal support*. Available at: https://base.garant.ru/402929258/ (August 30, 2022) (in Russian); O natsional'nykh tselyakh i strategicheskikh zadachakh razvitiya Rossiiskoi Federatsii na period do 2024 goda: Ukaz Prezidenta RF ot 07.05.2018 g. № 204 [On national goals and strategic tasks of the Russian Federation development for the period up to 2024: the RF President Order dated May 07, 2018 No. 204]. *Prezident Rossii*. Available at: http://kremlin.ru/acts/bank/43027 (June 25, 2020) (in Russian); Ob Osnovakh gosudarstvennoi politiki Rossiiskoi Federatsii v oblasti obespecheniya khimicheskoi i biologicheskoi bezopasnosti na period do 2025 goda i dal'neishuyu perspektivu: Ukaz Prezidenta RF ot 11 marta 2019 g. № 97 [On the basics of the RF state policy in the sphere of providing chemical and biological safety for the period up to 2025 and beyond: The RF President Order dated March 11, 2019 No. 97]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/553849979 (June 25, 2020) (in Russian).

cultural land spots; such objects tend to be polluted heavily as a result of former economic activities that took place at them in the past, etc.

It is noteworthy that the Russian scientific and methodical base for health risk assessment was largely well-prepared to be used in public administration when all the aforementioned issues were first set. Over the period starting from 90ties last century, certain postulates were developed, provided with methodical support and prepared for implementation in practical activities. These provisions further developed the theory of health risk analysis, first of all, health risk assessment.

There are several Russian scientific innovations in the field. The most interesting ones are:

– development of quantitative health risk assessment, non-carcinogenic health risks included;

– severity of health disorders taken into account within health risk assessment;

– methodical support provided for assessing integral risks associated with variable functional disorders in the body under exposure to heterogeneous environmental factors;

– health risk assessment methodology applied to estimate combined exposure to environmental factors and harmful working conditions.

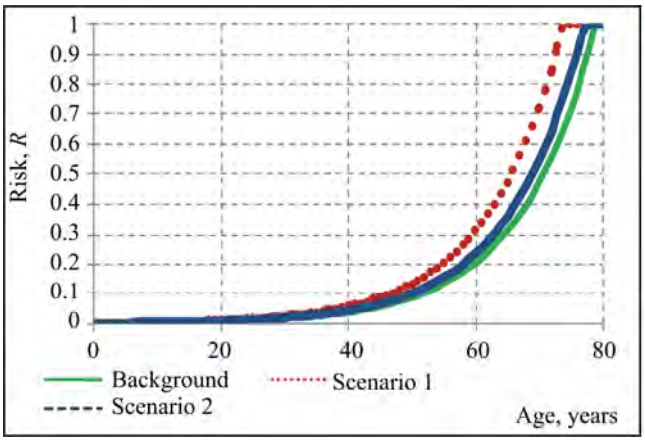
When developing quantitative risk assessment, Russian experts suggested and developed an idea that it was possible to model risk evolution and its growth under changing exposures [29, 30]. This approach was based on coordinated use of statistical and analytical models describing negative health outcomes caused by exposure to harmful environmental factors. Within this suggested approach, the human body was considered an open system consisting of a finite multitude of target organs that were tightly connected with each other and interacted with external factors. Risk evolution models were based on mathematical models that were repeatedly proven by experiments and epidemiological studies and were described in relevant research works. To implement the idea, differential calculus was needed. Essentially this new tool developed the risk assessment methodology and made it possible to perform numerical (virtual) experiments under preset exposure scenarios that involved any combination of harmful factors. Later the developed methodical approaches were applied to solve a whole set of managerial tasks.

Thus, the evolution model that described accumulating risks of functional disorders of various organs and systems was applied to substantiate a hygienic standard for ractopamine, an antibiotic used as a silage additive for farm animals, in foods [31]. The issue was associated with the necessity to give grounds for the opinion expressed by Russian hygienists who believed ractopamine should be strictly prohibited in any food. This was not in line with the *Codex Alimentarius* Decision stipulating allowable ractopamine contents from 0.01 to 0.09 mg/kg in various meat and meat products[6].

Russian hygienists used evolution modeling and made an effort to predict ractopamine accumulation in the body. This allowed them to prove that a maximum permissible daily dose taken as a basis for establishing maximum permissible level of ractopamine was within 0–1 μg/kg of body weight, that is, it did not differ authentically from zero and could not be used as a ground to establish hygineic standards for ractopamine contents in meet products (Figure 2). Basic postulates of the methodology were applied to substantiate maximum pertmissible levels of tetracycline antibiotics [32]. To do that, several models were used to describe how imbalance was developing in gut microbiota resulting in digestive diseases, dermatitis, or food allergy (Figures 3 and 4).

Overall, we have this available Russian methodology for health risk assessment harmonized with methodical approaches applied worldwide. Use of this methodology to substantiate hygienic standards has already become a considerable advantage in upholding the sovereign standards existing in Russia and the EAEU member states in discussions held by such international organizations as the FAO, WHO etc. Without doubt, this advantage will be retained in future.

[6] Joint FAO/WHO Food Standard Programme Codex Alimentarius Commission. 35th Session. Rome, Italy, July 2–7, 2012, pp. 87–120.



$$R_{t+1} = R_t + (\alpha \cdot R_t + \beta \cdot D)C$$

Recurrence equation showing accumulating risks of functional disorders of the cardiovascular system (non-carcinogenic risk)

R_{t+1} is a risk of disorders at the moment t+1;
R_t is a risk of disorders at the moment t;
α is a coefficient for risk evolution due to natural causes;
β is a coefficient for ractopamine effects;
C is a time empirical coefficient (C = 0.00274 for daily averaging);
D is a ractopamine dose [µg/kg].

Figure 2. Results obtained by modeling health risk evolution under various exposure scenarios

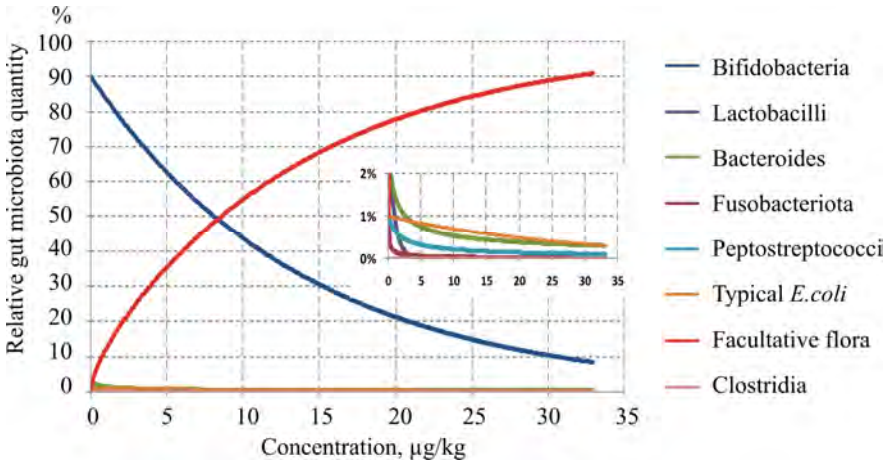


Figure 3. Dependence of relative gut microbiota abundance (%) on tetracycline concentration

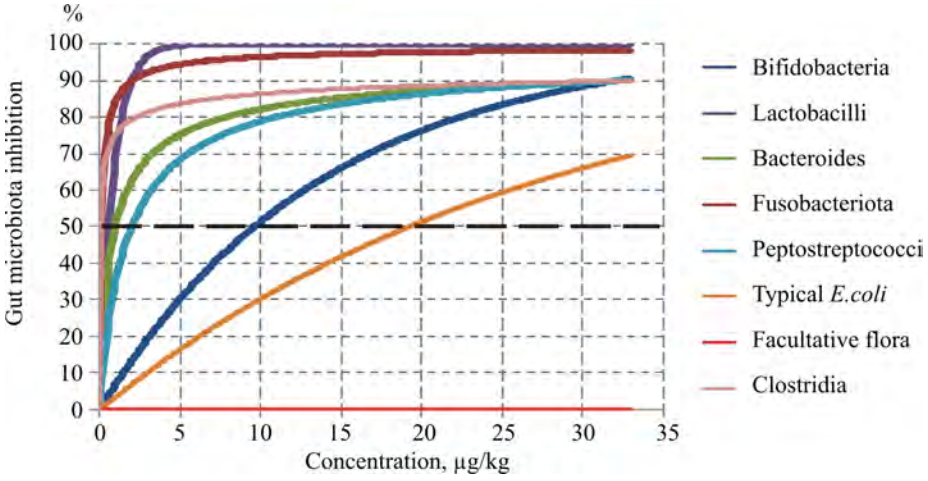


Figure 4. Models describing relationships between tetracycline concentrations and inhibition of growth for various bacteria

Efforts are being taken to develop practical use of the methodology for health risk assessment to solve tasks associated with hygienic standardization and establishing improved hygienic standards for concentrations of certain chemicals in the environment. Thus, a new type of maximum permissible concentrations has been developed and implemented, namely, maximum permissible concentrations of pollutants in ambient air with yearly averag-

ing ($MPC_{av.an.}$)[7]. Such MPC are substantiated with health risk criteria and they ensure acceptable (permissible) risks regarding both non-carcinogenic (HQ ≤ 1) and carcinogenic ($CR \leq 1 \cdot 10^{-4}$) effects [33, 34]. The methodical approaches applied to substantiate $MPC_{av.an}$ of chemicals in ambient air are fully harmonized with international approaches to developing hygienic standards, including reference concentrations used as indicators in risk assessment. By now, the Sanitary Rules and Norms SanPiN 1.2.3685-21 "Hygienic standards …"[7] contain average annual MPC for 72 chemical pollutants in ambient air. Conformity with these standards ensures life-time absence of unacceptable health risks for population, sensitive groups included.

Studies with their focus on effects produced by working conditions on workers' health have become another important trend in scientific development of the methodology for health risk assessment. This is due to a substantial contribution made by diseases associated with working conditions to losses of economic activity that were considerably higher than similar losses caused by occupational incidence [35].

A lot of attention is also given to developing methods for quantitative assessment of occupational risks as a function of likelihood and severity of negative health outcomes in workers. Experts have suggested methodical approaches to assessing health risks for workers considering cause-effect relations between health disorders and work and using epidemiological studies for such assessment [36].

Results of semi-quantitative (as per categories of working conditions, indexes of occupational diseases (I_{OD}) and work-related diseases (I_{WRD})) and quantitative risk assessment made it possible to substantiate new principles in determining a category of an occupational risk and analyzing its acceptability (Table).

As before, if a risk is assigned into "negligible" or "low" category, it means this risk is acceptable. Such an assessment fully correlates with the Guide "Human Health Risk Assessment from Environmental Chemicals" [8] where a risk level equal to $1 \cdot 10^{-3}$ is considered acceptable for occupational groups.

Table

Categories of occupational risks determined as per the results of its semi-quantitative and quantitative assessment

Category of working conditions	I_{OD}	I_{WRD}	Quantitative levels of occupational risks	Category of an occupational risk
Optimal – 1	Lower than 0.05	Lower than 0.05	Lower than $1 \cdot 10^{-4}$	Negligible risk
Permissible – 2	0.05–0.1	0.05–0.1	$1 \cdot 10^{-4}$–$1 \cdot 10^{-3}$	Low risk
Harmful – 3.1	0.1–0.2	0.1–0.2	$1 \cdot 10^{-3}$–$1 \cdot 10^{-2}$	Moderate risk
Harmful – 3.2	0.2–0.4	0.2–0.4	$1 \cdot 10^{-2}$–$3 \cdot 10^{-2}$	Average risk
Harmful – 3.3	0.4–0.6	0.4–0.6	$3 \cdot 10^{-2}$–$1 \cdot 10^{-1}$	High risk
Harmful – 3.4	0.6–0.8	0.6–0.8	10^{-1}–$3 \cdot 10^{-1}$	Very high risk
Hazardous – 4	Higher than 0.6	Higher than 0.6	$3 \cdot 10^{-1}$–1	Extremely high risk

[7] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya (utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha RF ot 28 yanvarya 2021 goda № 2) [Sanitary Rules and Norms SanPiN 1.2.3685-21. Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people (approved by the Order by the RF Chief Sanitary Inspector No. 2 dated January 28, 2021)]. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/573500115 (August 30, 2022) (in Russian).

[8] Guide R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals (approved and implemented by the Order of G.G. Onishchenko, the RF Chief Sanitary Inspector and the First Deputy to the RF Public Healthcare Minister on March 5, 2004). *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200037399 (August 30, 2022) (in Russian).

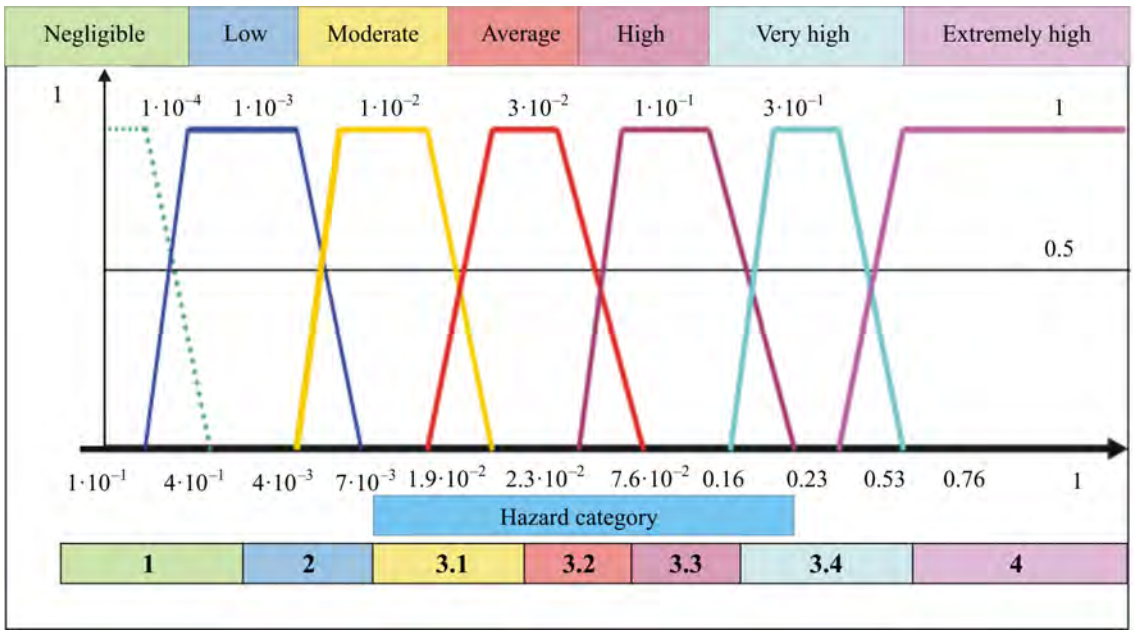


Figure 5. Graphic image of the scale showing trapezoid fuzzy numbers to determine an occupational risk category

Methods for assessing and predicting personified occupational risks are being developed to optimize occupational risk prevention. Such personified assessment considers age and work records of each worker. Results obtained by determining a category of a personified occupational risk can be clarified by applying probabilistic estimates, for example, the fuzzy set theory (Figure 5).

This method has great potential when it is used to create occupational risk groups for priority targeted medical and prevention activities given the predicted increase in risk levels.

An approach to risk assessment based on evolution models has turned out to be interesting, new and relevant when considering noise as a harmful environmental factor[9]. In contrast to models based on relative risk assessment or probit analysis, this approach offers to assess aggregated risks of cardiovascular disorders, disorders of the nervous system and the hearing organs. The assessment integrates both Russian and foreign data on how these effects are developing in dynamics against natural ageing of the body. Finding a solution to the system of recurrent equations made it possible to identify periods when exposure to noise was harmless (periods of acceptable risk) as well as to predict moments when a risk moved on to a fundamentally new level (a low risk became moderate; a moderate risk became high; etc.) [37]. Such assessments are in high demand by experts and ensure clear understanding when it can be or must be time to take sanitary-hygienic, technical, technological, or any other actions aimed at protecting population.

Studies that address assessment of risks associated with effects produced on health by lifestyle factors are also an interesting and promising new trend in the development of the risk assessment methodology [38]. A formalized social survey was included into the risk assessment algorithm. This stage in risk assessment was aimed at identifying risk factors and selecting those posing the highest threats, quantitative indicators considered, as well as estimating "factor – effect" relationships and

[9] MR 2.1.10.0059-12. Otsenka riska zdorov'yu naseleniya ot vozdeistviya transportnogo shuma (utv. rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka Glavnym gosudarstvennym sanitarnym vrachom RF G.G. Onishchenko 23 marta 2012 g.) [The Methodical Guidelines MR 2.1.10.0059-12. Assessment of health risks caused by exposure to transport noise (approved by G.G. Onishchenko, the RF Chief Sanitary Inspector and the Head of the federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing on March 23, 2012)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200095849 (August 30, 2022) (in Russian).

obtaining quantitative or semi-quantitative risk characteristics.

"Factor – effect" relationships were obtained for certain lifestyle factors (active and passive smoking, alcohol abuse, unhealthy diets) on the basis of evolutionary deterministic models that described relationships between lifestyle factors and both specific and aggregated health outcomes. These models were built based on the results of meta-analysis that covered foreign and domestic empirical studies (including those performed by the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), the US National Center for Health Statistics (NHANES)). The methodology was applied to assess risks associated with "traditional" lifestyle factors (smoking, alcohol abuse, poor physical and motor activity, and unhealthy diets) and we should note that previously such risks were predominantly assessed with "odds ratio", a statistical indicator. In addition to these factors, the suggested methodology also involved semi-quantitative assessment of risks associated with irresponsible medical and hygienic behavior, use of drugs and nonnarcotic psychoactive substances. Experts introduced a method to give score estimates to a risk-creating potential of specific components in the aforementioned factors. The method should be used when calculating separate and integrated indexes of health disorders probability. The approaches were fixed in the methodical document issued by Rospotrebnadzor[10] and implemented into practical activities performed by regional offices of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing (the Krasnoyarsk region, Arkhangelsk region, Irkutsk region, Voronezh region, etc.) [39–41].

The development of the methodology for health risk assessment also entailed providing scientific grounds for transition in spreading results of health risk assessment. This transition was from one-side informing of stakeholders (population, local authorities, economic entities etc.) about risk assessment results to a dialogue-based risk communication model. New approaches are based on transparency, trust, and mutual understanding; they ensure "communication between equals" and a partner dialogue. This corresponds to the contemporary concept of consensus-oriented public relations, which is very popular now in developed countries. These approaches have been fixed in several methodical documents approved by the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing[11].

It is noteworthy that progressive development of the risk assessment methodology taking place in 1990–2010 ensured operative, smooth, and effective transition of control and surveillance activities performed by Rospotrebnadzor onto a fundamentally new control platform that relies on the risk-based model. The old concept of control that previously stipulated unified frequency of inspections that should be performed at all economic entities at least once every three years[12] was replaced

[10] MR 2.1.10.0033-11. Otsenka riska, svyazannogo s vozdeistviem faktorov obraza zhizni na zdorov'e naseleniya (utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka Glavnym gosudarstvennym sanitarnym vrachom RF G.G. Onishchenko 31 iyulya 2011 g.) [The Methodical Guidelines 2.1.10.0033-11. Assessment of health risks associated with impacts exerted on public health by lifestyle-related factors (approved by G.G. Onishchenko, the RF Chief Sanitary Inspector and the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing on July 31, 2011)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200111974 (August 30, 2022) (in Russian).

[11] MR 2.3.2/2.3.7.0123-18. Sistema informirovaniya o riskakh ostatochnogo kolichestva antibiotikov v pishchevykh produktakh (utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom RF A.Yu. Popovoi 1 marta 2018 g.) [The Methodical Guidelines MR 2.3.2/2.3.7.0123-18. The system for informing about risks associated with residual contents of antibiotics in foods (approved by A.Yu. Popova, the RF Chief Sanitary Inspector and the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing on March 1, 2018)]. *Biblioteka normativnoi dokumentatsii*. Available at: https://files.stroyinf.ru/Data2/1/4293736/4293736537.htm (August 30, 2022) (in Russian).

[12] O zashchite prav yuridicheskikh lits i individual'nykh predprinimatelei pri osushchestvlenii gosudarstvennogo kontrolya (nadzora) i munitsipal'nogo kontrolya: Federal'nyi zakon ot 26.12.2008 № 294-FZ [On protecting rights of juridical persons and private entrepreneurs when accomplishing state control (surveillance) and municipal control: The Federal Law issued on December 26, 2008 No. 294-FZ]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/565415215 (August 30, 2022) (in Russian).

with a new one stating that frequency of inspections should correspond to actual risks of health harm created by a specific economic entity[13]. This replacement fully corresponded to goals and tasks the sanitary service in the country had to achieve and tackle.

Algorithms and methods with their aim to assign objects under sanitary-epidemiological surveillance into specific risk categories [42] facilitated substantial development of approaches to risk-based surveillance. They conformed to all the provisions fixed in the Federal Law "On protecting the rights of juridical persons and private entrepreneurs when performing state control …" that was valid at that moment.

The algorithm for risk assessment and assigning objects under surveillance into specific risk categories was based on two fundamental principles:

– a risk of health harm occurs when an object under surveillance violates the sanitary legislation;

– violation of the legislation that regulates sanitary-epidemiological welfare results in deteriorating quality of the environment (including lower safety of goods and services) and associated likelihood of health disorders in population, workers, or consumers.

A key idea in this innovative approach was an effort to avoid expert score estimates that were accepted by many federal authorities when they differentiated objects under surveillance as per risk categories.

It was offered to calculate a potential risk of health harm when determining a risk category of an object under surveillance $R_i\,(l)$ in full conformity with the classical definition of a risk as a combination of a probability that the sanitary legislation would be violated *p(l)* and severity of negative health outcomes (*u(l)* as an indicator describing health harm):

$$R_i\,(l) = p(l) \cdot u(l) \cdot M_i\,. \qquad (1)$$

The approach was based on analyzing long-term statistical data on the results of control and surveillance activities performed both at the federal level and in specific RF regions. A probability that the sanitary legislation would be violated was estimated as 95 % percentile of the distribution of regional relative frequency of violations detected during one inspection.

An indicator that described health harm when the sanitary legislation was violated at objects under surveillance was determined by performing system analysis of cause-effect relations in the "frequency of law violations – prevalence of health disorders" system. Targeted science-intensive studies accomplished specifically to solve issues related to creation of a model for risk-based control made it possible to obtain more than a thousand authentic relationships. These relationships confirmed that violations of the mandatory sanitary-epidemiological requirements produced negative effects on population mortality and incidence. Health disorders were differentiated as per their severity in accordance with the documents issued by the World Health Organization [43]. Severity for a group of diseases was calculated considering the structure of each category of nosologies in the Russian Federation over the last three years separately for children, adults of working age, and people older than working age. A scope of impacts exerted by an object under surveillance was considered a unique value typical for activities performed by a specific object under surveillance; this value was determined by a number of people influenced by a given object.

Such an approach to determining a risk category of an object under surveillance was quite new in the country and a practice when Rospotrebnadzor considered negative health outcomes in population was fundamentally different from those accepted by other surveillance authorities. The algorithm and assessment procedures were fixed in the methodical

[13] O gosudarstvennom kontrole (nadzore) i munitsipal'nom kontrole v Rossiiskoi Federatsii: Federal'nyi zakon ot 31 iyulya 2020 goda № 248-FZ [On the state control (surveillance) and municipal control in the Russian Federation: The Federal Law issued on July 31, 2020 No. 248-FZ]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/565415215 (August 30, 2022) (in Russian).

guidelines[14] where objects under surveillance were assigned into six different categories (starting form objects that caused an extremely high risk down to those with low risks) and were differentiated accordingly as per frequency and contents of scheduled control activities.

We should note that experts from the Higher School of Economics analyzed approaches to creating models of risk-based control accepted by different authorities and concluded that "*... the system for risk assessment used within sanitary-epidemiological surveillance is the only one assessment methodology that relies on a qualitative mathematical apparatus. This makes it possible to determine quantitative values of risks...*"[15]. These approaches were tested in pilot regions and then in the country as a whole and, as a result, it was determined that the share of objects that could create "extremely high risks" or, in other words, objects that were subject to the most strict (annual) control amounted to approximately 0.5–3.0 % of the total number of objects under surveillance in the country (depending on a region). Typically, such objects supplied drinking water to large cities or densely populated territories; they could also be industrial enterprises of the 1st or 2nd category according to the sanitary classification located within settlements or food-producing enterprises with high production outputs etc. From 4 to 9 % of objects under surveillance were classified as objects with high risks and they were subject to control every two years. From 20 to 40 % of all the registered objects under surveillance were determined as objects with low risks and any scheduled control activities were not mandatory for them. Thus, several years after the risk-based model was implemented into practice, scheduled surveillance was established to be unnecessary for approximately 54 % of transport infrastructure objects; approximately 44 % of objects rendering communal, individual and social services; approximately 33 % of industrial enterprises; etc. Overall, since 2017 a volume of scheduled inspections went down by 20 % in the country.

Businesses stated that the results were in line with their expectations; however, public values were not sacrificed in the process. Annual surveillance activities are performed exactly at those objects that can create the highest health risks [44].

This system is dynamic and "alive"; there are mechanisms for systemic review of risk assessment results. The latter is due to the developing legislative base, changes in violations of the mandatory sanitary requirements and "law-obedience" of economic entities all over the country.

The applied approaches turned out to be even in higher demand after the Federal Law "On state control (surveillance)" No. 248-FZ came into force on June 01, 2021. This law determines not only "activity" but also "production facilities" and "products" as objects under surveillance.

The risk calculation model was a universal one and this allowed developing an algorithm for determining hazard categories of products distrib-

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[14] MR 5.1.0116-17. Risk-orientirovannaya model' kontrol'no-nadzornoi deyatel'nosti v sfere obespecheniya sanitarno-epidemiologicheskogo blagopoluchiya. Klassifikatsiya khozyaistvuyushchikh sub"ektov, vidov deyatel'nosti i ob"ektov nadzora po potentsial'nomu risku prichineniya vreda zdorov'yu cheloveka dlya organizatsii planovykh kontrol'no-nadzornykh meropriyatii (utv. i vved. v deistvie Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom RF A.Yu. Popovoi 11 avgusta 2017 g.) [The Methodical Guidelines MR 5.1.0116-17. The risk-based model for control and surveillance activities in the sphere of providing sanitary-epidemiologic well-being. Ranking economic entities, types of activities, and objects under surveillance as per potential risks of damage to health for organizing scheduled control and surveillance activities (approved and implemented by A.Yu. Popova, the RF Chief Sanitary Inspector and the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing on August 11, 2017)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/555601296 (August 30, 2022) (in Russian).

[15] Plaksin S.M., Zuev A.G., Knutov A.V., Maksimova S.I., Polesskii E.A., Semenov S.V., Trifonov V.A., Chaplinskii A.V., Shabala Yu.I. Kontrol'no-nadzornaya deyatel'nost' v Rossiiskoi Federatsii: Analiticheskii doklad 2015 [Control and surveillance activities in the Russian Federation: Analytical report 2015]. Moscow, The analytical center of the RF Government, 2016, pp. 58 (in Russian).

uted on the consumer market and to fix it in the methodical guidelines issued by the Service[16].

Actual frequency of cases when mandatory requirements to product safety were violated, severity of outcomes caused by these violations and a number of consumers who used this or that product were considered in full conformity with the previously developed conceptual approaches. The methodology was flexible and objective and therefore different from subjective expert estimates typical for most classifications of consumer products as per risks of damage to health accepted abroad.

In addition, the methodology gave an opportunity to consider changing parameters of probability that mandatory requirements to product safety would be violated, severity of consequences and volumes in which this or that product was consumed. This made it even more relevant and provided a unified methodical ground for creating federal and regional registers of products assigned into different categories as per health risks they could cause.

The structure of these categorized registers was different in different regions (Figure 5) and this made it possible to spot out local priorities and adjust regional control and surveillance over products for the sake of providing safety for people living in a given region [45, 46].

Undoubtedly, the risk-based model of control and surveillance activities has good prospects for further development. A quite actual and relevant task is to create "risk profiles" of objects under surveillance as a systematized description of a risk area created by a typical object, risk indicators, and priority factors [47]. This will make it possible to raise predictive significance of risk assessment substantially, make control activities more targeted and reduce financial expenses necessary to perform them, laboratory tests included.

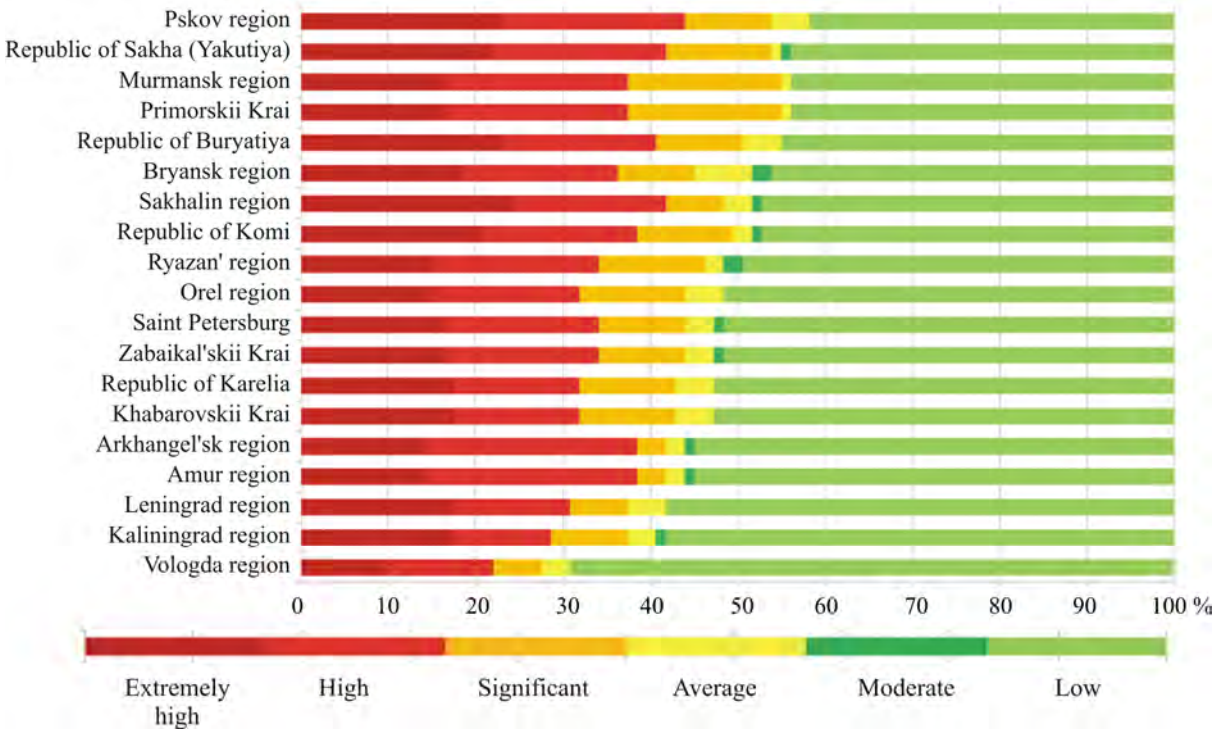

Figure 5. Comparative analysis of the structure of risk categories identified for foods distributed in the RF regions: a fragment (2021)

[16] O vnedrenii Metodicheskikh rekomendatsii «Klassifikatsiya pishchevoi produktsii, obrashchaemoi na rynke, po risku prichineniya vreda zdorov'yu i imushchestvennykh poter' potrebitelei dlya organizatsii planovykh kontrol'no-nadzornykh meropriyatii»: Prikaz Rospotrebnadzora ot 18.01.2016 № 16 [On implementation of the Methodical guidelines "Classification of foods distributed on the market as per health risks for consumers and risks of consumers' financial losses for organization of scheduled control and surveillance activities": The Order by Rospotrebnadzor dated January 18, 2016 No. 16]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/420332234 (August 30, 2022) (in Russian).

Any “risk profile” of an object under surveillance, be it an activity, a production facility, or a product, should be substantiated and provided with quantitative description. This requires complete and systemically collected data on typical objects and tools for analyzing them. Given that, when Rospotrebnadzor’s Unified Information and Analytical System is implemented and filled with data, this can become a starting point for a new stage in the development and practical application of the risk assessment methodology within activities performed by the Sanitary Service in the country.

Overall, the methodology for health risk assessment is becoming more and more relevant in variable spheres related to providing sanitary-epidemiological welfare. Primarily, this is due to public health being declared a key value in the country and a top criterion to estimate effectiveness of the public administration. Thus, for example, a health risk is considered a component in substantiating lists of priority chemicals within the “Clean Air” Federal project[17]. Emissions of such priority chemicals should be reduced immediately and their concentrations in ambient air require mandatory control and monitoring.

A risk for public health and life expectancy at birth is among basic arguments to label an object of accumulated environmental health as being subject to immediate elimination within the “General cleaning” Federal project[18].

There are multiple variable objects of accumulated environmental damage located all over the country. They often tend to have existed without an owner for a long time and this leads to substantial changes in their initial conditions. All this required fundamentally new approaches to assessing public health risks. The task got even more complicated due to the necessity to accomplish it in a very short time and insufficient information database on essence and levels of exposure. The suggested approaches based on the fuzzy set theory made it possible to include both quantitative and qualitative variables into risk assessment procedures. These variables fully described each given object and hazards posed by its existence for public health [48]. To assess influence exerted by each indicator on public health, experts applied scales that graded a health hazard considering weight contributions made by separate indicators and a group of indicators as a whole (component risks of separate indicators and a group as a whole) to the aggregated health risk created by a given object. Experts strictly followed the principle that types and severity of potential functional disorders of critical organs and systems should be considered when examining impacts of pollution created by a specific object. These approaches were fixed in the methodical document issued by Rospotrebnadzor[19] and they are being applied when more than 190 objects of accumulated environmental damage located all over the country are now being assessed and assigned into a specific category.

Undoubtedly, a promising trend in the development of the risk assessment methodology is integration of risk assessment and epidemiological studies, data on actual population incidence in a given city and (if available) results of specialized biomedical studies

[17] Natsional'nyi proekt «Ekologiya» (utv. Minprirody Rossii) [“Ecology” National project (approved by the RF Ministry of the Environment and Natural Resources)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_394077/0b83e7b8d6b58016a40c77f7619b332b159d076e/ (August 08, 2022) (in Russian).

[18] Pasport federal'nogo proekta «General'naya uborka» [The profile of the “General cleaning” Federal project]. *Pravitel'stvo Rossii*. Available at: http://static.government.ru/media/files/DoFhF6zbaji5mAKgkefAjTssLoyUOyS.pdf (August 08, 2022) (in Russian); Ob utverzhdenii kriteriev i sroka kategorirovaniya ob"ektov, nakoplennyi vred okruzhayushchei srede na kotorykh podlezhit likvidatsii v pervoocherednom poryadke: Prikaz Ministerstva prirodnykh resursov i ekologii RF ot 4 avgusta 2017 goda № 435 [On Approval of the criteria and the term categorizing objects of accumulated environmental damage elimination of which is the top priority: The Order by the RF Ministry of Natural Resources and the Environment issued on August 4, 2017 No. 435]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/456089663 (August 24, 2022) (in Russian).

[19] MR 2.1.10.0273-22. Otsenka vozdeistviya ob"ektov nakoplennogo vreda okruzhayushchei srede na zdorov'e grazhdan i prodolzhitel'nost' ikh zhizni, v tom chisle s vozmozhnost'yu ekspress-otsenki (utv. Glavnym gosudarstvennym sanitarnym vrachom RF 20.01.2022) [The Methodical Guidelines 2.1.10.0273-22. Assessment of impacts exerted by objects of accumulated environmental damage on people’s health and life expectancy, express estimations included (approved by the RF Chief Sanitary Inspector on January 20, 2022)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_423034/ (August 24, 2022) (in Russian).

on those health disorders that are classified as dependent on pollution levels or influence exerted by risk factors.

It seems advisable to share risk assessment results and discuss them with economic entities; these discussions should cover all the detected discrepancies between declared emissions, calculated pollution levels and an actual sanitary-hygienic situation in a given city. In case it is impossible to make health risks acceptable due to technical and / or organizational insufficiency, medical and preventive activities are recommended as compensatory actions until the environment is made truly safe and qualitative [49, 50].

Overall, we should note that analytical opportunities offered by the methodology for health risk assessment are quite extensive. Development of methodical grounds in hygiene and epidemiology as well as design of applied algorithms and approaches to risk assessment and management based on the fundamental methodology should involve several trends. They may be as follows:

– extending our knowledge on mechanisms of health disorders under exposure to heterogeneous environmental factors and work-related ones together with assessing likelihood of their occurrence;

– improving hygienic standardization of environmental and work-related factors;

– situational modeling and prediction of sanitary-epidemiological welfare under changing or preset conditions (economic, social, environmental, etc.);

– estimating probabilistic socioeconomic losses due to exposure to risk factors;

– providing substantiation for the strategic and tactical regulatory actions aimed at managing threats and risks for public health;

– anticipatory development of procedures for assessing and managing health risks associated with potentially hazardous risk factors created by new technologies and products (nanotechnologies, new foods etc.);

– assessing effectiveness of all the regulatory actions aimed at minimizing harmful impacts on human health.

The experience accumulated in developing the health risk assessment methodology in variable spheres should be considered a starting point for creating new risk assessment and risk management technologies. They should give an opportunity to solve any tasks related to providing sanitary-epidemiological welfare of the population in the Russian Federation.

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Review

SPECIFIC ENVIRONMENTAL HEALTH CONCERNS AND MEDICAL CHALLENGES IN ARCTIC AND SUB-ARCTIC REGIONS

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This systematic review surveys the results of studies that address the manifold influences of climate change on the health of populations in the Arctic and sub-Arctic regions. The review includes papers available in PubMed (maintained by The United States National Library of Medicine at the National Institutes of Health), Scopus (the largest abstract and citation database of peer-reviewed literature), WoS (the abstract and citation database of peer-reviewed literature) and BVS (Virtual Health Library) that were published between 1960 to 2021.

The review covers pressing environmental, sanitary-hygienic and social issues and identifies priority risk factors for human health and that of wildlife. Global pollution and communicable diseases are shown to pose threats for indigenous people living in the Arctic. These threats are likely to be greater than those faced by populations living elsewhere in the world.

We conclude that because climate is changing faster in the Arctic than anywhere else on the planet, there is an urgent need to address the issue. Global pollution and communicable diseases pose threats to public health, including the health of indigenous people living in the Arctic and sub-Arctic regions. It is necessary to intensify cooperation among different states to reduce external influences on the Arctic environment and to prioritize public health.

Keywords: *Arctic and sub-Arctic regions, global climate change, public health, risk factors, sanitary-epidemiological situation, ecological situation, local and imported threats, health losses.*

Most indigenous populations of the Arctic and sub-Arctic Regions are adapted to harsh natural environments, but these regions are subject to the effects of especially rapid climate change. Climate-related changes in circumpolar regions are affecting not only regional wildlife and human health but, from changes in permafrost, also threaten life across the planet. We examine some characteristics of Arctic and sub-Arctic regions from a geographical, demographic and cultural perspective and address the environmental chal-

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lenges and health threats faced by their populations.

Our research goal was to perform a systematic review of relevant studies that address environmental, sanitary-hygienic, social and other factors creating public health risks in the Arctic and sub-Arctic regions. The review aimed to reveal pressing challenges and issues that seek solutions as a top priority.

Materials and methods. The review included research articles published between 1960 and 2021 that are available in *PubMed* (maintained by The United States National Library of Medicine at the National Institutes of Health), *Scopus* (the largest abstract and citation database of peer-reviewed literature), *WoS* (the abstract and citation database of peer-reviewed literature) and/or *BVS* (Virtual Health Library). Articles addressed issues associated with climate change, pollution, and the influence on health and psychological state of populations living in the analyzed regions.

Results and discussion. *Geographic presentation of the Arctic and sub-Arctic regions.* The Arctic, following a geographical definition, is the region north of the Arctic Circle (about 66° 34' N latitude), the approximate southern limit of the midnight sun and the polar night. For ecologists, it is the region in the Northern Hemisphere where the average temperature for the warmest month (July) is below 10 °C (50 °F); the northernmost tree line roughly follows the isotherm at the boundary of this region. Whatever the definition, the Arctic region is a unique area among Earth's ecosystems consisting of the Arctic Ocean and adjacent seas, which contain seasonal sea ice in many places, and of land characterized by seasonal variation of snow and ice cover, with predominantly treeless permafrost (permanently frozen underground ice) containing tundra. The continental part of the Arctic belongs to Canada, Denmark (Greenland), Finland, Iceland, Norway, the Russian Federation, Sweden and the United States of America (Alaska). These eight countries have membership of the Arctic Council together with six Permanent Participants drawn from peoples indigenous to the Arctic. The sub-Arctic zone of the Northern Hemisphere refers to regions immediately south of the Arctic Circle or regions similar to these in climate or conditions of life. The sub-Arctic region (50°N and 70°N latitude) covers much of Alaska (USA), Canada, Iceland, the north of Scandinavia, Siberia (Russia), the Shetland Islands (UK), and the Cairngorms (Scotland, UK) [1].

The Arctic and sub-Arctic Regions have a very low population density. Permanent residents number ~4 million people, of whom approximately 500,000 are Indigenous Peoples[1]. Some population groups number > 100,000 inhabitants (e.g., Anchorage, Archangelsk, Reykjavik, Murmansk). The population is increasing in Alaska and Iceland and declining in the Russian Federation[2].

The Arctic states initiated a scientific and thereafter political cooperation in the late nineteen eighties to address an alarmingly fragile environmental state resulting from the arrival and accumulation of chemical and radionuclide pollution[3]. Despite the geopolitical differences of Members, the Arctic Council was formally established in 1996. Today, the Arctic Council is the leading intergovernmental forum promoting cooperation, coordination and interaction among the Arctic States, Arctic Indigenous peoples and other Arctic inhabitants. The Council addresses common Arctic issues, in particular those relating to sustainable development and environmental protection. The six Permanent Participants

[1] Permanent Participants. *Arctic Council Secretariat*. Available at: https://www.arctic-council.org/about/permanent-participants/ (June 08, 2022).

[2] IPCC, 2019: Summary for Policymakers. In: IPCC Special Report on the Ocean and Cryosphere in a Changing Climate. In: H.-O. Pörtner, D.C. Roberts, V. Masson-Delmotte, P. Zhai, M. Tignor, E. Poloczanska, K. Mintenbeck, A. Alegría [et al.] eds. Cambridge, UK and New York, NY, USA, Cambridge University Press, 2019, pp. 3–35. DOI: 10.1017/9781009157964.001

[3] The workhorses behind the success. *Arctic Council Secretariat*. Available at: https://www.arctic-council.org/news/the-workhorses-behind-the-success (June 08, 2022).

representing Arctic Indigenous Peoples include: the Aleut International Association, the Artic Athabaskan Council, the Gwich'in Council International, the Inuit Circumpolar Council, the Russian Association of Indigenous Peoples of the North, and the Saami Council. Thirteen non-Arctic states, as well as intergovernmental and interparliamentary organizations and non-governmental organizations have been approved as Observers to the Arctic Council[4].

An extreme environment challenged by climate change. The Intergovernmental Panel on Climate Change (IPCC)[5], a body of the United Nations responsible for advancing knowledge on human-induced climate change, issued a 2019 Special Report dedicated to the Polar Regions, the Ocean and Cryosphere in a Changing Climate. The Report noted that global warming has led to widespread shrinkage of the cryosphere (frozen components of the Earth system), with mass loss from ice sheets and glaciers (*very high confidence*), reductions in snow cover (*high confidence*) and Arctic Sea ice extent and thickness (*very high confidence*), and increased permafrost temperature (*very high confidence*).

Earlier, in April 2006, the impact of the progressive loss of Arctic Sea ice from global warming was powerfully illustrated by a photograph of an apparently stranded white polar bear on the front cover of *Time*, an American news magazine read around the world[6]. Titled "*Be worried. Be VERY worried*", this iconic illustration represents well the environmental and ecological challenges in the Arctic. "*Global warming is already disrupting the biological world, pushing many species to the brink of extinction and turning others into runaway pests. But the worst is yet to come*"[7]. Indeed, in 2013, Fitzgerald [2] stated, "*If trends continue and the ice continues to disappear, the effect on polar bears would be devastating*."

The remarkable degree of specialized adaptation to life on the sea ice that allowed the bears to be successful is the very reason that these animals are so vulnerable to the effects of climate change. Polar bears have few alternatives if their habitat (sea ice) and their access to ringed seal prey rapidly disappear. Predictions that polar bears may be able to adjust and sustain themselves on alternative food sources are not based on reality. Spring breakup of sea ice is happening much earlier and the Fall freeze-up is getting later, thereby prolonging the open-water period when the bears are shore bound. If these trends advance, and the ice continues to decline, the effect on polar bears could be devastating.

The plight of the polar bear may be more nuanced in that regional changes may actually favor survival. Studies (1990–97 and 2012–16) of the world's most northerly polar bear population in Kane Basin[8], which is transitioning to a seasonally ice-free region because of climate change, showed some beneficial effects, including range expansion, improved body condition, and stable reproductive performance, albeit in the setting of increased geographic and functional isolation [3, 4]. However, the authors concluded: "*The duration of these benefits is unknown because, under unmitigated climate change, continued sea-ice loss is expected to eventually have negative demographic and ecological effects on all polar bears*" [4].

The impact of climate change on biodiversity must take into account adaptation of the fauna in the northern terrestrial ecosystems, structured by a history of biotic and abiotic changes that overlie a complex geo-

[4] Arctic Council Observers. *Arctic Council Secretariat*. Available at: https://www.arctic-council.org/about/observers/ (June 08, 2022).

[5] The intergovernmental body of the United Nations responsible for advancing knowledge on human-induced climate change.

[6] TIME. Available at: http://content.time.com/time/magazine/0,9263,7601060403,00.html (June 08, 2022).

[7] Bjerklie D. Global Warming: Feeling the Heat. *Time*, 2006, vol. 167, no. 14. Available at: https://content.time.com/time/subscriber/article/0,33009,1176986,00.html (дата обращения: 08.06.2022).

[8] An Arctic waterway lying between Greenland and Canada's northernmost island, Ellesmere Island.

graphic arena. Since the Pliocene, Holarctic ecosystems have faced shifting climates (glacial and interglacial stages), resulting in cyclic animal distribution and demographics, with episodic dispersal / isolation and diversification of the fauna [1]. One example of this phenomenon is the apparent development of brown bears derived from a population of polar bears (*Ursus maritimus*) likely stranded by receding ice at the end of the last glacial period [5]. The Ancient Greeks named two constellations seen in the Northern Hemisphere, Ursus Minor and Ursus Major [6], and the word "Arctic" derives from the Greek "*arktikós*", meaning "of the Bear".

The Arctic climate and physical system is characterized by the cryosphere, defined by the IPCC as "*the components of the Earth System at and below the land and ocean surface that are frozen, including snow cover, glaciers, ice sheets, ice shelves, icebergs, sea, river and lake ice, permafrost and seasonally frozen ground*"[9]. The cryosphere, which represents 10 % of the Earth surface, has a major role in the climatic system owing to its high surface reflectivity or albedo. The increased melting of snow and ice induces a positive feedback, which in turn leads to more warming. This effect is named the snow- or ice-albedo feedback[10].

Climatologists have a special interest in the cryosphere as it acts as an historical archive of climatic behavior. Ice drilling and the analysis of ice cores in Greenland have allowed scientists to reconstruct previous periods of climatic changes [7], the evolution of global temperature over the past two million years, the cycles of nitrogen, carbon and methane, and even information on the former vegetation [8].

In the Arctic, the Greenland Ice Sheet covers an area of 1.7 million km^2, a sixth of the Antarctic Ice Sheet (12.3 million km^2, excluding the ice shelves). In the Arctic Ocean, sea ice reaches an average maximum of ~15 million km^2 at the end of winter, while Antarctic Sea ice reaches about 19 million km^2, usually in September. Thus, the Arctic ice sheet is an important contributor to the cryosphere.

Permafrost describes frozen soil (sand, ground, rock or sediment) – sometimes hundreds of meters thick. To be classified as permafrost, the ground has to have been frozen (when its temperature remains at or below 0 °C) continuously for at least two years. Since Arctic permafrost stores almost 1700 billion tons of carbon, it is an essential climate parameter[11]. The rise in global temperatures, which is higher in the Arctic than elsewhere, is causing the subsurface ground to thaw[12]. This releases greenhouse gases (carbon dioxide and methane) produced by biological material (e.g., remains of vegetation) and abruptly changes the landscape (ground subsidence)[10]. Climatologists closely monitor and model the climate change-associated evolution of permafrost (extension, thawing). It is estimated that, by 2011, up to two-thirds of the near-surface permafrost could be lost as a result of atmospheric warming[11].

The Arctic cryosphere, fragile and unique, is heavily impacted by climate change. In less than half a century, from 1971 to 2019, the Arctic's average annual temperature rose by 3.1 °C, compared to 1 °C for the planet as a whole. Stated otherwise, the Arctic is the fastest warming region on the planet, a phenomenon termed "Arctic amplification"[13]. On

[9] IPCC, 2019: Summary for Policymakers. In: IPCC Special Report on the Ocean and Cryosphere in a Changing Climate. In: H.-O. Pörtner, D.C. Roberts, V. Masson-Delmotte, P. Zhai, M. Tignor, E. Poloczanska, K. Mintenbeck, A. Alegría [et al.] eds. Cambridge, UK and New York, NY, USA, Cambridge University Press, 2019, pp. 3–35. DOI: 10.1017/9781009157964.001

[10] The cryosphere in the climate system. *Copernicus Europe's eyes on Earth*. Available at: https://climate.copernicus.eu/climate-indicators/cryosphere (June 08, 2022).

[11] Permafrost thaw: it's complicated. *ESA*. Available at: https://www.esa.int/Applications/Observing_the_Earth/FutureEO/Permafrost_thaw_it_s_complicated (June 18, 2022).

[12] The Arctic is warming four times faster than the rest of the world. *American Association for the Advancement of Science*. Available at: https://www.science.org/content/article/arctic-warming-four-times-faster-rest-world (June 18, 2022).

[13] Deshayes P.H. Arctic warming three times faster than the planet, report warns. Available at: https://phys.org/news/2021-05-arctic-faster-planet.html (April 28, 2022).

20 June 2020, a temperature of 38 °C was recorded in the Russian town of Verkhoyansk, a new Arctic high-temperature record according to the World Meteorological Organization (WMO)[14].

In summer 2019, hundreds of large wildfires ravaged the Arctic region (Russia, Alaska and Greenland). Wildfire burned an area covered with grass, shrubs, and peat for several weeks in the mountain slopes about 150 kilometers northeast of Sisimiut, Greenland's second-largest city. In Siberia, wildfires burned almost three million hectares of land, according to Russia's Federal Forestry Agency. The numerous fires produced plumes of smoke that reached the cities of Kemerovo, Tomsk, Novosibirsk, and the Altai regions, some even the North Pole and Mongolia! These fires were caused by record-breaking high temperatures and lightning, fueled by strong winds. In June 2019 alone, they released harmful pollutants, toxic gases and around 50 megatons of carbon dioxide into the atmosphere[15]. Summer 2020 set new emission records when wildfires in the Arctic Circle exceeded 2019 records for carbon dioxide emissions[16].

Dust and dust storms, which are commonly associated with deserts, also occur at high latitudes (≥ 50 °N and ≥ 40 °S, including the Arctic as a sub-region ≥ 60 °N). The sources of this High Latitude Dust (HLD) are various [9]. In Greenland, its origin is linked to glaciers grinding and pulverizing rock, which produces a fine-grained silt: the glacial flour. In the south, soil surface conditions are favorable for dust emission during the whole year. Human activities also generate dust; examples include mineral-rich dust from year-round mining operations and pavement traction sanding of roads in wintertime. At high latitudes, winds are occasionally strong enough to send plumes of sediment along coastal regions. Dust storms have often been observed in Greenland and were documented in its peninsula of Nuussuaq by the Copernicus Sentinel-2 satellites on 1 October 2020.

HLD impacts northern high latitudes of Alaska, Canada, Denmark, Greenland, Iceland, Russia, Sweden and Spitsbergen, Norway. Dust particles have numerous climatic and ecological impacts, ranging from the formation of clouds to alterations of atmospheric chemistry, marine environment, and bio-productivity. These alterations influence air quality and human health, acting at different levels (local, regional, and global) through climate change, air pollution, and deterioration of nutrient sources.

A holistic approach to the consequences of rapid climate changes in the Arctic and sub-Arctic regions and ecosystems is mandatory. Considering the Arctic biophysical system, Box and collaborators [10] propose the following indicators: air temperature; tundra biomass; local hydrology and permafrost thaw; increased ignition of wildfires; increased shrub biomass; timing mismatch between plant flowering and pollinators; increased plant vulnerability to insect disturbance; shifting animal distribution and demographics. Regular updates of these indicators can serve as reference points to assess environmental impacts associated with climate change.

The 2019 IPCC Special Report dedicated to the Polar Regions, the Ocean and Cryosphere in a Changing Climate focused mainly on climate-related modifications of the Arctic ecosystem and the several services provided by the ocean and the cryosphere to people. The services include food and water supply, renewable energy, cultural values, tourism, trade, and transport. Negative im-

[14] WMO recognizes new Arctic temperature record of 38 °C. *World Meteorological Organization (WMO)*. Available at: https://public.wmo.int/en/media/press-release/wmo-recognizes-new-arctic-temperature-record-of-38ºc (April 28, 2022).

[15] Siberian wildfires. *ESA*. Available at: https://www.esa.int/ESA_Multimedia/Images/2019/07/Siberian_wildfires (April 28, 2022); Huge fires in the Arctic and Siberia. *Eumetsat*. Available at: https://www.eumetsat.int/huge-fires-arctic-and-siberia (April 28, 2022).

[16] Copernicus reveals summer 2020's Arctic wildfires set new emission records. *Copernicus Europe's eyes on Earth*. Available at: https//atmosphere.copernicus.eu/copernicus-reveals-summer-2020s-arctic-wildfires-set-new-emission-records (April 28, 2022).

pacts of the Arctic induced by climate change, which are already observable, concern the ocean (sea level, ocean pH, temperature, kelp forest), the landscape (ground subsidence) and several ecosystems (rivers and streams). Impacts on human activities include a positive effect on tourism (Alaska and Scandinavia) and a negative impact on agriculture and infrastructure everywhere. The Report failed to address the health impact of climate change, in particular the impact on resident indigenous populations.

The threats of local and imported chemical pollution. In addition to climate change, global chemical contamination reaches the polar regions, allowing Sonne and coauthors to evoke "*the Arctic as a sink for pollutants*" [11]! Even though some sources of pollution are local (e.g., from mining and pesticide use), the majority arises from transport of sources located in lower latitudes through air, water (ocean currents) and terrestrial routes. For example, mercury (Hg) contamination was transported to the Arctic via the atmosphere, dominated by sources from East Asia [12]. These long-range environmental transportations (LRET) are major contributors to Arctic pollution by emerging organic contaminants (EOCs) and persistent organic pollutants (POPs), such as industrial organochlorines, polybrominated biphenyls (PCB) and diphenyl ethers (PCDE), polyfluorinated compounds (PFACs), and dioxins [13, 14]. The question of the effect of climate change on the transportation (LRET) and fate of these pollutants has arisen recently [11], and its remobilization has been confirmed [14]. The wide dispersal of pollutants, notably in the air and by sea, exposes the whole ecosystem and explains biotransformation, bioaccumulation and biomagnification. This adversely impacts Arctic fauna (zooplankton, marine invertebrates, fish, sea birds), notably mammals (e.g., seals, sled dogs, whales, polar bear). For example, POPs have multiple organ-system effects across taxa, including neuroendocrine disruption, immune suppression and bone density decrease [11].

Health challenges for the Arctic and sub-Arctic populations. From the nineteen fifties to 1990 in Alaska[17] and Canada [15], basic infectious diseases of humans included: Tuberculosis, Poliomyelitis, and parasitosis (worms, trichinosis, echinococcus linked with mammal flesh contamination). Eye-diseases (conjunctivitis, corneal opacities and blindness caused by UV light), poor diet and nutrition, addictions (alcoholism), and biting insects (requiring the use of DDT) were also prevalent. Sewage and waste disposal in permafrost areas presented additional health risks, including survival in very low ambient temperatures (-50 C°).

At the end of the 20th Century, the National Environmental Health Action Plan for Sweden [16] addressed new health concerns that included environmental pollutants, such as methyl mercury, brominated flame retardants, and radionuclides released from the Chernobyl Nuclear Power Plant in Soviet Ukraine.

Climate as a factor influencing public health. In 2010, Arbour and colleagues[18] (2010) provided a major introduction to some health issues in the Arctic, with a public health perspective.

Air temperature is a major meteorological factor influencing the human body. A change in air temperature alters the heat exchange between a person and the environment. Heat is primarily emitted through skin (approximately 82 %) and respiratory organs (13 %), and its emission depends on heat insulation by clothing. Wind increases heat emission. When air temperatures are low, wind can lead to body overchilling; wind stimulates more intense skin evaporation when air temperatures are high[18] [17]. A strong wind can provoke a hypertensive crisis and a stroke[19]. A drastic change in a

[17] Public Health Problems in Alaska. *Public Health Reports*, 1951, vol. 66, pp. 911–950.

[18] Boksha V.G., Bugutskii B.V. Meditsinskaya klimatologiya i klimatoterapiya [Medical climatology and climatic therapy]. Kiev, Zdorov'ya, 1980, 262 p. (in Russian).

[19] Grigor'ev I.I. Pogoda i zdorov'e [Weather and health]. Moscow, Avitsenna, YuNITI, 1996, 96 p. (in Russian).

wind direction can result in greater blood pressure variability[20] [18].

Air humidity strengthens impacts exerted by air temperature: the higher the air humidity, the more intensely the body reacts to it, both under high and low temperatures[21]. High air humidity combined with a low ambient temperature intensifies heat exchange and body chilling; when the temperature is high, air humidity helps promote body overheating that can result in heatstroke [19]. Elevated air humidity increases the likelihood of airborne diseases and exacerbates diseases of the respiratory and musculoskeletal systems [20].

Atmospheric pressure and changes thereof can promote physiological alterations expressed as headaches and functional disorders of the cardiovascular system (changes in blood pressure, vascular crises and internal bleedings, etc.) [21–23].

The Arctic and sub-Arctic climate typically involves the body being simultaneously exposed to several adverse weather-related factors. This is proposed to promote development of "polar strain syndrome" or "northern stress". This poly-syndrome includes several basic components such as oxidative stress, insufficient detoxification and poor functioning of the barrier organs, disorders of northern-type metabolism, northern tissue hypoxia, immune deficiency, blood hypercoagulation, poly-endocrine disorders, regenerative-plastic failure, impaired electromagnetic homeostasis, functional dissymmetry of interhemispheric communication, desynchronosis, psychoemotional strain, and meteoropathy. Chronic stress stimulates depletion of the body's functional reserves and often induces a cascade of deadaptation disorders that ultimately leads to pathology [24]. There is also a concept of a "geographic latitude syndrome", which describes differences in risk of morbidity and mortality among populations with respect to their distance from the Equator[22].

Living in the Arctic or sub-Arctic region can adversely affect human health. When comparing disease incidence rates among people living beyond the Polar Circle (68º N latitude) with those among populations living in the temperate region in Russia (56º N latitude), experts established the former to be higher both among children (by 1.5 times) and among adults (by 1.3 times). For children, there is a higher prevalence of respiratory diseases, diseases of the eye and adnexa, diseases of the musculoskeletal system and connective tissue, and endocrine, nutritional and metabolic diseases. The prevalence of circulatory diseases, diseases of the musculoskeletal system and connective tissue, and diseases of the eye and adnexa, is higher among adults living beyond the Polar Circle [25]. In addition, comparison of disease incidence among populations living in municipal settlements located beyond the Polar Circle (67° N latitude) and the temperate region in Russia (54° N latitude) showed that diseases of the musculoskeletal system were 2.5–2.6 times more frequent among adults living beyond the Polar circle; diseases of the eye and adnexa 2.7–2.0 times more frequent; diseases of the genitourinary system 2.6–2.4 times more frequent; diseases of the digestive system 1.5 times more frequent; and diseases of the circulatory system 1.3–1.6 times more frequent [26].

Primary hypertension was established to be much more frequent at higher latitudes[23] than at middle ones. Frequency increases as the period of living in polar regions lengthens [27–29]. Primary hypertension is peculiar in the Arctic and sub-Arctic region not only because it develops at a considerably younger

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[20] Kucher T.V., Kolpashchikova I.F. Meditsinskaya geografiya [Medical geography]. Moscow, Prosveshchenye, 1996, 160 p. (in Russian).

[21] Koiranskii B.B. Okhlazhdenie, pereokhlazhdenie i ikh profilaktika [Chilling, overchilling and their prevention]. Leningrad, Meditsina, 1966, 247 p. (in Russian).

[22] Gundarov I.A., Zil'bert N.L. Izuchenie regional'nykh razlichii v zabolevaemosti i smertnosti naseleniya s pozitsii sindroma geograficheskoi shiroty [A study on regional differences in population incidence and mortality considering the latitude syndrome]. *Vestnik AMN SSSR*, 1991, no. 11, pp. 52–56 (in Russian).

[23] High latitudes is a conventional denomination for polar regions on the Earth located to the north from approximately 65° N latitude and to the south from 65° S latitude.

age but also in regard to its clinical signs[24] and rapid progression. At high latitudes, primary hypertension tends to be more severe, more often involves hypertensive crises with a considerable increase in both systolic and diastolic blood pressure, and drastic disorders of higher nervous activity often result in strokes and myocardial infarctions [30–32]. There is even a peculiar "northern" primary hypertension described in the literature; the disease is associated with apparent weather sensitivity, crises typically developing as per the cerebral and cardiac types, strokes and myocardial infarctions [29].

O.N. Popova confirmed in her research work [33] that geographical latitude affected external respiration functioning in people who were born and lived beyond the Polar Circle. She established changes in the functional state of the respiratory system (lung vital capacity, inspiratory and expiratory reserve volumes being authentically higher than the physiological standards, an increase in lung volume). All these changes were compensatory and adaptive responses of the body under exposure to extreme weather and climatic factors. A moderate edema of inter-alveolar septa is considered the morphological basis of this functional shift; its occurrence in northern people was confirmed by electron microscopy.

According to K.N. Dubinin [34], impacts exerted by latitude on the endocrine system have been confirmed by multiple research works. They show that the "hypophysis–adrenal" system is activated at higher latitudes, thyroid hormones tend to be more labile, and the limits of the thyrotrophic hormone content shift towards smaller values. Adaptation strain in people living on the European North is combined with low levels of total triiodothyronine (T3) against an increase in concentrations of the most active free T3.

E.V. Tipisova established in her research [35] that men who lived in mid-latitude areas (59° 13' N latitude) had minimal activity of the "hypophysis – thyroid gland" system (triiodothyronine, free thyroxine) in comparison with that detected in people living in the Arctic area (66° N latitude) and close to it (64° N latitude). In addition, men who lived at 64–65° N latitude had lower reserve capabilities of the "hypothalamus – hypophysis – thyroid gland" system against more apparent activation of the "hypothalamus-hypophysis–adrenal cortex" system in comparison with people who permanently resided beyond the Polar circle. Prolactin content tended to decline and estradiol acted as an adaptation factor in the regulation of the "hypothalamus – hypophysis thyroid gland" system.

V.N. Petrov [25] showed that geographical altitude had its influence on a growing number of diseases of the eye and adnexa among people living beyond the Polar Circle due to low oxygen levels in ambient air. This results in oxygen deficiency in vessels that supply blood to the optic nerve, retina and lens leading to declining adaptation capabilities of the visual organs, especially during the polar night. Changes of the circulation in the central ophthalmic artery indicate there are certain vascular shifts and impaired cerebral hemodynamics.

Effects on health produced by the midnight sun, polar night and the day/night cycle. In the Arctic and sub-Arctic, an apparent change between day and night is absent for a long period of the year; there is also the polar night and midnight sun (contrasting seasons of light aperiodicity). These are specific northern factors typical for territories located higher than 67–68° N latitude. A.V. Enikeev and colleagues [36] showed that the polar night and midnight sun, as well as the long-term absence of a stable day/night cycle, could affect human health considerably by creating health risks for the respiratory organs, endocrine and circulatory systems.

Effects produced by the polar night on the respiratory organs were confirmed by

[24] Khamnagadaev I.I. Rasprostranennost' arterial'noi gipertenzii, ishemicheskoi bolezni serdtsa i ikh faktorov riska sredi sel'skogo korennogo i prishlogo naseleniya Severa i Tsentral'noi Sibiri [Prevalence of primary hypertension, ischemic heart disease and their risk afctors among rural indigenous people and alien population in the North and Central Siberia]: the thesis of the dissertation … for the Doctor of Medical Sciences degree. Tomsk, 2008, 49 p. (in Russian).

Yu.F. Shcherbina [37] who established that the external respiration apparatus had to work under greater strain during the polar night than during the midnight sun against apparently declining effectiveness of alveolar ventilation and reserve respiration capabilities. In addition, according to A.B. Gudkov [38], lung vital capacity became greater during the polar night than in the midnight sun, and large and middle-sized bronchi became more patent for airflow. This was a relevant compensatory and adaptive response of the body aimed not only at providing intensified metabolism but also at heating and moistening inhaled air.

V.N. Chesnokov established [39] that the polar night strained the adaptive mechanisms of the cardiovascular system. This strain became apparent through a growing contribution made by the cardiac and vascular components to the provision of adaptive reactions of the cardiovascular system. V.N. Pushkina[25] mentioned in her work that there was a strain in the blood supply to the brain against the elevated tone of cerebral vessels during the polar night.

According to data provided by Yu.Yu. Yuriev and E.V. Tipisov [40], as well as by A. Kauppila with colleagues [41], contrasting seasons of light aperiodicity affect the endocrine system by changing hormonal concentrations in the body. Thus, as daylight hours become longer, the "hypophysis–gonads" system is activated in people living in the Far North; this may result in various imbalances associated with both elevated activity of the system and depletion of its reserves.

K.E. Kipriyanova and colleagues [42] revealed both considerably elevated levels of testosterone and estradiol and abnormally low concentrations of globulin that bound sex hormones and total and free testosterone fractions in people living in the Far North under longer daylight hours.

E.V. Tipisova established in her study [35] that an elevated blood insulin level and a decrease in available adrenal cortical reserves was an adaptive reaction in men (living in the European North) under shorter daylight hours; these reserves recovered when daylight hours were the shortest. She also detected advanced adaptive reactions of the endocrine system in male children and adolescents.

K.N. Dubinin noted [34] that a specific hypophysis-thyroid system and dependence of thyroid gland hormones on photo periodicity had common adaptation significance for the human body under harsh climatic conditions in the European North.

V.N. Pushkina[26] confirmed that psychoemotional stress occurred during a period of the "biological polar night". This stress became apparent through elevated situational and personal anxiety, poorer health and lower activity against an obvious growth in aggressive reactions [39, 43].

Climate change has increased injuries, accidents and drownings. Rising ambient temperatures have disrupted ice formation and breakup patterns, leading to unsafe and unpredictable travel conditions which, in turn, have increased rates of injuries and death [44]. This was documented in Inuit communities of Canada: Search and Rescue (SAR) records from 1995 to 2010 showed an estimated annual SAR incidence rate of 19 individuals per 1,000. The incidence rate was six times higher for males than females; land-users aged 26–35 years had the highest incidence rate among age groups. Critical risk factors were environmental (weather and ice) conditions, particularly related to travel on sea ice during winter, as well as age and sex. In contrast with other studies, A. Durkalec and colleagues [45] noted that intoxication (alcohol) was the least common factor associated with SAR incidents. A study of over 4000 winter drownings in 10 Northern Hemisphere countries showed an exponential increase in regions with warmer winters (air temperatures near 0 °C). Risk factors were environmental conditions (winter air

[25] Pushkina V.N. Khronofiziologicheskie pokazateli funktsional'nogo sostoyaniya organizma studentov v usloviyakh Pripolyar'ya [Chronophysiological indicators of the body fucnitonal state in students living in reigons near the Polar Circle]: the thesis of the dissertation ... for the Doctor of Biological Sciences degree. Arkhangelsk, 2013, 37 p. (in Russian).

temperatures were between -5 °C and 0 °C, unstable ice), subject age (children and adults up to the age of 39), indigenous traditions and human behavior (livelihood requiring extended time on ice) [46].

Infectious diseases in the Arctic and sub-Arctic regions are impacted by climate change. Surprisingly, interest on the occurrence and distribution of communicable diseases in the Arctic and sub-Arctic is recent. In 2014, Hedlund and coauthors [47] underlined that few studies were available from Siberia and Alaska, and none from Greenland or Iceland. These authors suggested systematic surveillance with monitoring of extreme weather events after having reviewed the impact on common infectious diseases. These included food-borne diseases (salmonellosis, campylobacter), rodent-borne diseases (e.g., nephropathia epidemica), airborne diseases (respiratory pathogens) and vector-borne diseases (tick-borne encephalitis, TBE or borreliosis). The spirochete *Borrelia burgdorferi,* which causes Lyme disease, is the most common vector-borne disease (VBD) affecting humans in the temperate Northern Hemisphere. The number of Lyme disease cases in Europe was ~ 35,000 in the late 2000s [48]; left untreated, infection can spread to the joints, heart and nervous system.

Climate-sensitive infectious diseases in the Northern/Arctic Region, including borreliosis, leptospirosis, TBE, Puumala virus infection, cryptosporidiosis, and Q fever, show significant relationships with climate variables related to temperature and freshwater conditions. Whereas these infectious diseases represent increasing threats for humans, the risk of leptospirosis may decrease with increasing temperature and precipitation. "*At whole-region scale, the incidences of TBE are negatively correlated with all (hydro-) climate variables, while those of borreliosis are positively correlated with all climate variables*". This is notable because these diseases share the same vector, namely Ixodidae ticks [49]. Thus, the same vector can transmit a pathogenic bacterium (*Borrelia* spp.) and a neurotropic Flaviviridae virus (such as TBE).

Weather conditions, rainfall, moisture (at least 85 % relative humidity) and temperature affect the life cycle and habitat of Ixodes ticks. These factors contribute to the geographic expansion in association with vegetation communities and wild animal hosts (deer, other cervids, birds, and rodents), which carry tick vectors to new areas [48, 49]. For example, the sheep tick *Ixodes ricinus* has spread to the northern regions of Sweden and Norway [49]. In addition to this expansion, an increase in the incidence of tick bites has been linked with the increased annual temperature. Human contact with wild fauna due to urbanization and green zones in towns, as well as changing patterns of human behavior (increasing number of trekkers, wildlife and pet lovers), has augmented the risk of exposure to tick-borne pathogens [48].

The health of wildlife also has relevance to human health. Muskoxen and caribou (reindeer) are infected by a helminth parasite (*Varestrongylus eleguneniensis*, lungworm) that has rapidly extended its geographical range at high latitudes in the central Canadian Arctic; this is attributed to faster warming at high latitudes and altitudes, which allows the establishment of lungworms and their gastropod intermediate hosts [48]. Although not in direct relation with climate change, the propagation and geographic extension of Chronic Wasting Disease (CWD, an infectious and degenerative prion disorder) in the cervid population (deer, elk, moose, and caribou) is a major concern in Arctic areas. CWD, which was discovered in the 1980s in the western United States (U.S.), had expanded by 2012 to 19 U.S. states and 2 provinces in Canada [50] and, by 2021, to 26 U.S. states and 3 Canadian provinces [51]. After a decade of surveillance, the first case of CWD in reindeer was diagnosed in Norway in 2016, since that time, other cases have been reported in Norway, Sweden and Finland. Besides the threat to the cervid population across the Arctic region, the potential risk of transfer of a contagious prion to humans via food is considered. Ruscio and coauthors [52] recommend a regional One Health approach

to assess interactions at the human–animal–environment interface to augment understanding of, and response to, the complexities of climate change on the health of Arctic inhabitants.

Specific health risks related to permafrost thawing due to global warming. While organic matter in thawing permafrost is subject to microbial activity, with consequent release of greenhouse gases (carbon dioxide and methane), human health may also be impacted by the additional release of chemical and radioactive materials deposited in permafrost in recent times [53]. Biological risks associated with the permafrost thawing rank at the highest degree of uncertainty since all biological items are frozen before decomposition or degradation. This led Abramov and coauthors [54] to write "*Permafrost is used as a paleoarchive*". The story of preserved mammoth bodies, commonly found in Siberia permafrost, is known worldwide. Less widely known is that diverse microorganisms (Archaea, Bacteria and Eukarya), as well as viruses, are also isolated in permafrost. Some such organisms have been cultured, which demonstrates the preservation of life forms in permafrost [54]. A question of utmost importance is the potential health impact on modern humans if the multitude of unknown microorganisms that have been sequestered in permafrost for tens to hundreds of thousands of years were to be released into the environment[26].

The discovery of the H1N1 virus, which caused the global Spanish influenza epidemic, illustrates well the threats of sequestered microorganisms. The pandemic killed 20 to 50 million people in 1918–1919 [55]. Some key researchers, starting with Johan Hultin in 1951, have unsuccessfully attempted to obtain the 1918 virus from bodies of victims buried in permafrost at Alaska's Brevig Mission burial site. He was again involved in 1997, at age 72, during his second trip to the Brevig Mission burial ground. He provided unfixed lung tissue to U.S. scientists Dr. Jeffery Taubenberger and Dr. Ann Reid who isolated RNA material. With genomic RNA of the 1918 virus isolated from archived formalin-fixed lung autopsy materials, the sequencing the genome of the 1918 virus was at last possible [56]. Microbiologist Dr. Peter Palese and his New York team created the plasmids used by Dr. Terrence Tumpey at the U.S. Center for Disease Control & Prevention to reconstruct the 1918 pandemic virus [57].

Contrary to the H1N1 influenza virus, which has been reconstructed, some viruses can "*survive intact in ice patches for at least this period and retain their infectivity*" [58]. This was demonstrated for the caribou feces-associated virus (aCFV) that was probably present in the animal's plant diet and isolated from a 700 ± 40 year-old caribou fecal sample [59].

The study of the Siberian permafrost virome allowed the detection of a giant virus, named *Pithovirus sibericum*, which was isolated from a > 30,000 year-old radiocarbon-dated sample. A previous study reported the detection of genomic signatures of a tomato mosaic tobamovirus in 140,000 year-old glacial ice in Greenland, but did not address the question of viability [60].

The risk of mammalian infectious diseases linked to the release of microbes in thawing permafrost was realized in 2016 when *Bacillus anthracis* (anthrax bacterium) killed thousands of reindeer and affected dozens of humans in the Yamal peninsula in the northern part of Russia's Western Siberia. After 70 years free of anthrax, this outbreak was related to former severe and recurring regional epizootics of anthrax in the early 20th century. The activation of spores in 2016 had several causal factors, including 6 years of relatively warm weather followed by cold years during which a thick snow cover prevented soil from freezing. The summer 2016 heat wave accelerated the permafrost thaw, and the situation became even worse due to a reduced rainfall in July 2016 (less than 10 % of its 30-year mean value) [61].

[26] Permafrost thaw could release bacteria and viruses. *ESA*. Available at: https://www.esa.int/Applications/Observing_the_Earth/Permafrost_thaw_could_release_bacteria_and_viruses (June 26, 2022).

Arctic pollution impacts humans through water and food consumption. Awareness of the human impact of pollution in the Northern Hemisphere led to the creation of a dedicated research program in 1997. The Arctic Monitoring and Assessment Programme (AMAP) launched ongoing surveillance of environmental POPs in the Arctic ecosystem. In 1998, 2002, and 2009, AMAP published reports on the results and the health risks of POPs for Arctic populations [62].

The cultural behaviors of indigenous populations are a key to understanding the routes by which pollutants can enter the body. The first example is the population living in the Faroe Islands who traditionally consume marine mammals (whales), seabirds and other seafood and, in Greenland even polar bears. These animals are contaminated with pollutants such as mercury, metals and POPs (e.g., PCB, organochlorine pesticides), and consuming their flesh exposes subjects to pollutants with neurotoxic [63, 64], genotoxic and reproductive toxic potential [62, 65]. Human plasma organochlorine levels were elevated in an Arctic population, and the mean plasma concentration of DDE, the breakdown product of DDT, was found to be elevated in subjects with idiopathic Parkinson disease (PD). The age-adjusted prevalence of PD in the Faroe Islands (209 per 100,000 inhabitants) and in Greenland (187.5 per 100,000 inhabitants) is higher than in a Baltic Sea Island in Denmark (98.3 per 100,000 inhabitants); patients were younger in Greenland and a higher proportion of patients had cognitive decline [63, 64].

Exposure to methyl mercury from marine mammals and other seafood can affect human brain development. The average mercury concentration of hair was greater in children (5 micrograms/g) than their mothers (1.5 micrograms/g) in a traditional Inuit community in Qaanaaq (Greenland). While the children were clinically unremarkable, neuropsychological tests showed possible exposure-associated deficits. Additionally, in conjunction with data from other studies (Faroese Islanders), peak latencies on brainstem auditory evoked potentials tended to be prolonged at increased exposure levels [66].

In the same study, Inuit had significantly lower sperm DNA damage. Further studies are required to elucidate whether the serum POP-related effects on hormone receptors and / or AhR are explanatory factors. 'The Arctic dilemma' is that along with the intake of the Greenlandic traditional diet that contains POPs, there is also a number of important nutrients, such as trace elements/antioxidants and marine unsaturated fatty acids that have favorable health effects. However, several studies suggest that an increase in Western food items in the diet can lead to other health risks, such as the metabolic syndrome and its sequellae, namely body weight increase, hypertension, diabetes type 2, cardiovascular disease, and cancer, including breast cancer.

Further studies are required to elucidate these phenomena, including research focused on biomarkers of exposure and effects, epigenetic changes and the determination of relevant genetic polymorphisms, case-control as well as generation studies. There is also a need for the development of new biomarkers to study the potential POP effects that inhibit the immune system and affect the development of the central nervous system. Although the traditional Greenlandic diet, together with cigarette smoking, is associated with a high POP intake relative to that of Europeans, male Inuit have significantly lower levels of sperm DNA damage. A possible explanation is the relatively rich selenium and n-3 unsaturated fatty acids in the Arctic diet [62]. However, the exposure of pregnant women in Greenland to metal pollutants (tested in blood) over the admitted normal range, can "*adversely influence fetal development and growth in a dose-response relationship*". Abnormal fetal outcomes have been noted, including reduced birth weight, reduced head circumference, and preterm birth [65].

The second example of cultural tradition of many northern indigenous peoples is related to diet and water consumption. In addition to a cultural preference, drinking untreated water (e.g., from lakes, ponds, rivers, melted snow or

ice) is not an uncommon practice, especially when northern residents are visiting cabins, hunting, fishing, trapping, and gathering [67]. For the Indigenous Peoples of North-Western Siberia, typically in the season of fishing or reindeer slaughter, "*This diet provides a ready-made set of macro- and micro-elements necessary for life in the challenging conditions of the Arctic"* [68]. An example of the benefit of traditional food is the consumption of reindeer venison meat, which has been shown to reduce hypertension and the risk of chronic non-obstructive bronchitis. Nowadays, as shown by Bogdanova and coauthors [69], the consumption of traditional reindeer food has decreased by almost 50 %, in part from the export of such products and the effects of climate change, which modifies seasonal fishing and disrupts the traditional migration routes of the reindeers [68]. The safety of food and water in relation to chemical/microbiological contamination is a major issue for Arctic populations, as are waterborne illnesses.

Suicide in the Arctic as an additional risk factor. We discovered the drama of suicide among adolescents when one of us (JR) visited the cemetery of Ammassalik-Tasilaq (Greenland) in summer 1994. Catherine Enel, a late French ethnologist who lived in the community explained the suicidal ideation of local adolescents and evoked Robert Gessain who, with alarm about the fate of the Inuit population, wrote in 1969 "*The Ammassalimiut will culturally disappear from the world, leaving more numerous descendants. Cultural death and population explosion, ethnocide and genoboom, are the by-products on these Arctic shores of Western expansion*"[27]. In fact, suicidal behaviors and thoughts are a major public health issue across Arctic States and their northern regions [70]. Excess risk is related to ethnicity (indigenous groups), age and sex. The suicide rate in the Norwegian Sami people is higher among males aged 15–24 and more than double in males than females. The mean age-standardized suicide rate shows great variations in the Arctic States for the decade 2000–2009. In the Western countries (Europe and America), the median age is < 20 years: suicide impacts a young population. To the contrary, in the Russian Federation, as well as in Greenland and Nunavut (Canada), where the indigenous population constitutes the majority of inhabitants, suicide occurs more in older people (> 40 years). Young and coauthors [70], who emphasize the need for suicide prevention, propose few explanations for the problem of suicidal behaviors and thought from a circumpolar perspective.

Conclusion. The Arctic and sub-Arctic populations are victims of the Anthropocene Epoch of human activity and the extension of a Westernized lifestyle that endangers local resources and indigenous cultures.

What can be done? Bring better research and information to allow remediation and resilience!

How? Increased cooperation among states is mandatory, as underlined by Margareta Johansson, a research coordinator in the Department of Physical Geography and Ecosystem Science at the University of Lund (Sweden) who concluded her document with the following sentence: "*the climate knows no national borders*"[28]. As climate changes faster in the Arctic than elsewhere, global pollution and infectious diseases threaten to challenge the health of its indigenous peoples to a degree perhaps greater than faced by humans in other parts of the world.

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Competing interests. The authors declare no competing interests.

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Research article

CLIMATIC AND CHEMICAL HEALTH RISK FACTORS FOR PEOPLE LIVING IN ARCTIC AND SUB-ARCTIC REGIONS: POPULATION AND SUB-POPULATION LEVELS

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The article dwells on climatic and chemical risk factors that influence health of people living in the RF Arctic and sub-Arctic regions on population and sub-population levels. We used a model describing cause-effect relations between environmental factors and life expectancy at birth based on an artificial neural network to predict a future medical and demographic situation in territories with Arctic and sub-Arctic climate in the RF.

Children's health was examined profoundly due to a participating representative sampling. We comparatively analyzed clinical, biochemical and general clinical indicators in the test and reference groups using standard statistical procedures and statistical software packages.

We established that average monthly temperatures in July grew on average by 3.4 % over 2010–2019 on the examined territories in the RF; precipitations in January and July grew by 13.0–15.1 %. The article presents differentiated estimates of emerging influence on life expectancy at birth (LEB) exerted by weather and climatic conditions on the analyzed territories with Arctic and sub-Arctic climate. Losses in LEB vary from 164 days in Yakutia to 349 days in Chukotka. Aggregated influence of weather and climatic factors in the Arctic and sub-Arctic zones in 2010–2019 produced variable effects on LEB, starting from negative ones that resulted in its decline in the Magadan region, the Nenets Autonomous Area, Chukotka, and the Yamal-Nenets Autonomous Area (-254; -211; -109 and -8 days accordingly) and to positive ones that led to the growth in LEB by up to 111 days in Yakutia.

Children who are simultaneously exposed to adverse weather and climatic factors in the sub-Arctic zone and substantial chemical pollution in ambient air have more frequent and more apparent negative changes in their health indicators in comparison with children from the reference group. Thus, respiratory diseases and diseases of the nervous system were by 5.6 times more frequent in the test group; levels of leukocytes, ESR, TSH, Apo-B and Apo-B/ApoA1 in blood were by 1.3–1.7 times higher, $p = 0.0001$. Levels of Apo A1, hydrocortisone, and serotonin in blood were by 1.2–2.5 times lower, $p = 0.0001–0.040$, etc. A share contribution made by chemical factors to associated respiratory diseases and diseases of the nervous system amounted to 25–31 %; adverse climatic factors, 10–15 % .

Keywords: *climate in Russia, Arctic, public health, children, life expectancy at birth, LEB, health risk factors, socio-hygienic determinants, ambient air quality, neural networks, prediction of potential LEB growth, profound examinations.*

Human health is influenced by a complex set of interrelated factors such as environmental, climatic, geographic, social and behavioral ones. The human body has to adapt to them to maintain proper functioning [1]. Climate is among the most important factors that determine live activity of the human body including preservation and development of its biological, psychological and physiological functions. These functions are of vital

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importance since they influence a person's working ability and social activity. Climate on a given territory is determined by its geographical position, namely, its latitude, height above sea level, sea to land ratio, topographic peculiarities etc. Climate is the weather conditions prevailing on a given territory over a long-term period[1]. There is another definition stating that climate is the average weather for a particular region taken over a long-term observation period[2]. Climate consists of multiple specific and instant atmospheric conditions, so to say, of multiple variable "weathers" over a long-term period (usually from 50 to 100 years)[3]. Therefore, we can consider climate to be a certain background for a person's live activity and health [2], and the weather is a set of meteorological elements (factors) taking turns according to laws and regularities of specific climate.

Impacts exerted by the weather on the human body can be both positive and negative. They become apparent as meteosensitivity, meteolability or meteotropic reactions, in other words, pathological responses of the human body caused by exposures to adverse weather factors[4]. Meteopathic reactions can occur in the body under exposure to such meteorological factors as air temperature, humidity, pressure, wind speed, solar radiation (including spectral distribution of energy), longwave solar radiation, precipitations (their type and intensity), air composition, atmospheric electricity, atmospheric radiation, infrasound, etc. [2].

Several basic meteorological factors exert the most substantial influence on the human body. First, we should mention *air temperature*, including its peak values in summer and winter seasons, and its fluctuations; then, *air humidity*, which enhances effects produced by air temperature; *atmospheric pressure* and its changes; *precipitation quantities* in various seasons; *insolation*; and some others. Meteorological factors (air temperature and humidity, wind speed, atmospheric pressure, solar radiation intensity etc.) produce combined effects on the human body and can either enhance or weaken each other's influence. The human body tends to bear additional loads under combined adverse exposure to climatic factors [3].

Results of multiple domestic and foreign studies with their focus on assessing influence of weather and climate on human health indicate and predict wide-scale, or even disastrous, effects such as elevated incidence and mortality and, consequently, a reduction in life expectancy at birth (hereinafter LEB) [4–7]. Thus, climate change influences social and ecological determinants of health, namely, clean air, safe drinking water, sufficient amounts of food products and safety (integrity) of housing. According to the WHO [8] over a period from 2030 to 2050 the climate change is expected to cause a growth in a number of deaths by approximately 250 thousand annually because of insufficient nutrition, malaria, diarrhea and exposure to high air temperatures. Direct costs due to negative impacts exerted by climate on health are predicted to reach 2–4 billion US dollars per year by 2030. They do not include costs in some sectors of the economy that govern human health such as agriculture, water supply and sanitation. Areas where public healthcare is underdeveloped (mostly, developing countries) are likely to be unable to cope with this dangerous situation without relevant preparation and equipment. A reduc-

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tion in greenhouses gases emission due to modernization of vehicles, food products and energy consumption can result in health improvement, especially due to lower levels of ambient air pollution [8].

According to the Report[5] on climatic peculiarities in Russia in 2019, climate changes that have been observed in the country over the last decades follow the overall warming trends. Average annual temperature anomalies (a deviation from the average level in 1961–1990) equaled +2.07 °C. In 2019, average annual temperatures were among five highest ones over the whole observation history in almost every RF region. Negative anomalies were observed only in summer in the North-Western Federal District and Volga Federal District. Growing concentrations of greenhouse gases, primarily carbon dioxide and methane, are considered the basic driver of contemporary warming. Although the global society has been taking substantial efforts to confine greenhouse gases emission into ambient air, their concentrations are only growing further. In 2019 background CO_2 concentrations reached another peak in ambient air at northern latitudes.

We cannot give any unambiguous estimates to influence exerted by warming on climatic conditions for people's lives and activities in Russia. Thus, on one hand, changes in the cryosphere involve a substantial improvement of navigation along the Northern Sea Route. On the other hand, permafrost degradation can result in destruction of house footings and infrastructure. A longer vegetation period created by warming is an obvious bonus for agriculture but it usually entails elevated risks of drought in basic grain-producing regions in the European part of Russia due to precipitation deficiency and higher air temperatures. An observed trend of a shorter heating period and its growing average temperature (up to 0.8 ºC over 10 years in the central Yakutia) makes the existing buildings more thermally effective and stimulates a reduction in energy consumption[6]. Predicted changes in various economic branches due to the observed climate change can become apparent through changes in emerging medical and demographic risks and public health indicators. Regular climatic monitoring and climate change modeling should produce detailed and reliable data about the existing trends in climate change. These data provide the necessary grounds for developing relevant activities aimed at adapting economic branches and human environment to changing climate thereby minimizing climate-induced risks and health harm.

In medicine, cold climate in northern areas is considered an irritating type of climate with typical apparent daily and seasonal ranges of meteorological elements. This climate makes higher demands to adaptation mechanisms. Cold climate in the North is remarkable for its low air temperatures, high relative air humidity, permafrost, polar nights without any solar radiation, strong harsh winds, etc. Peculiarities of this climate induce tension of thermal regulation and hemodynamics in the human body; intensify the basic metabolism and the stomach hypersecretion. They also stimulate adverse changes in the nervous system such as reinforced inhibitory processes, lower conditioned reflex activity, lower working abilities, and sleeping disorders (during the midnight sun). People's reactions and health under exposure to weather factors can be considered disorders of physiological adaptation and outcomes created by an acute meteorological stress. We should note that adverse effects produced by weather are related not so much to absolute values of meteorological parameters but to drastic changes in them. These

[5] Doklad ob osobennostyakh klimata na territorii Rossiiskoi Federatsii za 2019 god [The report on climatic peculiarities in Russia in 2019]. Moscow, Rosgidromet, 2020, 97 p. (in Russian).

[6] Vtoroi otsenochnyi doklad Rosgidrometa ob izmeneniyakh klimata i ikh posledstviyakh na territorii Rossiiskoi Federatsii. Razdel 6. Vozdeistviya izmeneniya klimata na khozyaistvennye ob"ekty i zdorov'e naseleniya. Mery adaptatsii k etim vozdeistviyam [The second estimation report by Rosgidromet on climatic changes and their consequences in the Russian Federation. Section 6. Impacts exerted by climatic change on economic entities and public health. Adaptation to these impacts]. Moscow, The Russian Federal Service for Hydrometeorology and Environmental Monitoring, 2014, pp. 43–56 (in Russian).

changes make higher demands for homeostasis-supporting systems and lead to desynchronization of the internal biorhythms [3].

So, most RF regions are considered territories with adverse climatic conditions. In addition to that, approximately 15–20 % of them are located in zones where high levels of chemical pollution in ambient air (more than 5 $MPC_{av.daily}$) are combined with adverse weather and climatic factors (abnormally low air temperatures, harsh winds, and low insolation). Several priority pollutants are usually detected in ambient air in settlements in such regions. They include benz(a)pyrene, formaldehyde, hydrogen sulfide, particulate matter, hydrogen fluoride, metals (including nickel, copper, aluminum, chromium (VI)), hydrogen chloride, aromatic hydrocarbons etc. They predominantly belong to the 1st or 2nd hazard category[7]. All the aforementioned chemicals and extreme weather and climatic factors can induce restructuring of homeostatic systems in the body; intensify developing deadaptation and strain of the immune-hormone regulation, circulation, and the bronchopulmonary system. They can also make redox processes faster and impair functional state of the barrier organs (liver, kidneys, spleen, lungs, and the immune system) [9–19].

According to the data taken from the IPCC report "Global Warming of 1.5 °C"[8] the most serious and widely spread risks for people, economy and ecosystems are predicted for the Arctic region (Figure 1).

Combined exposure to negative heterogeneous factors can lead to elevated chronic incidence among population. It is especially true for children as they are the most sensitive subpopulation. This is confirmed by higher incidence rates detected on these territories regarding the respiratory diseases, diseases of the nervous and cardiovascular systems. They are by 1.5–2.5 times higher than on average in the country [16].

The outlined problem is rather pressing. This calls for more profound examination of changes in homeostasis indicators that describe negative effects in target organs. This examination makes it possible to substantiate effective prevention of non-communicable diseases associated with combined exposure to chemical and adverse (extreme) climatic factors. The necessity to pay closer attention to impacts exerted by "harsh" weather and climatic factors on public health in the Arctic and sub-Arctic zones in the RF determined topicality of the present study and its goal.

Our research goal was to identify and estimate modifying influence exerted by chemical and climatic health risk factors in the Arctic and sub-Arctic zones at the population and sub-population levels.

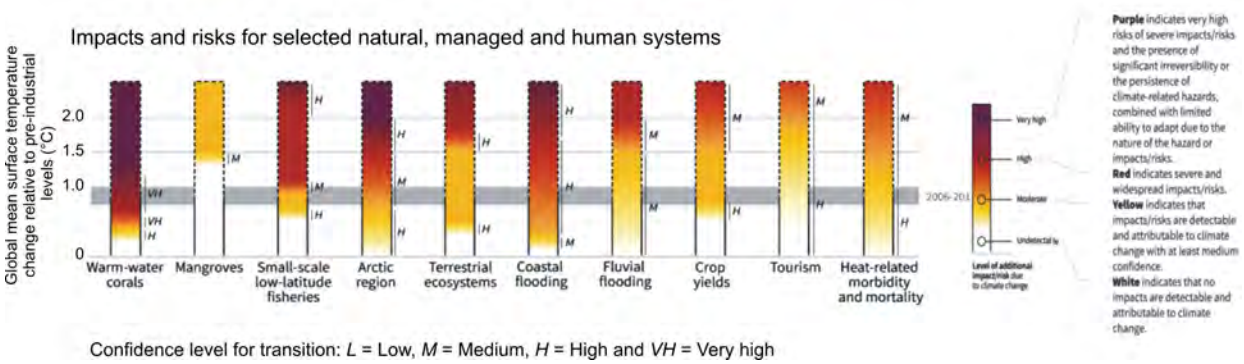

Figure 1. Impacts and risks created by global warming for selected natural, managed and human systems (estimates are based on scientific research and experts' opinions by the IPCC experts)[8]

[7] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2019 godu: Gosudarstvennyi doklad [On sanitary-epidemiological welfare of the population in the Russian Federation in 2019: the State report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2020, 299 p. (in Russian).

[8] Global Warming of 1.5 °C. *IPCC*. Available at: https://www.ipcc.ch/sr15/ (April 15, 2022).

To achieve that, we set the following research tasks: 1) to quantify influence exerted by climatic risk factors on public health in RF regions located in the Arctic and sub-Arctic zones (the population level); 2) to assess children's health (the sub-population level) under combined exposure to aerogenic chemical factors and adverse climatic factors.

Materials and methods. We took all the initial data for statistical analysis from open and verified sources including statistical forms and reports issued by Rosstat, Rospotrebnadzor, and the RF Public Healthcare Ministry.

We estimated influence exerted by weather and climate on LEB in RF regions that were geographically located in the Arctic and sub-Arctic zones. Our estimates were based on scenario modeling that involved using a digital (neuronet) model in accordance with the Methodical guidelines MR 2.1.10.0269-21[9]. The applied model was based on a matrix with data collected in 2010–2019. The matrix consisted of 148 indicators that were conditionally consolidated into 6 groups: 53 indicators describing sanitary-epidemiological welfare on a given territory; 9 indicators, a public healthcare system; 14 economic indicators; 30 lifestyle-related indicators; 34 sociodemographic indicators; 8 indicators describing weather and climate. The analyzed weather and climate indicators[10] included average monthly air temperatures and precipitation quantity in July and January as well as their deviations from average long-term levels in different RF regions over 2010–2019. Life expectancy at birth (LEB) in a given region was considered a dependent variable. It was estimated based on data[11] collected in 2010–2019 and provided by the Federal Statistic Service.

We took four regions located in the Arctic zone and three regions located in the sub-Arctic zone as example ones in accordance with our goal. The Arctic regions were Yakutia (the northern part), Chukotka (the northern part), the Yamal Nenets Autonomous Area (the northern part), the Krasnoyarsk region (the northern part, more exactly, Norilsk municipal district and Taimyr Dolgan-Nenets municipal district). The sub-Arctic regions were the Magadan region (its continental part), Murmansk region (the northern part), and the Nenets Autonomous Area.

Estimating influence exerted by weather and climate factors on public health in the Arctic and sub-Arctic regions in the RF. Influence exerted by weather and climate on LEB losses was determined by conducting a series of numerical experiments using three sequential computation stages described in our previous article [20]. At the first stage, we substituted values of indicators reflecting weather and climatic conditions in a specific region (a reference region) for all the regions in the RF. All the other variables (determinants) retained their basic value. The second stage involved determining a region in the RF with the greatest losses in LEB, which was conditionally considered the most "favorable" against weather and climatic conditions in a reference region. At the third stage, we determined losses in LEB against a "favorable" region, which were caused by weather and climatic conditions; the procedure was repeated for all Arctic and sub-Arctic regions in the RF. The algorithm was sequentially applied to examine each RF region used as a reference one against other regions in the country. Resulting losses in LEB for each examined Arctic or sub-Arctic region were estimated by averaging values obtained at the third stage.

We established what effects weather and climate produced on LEB over 2010–2019 by

[9] MR 2.1.10.0269-21. Opredelenie sotsial'no-gigienicheskikh determinant i prognoz potentsiala rosta ozhidaemoi prodolzhitel'nosti zhizni naseleniya Rossiiskoi Federatsii s uchetom regional'noi differentsiatsii: Metodicheskie rekomendatsii [MR 2.1.10.0269-21. Identification of socio-hygienic determinants and predicted potential growth in life expectancy at birth for the RF population considering regional differentiation: The Methodical guidelines]. Moscow, 2021, 113 p. (in Russian).

[10] Rossiiskii statisticheskii ezhegodnik. 2019: Statisticheskii sbornik [Russian annual statistical data collection. 2019: Statistical data collection]. *Rosstat*. Moscow, 2019, 708 p. (in Russian).

[11] Regiony Rossii. Sotsial'no-ekonomicheskie pokazateli. 2019: R32 Statisticheskii sbornik [Regions in Russia. Socioeconomic indicators. 2019: P32 Statistical data collection]. *Rosstat*. Moscow, 2019, 1204 p. (in Russian).

using scenario neuronet modeling. We took actual data on socio-hygienic determinants registered in 2010 as our baseline scenario. A target scenario was set by keeping all the social and hygienic determinants at their baseline level except from indicators that characterized weather and climatic conditions in the analyzed RF regions. These indicators were set at their values determined for 2019. We determined effects produced by weather and climate on changes in LEB in the analyzed RF regions by calculating a difference between a baseline and target scenario.

Krasnoyarsk region has a huge territory and is located in different climatic zones. Bearing this in mind, we selected one representative territory to estimate influences exerted by weather and climate on LEB in the Arctic zone in this region. This territory was Norilsk. The algorithm applied to calculate influence exerted by weather and climate on LEB was similar to calculations performed for other analyzed RF regions. To determine climatic peculiarities in Norilsk, we took the data on average air temperature and precipitations in July and January obtained at "Norilsk. Alykel" monitoring post (No. 23078). We took statistical data obtained for the whole Krasnoyarsk region for the remaining analyzed indicators.

Changes in weather and climatic indicators were analyzed in dynamics as per their average growth rates over the period from 2010 to 2019.

Assessing health of children living under combined exposure to weather and climatic factors in the Arctic / sub-Arctic zone and high levels of aerogenic chemical exposure. This stage involved examining health of children aged 3–6 years. They lived in regions with either isolated exposure to adverse weather and climatic factors typical for a sub-Arctic zone (the test group A was made of 72 children) or with combined exposure to high levels of chemical pollution in ambient air and adverse weather and climatic factors (the test group B included 184 children). Our reference groups included children of the same age who lived in regions with moderate continental climate (the reference group A for the test group A) and in regions with sub-Arctic climate where chemical aerogenic exposure was either absent or negligible (the test group A as a reference group for the test group B). All the children were examined in full conformity with the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, 2013. The examinations were approved according to the conventional procedure by the Committee on Biomedical Ethics of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies. Legal representatives of all the participating children gave their informed voluntary consent to the participation prior to the examinations.

We estimated combined aerogenic exposure to chemicals in ambient air as per contents of aluminum, fluoride-ion, copper and nickel in biological media. According to the Methodical guidelines MUK 4.1.773-99, 4.1.3230-14, 4.1.3589-19 that are valid in the RF, chemical and analytical tests to determine copper and nickel in blood and aluminum and fluoride-ion in urine were performed by using mass spectrometry and ion-selective potentiometry with the following equipment: Agilent 7500cx mass spectrometer with inductively coupled argon plasma (Agilent Technologies, USA), ILA-2 laboratory automated ionometer (Izmeritelnaya tekhnika, Russia). We comparatively assessed indicators in the children from the test groups and those in the children from the reference ones. The assessment involved calculating significance of difference between two independent samplings with using non-parametric Mann – Whitney test ($U \leq U_{cr}$). The level of significance was taken as $p \leq 0.05$ when statistical hypotheses were tested.

To identify possible negative effects in target organs, we examined relevant biochemical and general clinical indicators. They included levels of erythrocytes, leucocytes, and hemoglobin; erythrocytes sedimentation rate (ESR); eosinophils and neutrophils in nasal secretions; eosinophilic index; apolipoproteins A1 (*Apo-A1*) and B100 (*Apo-B*); contents of the thyrotrophic hormone (*TTH*), thyroxin (*T4*), hydrocortisone, and neurotropin-3 in blood serum; levels of

catecholamines (adrenaline, dopamine, noradrenaline, and serotonin) in blood plasma.

Data on incidence among the examined children were analyzed as per results obtained by a complex objective medical examination[12]. It fully met the criteria of the International Classification of Diseases (ICD-10) and involved identifying a number of disease cases at the moment the examination took place. Priority diseases, critical organs and system taken into account, were identified based on authentically higher prevalence in a test group against a reference one ($p \leq 0.05$).

Complex impacts exerted by weather and climatic factors in the sub-Arctic zone (air temperature and humidity, wind speed) were estimated as per the normal equivalent effective temperature (NEET). The NEET was calculated as per the formulas introduced by A. Missenard[13] and I.V. But'eva[14]. The NEET values varying from 12 to 24 °C were considered comfortable and sub-comfortable [11]. Hygienic assessment of ambient air quality was performed using data obtained at control points within social and hygienic monitoring activities in 2014–2018.

Statistical analysis and calculations were performed in mathematical computation packages for PC (Statistica 10, RStudio, MS Excel 2010). We applied geoinformation systems (ArcGIS 9.3.1) to visualize our cartographic materials.

Results and discussion. Most RF regions are located in zones with relatively harsh climate. According to the classification[15] created by B.P. Alisov, a scientist and climatologist, Russia is located in three climatic zones, namely, Arctic, sub-Arctic and moderate one. The Arctic Ocean seaboard in Siberia and its islands (the southern island of the Novaya Zemlya excluded) as well as some islands in the Barents Sea are located in the Arctic zone[16] (Figure 2).

In 2019, the lowest average monthly temperatures among all the analyzed RF regions were registered in Yakutia, Magadan region and Chukotka (-34.1 ºC; -27.4 ºC; -23.6 ºC accordingly). The highest average monthly temperatures in July were registered in the Yamal Nenets Autonomous Area, Yakutia, and Magadan region (15.2 ºC; 14.3 ºC; 12.7 ºC accordingly). The greatest average monthly precipitation in January was registered in Murmansk region, the Nenets Autonomous Area and the Yamal Nenets Autonomous Area (37.7; 23.1; 22.6 mm accordingly); in July, in Magadan region, Murmansk region and Yakutia (60.5; 60.4; 52.6 mm accordingly).

If we take basic weather indicators in dynamics over 2010–2019 in the analyzed RF regions in the Arctic and sub-Arctic zones, we can see that average monthly temperatures in July grew by 3.4 % on average (within a range from 0.3 to 5.9 %). Average monthly precipitation in July and January also increased, by 15.1 % and 13.0 % accordingly. Average monthly temperatures in January and July grew by 4.5 % and 1.9 % accordingly on the territories located predominantly in the sub-Arctic climatic zone (Murmansk and Magadan regions). These temperature indicators increased by 2.1 % and 4.2 % accordingly on the mixed-type territories (located in both Arctic and sub-Arctic zones) (Table 1). Average monthly temperatures in July and January grew by 1.2 ºC and 1.9 ºC on average against average long-term values in all the analyzed regions.

[12] The field medical examination was performed by experts from the Department for Children and Adolescents Hygiene (headed by S.L. Valina, Candidate of Medical Sciences).

[13] Missenard A. L'homme et le climat. Paris, Plon, 1937, 270 p. (in French).

[14] But'eva I.V., Sheinova T.G. Metodicheskie voprosy integral'nogo analiza mediko-klimaticheskikh uslovii [Methodical issues in integral analysis of medical and climatic conditions]. *Kompleksnye bioklimaticheskie issledovaniya*, 1988, pp. 97–108 (in Russian).

[15] Khromov S.P., Petrosyants M.A. Meteorologiya i klimatologiya: uchebnik, 7-e izd. [Meteorology and climatology: manual, 7th ed.]. Moscow, The Moscow University Publ.; Nauka, 2006, 582 p. (in Russian).

[16] O sostoyanii i ob okhrane okruzhayushchei sredy Rossiiskoi Federatsii v 2018 godu: Gosudarstvennyi doklad [The State Report "On the ecological situation and environmental protection in the Russian Federation in 2018"]. Moscow, The Ministry of the Environment and Natural Resources; NPP "Kadastr", 2019, 844 p. (in Russian).

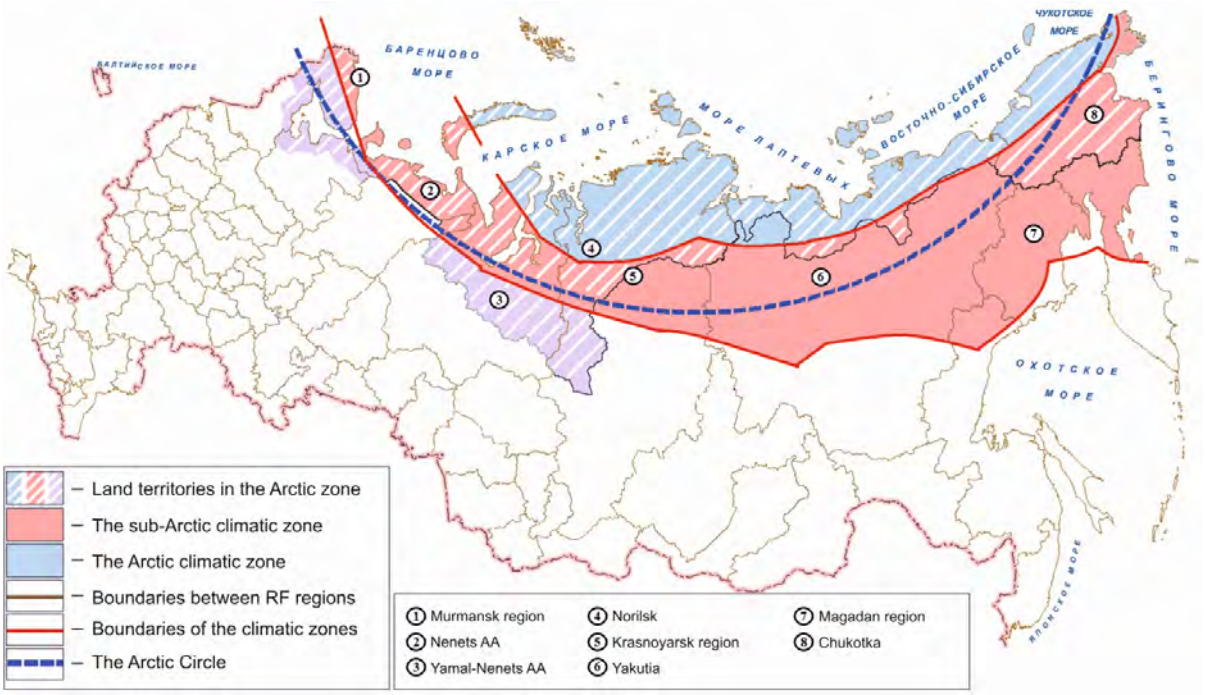

Figure 2. A map showing Arctic and sub-Arctic climatic zones in the RF

Table 1

Changes in weather and climatic indicators taken in dynamics over 2010–2019 as per average growth rates, %

RF region	Climate	Average monthly temperature (January, ºC), % (as per module)	Average monthly temperature (July, ºC), %	Average monthly precipitation (January, mm), %	Average monthly precipitation (July, mm), %
Krasnoyarsk region (the northern part)	Arctic and sub-Arctic	1.0	+1.6	+8.6	+7.0
Nenets AA	Arctic and sub-Arctic	5.6	+5.8	+5.8	+24.2
Yakutia (the northern part)	Arctic and sub-Arctic	1.1	+1.4	+5.4	+1.6
Chukotka	Arctic and sub-Arctic	0	+3.8	+10.1	+6.5
Yamal Nenets AA (the northern part)	Arctic and sub-Arctic	1.7	+5.9	+6.4	+30.9
Magadan region (the continental part)	Sub-Arctic	1.0	+0.3	+44.1	+24.3
Murmansk region (the northern part)	Sub-Arctic	8.0	+3.4	+6.3	+3.2

We accomplished scenario modeling using actual data on the analyzed climatic features. Its results allowed us to obtain differentiated estimates of emerging influence exerted on LEB by Arctic and sub-Arctic weather and climate on the analyzed territories. Climate-induced losses in LEB vary from 164 days in Yakutia to 349 days in Chukotka (Figure 3). Average loss in LEB due to weather and climate amounted to 191.7 days in the RF as a whole[4].

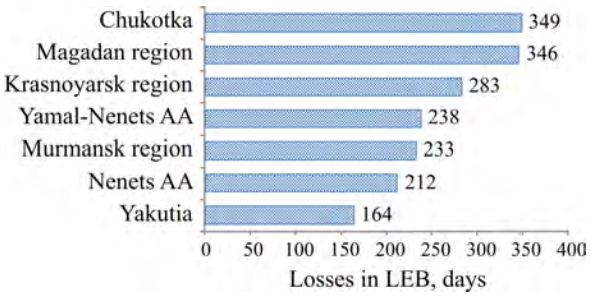

Figure 3. Losses in LEB due to weather and climate, 2018, days

The climate change observed over the last decade in the Arctic and sub-Arctic zones has produced an apparent effect on the integral health indicator, life expectancy at birth. Over 2010–2019 LEB grew on average by 9.7 % in all the RF regions located in the Arctic and sub-Arctic zones. This growth appeared within a range from 4.9 % in Murmansk region up to 18.4 % in Chukotka. The LEB levels were 68.1–74.2 years in these regions (Table 2). The greatest growth in LEB in the analyzed period was established in Chukotka where it equaled 10.6 years; it should be noted that in 2010 the regional LEB there was the lowest in the RF and was equal to 57.5 years.

All the influence of weather and climate in the analyzed period produced variable effects on LEB, either negative, such as its decline in Magadan region, the Nenets Autonomous Area, Chukotka and the Yamal Nenets Autonomous Area (-254; -211; -109 and -8 days accordingly), or positive ones as the growth in it by 111 days in Yakutia. A contribution made by influence of weather and climate to the actual LEB levels varied from -13.2 % (Magadan region) to 4.9 % (Yakutia) according to the results produced by scenario modeling (Table 2). The greatest positive influence exerted by the registered changes in weather and climate was detected in Yakutia where it equaled 111 days. The actual growth in LEB in this region was among the highest detected on the analyzed territories over 2010–2019 (6.3 years). This can be due to both complex and systemic improvement in the sanitary-epidemiological wellbeing on the territory, the socio-demographic situation and people's lifestyle and to gradual changes in weather and climate that have become warmer.

Mostly favorable effects of changes in weather in climate on LEB can probably be due to more favorable navigation conditions along the Northern Sea Route, a longer vegetation period necessary for agriculture, and a declining pressure on regulatory systems in the human body that maintain its adaptation capabilities etc[6]. Still, this influence by weather and climate on LEB turned out to be negative on some territories (Magadan region, the Nenets Autonomous Area, Chukotka, and the Yamal Nenets Autonomous Area). This is probably due to several reasons including soil degradation due to permafrost transformation and thawing followed by destruction of house footings and civil engineering infrastructure; greater areas where blood-sucking arthropods occur; violated balance between local ecosystems; some other reasons for growing population incidence and mortality [8]. Besides, the highest amplitudes were established in Magadan region over 2010–2019 regarding average monthly precipitation in January and July (47 and 96 mm); and there was one of the highest amplitudes of average monthly temperature in January (10.6 ºC) in the region. This indicates there were drastic differences in weather and climatic conditions over the analyzed decade. Such changes can produce negative effects on human health as they exacerbate chronic diseases, create additional burden on adaptation systems in the human body and make socioeconomic conditions worse.

Table 2

Assessment of probabilistic influence exerted by weather and climate on LEB in 2010–2019

RF region	Climate	LEB in 2019 in a given RF region, years	Actual change in LEB over 2010–2019, days (years)	Influence by weather and climate and its contribution to change in LEB over 2010–2019, days (%)
Krasnoyarsk region (the northern part)	Arctic and sub-Arctic	69.8	821.3 (2.3)	49.0 (5.9)
Nenets AA	Arctic and sub-Arctic	73.2	3 019.0 (8.3)	-211.0 (-7.0)
Yakutia (the northern part)	Arctic and sub-Arctic	73.0	2 281.0 (6.3)	111.0 (4.9)
Chukotka	Arctic and sub-Arctic	68.1	3 869.0 (10.6)	-109.0 (-2.8)
Yamal Nenets AA (the northern part)	Arctic and sub-Arctic	74.2	1 507.0 (4.1)	-8.0 (-0.5)
Magadan region (the continental part)	Sub-Arctic	69.7	1 675.0 (4.6)	-254.0 (-13.2)
Murmansk region (the northern part)	Sub-Arctic	71.8	1 212.0 (3.3)	13.0 (1.1)

Table 3

Indicators of negative effects in children exposed to adverse weather and climatic factors in the sub-Arctic zone

Indicator	The test group A, $\bar{X} \pm SEM$	The reference group A, $\bar{X} \pm SEM$	Authenticity of differences $p \leq 0.05$
Blood			
Erythrocytes, 10^{12}/dm^3	4.71 ± 0.06	4.41 ± 0.07	0.0001
Hemoglobin, g/dm^3	132.87 ± 1.72	132.71 ± 1.63	0.900
Leucocytes, 10^9/dm^3	6.68 ± 0.35	5.85 ± 0.38	0.0001
ESR, mm/hour	7.53 ± 0.65	4.35 ± 0.38	0.0001
Blood serum			
TTH, μIU/cm^3	3.45 ± 0.22	2.43 ± 0.23	0.0001
Free T4, pmol/dm^3	12.37 ± 0.29	13.76 ± 0.32	0.0001
Apo-B/ApoA1, g/dm^3	0.57 ± 0.027	0.45 ± 0.035	0.0001
Apo A1, g/dm^3	1.42 ± 0.03	1.69 ± 0.09	0.0001
Apo-B, g/dm^3	0.82 ± 0.03	0.72 ± 0.04	0.0001
Hydrocortisone, nmol/cm^3	241.59 ± 18.71	281.85 ± 31.89	0.040
Blood plasma			
Adrenaline, pg/cm^3	79.49 ± 2.01	69.55 ± 3.97	0.0001
Dopamine, pg/cm^3	58.44 ± 2.9	59.35 ± 3.91	0.710
Noradrenaline, pg/cm^3	383.99 ± 19.29	384.23 ± 24.22	0.990
Serotonin, ng/cm^3	99.18 ± 13.57	250.06 ± 29.05	0.0001

We assessed influence exerted by weather and climate on LEB on the territories in Krasnoyarsk region located in the Arctic and sub-Arctic zone. The assessment revealed that, in spite there was a certain decline in average monthly temperatures in January (from -23.2 ºC in 2010 to -24.8 ºC in 2019 in Norilsk) and a significant increase in average monthly temperatures in July (from 12.3 ºC to 17.2 ºC), the detected climatic trends resulted in a growth in LEB that equaled 49 days over the analyzed period (Table 2).

We assessed how weather and climate influenced children's health. The assessment revealed that children living in the sub-Arctic zone were exposed to adverse weather and climatic factors (the NEET index being lower by 4.3 times and daily drops in atmospheric pressure being by 2.4 times higher and with a greater amplitude), which were absent on the reference territory (with moderate continental climate).

The children from the test group A had statistically significant changes in blood indicators under exposure to the analyzed adverse weather and climatic factors. Levels of leucocytes and ESR in blood were by 1.7 times higher in them than in the children from the reference group A (Table 3). This may indicate developing inflammatory reactions, first of all, in the upper airways.

We discovered strain in the thyroid function indicated by 1.4 times higher TTH levels in blood serum against the same indicator in the reference group A (p = 0.0001). According to data available in peer-reviewed sources, levels of thyroid hormones in blood tend to grow under exposure to low air temperatures and especially to drops in them. These hormones facilitate compensatory tolerance to effects produced by low temperatures due to growing oxygen consumption and greater heat production [14, 15]. Long-term strain in the thyroid function can disrupt ventricle relaxation and induce supraventricular arrhythmia, elevated blood pressure and a further cascade of pathological processes that ultimately lead to vascular disorders [21].

We comparatively assessed certain indicators of the lipid spectrum in the children from the test group A and the reference group A. As a result, we revealed that *Apo A1* levels were by 1.2 times lower and *Apo-B* and *Apo-B/ApoA1* levels were by 1.3 times higher in blood serum in the test group A (p = 0.0001). This can be considered a risk of early developing vascular disorders. Detected changes in apolipoproteins are confirmed by the results of proteome profile analysis, which allow assuming probable negative effects concerning endothelial dysfunction. We established changes in apolipoprotein A1

(*APOA1* gene), apolipoprotein C-II (*APOC2* gene), apolipoprotein C-III (*APOC3* gene), amyloid protein A-1 (*SAA1* gene), and P2Y purinoceptor 12 (*P2RY12* gene).

Atherosclerotic changes in vessels develop from early endothelial dysfunction to atherosclerotic plagues. These processes involve cardiac muscle hypoxia and production of pro-inflammatory cytokines that induce local arrhythmogenic activity. The latter develops with participating disorders of the sympathoadrenal regulation [22]. Given that, we should mention rather alerting changes in certain hormones and neuromediators. They indicate that the sympathoadrenal system has been deregulated. Thus, the children in the test group A had by 1.2–2.5 times lower levels of hydrocortisone and serotonin (p = 0.0001–0.040) together with elevated adrenaline contents in blood (p = 0.0001) against their counterparts from the reference group A. Low hydrocortisone correlates with impaired central regulation of corticotrophin-releasing factor production. This regulation is performed by the limbic system of the brain linked with production of neurotransmitters, serotonin included [23]. Imbalance between catecholamines and serotonin secretion in blood under exposure to adverse climatic factors is probably a sign that the protective and adaptive functions of the body have been impaired. This makes for lower resistance to hyperthermia and hypoxia as well as deteriorated endogenous vasomotion in the cardiac muscle tissues and impaired metabolism of cardiomyocytes [24].

The next step was to perform comparative analysis of chemical contents in blood under aerogenic exposure to chemical factors (copper, nickel, aluminum, and gaseous fluorides in concentrations from 0.005 mg/m^3 to 0.02 mg/m^3 or from 1.5 to 7.5 $MPC_{av.daily}$). We established that the exposed children had elevated copper and nickel concentrations in blood and aluminum and fluoride-ion in urine that were by 1.2–3.0 times higher and by 2.5–4.0 times higher accordingly than the same indicators in the non-exposed children and by 3.5–6.0 times higher than the reference levels. Elevated contents of toxic chemicals in biological media can result in a wider range and more apparent negative health outcomes in exposed children. We identified a set of indicators with their deviation clearly showing that negative effects were developing as a response to combined exposure to chemical and adverse climatic factors. These effects included sensitization of the upper and lower airways (eosinophils being by 1.2 times higher in nasal secretion and elevated total IgG in blood); impaired balance of neuromediators (acetylcholine being lower by 1.2 times and serotonin being by 1.9 times higher in blood serum); changes in the humoral immunity (lower *IgA*, *IgM* levels in blood); disrupted recovery of damaged neuronal structures (neurotropin-3 being by 1.3 times higher in blood serum) (Table 4).

The established changes occur in biochemical indicators that characterize developing negative effects in target organs, namely, the endocrine, nervous and circulatory systems. These changes are actually confirmed by elevated frequency of developing relevant diseases. Thus, the children who live under combined exposure to chemical and adverse weather and climatic factors suffer from respiratory diseases (hypertrophy of tonsils, chronic rhinitis) by 1.7 times more frequently than their counterparts from the reference group (p = 0.010–0.024); circulatory diseases (sick sinus syndrome), by 5.6 times more frequently (p = 0.0001–0.007); diseases of the nervous system (functional disorders), by 2.6 times more frequently (p = 0.031); diseases of the endocrine system (other disorders of thyroid), by 1.2 times more frequently (p = 0.033) (Table 5).

We established rather alerting frequency of thyroid diseases (5.9 %) and cardiomyopathy (5.9 %) in the children from the test group B whereas the children from the test group A did not have these diseases at all (p = 0.010). The data on frequency of certain diseases in the examined children are consistent with the results of foreign and Russian studies indicating that adverse climate and chemical factors contribute to developing respiratory and neuroendocrine diseases. A share contribution made by chemical factors to associated respiratory diseases reached 31.0 %; diseases of the nervous system, 25 %. A contribution made by adverse weather and climatic factors to associated respiratory diseases and diseases of the nervous system equaled 12 % and 10 % accordingly.

Table 4

Indicators of negative effects in children under combined exposure to adverse weather and climatic factors in the sub-Arctic zone and aerogenic chemical factors

Indicator	Average group value, $\bar{X} \pm SEM$		Authenticity of inter-group differences, $p \leq 0.05$
	The test group B	The test group A	
Nasal secretion			
Eosinophilic index, %	1.890 ± 0.426	2.001 ± 0.682	0.789
Neutrophils, units in field of view	22.806 ± 1.621	21.956 ± 2.753	0.602
Eosinophils, units in field of view	5.931 ± 1.874	5.112 ± 1.029	0.046
Blood			
Hemoglobin, g/dm^3	133.27 ± 1.36	132.87 ± 1.72	0.721
Erythrocytes, 10^{12}/dm^3	4.77 ± 0.05	4.71 ± 0.06	0.127
Leucocytes, 10^9/dm^3	6.28 ± 0.32	6.68 ± 0.35	0.104
ESR, mm/hour	5.79 ± 0.82	7.53 ± 0.65	0.002
Blood serum			
Total IgE, IU/cm^3	106.92 ± 29.45	100.60 ± 18.724	0.039
Neurotropin-3, pg/cm^3	8.39 ± 1.26	6.74 ± 1.05	0.048
Acetylcholine, pg/cm^3	28.18 ± 1.33	33.02 ± 2.09	0.0001
IgG, g/dm^3	10.23 ± 0.22	11.39 ± 0.38	0.0001
IgM, g/dm^3	1.39 ± 0.04	1.49 ± 0.06	0.011
IgA, g/dm^3	1.22 ± 0.05	1.34 ± 0.08	0.022
ApoB/ApoA1, g/dm^3	0.59 ± 0.03	0.57 ± 0.03	0.191
Apolipoprotein A1, g/dm^3	1.61 ± 0.09	1.42 ± 0.03	0.0001
Apolipoprotein B-100, g/dm^3	0.89 ± 0.03	0.82 ± 0.03	0.001
Free T4, pmol/dm^3	13.43 ± 0.16	12.42 ± 0.36	0.095
TTH, μIU/cm^3	2.93 ± 0.15	3.20 ± 0.25	0.069
Hydrocortisone, nmol/cm^3	277.28 ± 20.60	241.59 ± 18.71	0.141
Blood plasma			
Dopamine, pg/cm^3	62.35 ± 2.01	58.44 ± 2.94	0.034
Noradrenaline, pg/cm^3	389.46 ± 12.75	383.99 ± 19.29	0.637
Adrenaline, pg/cm^3	77.49 ± 1.54	79.49 ± 2.01	0.122
Serotonin, ng/cm^3	185.24 ± 14.88	99.18 ± 13.57	0.0001

Table 5

Frequency of diseases in the groups: comparative analysis, %

Category of diseases / Nosology (ICD-10)	Frequency in the test groups, %		Authenticity of inter-group differences ($p \leq 0.05$)
	The test group B	The test group A	
Diseases of the respiratory system (J00–J99), including:	59.2	44.9	0.010
- hypertrophy of tonsils (J35.1)	24.8	14.7	0.024
- chronic rhinitis (J31.0)	19.3	8.7	0.003
Diseases of the circulatory system (I00–I99), including:	18.8	5.5	0.0001
- cardiac murmur, unspecified (R01.0)	5.9	0.0	0.010
- sick sinus syndrome (I49.5)	10.1	1.8	0.007
Endocrine diseases (E00–E920), including:	53.7	44.95	0.033
- other disorders of thyroid (E07)	5.9	0.0	0.010
Functional disorders of the CNS and ANS including: - autonomic dysfunction (G90.8); - asthenoneurotic syndrome (G93.8)	11.9	4.6	0.031

Conclusions:

1. Over 2010–2019 average monthly air temperatures grew by 3.4 % on average (within a range from 0.3 to 5.9 %) on the analyzed territories in the RF regions located in the Arctic and sub-Arctic zones. Average monthly precipitation grew by 15.1 % and 13.0 % in July and January accordingly. Average monthly temperatures in January and July grew by 4.5 % and 1.9 % accordingly on the territories located

predominantly in the sub-Arctic climatic zone (Murmansk and Magadan regions). On the mixed-type territories (located in both Arctic and sub-Arctic zones), these temperatures grew by 2.1 % and 4.2 % accordingly. Air temperatures in July and January deviated from average long-term values towards growth by 1.2 ºC and 1.9 ºC accordingly. Overall, the detected changes, namely, growing average monthly temperatures and precipitations as well as their average annual deviations are well in line with the current climatic theory on global warming.

2. We established losses in LEB due to weather and climate on the analyzed territories against the background influence exerted by a set of social-hygienic determinants within a range from 349 days (Chukotka) to 164 days (Yakutia). The greatest losses were detected in Chukotka and Magadan region (349 and 346 days accordingly)

3. Climate warming detected over the last decade in the Arctic and sub-Arctic zones has resulted in variable effects produced by weather and climate on LEB. The greatest positive effects are detected in Yakutia (the northern part) where LEB has grown by 111 days and Krasnoyarsk region (the northern part), growth by 49 days. The greatest negative effects are detected in Magadan region where LEB has declined by 254 days

4. The established effects produced by weather and climate on human health are in line with the current estimates given by experts from the governmental and international organizations. The experts believe these effects to be rather ambiguous given the future prospects in global warming development. This requires further research aimed at establishing multiple effects produced by weather, climatic and meteorological factors on the medical-demographic situation including that existing on the arctic territories in the Russian Federation.

5. Long-term combined exposure to aerogenic chemical and adverse weather and climate factors has resulted in negative health outcomes in children aged 3–6 years. We established changes in biochemical and clinical indicators that characterized these effects. They included strain in the thyroid function, developing inflammatory processes, a risk of early vascular disorder, impaired endogenous vasomotion in the cardiac muscle tissues and neuroendocrine regulation. These negative effects were confirmed by elevated prevalence of respiratory lymphoproliferative diseases, functional disorders of the nervous, endocrine and circulatory systems. It was by 5.6 times higher than in the reference group. A contribution made by chemical factors to respiratory diseases and diseases of the nervous system equaled 25–31 %; a contribution made by adverse weather and climatic factors was 10–12 %.

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Research article

ASSESSING HEALTH RISKS CAUSED BY EXPOSURE TO CLIMATIC FACTORS FOR PEOPLE LIVING IN THE FAR NORTH

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Extreme climatic conditions in the Far North region create health risks for people living there. Given the necessity to adapt to these conditions, it seems vital to assess health risks caused by exposure to extreme climatic factors. Such an assessment will give an opportunity to establish and quantify influence exerted by climatic factors on public health.

The task was to assess risk rates for adults and children living in the Far North region in Russia. To do that, we analyzed the "exposure – effect" relationship for previously established climatic factors (atmospheric pressure and atmospheric air temperature, air humidity, and wind speed (as an index of the normal equivalent-effective temperature – NEET). Additional likelihood of incidence associated with exposure to climatic factors and occurring risk rates were calculated and then characterized based on the results of the analysis using mathematical modeling techniques.

As a result, we identified parameters of a cause-effect relation between average monthly NEET, daily pressure drops and incidence among population living in the Far North. We established unacceptable health risks for adults caused by diseases of the circulatory system that were associated with effects produced by NEET and atmospheric pressure, diseases of the respiratory system, injury, poisoning and certain other consequences of external causes associated with effects produced by NEET. We also established unacceptable health risks for children caused by diseases of the respiratory system, injury, poisoning and certain other consequences of external causes associated with effects produced by NEET. The results produced by this study can provide a guideline for developing activities aimed at facilitating adaptation to the existing climatic conditions in order to preserve public health.

Keywords: *risk assessment, climatic factors, risk characteristic, analysis of the "exposure – effect" relationship, atmospheric pressure, NEET index, adaptation, climate change, public health.*

The RF President Order issued on December 17, 2009 No. 861-rp "On the Climatic Doctrine of the Russian Federation" identifies certain negative outcomes caused by expected climate change; elevated public health risks (growing mortality and morbidity) are among them[1]. Given that, a priority task within the climate policy is to develop and implement activities that facilitate adaptation to occurring climate change [1–3]. To do that, a national action plan on adaptation to climate change was developed in the country. It was approved

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[1] O Klimaticheskoi doktrine Rossiiskoi Federatsii: Rasporyazhenie Prezidenta Rossiiskoi Federatsii ot 17.12.2009 № 861-rp [On the Climatic Doctrine of the Russian Federation: The RF President Order issued on December 17, 2009 No. 861-rp]. *The RF Government*. Available at: http://government.ru/docs/all/70631/ (May 20, 2022) (in Russian).

by the RF Government Order issued on December 25, 2019 No. 3183-r[2]. Risk assessment is a most significant component in developing and planning actions that facilitate adaptation to climate change. Use of it makes it possible to quantify and predict outcomes for public health caused by exposure to climatic factors [4, 5].

Extreme natural and climatic factors are quite typical for the Far North regions. They create health risks for people living there. These factors include low atmospheric air temperatures that persist over a long period, drastic atmospheric air pressure drops with high amplitudes, high air humidity, squalls, etc. [6–9]. Effects produced by them make for greater functional strains of specific organs and systems, reduce biological stability of the body and lead to changes in those organs and systems where adaptation resources are engaged most intensely and adaptive restructuring is the most obvious [10, 11]. All this creates health risks for adults and children living in the Far North. At the same time, climate change is developing significantly faster in this region than anywhere else on the planet [12, 13]. Given that, when people have to adapt to the existing conditions, it is vital to assess health risks caused by exposure to climatic factors. Such an assessment allows quantifying effects produced on public health by climatic factors, establishing and estimating comparative significance of the existing threats for public health.

Previously, we identified hazards for health and established that it was advisable to use the normal equivalent effective temperature (NEET) index and daily atmospheric pressure drops as key indicators for estimating effects produced by climatic factors on health of people living in the Far North. These selected factors have predominantly complex effects and this gives an opportunity to comprehensively assess their influence on public health without overestimating occurring health risks. We established that the selected key indicators had authentic cause-effect relations with diseases of the respiratory system (J00–J99), diseases of the circulatory system (I00–I99), endocrine, nutritional and metabolic diseases (E00–E90), mental and behavioral disorders (F00–F99), as well as injury, poisoning and certain other consequences of external causes (S00–T98) [7, 10].

Our research goal was to calculate and assess risk rates associated with effects produced by atmospheric pressure (daily drops) and atmospheric air temperature, air humidity and wind speed (NEET index) for adults and children living in the Far North.

Materials and methods. We calculated and assessed public health risks associated with atmospheric pressure (daily drops) and atmospheric air temperature, air humidity and wind speed (NEET index) that were previously established as key indicators at the hazard identification stage [7, 10]. Calculations and assessment covered both adults and children living in a large industrial city located beyond the Polar Circle (69 degrees north latitude).

To achieve our goal, we analyzed the "exposure – effect" relationship for the examined climatic factors. The analysis results gave grounds for calculating additional likelihood of incidence associated with effects produced by climatic factors. The calculations were performed by using mathematical modeling techniques and their results were used as a basis for calculating risk rates. These risks rates were a product of additional likelihood of incidence associ-

[2] Ob utverzhdenii natsional'nogo plana meropriyatii pervogo etapa adaptatsii k izmeneniyam klimata na period do 2022 goda: Rasporyazhenie Pravitel'stva RF ot 25.12.2019 № 3183-r (red. ot 17.08.2021) [On approval of the national action plan at the first stage of adaptation to climate change for the period up to 2022: The RF Government Order issued on December 25, 2019 No. 3183-r (last edited on August 17, 2021)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_342408/f62ee45faefd8e2a11d6d88941ac66824f848bc2/ (May 20, 2022) (in Russian).

ated with exposure to climatic factors multiplied by weighted average severity of diseases used as health outcomes in exposed population.

The stage when the "exposure – effect" relationship was estimated involved establishing quantitative associations between exposure to climatic factors (atmospheric pressure and atmospheric air temperature, air humidity and wind speed (as the NEET index)) and categories of diseases that were previously determined at the hazard identification stage (diseases of the respiratory system (J00–J99), endocrine, nutritional and metabolic diseases (E00–E90), diseases of the circulatory system (I00–I99), injury, poisoning and certain other consequences of external causes (S00–T98), mental and behavioral disorders (F00–F99)). We additionally specified nosologies that could be used as health outcomes when assessing effects produced by the analyzed climatic factors within previously established categories of diseases. To do that, we analyzed more than 100 literature sources that included up-to-date research works covering results produced by both fundamental and applied studies. All they were found in universally recognized citation databases (Google Scholar, Web of Science, Scopus, NCBI PubMed etc.) and were considered relevant for the subject of this study. We also used the methodical guidelines "Assessment of risks and damage caused by climate change that influences growing mortality and morbidity in high-risk population groups"[3] to specify relevant nosologies.

We analyzed data available in research works and established exposure levels regarding the NEET index and the atmospheric air pressure (daily drops) that would not probably lead to the established health outcomes in exposed population.

We calculated additional likelihood of incidence among adults and children to quantify risk rates associated with effects produced by atmospheric air pressure and atmospheric air temperature, air humidity and wind speed (as the NEET index). The calculation was based on a system of parameterized relationships between average monthly incidence among population due to the aforementioned causes and an average monthly NEET and a number of days with daily pressure drops exceeding the established no-effect exposure (that did not produce any unfavorable effects as established at the stage of estimating the "exposure – effect" relationship) per month.

We took our initial data on climatic parameters from databases with the results produced by observations at meteorological stations located in the analyzed region over the period from January 01, 2014 to December 31, 2018 (daily averaging): atmospheric air pressure (inter-daily drops) at the level at which a station was located (GPa), atmospheric air temperature (°C), relative air humidity (%), and wind speed (m/sec). Based on these data, we calculated average monthly indexes of the normal equivalent effective temperature (NEET) [14, 15].

Initial data on incidence were taken from databases provided by the Fund for Mandatory Medical Insurance. We used data on a number of insured people who lived on the analyzed territory and applied for medical assistance there over 2014–2018. The data were taken as per age groups (adults and children) and as per specific nosologies falling within several categories of diseases including diseases of the respiratory and circulatory systems, injury, poisoning, and certain other consequences of external causes. Relative incidence rates (per 1000 people).

[3] MR 2.1.10.0057-12. Otsenka riska i ushcherba ot klimaticheskikh izmenenii, vliyayushchikh na povyshenie urovnya zabolevaemosti i smertnosti v gruppakh naseleniya povyshennogo riska [Assessment of risks and damage caused by climate change that influences growing mortality and morbidity in high-risk population groups: methodical guidelines]. Moscow, Rospotrebnadzor's Federal Center for Hygiene and Epidemiology, 2012, 48 p. (in Russian).

Table 1

Formulas for modeling cause-effect relations between the NEET, atmospheric pressure and incidence among population

№	Formula	Designation
1	$Y^j = a_0{}^j + \sum_i a_1{}^{ij} X^{ij}$	Y^j is relative incidence or mortality among population due to the *j*-th cause, cases per 1000 people; $a_0{}^j$, $a_1{}^{ij}$ are the model coefficients; X^{ij} is the *i*-th factor influencing the *j*-th health outcome
2	$\Delta Y^{ij} = a_1{}^{ij}(X^{ij} - X_N^{ij})$	ΔY^{ij} is additional incidence or mortality among population due to the *j*-th cause associated with exposure to the *i*-th factor, causes per 1000 people; $a_1{}^{ij}$ is the model coefficient; $X_N{}^{ij}$ is a value of a factor that would not probably cause adverse health outcomes in a person exposed to this factor
3	$P^j = 1-(1-1/1000)^{Y^j}$	P^j is likelihood of a disease due to the *j*-th cause during a calendar year
4	$\Delta P^{ij} = P^j(X^{ij}) - P^j(X_N{}^{ij})$	ΔP^{ij} is additional likelihood of a disease due to the *j*-th cause associated with exposure to the *i*-th factor

were calculated based on the absolute number of cases by dividing this absolute number by the number of insured people and multiplying by 1000

Cause-effects relations between the NEET, atmospheric air pressure and incidence among population were modeled by using mathematical statistics methods. All the models were tested to check statistical significance of the established relations ($p < 0.05$) and to perform expert estimates of their conformity with biomedical concepts.

An overview of cause-effects relations is given with a linear multiple regression model (Table 1, Formula 1). Incidence associated with exposure to the analyzed climatic factors was calculated as a difference between estimates obtained with an actual value of a factor and a value of a factor that would not probably cause any adverse health outcomes in an exposed person (Table 1, Formula 2). Likelihood of a disease during a year was calculated based on the obtained data (Table 1, Formula 3). Additional likelihood of a disease associated with exposure to effects produced by atmospheric pressure and NEET was determined as a difference between estimates of incidence calculated with an actual value of a factor and a value of a factor that would not probably cause any adverse health outcomes in an exposed person (Table 1, Formula 4).

Risk rates were calculated as a product of additional likelihood of incidence associated with exposure to climatic factors multiplied by weighted average severity of diseases as per their categories that were applied in the formulas as health outcomes. Severity of diseases was determined in accordance with the “WHO methods and data sources for global burden of disease estimates 2000–2019” and was measured as a dimensionless coefficient with its value falling within the range from 0 to 1[4].

Results and discussion. We analyzed relevant research data to estimate the “exposure – effect” relationship. As a result, we established that atmospheric air pressure or, to be exact, such a parameter of the factor as daily drops produced adverse effects on the circulatory system. These effects induce

[4] WHO methods and data sources for global burden of disease estimates 2000–2019: Global Health Estimates Technical Paper WHO/DDI/DNA/GHE/2020.3. Geneva, WHO, 2020, 47 p.

functional disorders of the cardiovascular system (including changes in blood pressure, vascular crises and internal hemorrhages etc.) [16–18]. According to data obtained by several relevant foreign studies, daily drops in atmospheric air pressure that equal 7.5 mm Hg can lead to acute cardiovascular diseases including acute myocardial infarction, subarachnoid hemorrhage, hypertensive crises, acute cerebrovascular accidents, acute coronary diseases etc. [19–21]. Therefore, we established that atmospheric air pressure as a specific climatic factor produced certain effects on the cardiovascular system and it was advisable to link it to acute cardiovascular diseases as health outcomes (effects) occurring due to exposure to it. These diseases include essential (primary) hypertension (I10), hypertensive heart disease (I11), angina pectoris (I20), acute myocardial infarction (I21), subarachnoid hemorrhage (I60), and stroke, not specified as hemorrhage or infarction (I64). These effects are the most likely to occur when daily drops in atmospheric air pressure are equal to 7.5 mm Hg or more. Given that, it is advisable to use this value as an exposure level, which does not probably produce harmful effects on public health that are associated with exposure to this factor. Averaging over five years completed, we established that a number of days with inter-daily drops in atmospheric air pressure being equal to 7.5 mm Hg or more amounted to 80.4 days per year.

The identified nosologies have been established to be more typical for adult population [19–23]; therefore, further calculations and identification of risk rates associated with exposure to atmospheric air pressure as an influencing climatic factor will be performed exclusively for adults living on the analyzed territory.

Having analyzed relevant data available in literature, we established that a range from 17.0 to 22.0 °C was considered comfortable for the NEET index. Any temperature that is beyond this range imposes stricter demands to thermoregulation mechanisms [3, 8]. Given that, an air temperature of 17 °C can be applied as an exposure level that does not probably produce any harmful effects on public health associated with exposure to this factor. The NEET index value did not exceed this level on the analyzed territory over the examined period.

We made a more precise list of nosologies within the previously identified categories that would probably be the most climate-sensitive health outcomes caused by effects of the NEET. It is advisable to use acute respiratory infections (J00–J22) and chronic lower respiratory diseases (J40–J44) as health outcomes associated with exposure to the NEET within the category that comprises diseases of the respiratory system; diabetes mellitus (E10–E14), with the category of endocrine, nutritional and metabolic diseases; hypertensive diseases (I10–I15) and ischemic heart diseases (I20–I25), within the category comprising diseases of the circulatory system; mental and behavioral disorders due to use of alcohol (F10), neurotic, stress-related and somatoform disorders (F40–F48), behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F90–F98), within the category of mental and behavioral disorders; frostbites, within the category covering injuries, poisoning and certain other consequences of external causes (T33–T35) [24–35].

Table 2 provides the results produced by correlation and regression analysis (a_0, a_1 are the model parameters, R^2 is the determination coefficient). We selected only statistically significant correlations ($p < 0.05$). A negative value of the coefficient a_1 means that the related incidence grows as the NEET value decreases.

The accomplished calculations made it possible to establish that additional probable incidence regarding diseases of the circulatory system amounted to $1.1 \cdot 10^{-2}$ among adults living in a large industrial city located beyond the Polar Circle. A health risk caused by diseases of the circulatory system was equal to $6.33 \cdot 10^{-3}$.

Table 2

Parameters of statistically significant linear regression models ($p < 0.05$)

Category of diseases as per ICD-10	Risk factor	a_0	a_1	R^2
Diseases of the circulatory system (I00–I99)	Atmospheric air pressure drops	93.23	0.205	0.04
Diseases of the respiratory system (J00–J99)	NEET	308.230	-7.808	0.3
Diseases of the circulatory system (I00–I99)		103.651	-1.051	0.2
Injuries, poisoning and certain other consequences of external causes (S00–T98)		0.72	-0.078	0.59

Table 3

Risk rates for children and adults associated with exposure to the NEET

Category (ICD-10)	Age	Additional likelihood of diseases	Risk rate
Diseases of the respiratory system	Children	$3.91 \cdot 10^{-1}$	$4.70 \cdot 10^{-2}$
Injury and poisoning		$7.06 \cdot 10^{-4}$	$2.63 \cdot 10^{-4}$
Diseases of the respiratory system	Adults	$1.56 \cdot 10^{-1}$	$3.34 \cdot 10^{-2}$
Diseases of the circulatory system		$2.51 \cdot 10^{-2}$	$1.45 \cdot 10^{-2}$
Injury and poisoning		$9.59 \cdot 10^{-4}$	$4.24 \cdot 10^{-4}$

Table 3 provides the results produced by calculating risk rates for adults and children associated with exposure to air temperature, humidity and wind speed (as the NEET index).

The calculations revealed that additional likelihood of respiratory diseases associated with effects produced by the NEET amounted to $3.91 \cdot 10^{-1}$ for children and $1.56 \cdot 10^{-1}$ for adults; additional likelihood of circulatory diseases, $2.51 \cdot 10^{-2}$; for adults; additional likelihood of injury and poisoning (frostbite), $7.06 \cdot 10^{-4}$ for children and $9.59 \cdot 10^{-4}$ for adults. The calculated health risk caused by diseases of the respiratory system amounted to $4.7 \cdot 10^{-2}$ for children and $3.34 \cdot 10^{-2}$ for adults; diseases of the circulatory system, $1.45 \cdot 10^{-2}$ for adults; injury, poisoning and certain other consequences of external causes (frostbite), $2.63 \cdot 10^{-4}$ for children and $4.24 \cdot 10^{-4}$ for adults.

The following classification was applied to characterize the calculated risk rates:

1) $1.0 \cdot 10^{-6}$ or below, minimal risk;

2) $1.1 \cdot 10^{-6}$–$1.0 \cdot 10^{-4}$, permissible (acceptable) risk;

3) $1.1 \cdot 10^{-4}$–$1.0 \cdot 10^{-3}$, alerting risk;

4) $> 10^{-3}$, high risk.

Alerting and high risks are characterized as unacceptable; in case such risk rates are identified, it is advisable to develop certain actions aimed at preventing health disorders and preserving public health. Such actions should always concern those organs and systems for which these unacceptable risk rates have been identified.

According to the suggested classification, we established unacceptable health risks for adults living in a large industrial city located beyond the Polar Circle. These health risks were caused by diseases of the circulatory system associated with effects produced by the NEET and atmospheric air pressure as well as diseases of the respiratory systems, injury, poisoning and certain other consequences of external causes that were associated with exposure to the NEET. We established unacceptable health risks for children caused by diseases of the respiratory system, injury, poisoning and certain other consequences of external causes that were associated with exposure to the NEET.

Conclusion. We estimated the "exposure – effect" relationship by analyzing relevant data available in research works and established certain exposure levels for the analyzed climatic factors that would produce certain harmful effects associated with exposure to them on public health. Thus, it is advisable to use an average monthly NEET value equal to 17 °C and lower and inter-daily atmospheric air pressure drops equal to 7.5 mm Hg and more as exposure levels that would certainly lead to negative health outcomes in exposed population.

Having calculated and estimated risk rates for people living in the Far North, we established unacceptable health risks for adults caused by diseases of the circulatory system that were associated with exposure to the NEET and atmospheric air pressure ($1.45 \cdot 10^{-2}$ and $6.33 \cdot 10^{-3}$ accordingly); diseases of the respiratory system ($3.34 \cdot 10^{-2}$) and injury, poisoning and certain other consequences of external causes that were associated with exposure to the NEET ($4.24 \cdot 10^{-4}$). We also established unacceptable health risks for children caused by diseases of the respiratory system ($4.70 \cdot 10^{-2}$) and injury, poisoning and certain other consequences of external causes ($2.63 \cdot 10^{-4}$) that were associated with exposure to the NEET.

These research results make it possible to predict negative health outcomes in people living in the Far North. These health outcomes occur under combined exposure to climatic factors (atmospheric air pressure (daily drops) and atmospheric air temperature, air humidity and wind speed (as the NEET index)). They can also serve as a guideline for developing actions aimed at facilitating adaptation to the existing conditions in order to preserve public health.

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Research article

PROBLEMATIC INTERNET USE AS YOUTH'S RISKY BEHAVIOR UNDER DISTANCE LEARNING DURING THE COVID-19 PANDEMIC

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We selected Problematic Internet Use (PIU) as our research object. PIU is a behavioral addiction or a type of addictive behavior that can have negative influence on users' emotional and social functioning. In our case, these users were students who had to learn distantly.

The aim of this pilot study was to estimate use of the Internet by students and associated risks by performing the validated screening (Problematic Internet Use – PIU). The first stage was accomplished under routine full-time education; the second stage took place during the COVID-19 pandemic under the forced lockdown in the spring term 2020.

Medical students who participated in this pilot study were asked to estimate how much time they spent using the Internet on their mobile devices or PC and to report risks associated with problematic Internet use, both under ordinary circumstances and under forced self-isolation during the COVID-19 pandemic. We applied Problematic and Risky Internet Use Screening – PRIUSS, Midwestern University, USA, both paper version and Google survey, to question the participants. Overall, 230 students took part at the first stage of the survey; one year after there were 90 students participating in the survey.

The research results show it is truly vital to examine risky behavior since it can pose certain threats for young students' health due to growing volumes and shares of information obtained from information network channels and Internet resources. In addition, we established an increasing share of risky behavior when using the Internet under restrictions associated with the COVID-19 pandemic. There was a substantial growth in the number of students exposed to the intensive Internet use. The scores as per the subscales "social disorders" and "emotional disorders" grew by 2.7 and 2.1 times accordingly. The score describing risky / impulsive Internet use went up from 7.8 to 16.3. All the differences were statistically significant ($p < 0.001$).

Keywords: *preventive medicine, distance learning, COVID-19, students, risks of Internet use, behavioral addictions, Internet use screening, public health.*

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At the end of the 20th century, some reports started to appear in research works about people with certain medical and social issues occurring due to their use of a PC or the Internet. Problematic Internet use (PIU) is usually defined as excessive or risky use of the Internet [1]. Multiple contemporary studies have noted that Internet use can evoke anxiety, attention deficit and hyperactivity disorder, hostility, aggression and depression. It can produce negative effects on academic progress; moreover, it can stimulate impairments in various aspects of a person's everyday life and create elevated behavioral health risks [1–3]. Excessive Internet use by young people often involves negative social consequences including poor progress in studies, stress and risky behaviors and attitudes towards health.

Young people are especially susceptible to a risk of developing addiction to the Internet or problematic Internet use as it was reported by 5–10 % of students [4–6].

Young people see the Internet, hardware and gadgets as habitual and comfortable parts of their lives. Youth lifestyles are shaped under influence exerted by network and mobile technologies. This concerns pastime, routine activities, habitual channels to get information from, ways to work with information resources, and the nature of interpersonal relations. Young students use the Internet to search for useful data, to view the latest news or ratings, to find job, to communicate with friends, to download music and watch movies or clips, to purchase something in online shops. The Internet has become the basic information source and the major communication tool for young people. On one hand, the Internet is a powerful information field with abundant resources (interactive sites, portals, electronic libraries, databases, web-classrooms and networks societies) and variable ways to present them (from a text to multimedia). It provides an opportunity to move freely and non-linearly in a hypertext space, to promptly find, process, enrich, store and redirect any information. On the other hand, there is redundancy and variability of materials that are renewed too fast; this accelerates information exchange, makes obtaining new knowledge much easier and enlarges data communications [7].

Use of social networking services (SNS) is a most popular activity in the Internet among young people. Excessive involvement in certain online activities such as gambling, watching porn, videogames, social networking, or online purchases can lead to serious issues and create elevated risks of chaotic or even addictive Internet use [8, 9]. The COVID-19 pandemic resulted in drastic changes in lifestyles, both worldwide and in Russia. Many countries had to introduce a lockdown to prevent the infection from spreading. A lot of people had to switch to remote work or studies and, accordingly, start using the Internet as a major communication tool. They were forced to replace real communication with network one and information and communication technologies thereby became much more significant for them [10–12]. Some studies have established that social networks can also be an important tool for providing social support during self-isolation [11, 13].

Contemporary Internet use provides wide opportunities to obtain necessary data, communicate in social networks, do shopping online, play games or trade anything. There are enough studies reporting about people who have certain issues associated with using a PC or the Internet due to addictive behavior regarding electronic devices. Problematic Internet use is a topical issue for public healthcare since it can produce negative effects on emotional and social functioning. The COVID-19 pandemic that started in 2019 influenced public health all over the world and largely exerted significant negative impacts on children and teenagers, Internet abuse being among their outcomes.

For most people, use of information and communication technologies remains within natural and physiological reactions. However, when use of social networking becomes too intense, this creates an elevated risk of additive behavior. A risk of becoming addicted is caused by the fact that Internet use by young people is often impulsive in its essence and leads to adverse outcomes, in particular, for physical health, emotional state, and social relationships.

Excessive Internet use has not been recognized as a health disorder by the World Health Organization so far and it is not included into the International Classification of Diseases (ICD-11). However, gaming disorder is included into the ICD-11 but experts are still arguing about how to diagnose it. Is this disorder a specific clinical case or is it just a sign of underlying mental disorders?

At the same time, results of multiple studies addressing early detection of Internet addiction have confirmed that there are available instruments for screening of issues related to Internet use [4, 8, 14, 15]. It has also been noted, that if such issues are detected early, this can motivate people to change their behavior [16].

Teenagers are vulnerable due to incomplete morphofucntional development of their organs and systems and elevated sensitivity to factors that influence them. Teenagers often have to face unpleasant aspects related to Internet technologies [4]. Digital media can create certain unique problems regarding problematic or excessive use and teenagers have rather specific psychological vulnerability [5]. Bearing this in mind, we assume that an effort to change one's behavior given excessive Internet use is a vital issue in studies with their focus on online behavior.

Situations with high health risks are mostly associated with a significant growth in Internet use. Thus, questioning results published by the PIU research center in 2015 indicated that 24 % of young people aged from 13 to 17 years had a constant Internet connection and 56 % connected to the Internet several times a day [17]. CIBERASTUR, a survey that was conducted in Spain and covered 25,000 teenagers aged 11–18 years, established that 95.7 % of its participants had a smartphone and 86.6 % of them used it every day.

In future, a procedure for assessing health risks for young people which we suggest in this study can be included into the system for social-hygienic monitoring.

Our goal in this pilot study was to assess Internet use by medical students with a Problematic Internet Use (PIU) screening tool.

Materials and methods. ***The study design.*** This study was accomplished in a medical higher educational institution over the period from November 2019 to November 2020 in two stages. The first stage in November 2019 involved filling in a paper version of the questionnaire; in November 2020 we had to use a Google survey due to self-isolation caused by the COVID-19 pandemic.

Research object and organization. The survey took place within the research work accomplished by the Children and Teenagers Hygiene Department at F.F. Erismann's Federal Research Center for Health. The research work was entitled "Provision of hygienic safety of the information and educational environment for students in digital economy". The survey was approved by the Local Ethical Committee at Sechenov University (the meeting report No. 34-20) and aimed at identifying whether students had any risky behavior regarding Internet use under routine conditions and under self-isolation. Participants were selected randomly out of students who attended the chosen medical HE institution. They were aged from 17 to 21 years. All the participating students did not have any financial or any other interest in taking part in the survey.

The survey procedure. We used PRIUSS as a validated tool for assessing problematic Internet use[1] in adolescents and young adults.

PRIUSS consists of 18 questions and has three sub-scales that make it possible to identify social impairments, emotional impairments and risky / impulsive use (six, five and seven questions for each sub-scale accordingly).

Social impairments are revealed by questions that enable estimating problems arising in online or personal communication, developing excessive anxiety due to probable negative estimates given by other members of the Internet society, inability to enter any real relation-

[1] Jelenchick L.A., Eickhoff J., Zhang C., Kraninger K., Christakis D.A., Moreno M.A. Screening for Adolescent Problematic Internet Use: Validation of the Problematic and Risky Internet Use Screening Scale (PRIUSS). *Acad. Pediatr.*, 2015, vol. 15, no. 6, pp. 658–665. DOI: 10.1016/j.acap.2015.07.001

ships due to predominant Internet use, as well as some other consequences of excessively enthusiastic network socializing, for example, failure to participate in important events or difficulties in interpersonal communications.

Emotional impairments are estimated by analyzing answers to questions about arising irritation, anger, anxiety, vulnerability, feeling oneself isolated from the world and friends in case it is impossible to get access to the Internet. Emotional vulnerability also covers a situation when a person thinks Internet use to be more important than his or her routine activities.

Risky / impulsive Internet use was identified in case certain negative trends in students' behavior were established due to positive answers to certain questions. For example, students stated they tried to avoid any other activity so that they could stay online; they neglected their direct responsibilities, lost motivation to fulfill important tasks and had sleeping disorders due to their wish to remain online, even at night. If time spent by a user in the Internet produces negative effects on his or her academic progress, this also indicates risky and excessive Internet use.

The respondents chose answers that described how they behaved and what they felt concerning Internet use over the last six months. Questions starting with "how often?" concerned variable online contacts, emotional state caused by Internet absence, motivation to go on living in case the Internet was absent etc. The students filled in the 18-score screening scale for problematic Internet use (PRIUSS); it was a paper version in November 2019 and a Google survey in November 2020 under self-isolation. The scale had scores from 0 to 72. If a result was equal to 25 scores or higher, a respondent was included into a risk group as per problematic Internet use.

Analysis. We applied ANOVA test to compare qualitative indicators and χ^2 test for nominal data (sex, age, and a share of the respondents with the final score higher than 25).

There could be shifts in final results due to differences in the structure of two respondents' groups. To eliminate them, we performed logistic regression analysis with problematic Internet use (the final score higher than 25) as a dependent variable and the number of survey, sex and age as covariants. The analysis was performed both as per the whole scale and three sub-scales, namely, social impairments, emotional impairments, risky / impulsive Internet use.

Statistical analysis was performed with SPSS Statistics 22.0 software package.

Results and discussion. Overall, 320 students took part in our pilot study; 230 participated in the first survey and 90 in the second one. Females prevailed in both groups since they accounted for 84.3 % in the first survey group and for 86.7 % in the second one, the overall share being 85.0 %. The first stage in the screening took part in November 2019 under routine full-time education; the second one was performed during the COVID-19 pandemic and the respondents estimated their Internet use (in November 2020) considering forced self-isolation during the lockdown which was introduced in the spring term in 2020.

There were no statistically significant sex-specific differences between the groups ($p = 0.601$).

There were age-specific differences between the groups. The second group was substantially younger since 37.8 % of the participants in it were aged 17–19 years whereas people of the same age accounted for only 5.7 % in the first group. On the contrary, people aged 23–25 years accounted for 5.6 % in the second group and for 17.4 % in the first one ($p < 0.001$).

The first survey revealed only 25.2 % of the respondents with their final score being higher than 25; that is each fourth respondent had a high health risk, namely, a risk of social and emotional impairments as well as risky / impulsive Internet use.

The share of people who had the final score higher than 25 grew to 93.3 % in the second survey. The difference was statistically significant, odds ratio (OR) was equal to 41.5; 95 % CI: 17.2–100.1; $p < 0.001$. Our comparison of the survey results showed that the average final score was significantly higher in the second survey, 40.5 against 19.3 in the first

one. Statistical significance was estimated with ANOVA test (one-factor dispersion analysis). Differences were considered significant at $p < 0.001$ (Table 1).

Obviously, results of the two surveys show there is a significant and authentic growth in a health risk for students caused by intensive Internet use.

We performed profound analysis of the results obtained for three screening sub-scales: social impairments, emotional impairments, risky / impulsive Internet use. Table 2 provides the results.

The mean score was higher as per all three scales in the second survey against the first one.

We established a growth as per the sub-scale "social impairments" that included first 6 questions and the sub-scale "emotional impairments" that included the next 6 questions: from 4.7 to 12.8 and from 6.6 to 11.3 accordingly. The score reflecting risky / impulsive Internet use grew from 7.8 to 16.3. All these differences were statistically significant ($p < 0.001$). The first survey revealed only 25.2 % of the respondents with their final score being higher than 25; that is each fourth respondent had health risks associated with problematic Internet use. The share of people who had the final score higher than 25 grew to 93.3 % in the second survey. The difference was statistically significant, odds ratio (OR) was equal to 41.5; 95 % CI: 17.2–100.1; $p < 0.001$.

There could be shifts in final results due to differences in the structure of two respondents' groups. To eliminate them, we performed logistic regression analysis with problematic Internet use (the final score higher than 25) as a dependent variable and the number of survey, sex and age as covariants (Table 3).

This logistic regression analysis revealed that a share of the respondents with their final score exceeding 25 had a statistically significant association only with the number of the survey (the first or the second one)

Table 1

Comparison of the results obtained by surveys 1 and 2 addressing problematic Internet use

Survey	*N*	Mean value	Standard deviation	Standard error of the mean	Median value
The first survey (1.0)	229	19.27	9.43	0.62	18.00
The second survey (2.0)	90	40.52	11.02	1.16	39.00
Total	319	25.27	13.76	0.77	23.00

Table 2

Analysis of mean scores as per the sub-scales (social impairments, emotional impairments, risky / impulsive Internet use)

Survey	Statistical indicators	Social impairments	Emotional impairments	Risky / impulsive Internet use
1.0	N	230	229	230
	Mean value	4.7	6.6	7.8
	Standard error of the mean	0.20	0.27	0.30
	Standard deviation	3.1	4.2	4.6
	Median value	4.00	6.00	7.00
2.0	N	90	90	90
	Mean value	12.8	11.3	16.3
	Standard error of the mean	0.45	0.52	0.56
	Standard deviation	4.2	5.0	5.3
	Median value	12.00	10.00	16.00
Total	N	320	319	320
	Mean value	7.0	7.9	10.2
	Standard error of the mean	0.28	0.27	0.34
	Standard deviation	5.0	4.9	6.1
	Median value	6.00	7.00	9.00

Table 3

Results of statistical analysis as per three variables: the survey number, age and sex

Variable	*p*	Adjusted odds ratio	95 % confidence interval for OR
Survey number	< 0.001	35.60	14.52–87.28
Sex	0.89	1.05	0.47– 2.33
Age	0.15	0.64	0.35–1.18

($p < 0.001$). Adjusted odds ratio amounted to 35.6 with 95 % CI: 14.5–87.3. We did not detect statistically significant influence exerted by sex or age ($p > 0.05$).

The results obtained by the regression analysis indicate that there was a substantial decline in the share of people who did not have any health risks associated with Internet use from the first survey to the second one.

Extensive Internet use for studying, work, communication and pastime is becoming one of major concerns in public healthcare. As excessive dependence on electronic technologies is growing, its impacts are more and more likely to lead to negative health outcomes. It was especially true at that time when the world society was fighting against the COVID-19 pandemic and had to reconstruct the online environment in the process to make it more suitable for remote work, study, social relations and entertainments [11]. Students found themselves in an unusual situation when they had to study remotely under self-isolation. On one hand, they were able to communicate with their friends by using electronic teaching and learning aids. On the other hand, self-isolation induced certain strain in their emotional sphere, led to greater loads on them and impaired their health. There was a national study that addressed issues related to studying and obtaining necessary information under self-isolation during the COVID-19 pandemic. It revealed that children who had to study remotely spent more time on doing their homework in comparison with traditional full-time education; children also had to spend more time working with electronic devices with a screen and this resulted in longer exposure to them and a growing number of health complaints [18]. A study performed in China aimed to determine peculiarities of Internet use during the COVID-19 pandemic. It also established increasing Internet use including both frequency and duration, especially when the Internet was used to relax. Long periods of Internet use also became much more frequent. The study showed that female sex, age, depression and stress had an authentic correlation with total scores of Internet addiction; it was also noted that prevalence of depression, anxiety and stress with variable intensity correlated authentically with groups of addicted Internet users, problematic Internet users and adequate Internet users [19, 20].

Our pilot study made it possible to estimate how frequently the Internet was used by medical students before self-isolation and under it. Prevalence of intense Internet use among students is consistent with data obtained by other authors. Recent studies have also established growing health risks caused by longer time spent on working with electronic devices, a significant decline in physical activity, as well as with probable developing addictive online behavior [9, 16, 19, 21].

Sex-specific differences seem quite interesting in relation to Internet addiction. Some research results indicate that both women and men can become “addicted” to technologies but men and women indulge in rather different online activities [4]. However, a share of men who are addicted to electronic technologies is often higher against women [16, 22, 23]. We did not detect any authentic effects produced by sex on problematic Internet use in this study.

We should remember that the issue is urgent. It is necessary to standardize the test we applied in this study and facilitate it for use in studies on Russian students as a specific population. This will give an opportunity to examine intense and problematic Internet use among students and to develop relevant programs aimed at correcting deviations.

Conclusion. The first stage in our study was performed among full-time medical students who used the Internet and social networks in a routine situation. As a result, only each fourth student turned out to have social and emotional impairments and his or her Internet use could be described as risky / impulsive thus indicating apparent problems related to this use. The picture changed drastically during the COVID-19 pandemic when students had to switch to distant learning. At the second stage, 93.3 % of the participating students were established to be problematic Internet users. The PRIUSS survey allowed establishing a growth in risky / impulsive Internet use and social impairments, by 2.1 and 2.7 times accordingly. Logistic regression analysis revealed that students' age or sex did not have any authentic effects on problematic Internet use whereas there was an authentic association between more apparent problematic Internet use and the number of the survey, namely, higher shares of problematic Internet use were detected in the second one that was performed under self-isolation during the COVID-19 pandemic.

Various health disorders that are caused by problematic Internet use are highly prevalent among students and they are detected easily with the PRIUSS tool. This allows recommending this screening tool to perform operative diagnostics of problems, to identify risk groups with people susceptible to problematic Internet use, and to develop relevant preventive programs.

Education can move to a new qualitative level under certain conditions that make for preservation and improvement of students' health and creation of new relevant approaches to managing health risks. Our research results indicate it is important to examine risky behavior that poses threats for students' health due to due to growing volumes and shares of information obtained from information network channels and Internet resources. Besides, such risky behavior becomes much more frequent when the Internet is used under restrictions associated with the COVID-19 pandemic. This may become a huge issue for public healthcare. Activities aimed at mitigating these health risks should rely on fundamental studies and opinions of experts in protection, preservation and improvements of children's, adolescents' and young adults' health. We have shown in our study that Internet use did not only become more intense in a complicated social situation (self-isolation during the pandemic) but also involved negative emotional experiences and was risky in its essence (the average final score grew by 3 times as per the sub-scales "social impairments", "emotional impairments" and "risky / impulsive Internet use" in the second survey). It is necessary to use and standardize "problematic Internet use" screening tool to make it more suitable for population studies. This will make it possible to accomplish studies on effective correction of problematic Internet use among students. It is necessary to prevent health risks, including those associated with exposure to electronic devices with a screen, both during a pandemic and in an epidemiologically safe situation.

Active Internet use is becoming quite usual both among adolescents and even children. Doctors who are responsible for primary healthcare should have available tools to perform early screening aimed at detecting problematic or risky Internet use (PRIUSS). Such screening can become another effective tool for monitoring of adolescents' health. Use of screening tools to identify an association between problematic (excessive) Internet use and health issues will make it possible to detect health disorders at their early stages and to develop strategies for mitigating health risks. This includes, among other things, prevention of secondary victimization in relation to Internet-risks and development of variable cyber-addictions. Resistance to problematic Internet use by youth will reduce possible dysfunctions related to social, emotional and risky / impulsive behavior that can result from problematic Internet use thereby improving quality of their lives.

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Research article

CHEMICAL AIR POLLUTION IN RESIDENTIAL PREMISES AS A HEALTH RISK FACTOR

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Up-to-date techniques applied in physical-chemical studies made it possible to identify and quantify chemical pollutants in the air inside contemporary residential premises in a large megacity and then create a database on them. This database has a list of more than 600 chemicals from 18 groups of volatile hydrocarbons and covers hygienic standards for their contents, their hazard category, and ranges of detected concentrations. Major sources of air pollution with these chemicals in residential premises were also identified. From the hygienic point of view, a significant fact is that there are no hygienic standards for more than 60 % of chemicals detected in air in residential premises. Formaldehyde, phenol, and styrene are priority chemicals for quality monitoring and risk-based control of hazards posed by chemical air pollution both in newly built houses that are at the approval stage and already exploited ones. Formaldehyde, benzene, phenol, styrene, acetophenone, ethylbenzene, hexanal, nonanal, butyl acetate, ethyl acetate, isopropanol, and trimethylbenzene are the most hygienically significant volatile organic compounds for quality control and health risk assessment considering frequency of their occurrence, concentration levels, concentrations exceeding MPC, group affiliation, hazard category, and ability to transform. When controlling natural chemicals that occur in air in residential premises due to some internal pollution sources, we should bear in mind that transformation may result in a new structure of pollution and new occurring chemicals can be more toxic and hazardous than original ones.

To minimize risks associated with exposure to chemical pollution and to assess chemical safety of air in residential premises, we recommend wider use of up-to-date physical and chemical methods for qualitative and quantitative analysis thereby securing identification of a wide range of pollutants including potentially hazardous ones. Since certain chemicals have been detected for which no safety criteria have been developed so far, it is especially vital to perform research in the sphere of hygienic standardization and to develop methodical documents aimed at providing adequate hygienic assessment of quality and chemical safety of internal environment in residential premises.

Keywords*: residential premises, air, chemical pollution, chromatography-mass spectrometric studies, environmental health risks.*

At present, the residential real estate market is developing quite actively in many regions throughout the country. Any type of housing, be it an individual low-rise house, an apartment or a room in a high-rise building, is not only a construction object but primarily an environment where people spend most of their lives. Given that, issues related to quality and hygienic safety of this environment are quite topical and significant [1–5].

A pressing issue the hygienic science has to resolve now is establishing regularities in how the environment in residential premises becomes qualitative and safe [6–8]. Chemical air pollution in residential premises is among the most significant risk factors for public health due to several reasons. Chemicals can be emitted into air simultaneously from several internal sources and air exchange in small rooms is rather weak and insufficient to attenuate pollution; chemicals persist in residential premises for a long time and chemical structure of this pollution is stable, and this gives certain priority to air in residential premises over other environments. Therefore, many experts believe residential premises to make a major contribu-

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tion to the total chemical burden on people associated with air pollution[1] [9–12].

Undoubtedly, ambient air is an external source of air pollution in residential premises. High levels of ambient air pollution can exert their influence on growing incidence of respiratory diseases, diseases of the central nervous system, cardiovascular system, blood system, and oncological pathologies [13–17]. Previous studies, both ours and accomplished by other experts, revealed more than 10 various internal sources of air pollution in residential premises, apart from ambient air as an external source. Primarily, these sources are construction and finishing materials made of polymer and polymer-containing components. House dust is another significant source of pollution since non-organic and organic chemicals are sorbed on its particles. These chemicals include street dust, particles of pets' skin and fur, particles of pets' food etc. Air pollution in residential premises can partially occur due to improper functioning of ventilation, sewage, and rubbish chutes; natural gas combustion contributes to it. Household washing powders, cleaners, polishes, glues, varnishes, paints, perfumes, cosmetics etc. also make a certain contribution. Results obtained by multiple studies confirm that indoor chemical air pollution is by 1.5–4.0 times higher than outdoor air pollution on the same territory [18–20].

There are so called "phenol buildings" described in literature; 50 years ago, the World Health Organization introduced a specific term "Sick Building Syndrome". This term comprises various health disorders that develop in people who have just moved into new residential buildings. These health disorders often become apparent through lower working capacity, variable allergic reactions, rapid fatigability, frequent headaches etc. [19–22]. "Sick Building Syndrome" probably occurs due to chemical air pollution inside buildings and, first of all, such pollutants as volatile organic compounds. Higher air tightness is considered the principal cause of "Sick Building Syndrome" since it reduces outdoor air supply; another important cause is more intense use of polymer and synthetic materials in construction as well as in decorating and furnishing. Some studies describe results obtained by profound biomedical examinations of people who live under long-term exposure to formaldehyde pollution inside their residential premises and provide substantiation for authentic mathematical models of a relationship between people's health and exposure to this chemical in the living environment [23].

Negative influence exerted by chemicals on human health is an indisputable fact and the necessity to search for sources of air pollution in residential premises and to examine than is just as obvious. Our present study concentrates exactly on this matter.

The research goal was to identify and quantify the maximum possible range of organic compounds that pollute air in residential premises; to reveal their sources; to determine the list of the most hygienically significant chemicals in order to minimize health risks and accomplish risk-based control over safety of the environment in residential premises.

Materials and methods. Air inside contemporary residential buildings was selected as a research object. We examined air inside 207 apartments located in high-rise apartment blocks, both typical and individually designed. We also examined air inside low-rise cottages and townhouses. The research design made it possible to obtain qualitative and quantitative description of chemical air pollution in different types of residential buildings in a large megacity.

Air samples for chemical analysis were taken in the center of a living room with all the windows closed and air conditioning switched off. Prior to air sampling, apartments had not been ventilated for 12 hours.

Volatile organic compounds were identified and quantified in air in residential premises by using chromato-mass-spectrometry. The sensitivity of the method is at the same level or below than the existing hygienic standards for contents of organic compounds

[1] Novikov S.M. Khimicheskoe zagryaznenie okruzhayushchei sredy: osnovy otsenki riska dlya zdorov'ya naseleniya [Chemical pollution of the environment: basic of health risk assessment]. Moscow, 2002, 24 p. (in Russian).

C_1–C_{20} in air with unidentified chemical pollution. The analysis was performed on a chromato-mass-spectrometry system manufactured by Thermo Fisher Scientific (USA) that included Focus GC gas chromatographer (USA) with electronic gas flow control, DSQ II mass spectrometric detector with quadrupole mass analyzer (a range of measured atomic mass numbers is from 1 to 1050), as well as ACEM 9300 thermal desorber with gas sample cryofocusing. We applied specific software package to collect and store mass spectra, to analyze measurement results, and to perform quantitative analysis. All the obtained results were compared with data taken from the NIST 08 Mass Spectral Library (more than 220 thousand spectra for more than 190 thousand chemical compounds).

Air samples were taken into sorption tubes on a polymer sorbent (Tenax TA, the granulation is 0.20–0.25 mm, the specific surface area is 35 m^2/g) with following thermal desorption. The results were statistically analyzed in Microsoft Excel. This article dwells on the averaged results of analytical replications. Data error does not exceed its allowable level ($M \leq 5$ %).

Formaldehyde was identified in air in residential premises by using our own high performance liquid chromatography (HP-LC) method in accordance with the methodical guidelines[2].

Heavy metals in their aerosol form were identified in air in residential premises by using a Beckman atomic-absorption spectrophotometer equipped with Massmann Cuvette and graphite tubes.

To assess hazards, the identified concentrations of chemicals were compared with average annual and average daily maximum permissible concentrations (MPC) established for ambient air in settlements. In case no such MPC were established for a specific chemical, we took maximum single MPC and tentatively safe exposure levels (TSEL)[3].

Results. Air inside each analyzed residential premises had a wide range of chemicals, namely, approximately 600 volatile organic compounds. Their qualitative and quantitative structure depended on purposes of a specific room and characteristics of internal pollution sources.

Air quality in enclosed spaces was established to depend on ambient air pollution regarding certain chemicals. Thus, concentrations of nitrogen oxides, carbon oxide and dust inside residential buildings corresponded to their concentrations in outdoor air, excluding situations when internal pollution sources were also present.

Lead, sulfur dioxide and ozone were identified in air in residential premises mostly in concentrations lower than in ambient air outdoors.

Overall, we identified 609 chemicals from 18 groups of volatile organic compounds in air in residential premises. Table 1 provides data on basic groups of volatile organic compounds identified in analyzed air and their major sources.

Concentrations of volatile organic compounds were higher in practically all samples taken in residential premises than in those taken outside. Contents of toluene, xylene, benzene, acetaldehyde, methyl ethyl benzene, propyl benzene, ethanol, ethyl acetate, acetone, phenol, and some saturated hydrocarbons (in particular, pentane, hexane, octane, and nonane) were higher inside buildings than in ambient air, the difference reaching 10 times or even higher.

Figure 1 shows typical group structure of organic compounds in air in residential premises as per their number in each group. Saturated, unsaturated, aromatic and cyclic hydro-

[2] MUK 4.1.1045-01. VEZhKh opredelenie formal'degida i predel'nykh al'degidov (S2–S10) v vozdukhe (utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii Pervym zamestitelem Ministra zdravookhraneniya Rossiiskoi Federatsii G.G. Onishchenko 5 iyunya 2001 g.) [The Methodical Guidelines MUK 4.1.1045-01. HP-LC to identify formaldehyde and saturated aldehydes (C_2–C_{10}) in air (approved by G.G. Onishchenko, the RF Chief Sanitary Inspector, the First Deputy to the RF Public Healthcare Ministry on June 5, 2001)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200029341 (May 17, 2022) (in Russian).

[3] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya (utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28 yanvarya 2021 goda № 2) [Sanitary Rules and Standards 1.2.3685-21. Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people (approved by the Order of the RF Chief Sanitary Inspector issued on January 28, 2021 No. 2)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (May 17, 2022) (in Russian).

Table 1

Groups of volatile organic compounds and sources of their entry into air in residential premises

Groups of compounds		The number of identified compounds	A share of compound for which hygienic standards are established, %	Ranges of identified concentrations, mg/m^3	Sources*	Hazard categories
Saturated hydrocarbons	Normal	19	56	0.05–2.52	1–7	4
	Branched	34	0	0.004–4.15	1–5, 7	–
Unsaturated hydrocarbons		65	18	0.001–0.938	1–3, 5, 6	3–4
Aromatic hydrocarbons		63	43	0.001–1.524	1–7	2–4
Cyclic hydrocarbons		45	15	0.008–0.52	1, 3, 5	–
Simple and complex ethers		55	54	0.001–0.786	1, 5, 7, 9	3–4
Ketones		49	13	0.002–4.05	1–5, 9, 11	3–4
Aldehydes (saturated and unsaturated)		43	41	0.004–0.558	1–6, 9, 11	2–4
Alcohols		42	49	0.005–1.12	1, 4, 5, 7, 9	3–4
Terpenes		29	17	0.002–0.790	3, 4, 7–9	–
Organic acids		17	58	0.001–0.958	2, 5, 9, 11	2, 3
Furans		17	20	0.012–0.552	1–4, 9	–
Indane compounds		15	0	0.004–0.23	2, 3, 5–7	–
Phenols		7	40	0.001–0.323	1, 2, 5	2
Oxygen-containing compounds		7	0	0.035–0.045	5, 7	–
Nitrogen-containing compounds		48	23	0.001–0.421	3–6, 11	2–4
Halogen-containing compounds		29	54	0.011–1.400	1, 3–5, 7, 10	2–4
Sulfur-containing compounds		25	40	0.005–0.365	1, 2, 4, 5, 9	1–4

N o t e : *Major sources that create chemical pollution in air in residential premises include: **1** – construction and finishing materials; **2** –polluted ambient air; **3** – tobacco smoke; **4** – house dust; **5** – anthropogenic toxins and pets' vital activity products; **6** – products of incomplete gas combustion; **7** – household chemicals including washing powders, polishes for furniture and floor, glues for floor boards, varnishes and paints, aerosol air fresheners; **8** – perfumes and cosmetics, flowers and plants; **9** – cooking; **10** – tap water usage (showering, drinking, laundry, boiling, doing the dishes, cleaning etc.); **11** – products created by transformation of pollutants.

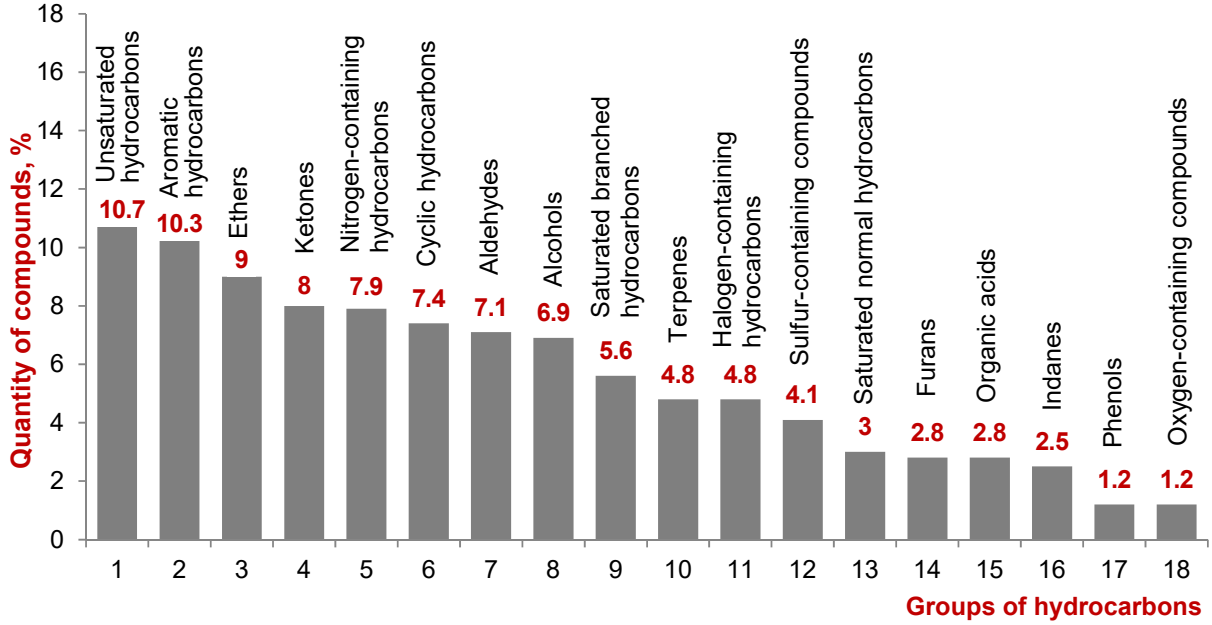

Figure 1. Group structure of organic compounds in air in residential premises distributed as per group shares (determined as per a number of compounds in each group)

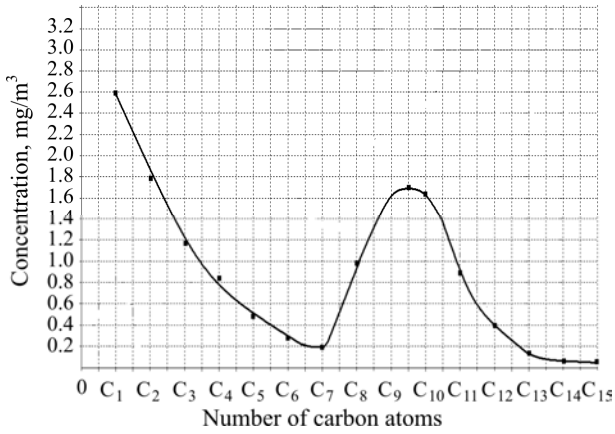

Figure 2. Contents of saturated hydrocarbons in air inside apartments depending on the number of carbon atoms in their chemical formula

carbons accounted for 44 % of the total quantity of volatile organic compounds. Saturated and aromatic hydrocarbons accounted for more than one third (34 %). Variable functional groups also had significant shares in the structure of compounds in air in residential premises; in particular, this concerns oxygen-, nitrogen-, sulfur-, and halogen-containing compounds.

Hydrocarbon contents went down from the simplest representative C_1 (methane) to C_7 (heptane), then increased reaching its peak for C_9 (nonane) and then went down again (Figure 2).

The established trend is in line with distribution of normal saturated hydrocarbons in ambient air in industrial areas with low pollution levels. An increase in contents of hydrocarbons C_8–C_{12} might be due to their migration into air from construction and finishing materials and household chemicals.

It seemed rather difficult to assess hazards posed by a wide range of organic compounds occurring in air in residential premises since there were no existing hygienic standards for a significant number of them.

As for compounds with established safety levels of their concentrations, their total contents could hardly be considered hazardous since they occurred in concentrations not exceeding MPC. Most such compounds belonged to the fourth hazard category regarding their toxicological properties.

Special attention was given to chemicals from aromatic hydrocarbons group. Benzene, toluene, ethylbenzene, xylenes, propyl benzene, methyl ethyl benzenes, and trimethylbenzene occurred practically in all analyzed residential premises. They belong to the group of the most hazardous chemicals out of those identified in air given their hygienic significance and ability to transform by oxidation thereby generating products that are more toxic [18]. Some aromatic hydrocarbons occurred in concentrations that were significantly higher than average daily MPC. Thus, if an apartment was just after repairing and had new furniture, or a room was polluted with tobacco smoke, benzene concentration reached 15 average daily MPC; ethylbenzene, 8 average daily MPC; trimethylbenzene, 8 average daily MPC; etc. (Table 2).

This indicates it is necessary to control these compounds in air in residential premises.

We detected a trend for aromatic hydrocarbons, similar to saturated ones, to distribute

Table 2

Aromatic hydrocarbons identified in air in residential premises and their hygienic significance

Compound	The number of carbon atoms in the molecule	Ranges of concentrations, mg/m^3	Concentrations exceeding average daily MPC, maximum number of times
Benzene	C_6	0.006–1.524	15.2
Toluene	C_7	0.001–0.963	1.6
Ethylbenzene	C_8	0.001–0.854	43.0
Xylenes	C_8	0.004–0.792	4.0
Methyl ethyl benzene	C_9	0.002–0.602	20.1
Trimethylbenzene	C_9	0.002–0.520	34.7
Methyl isopropyl benzene	C_{10}	0.002–0.125	8.9
Naphthalene	C_{10}	0.0–0.150	21.4
Styrene	C_8	0.001–0.135	68.0
Diethylbenzene	C_{10}	0.002–0.077	15.4
Tetramethylbenzene	C_{10}	0.003–0.280	28.0

depending on their molecular structure. Their contents were shown to go down as the number of carbon atoms in their formula grew and the simpler hydrocarbons occurred in larger quantities than their high-molecular homologs.

Aldehydes were the most hygienically significant compounds among oxygen-containing ones. We identified a wide range of saturated normal aldehydes (from formaldehyde to dodecanal) and their isomers as well as unsaturated (acrolein, methyl acrolein) and aromatic aldehydes (benzaldehyde, 4-methylbenzaldehyde); in some cases their concentrations exceeded maximum permissible ones.

Hexanal, formaldehyde, acetaldehyde, and nonanal were the most hygienically significant aldehydes. These compounds can be found in various solvents, construction and finishing materials, household chemicals, perfumes, and some other substances that are commonly stored and used in residential premises.

Formaldehyde and hexanal were identified in air inside practically all the examined rooms. Formaldehyde occurred in concentrations from 0.001 mg/m³ (in ecologically clean apartments) to 0.170 mg/m³ (in apartments with new furniture made of wood chipboards). Hexanal was identified within the range of concentrations 0.001–0.08 mg/m³. We should note that the aforementioned aldehydes occur in air not only due to migration from variable internal sources but also due to transformation of other organic compounds.

When it comes down to ketones, acetophenone, acetone and methyl ethyl ketone (butanone) are the most significant ones given their prevalence, total contents, the number of representatives and concentrations. Acetone concentration reached 5.6 average daily MPC in some places (in particular, close to where household chemicals were stored). Acetophenone concentrations (comes from perfumes and cosmetics) reached nine average daily MPC.

Some ketones do not have hygienic standards established for them. Among such compounds, 2-heptanone, 2-butanone, 2-octanone, and 2-hexanone occurred frequently and in the highest concentrations.

As for alcohols, 2-pentanol, n-butanol, isobutanol, 2-butanol, 1,4-dioxane, diphenyl ether, ethyl- and butyl acetates were the most hygienically significant. Alcohols occur in air in residential premises from such sources as people and pets' vital activity products, cooking, household chemicals, plants, and perfumes.

Furans also should be given similar attention among other oxygen-containing compounds. They are contained in tobacco smoke, motor transport exhausts, gas combustion products, etc. Furan, 2- and 4-mehtylfuran have high hygienic significance. Furan was identified in concentrations reaching eight MPC in rooms that were heavily polluted with tobacco smoke. Some compounds from the furan group do not have hygienic standards established for them. Among such compounds, 2-pentyl- and 2-butyltetrahydrofuran were identified in the highest concentrations.

Nitriles and nitrogen-containing compounds is another group of chemicals with certain hygienic significance. Nitrogen-containing compounds are applied as plasticizers and modifiers when colorants and finishing polymer materials are manufactured. Nitrogen-containing compounds occur in air due to tobacco smoking or they can sorb on house dust; apart from that, nitriles and nitrogen-containing compounds can also be final products resulting from transformation. Since their reaction abilities are rather weak, we can expect these compounds, just like ketones, to accumulate in air in enclosed spaces, which means their contents should be controlled. However, hygienic standards are established for only 23 % of the all nitrogen-containing compounds identified in air in residential premises.

We should emphasize that it was extremely difficult to assess hazards posed by the whole range of identified chemicals since there were no established hygienic standards for a significant part of them. Hygienic standards are available only for 31 % of the identified chemicals. Hygienic standards exist for only 20 % of all the identified toxic furans; cyclic hydrocarbons, 15 %; aldehydes, 41 %; phenols, 40 %; alcohols, 49 %; sulfur-containing compounds, 40 %; halogen-containing compounds, 54 % (Table 1). Meanwhile, these compounds penetrate air in residential premises from polymer materials or with tobacco smoke, due to tap water consumption or as final products when basic pollutants transform. Given their extremely weak reaction abilities and ability to transform,

these compounds can accumulate in air in residential premises in significant amounts.

It seemed very important to identify major sources of various chemicals. Table 3 provides the list of 10 major sources that create air pollution in residential premises as well as summarized results obtained by examining spectra of variable compounds that come from these sources into air in residential premises.

We estimated pollution levels as per the total MPC excess (K_{total}) and obtained the following results. K_{total} determined for volatile organic compounds reached 79 for air inside rooms that were heavily polluted with tobacco smoke; 70, for a room with new linoleum on the floor. We calculated several values for rooms in a comfortable apartment after it has been repaired using all the advanced technologies and materials: bedrooms, up to 42; rooms without any furniture, up to 30; living rooms, 17; children's rooms, up to 20. For reference, K_{total} calculated inside cottages located in the countryside was often lower than 5 and never exceeded 10.

Table 4 provides the list of compounds with their concentrations exceeding hygienic standards in more than 10 % of the analyzed apartments.

Formaldehyde, phenol, and styrene are obviously the most widely spread chemical pollutants occurring in air in residential premises.

Formaldehyde migrates into air in residential premises from furniture made of wood chipboards and the process may persist for many years. Besides, formaldehyde can be found in heat insulating materials, linoleums,

Table 3

Quantitative assessment of volatile organic compounds entering air in residential premises from major internal sources of pollution

Internal sources of pollution	The number of compounds	The number of groups	The share of compounds without any hygienic standards established for them, %
Construction and finishing materials	154	13	39
Vital activity products	157	18	59
Tobacco smoke	121	18	72
Cases of household appliances	33	8	48
Household chemicals	83	12	34
Products of natural gas combustion and cooking	67	13	67
Perfumes and cosmetics	58	10	45
House dust	80	13	63

Table 4

Chemicals identified in air in residential premises in concentrations higher than hygienic standards

Chemical	A share of samples with concentrations higher than MPC, %	MPC exceeded by (times)
Styrene	35	1.5–18.0
Formaldehyde	32	1.2–17.0
Phenol	20	1.0–5.0
Hexanal	17	1.2–6.5
Nonanal	15	1.2–4.5
Ethylbenzene	14	1.8–8.2
Butyl acetate	10	1.0–2.2
Ethyl acetate	10	1.0–3.2
Isopropanol	15	1.0–2.5
Benzene	12	1.2–5.0
Acrolein	10	1.0–7.0
Octanal	11	1.2–2.5
Dichlorobenzene	10	1.3–3.3
Trimethylbenzene	15	1.3–3.3
Acetophenone	10	1.0–9.5

cosmetics, household chemicals, and shrink-proofing agents used to manufacture up-to-date textiles etc. This chemical produces general toxic, irritating and allergenic effects. It is noteworthy that formaldehyde is not only capable to directly induce allergy but also stimulate allergic reactions to other allergens.

Several research works provide data on a relationship between formaldehyde contents in air and abundance of polymer materials (the correlation coefficient equals 0.67) [18, 19]. The highest formaldehyde concentrations (0.062–0.077 mg/m^3) were detected in rooms with new furniture made of wood chipboards. Natural gas combustion is also a source of this chemical. It was established that if a 4-burner gas cooker was working for one hour, this resulted in 1.5–2.0 times increase in formaldehyde concentration in air inside a kitchen. Tobacco smoke is another source of formaldehyde. Smoke from just one cigarette was established to contain 0.035 mg/m^3 of formaldehyde. After three cigarettes have been smoked, formaldehyde concentrations in air on average grow by 42 %.

Phenol is another most widely spread and hazardous pollutant that occurs in air in residential premises. Phenol mostly comes into air in residential premises from construction materials that contain phenol-formaldehyde components (plastic coverings, certain polishers and varnishes for parquet, wood chipboards, fiberboards, plywood); paints and solvents used as protective coatings for wood; insulation materials based on foam carbamide resins; disinfectants.

Formaldehyde and phenol concentrations may largely occur in air in residential premises due to polluted ambient air since they can easily be found in industrial emissions and exhaust gases.

Styrene can also be considered a most widely spread pollutant in air in residential premises. Styrene concentrations, either equal to MPC or higher, were detected in most analyzed residential premises. Styrene comes into indoor air mostly from heat insulating and finishing materials, PC cases and cases of other electronic appliances that are made from polystyrene or polystyrene-based materials, as well as plastic coatings on kitchen furniture.

Discussion. We identified 609 compounds from 18 groups of volatile hydrocarbons in air in residential premises. Aromatic hydrocarbons and aldehydes with styrene and formaldehyde as their main representatives should be considered priority compounds for chemical-analytical control as per their contents in air, the number of identified chemicals from the group and hygienic significance. Phenol pollution in air in residential premises is another risk factor for public health.

Formaldehyde, phenol, and styrene are major indicators applied within monitoring activities aimed at assessing quality and performing risk-based control of hazards posed by chemical air pollution both in newly built residential houses that are at the approval stage and already exploited ones. These compounds, which are able to produce not only general toxic effects on human health but also allergenic (formaldehyde) and carcinogenic effects, were identified in air in most analyzed residential premises. Their concentrations exceeded MPC established by hygienic standards more frequently than concentrations of other pollutants and multiplicity of this excess was also higher (Table 5). Besides, several sources of these compounds were often found in apartments at the same time. We should bear in mind that these chemicals could be released into air from each construction material or any other source in permissible concentrations whereas the total concentration that occurs in air from different sources could well be significantly higher than the maximum permissible one as it was shown when considering formaldehyde [23]. Given that, we recommend performing mandatory control over formaldehyde, phenol, and styrene concentrations both when a new residential building or a repaired one is being commissioned and when people complain about an unsatisfactory low-quality environment. This mandatory control should also be included into risk-based surveillance over safety of the environment in residential premises.

Apart from formaldehyde, styrene, and phenol, the most hygienically significant compounds are acetophenone, ethylbenzene, hexanal, nonanal, butyl acetate, ethyl acetate, isopropanol, benzene, and trimethylbenzene (Table 5).

Contents of these chemicals should primarily be controlled in order to perform proper assessment of hygienic safety inside contemporary residential premises with unknown pol-

lution sources; this control is also necessary when people complain about some alien smells inside their apartments or worsening health due to living there as well as when calculating risks associated with effects produced on health by volatile organic compounds occurring in the living environment.

Therefore, the results of this study as well as earlier ones made it possible to identify the maximum widest range of chemical pollutants in air in residential premises; to quantify them and to determine the actual structure of air pollution; to establish major sources of chemical pollutants in air in residential premises. We determined quantitative parameters of chemical air pollution depending on ambient air pollution, abundance of polymer materials in a given room, a number of people in a given room, a period during which a given building was exploited, air temperature and humidity, and air exchange intensity [6, 9, 19].

However, several issues have remained unresolved by now and this makes it impossible to accomplish proper sanitary-epidemiological control of chemical air pollution in residential premises supported by a relevant methodical base.

The most significant problem is lacking methodical and regulatory support for assessing hazards or safety in case the identified chemicals occur in air. In particular, it is rather unclear what a period any hygienic standards should be averaged over when we use them as reference ones within sanitary-epidemiological surveillance of chemical air pollution in residential premises, namely, average annual, average daily, or single maximum ones. Thus, there was an item in this formerly valid document[4] pointing out that chemical concentrations in air in residential premises should not exceed average daily MPC established for air in settlements when a building is being commissioned. In case there are no such MPC established for a given chemical, its concentration should not exceed maximum single MPC or TSEL. Still, there is no such requirement in recently developed documents that are valid now.

There is another important issue. How many samples should be taken, where they should be taken and what sampling conditions are proper? If we want to obtain adequate results, we need unified methodical requirements to sampling points, a number of samples, and sampling conditions and we should determine under what conditions results of one-time sampling in residential premises can be compared with average daily MPC.

Table 5

Basic hygienically significant chemical pollutants in air in residential premises

Chemical	Hazard category	Frequency, %	MPC exceeded by (times)	Major pollution sources
Styrene	2	80	1.5–18.0	Construction and finishing materials, toys, household appliances
Formaldehyde	2	100	1.2–17.0	Furniture, construction and finishing materials
Phenol	2	70	up to 4.2	Construction and finishing materials, disinfectants
Acetophenone	3	50	1.0–4.0	Furniture, resins, perfumes
Ethylbenzene	3	80	up to 3.0	Ambient air, construction and finishing materials
Benzene	2	78	1.0–6.9	Varnishes, paints, natural gas, ambient air
Hexanal	3	64	1.0–5.4	Furniture, varnishes, paints, construction materials, perfumes
Nonanal	3	60	1.0–5.4	Furniture, varnishes, paints, construction materials, perfumes
Isopropanol	3	50	up to 2.0	Household chemicals, varnishes, paints
Trimethylbenzene	3	74	1.3–3.3	Polymer construction and finishing materials
Butyl acetate	3	54	1.0–2.2	Polymer construction and finishing materials, varnishes, paints
Ethyl acetate	3	48	1.0–3.2	Polymer construction and finishing materials, varnishes, paints

[4] SanPiN 2.1.2.2645-10. Sanitarno-epidemiologicheskie trebovaniya k usloviyam prozhivaniya v zhilykh zdaniyakh i pomeshcheniyakh (utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 10 iyunya 2010 goda № 64) [Sanitary Rules and Standards 2.1.2.2645-10. Sanitary-epidemiological requirements to living conditions in residential buildings and residential premises (approved by the Order of the RF Chief sanitary Inspector on June 10, 2010 No. 64)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (May 17, 2022) (in Russian).

In addition, it is necessary to substantiate a list of procedures for chemical tests. These procedures, along with being cost-effective and available, should be highly sensitive since this gives an opportunity to ensure that test results are comparable with hygienic standards.

Therefore, adequate hygienic assessment of air quality and chemical safety under exposure to chemical pollution in residential premises requires further development of regulatory and methodical documents aiming to improve sanitary-epidemiological examinations with their focus on air.

Conclusion. We applied up-to-date physical and chemical research techniques and this allowed us to identify and quantify chemical pollutants in air inside contemporary residential premises and to create a database on chemical pollution in a large megacity. The database contains data on more than 600 chemicals from 18 different groups of volatile hydrocarbons stating their hygienic standards, a hazard category, and ranges of detected concentrations. In addition, we identified major sources of air pollution with these chemicals. It is noteworthy that there are no established hygienic standards for more than 60 % of all the chemicals identified in air in residential premises.

Formaldehyde, phenol, and styrene are priority chemicals for quality monitoring and risk-based control of hazards posed by chemical air pollution both in newly built houses that are at the approval stage and already exploited ones.

Apart from formaldehyde, styrene, and phenol, such compounds as acetophenone, ethylbenzene, hexanal, nonanal, butyl acetate, ethyl acetate, isopropanol, benzene, and trimethylbenzene are the most hygienically significant volatile organic ones for quality control and health risk assessment considering frequency of their occurrence, concentration levels, concentrations exceeding MPC, group affiliation, hazard category, and ability to transform.

When controlling natural chemicals that occur in air in residential premises due to some internal pollution sources, we should bear in mind that transformation might result in a new structure of pollution that includes new occurring chemicals, for example, aldehydes or ketones that can be more toxic and hazardous than original ones.

To minimize risks associated with exposure to chemical pollution and to assess chemical safety of air in residential premises, we recommend wider use of up-to-date physical and chemical analysis methods for identification of a wide range of pollutants. It is especially vital to develop hygienic standardization in order to minimize environmental risks and to develop methodical documents aimed at providing adequate hygienic assessment of quality and chemical safety of internal environment in residential premises.

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Research article

IDENTIFICATION OF GENETICALLY MODIFIED ORGANISMS IN FOODS OF PLANT ORIGIN AS A WAY TO CONTROL HEALTH RISKS FOR CONSUMERS

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Uncontrolled distribution of goods produced by genetically modified plants should be prevented by the state in order to secure food safety in the Russian Federation and to minimize health risks for consumers.

We analyzed foods of plant origin for children to identify components of genetically modified organisms in them. It was done to ensure safety of such foods. The highest specific weight among the analyzed foods belonged to nectars (40.0 %) and juice-containing drinks (36.0 %). Juices and fruit drinks accounted for 12 % each. Genetically modified organisms were determined in foods by identifying regulatory sequences (35S promoter, FMV promoter and NOS terminator) that are widely used in constructions of genetically modified plants. Occurrence of regulatory genetic elements specific for genetically modified organisms was checked in juice products for children by the polymerase chain reaction in real-time mode with hybridization-fluorescent detection of amplification products and with the use of the "AmpliSens GM Plant-1-FL" and "AmpliKvant GM soya-FL" test systems.

The results of this study showed that no analyzed foods of plant origin contained any regulatory sequences (35S, NOS u FMV) indicating presence of genetically modified organisms. Fluorescence through the FAM, Cy5 and ROX channels did not exceed its threshold value. Therefore, we did not detect any violations of the established requirements to occurrence of genetically modified organisms in foods for children. Further investigation that would involve examining a more extensive material is required to ensure proper assessment and control of food contamination with genetically modified organisms in order to ensure food safety.

Keywords: *transgenic plants, genetically modified organisms, promoters, terminators, polymerase chain reaction, food safety, juice foods for children.*

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At present, food safety is a pressing issue given the global population growth [1, 2]. It is an integral component of national security in any state [3]. The Food Safety Doctrine of the Russian Federation was approved by the RF President Order issued on January 21, 2020 No. 20. The item 7z in it stipulates the necessity to prevent any imports of genetically modified organisms into the country as a key national interest in providing food safety. It is prohibited to sow, grow, cultivate or distribute such products in Russia; the Order also highlights the necessity to control imports and distribution of foods produced with using genetically modified organisms[1].

Genetically modified cultures are being used more and more often to increase crop capacity of plants and make them more resistant to harmful factors [4–6]. There are varieties of fruit and vegetables that have been created in laboratories by up-to-date genetic engineering technologies [7–9]. Nowadays genetically modified organisms can be found in most foods, juice products included.

The juice products market is developing dynamically and it can provide consumers with a wide and diverse range of juices, nectars, juice-containing drinks and fruit drinks[2] [10–12]. Juice products are considered a source of necessary nutrients and biologically active compounds [13–16]. Manufacturers issue multiple innovative products on the market all over the world. They are currently switching to more healthy ingredients in the process given a growing consumer interest in healthy diets. Technological processes and receipts are being developed and juice products are being enriched with vegetable components and vitamins [17].

Since 2016, the legislation in Russia strictly forbids any commercial growing of genetically modified cultures; still, their imports are allowed provided they have been registered in full conformity with the state registration procedure[3]. However, it is forbidden to use genetically modified organisms in foods for children, juices included. At present, the mandatory requirements aimed at providing juice products safety are stipulated in the Technical Regulations of the Customs Union CU TR 023/2011 “The Technical Regulations for juice products made of fruit and vegetables”[4]. Most juices and juice-containing drinks that are sold in the country are manufactured in Russia from imported concentrated purees and juices. Imported raw materials account for 80 % in juice products manufactured in the country [18] and this share has remained stable over the last 20 years. Many fruit cultures that are used in juice products manufacturing cannot be grown in Russia due to unsuitable climatic

[1] Ob utverzhdenii Doktriny prodovol'stvennoi bezopasnosti Rossiiskoi Federatsii: Ukaz Prezidenta RF № 20 ot 21.01.2020 g. [On Approval of the Food Safety Doctrine of the Russian Federation: The RF President Order No. 20 issued on January 21, 2020]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/564161398?section=text (June 07, 2022) (in Russian).

[2] Rynok sokov i nektarov v Rossii. Tekushchaya situatsiya i prognoz 2022–2026 gg. [Juice and nectar market in Russia. The current situation and forecasts for 2022–2026]. *Alto Consulting Group (ACG)*. Available at: https://alto-group.ru/otchot/rossija/285-rynok-sokov-i-nektarov-v-rossii-tekuschaja-situacija-i-prognoz-2021-2025-gg.html (June 03, 2022) (in Russian).

[3] O vnesenii izmenenii v otdel'nye zakonodatel'nye akty Rossiiskoi Federatsii v chasti sovershenstvovaniya gosudarstvennogo regulirovaniya v oblasti genno-inzhenernoi deyatel'nosti: Federal'nyi zakon № 358-FZ ot 03.07.2016 g. [On making alterations into certain legislative acts of the Russian Federation regarding development of state regulation in the sphere of genetic engineering: The Federal Law No. 358-FZ issued on July 03, 2016]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/420363719?section=text (June 08, 2022) (in Russian).

[4] TR TS 023/2011. Tekhnicheskii reglament na sokovuyu produktsiyu iz fruktov i ovoshchei (utv. Resheniem Komissii Tamozhennogo soyuza ot 9 dekabrya 2011 goda № 882) [CU TR 023/2011. The Technical Regulations for juices made of fruit and vegetables (approved by the Decision of the Customs Union Commission on December 09, 2011 No. 882)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902320562?section=text (June 08, 2022) (in Russian).

conditions. Therefore, there is a risk that genetically modified organisms can penetrate the Russian food market without any proper state registration. Besides, there are risks that some products might be falsified, counterfeited or declared inadequately. It is necessary to implement new techniques for determining quality, safety and authenticity of juice products that are more effective than the existing ones.

Our research goal was to identify probable occurrence of genetically modified organisms in foods of plant origin for children in order to ensure food safety.

Materials and methods. Genetically modified organisms were identified in foods by the polymerase chain reaction in real-time mode with hybridization-fluorescence detection. Overall, we analyzed 50 samples of foods of plant origin for children. The highest specific weight among the analyzed foods belonged to nectars (40.0 %) and juice-containing drinks (36.0 %). Juices and fruit drinks accounted for 12 % each.

The first stage involved DNA extraction in accordance with the recommendations provided by the manufacturer of the "MagnoPrime FITO" reagent kit ("NekstBio" LLC. Moscow). At the next stage, the obtained samples were amplified with CFX96 (Bio-Rad, USA) as per the following program: 1 cycle: 95 °C for 900 sec; 2 cycles: 95 °C for 15 sec, 59 °C for 60 sec. We applied the "AmpliSens GM Plant-1-FL" and "AmpliKvant GM soya-FL" test systems (Rospotrebnadzor's Central Scientific Research Institute for Epidemiology) in the process for qualitative and quantitative determination of genetically modified ingredients of plant origin in foods accordingly. Amplification completed, we then detected intensity of fluorescence as per channels that corresponded to the FAM, HEX, ROX, Cy5 dyes. The results were estimated as per an intersection between the fluorescence curves with the threshold line preset at a certain level. The result was considered valid in case correct results were obtained for positive and negative controls of DNA extraction and amplification in accordance with the instructions provided with the reagent kit. Fluorescence curves were analyzed with CFX Manager software package.

Results and discussion. A wide variety of fruits, vegetables and berries are used as raw materials in juice manufacturing. Most analyzed juice products were samples made from apple, peach, tomato or orange concentrated juice and (or) purees as well as from multi-fruit concentrated products. Rather few samples contained grapes, cherry, black current, bananas, apricots, peaches, pears, grapefruits, cowberries, blackberries, litchi, and granadilla.

Our study focused on identifying DNA promoters 35S, FMV and NOS terminator in juice products for children. Their occurrence would indicate that genetically modified organisms were present. The results showed that the analyzed samples did not contain any specific sequences and that fluorescence as per FAM, Cy5 and ROX channels did not exceed the threshold level. Still, as we performed the polymerase chain reaction in real-time mode, we detected accumulating fluorescence as per the channel for controlling plant DNA (HEX) occurrence in 86.0 % of the analyzed samples. Nectars accounted for 39.5 % of such samples; juice-containing drinks, 37.2 %; juices, 14.0 %; and fruit drinks, 9.3 %. The Figure shows levels of fluorescence at the last amplification cycle for five food samples as per all the analyzed channels. Obviously, these levels exceed the threshold value only as per HEX channel indicating that plant DNA occurs in the analyzed samples.

Our examination with using "AmpliKvant GM soya-FL" did not establish any growth in fluorescence signals as per FAM and HEX channels. This confirms absence of any regulatory sequences typical for genetically modified organisms and soya DNA in all the analyzed samples of juice products for children.

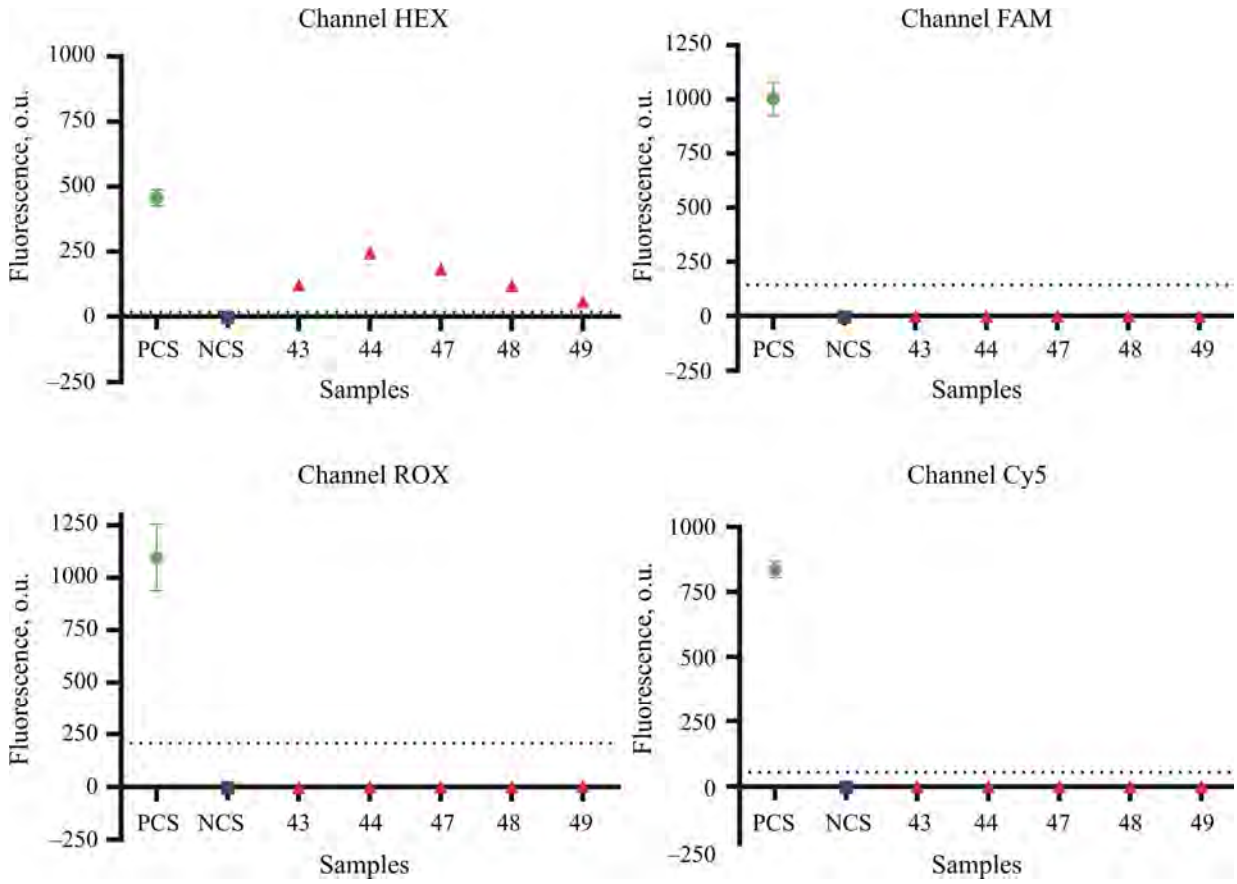

Figure. Levels of fluorescence at the last amplification cycle as per HEX, FAM, ROX, and Cy5 channels: o.u. is optical units; PCS is positive control sample; NCS is negative control sample

An issue related to probable risks of using genetically modified organisms is still being discussed [19, 20]. Food safety should include concerns for health of elderly people, pregnant women and nursing mothers as well as children. In the Russian Federation, there is the valid moratorium on use of genetically modified organisms in foods for children[5]. In this study, we did not detect genetically modified organisms in any sample of juice products for children. This means that all the analyzed products conform to the requirements stipulated in the existing RF legislation.

Similar results were obtained in an earlier study accomplished in Astrakhan that did not detect any NOS terminator sequences in foods for children, juices included [21]. Most juices do not contain any genetically modified organisms since transgenic fruit and vegetables are grown in much smaller quantities than basic agricultural crops. However, recently there has been an ascending trend in use of biotechnologies in fruit and vegetable production [22, 23]. Thus, a new apple variety grown with using biotechnologies is already available on the US market. This pro-

[5] TR TS 021/2011. O bezopasnosti pishchevoi produktsii (s izmeneniyami na 14 iyulya 2021 goda) (utv. Resheniem Komissii Tamozhennogo soyuza ot 9 dekabrya 2011 goda № 880) [CU TR 021/2011. On food products safety (last amended on July 14, 2021) (approved by the Decision of the Customs Union Commission on December 09, 2011 No. 880)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902320560?section=text (June 09, 2022) (in Russian).

duct's name is "Arctic apple"; it was genetically modified to prevent browning after slicing thus making a fruit look fresh. In October 2020, a genetically modified pineapple was introduced on the market. The fruit is sweeter and has bright pink pulp [23]. Transgenic papaya was first produced as far back as in 1990ties; a GMO-containing variety of this fruit is more resistant to the papaya ringspot virus [24]. While citrus production in the USA is trying to overcome the incurable bacterial disease known as Huanglongbing ("citrus greening disease") that destroys orange trees in the country, experts in the field are searching for a similar solution to the issue [25, 26].

Conclusions. We analyzed juice products for children in this study. As a result, we did not detect any regulatory genetic elements typical for genetically modified organisms. Therefore, the existing legislative requirements regarding occurrence of genetically modified components in foods for children have not been violated. Further investigations on wider samplings are required for proper assessment and control of food contamination with genetically modified organisms in order to ensure food safety.

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Competing interests. The authors declare no competing interests.

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Research article

IDENTIFICATION AND CHARACTERIZATION OF 1-HYDROXYPYRENE CONTENTS IN URINE AS A MARKER OF EXPOSURE TO PAH IN WORKERS OF ELECTROLYSIS WORKSHOPS AT ALUMINUM PRODUCTION

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Potential harmful effects produced by highly toxic aromatic hydrocarbons (PAH) on health of workers employed at aluminum production make it necessary to identify biomarkers of exposure to the toxicants and to assess health risks.

Our research goal was to identify and assess contents of 1-hydroxypytene (1-OHPyr) as a biomarker of exposure to PAH. The chemical was identified in urine of workers from electrolysis workshops where either conventional or updated aluminum production technologies were employed. We comparatively examined contents of the marker metabolite 1-OHPyr in urine of 142 workers with basic occupations employed at electrolysis workshops with different aluminum production technologies (the test group) and 14 people who were included in the reference group. The chemical was identified with the authors' high-sensitivity gas chromatography-mass spectrometry method for 1-OHPyr identification in urine with the lower limit of detection being equal to 0.1 μg/l and total error not exceeding 15 %.

The research results revealed high 1-OHPyr contents in urine of workers employed at electrolysis workshops. These contents were by 2–30 times higher than the permissible value of the biological exposure index (BEI) and were associated with exposure to PAH components, an aluminum production technology applied in a given workshop and a worker's occupation. The highest PAH burdens as per 1-OHPyr contents in urine and associated health risks were determined for workers who handled anodes of electrolyzers and crane operators in workshops that employed a conventional technology with self-baking anodes. The lowest ones were established for electrolysis operators and anode frame operators in workshops that employed an updated technology with prebake anodes. It is noteworthy that 1-OHPyr contents were by 2.7–4.7 times higher than permissible BEI value in urine of EOT (bridge) crane operators since these cranes were located in the upper zone of the analyzed electrolysis workshops.

Our research results allow us to recommend the inclusion of biological monitoring of 1-OHPyr contents in urine of workers employed at electrolysis workshops of aluminum productions into periodical medical examinations. This is necessary for developing activities aimed at primary and secondary prevention of occupational and work-related diseases.

Keywords: *aluminum production, polycyclic aromatic hydrocarbons, biomarker of exposure, 1-hydroxypyrene, workers, gas chromatography-mass spectrometry, biological monitoring, biological media.*

Polycyclic aromatic hydrocarbons (PAH) are among priority and the most hazardous persistent organic pollutants. They are highly toxic and produce strong mutagenic and carcinogenic effects. Their influence on the human body is a serious threat to health and a risk factor of oncologic diseases. All this calls for monitoring of biomarkers of exposure to toxicants belonging to the PAH group [1–3]. Exposure to technogenic PAH occurs due to functioning of various metallurgical, petrochemical and coal-processing industries (aluminum, cast iron and steel smelting; coke, bitumen and asphalt production, etc.) [4, 5].

In aluminum production, PAH occur due to anode mass smelting in electrolyzers where aluminum is manufactured using the Soderberg technology with either self-baking or prebake

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charcoal electrodes. Coal-tar pitch sublimes (tarry matter) account for a big share of PAH that are emitted in workplace air. More than 12 PAH with different carcinogenic potential are determined in these emissions including benz(a)pyrene, chrysene, dibenz(a,i)pyrene, benzo(k)fluoranthene, phenanthrene, pyrene, anthracene and others [6–8].

In Russia and in most other countries effects produced by PAH are assessed and their contents are standardized as per benz(a)pyrene since it is the most hazardous and the most profoundly studied chemical in this group. At the same time, to assess an actual chemical burden and associated health risks, not only PAH contents are controlled in workplace air, but also biomonitoring is performed with its aim to identify contents of the actual substances or their metabolites in substrates in the human body. Biomonitoring results allow quantifying contents of toxicants that have actually entered the body and affect it [9, 10].

In world practice, biomonitoring of PAH is usually accomplished by identifying 1-hydroxyperen (1-OHPyr), a conventionally accepted marker metabolite, in urine. This is due to pyrene being the basic component in PAH mixtures and contents of its metabolite correlating with total PAH contents in ambient air and damage to DNA in people exposed to benz(a)pyrene [11–15]. The American Conference of Governmental Industrial Hygienists (ACGIH) established the maximum permissible value of the biological exposure index (BEI) for 1-OHPyr contents in urine, which equals 2.5 μg/dm^3 [1]. Biomonitoring studies that were accomplished at aluminum productions abroad established high 1-OHPyr contents in urine of workers who dealt with electrolyzer maintenance and made charcoal anodes [11, 12, 16, 17]. In Russia, similar studies have not been performed so far. There are also no available data on comparative assessment of 1-OHPyr contents in workers with basic occupations from workshops where different aluminum production technologies are applied.

Measuring of 1-OHPyr contents in urine is a significant stage in biomonitoring studies. Gas chromatography-mass spectrometry (GC-MS) is a promising and reliable method for identifying 1-OHPyr in urine. It is highly effective, employs selectivity in separation of components on a column and gives a possibility to use the deuterated internal standard 1-OHPyr-d9. Moreover, we tested and implemented our own high-sensitivity GC-MS method for determining 1-OHPyr in urine. The method was developed based on available foreign GC-MS procedures [12, 18, 19] and metrologically certified in the RF [20]. The use of it will allow performing authentic assessment of exposure to PAH and its effects on the human body within biomedical monitoring.

Our research goal was to identify and assess contents of 1-hydroxypytene (1-OHPyr) as a biomarker of exposure to PAH in urine of workers employed at electrolysis workshops with either conventional or updated aluminum production technologies.

Materials and methods. Our study was accomplished at a large aluminum production enterprise located in the Eastern Siberia. The enterprise employed both a conventional aluminum production technology with self-baking anodes and an updated one with pre-bake anodes.

We estimated contents of coal-tar pitch sublimes and benz(a)pyrene in workplace air inside electrolysis workshops at the analyzed aluminum production enterprise. The assessment was performed by analyzing the results obtained by our own examinations and measurements accomplished by a sanitary-industrial laboratory of the enterprise [21] as well as data available in Russian and foreign research works [22, 23].

A chemical analytical examination of PAH metabolite 1-hydroxypyrene contents in urine consisted of two stages. The first one involved collecting urine samples and preparing them; at the second stage, the metabolite

[1] 2020 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, ACGIH, 2020, 292 p.

was analyzed by using GC-MS and the obtained results were assessed.

1-OHPyr was identified and quantified in urine on Agilent 7890A gas chromatographer with Agilent 5975 mass selective detector, HP-5MS capillary column (30×0.25×0.25 μm), and Agilent 7693 automatic liquid sampler according to the suggested procedure [20]. Sample preparation was performed by optimized enzymatic hydrolysis of a conjugated metabolite with β-glucuronidaze at 55 °C for 60 minutes, liquid-liquid analyte extraction with hexane with evaporation in an inert gas, derivatization with a silylating solution of N, O-bis trifluoroacetamide (BSTFA) into trimethylsilyl ether under the room temperature, and gas chromatography operating in the selected ion monitoring (SIM) mode with m/z 290, 275, 299, 284 [24]. 1-OHPyr quantification in urine was performed with the isotope-labeled internal standard 1-OHPyr-d9. Chromatograms of individual 1-OHPyr identification in workers' urine are shown in Figure 1.

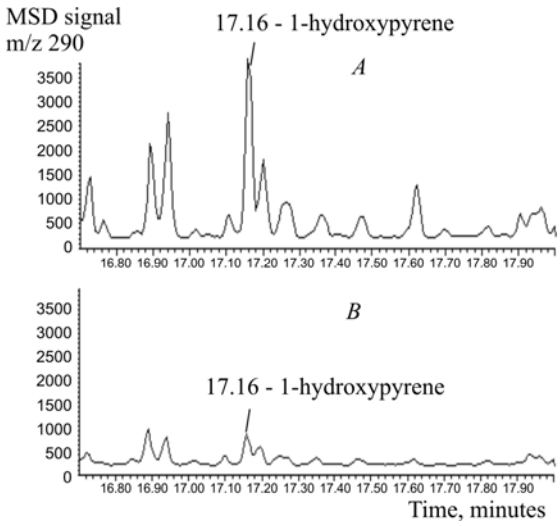

Figure 1. Chromatograms of urine samples from the test and reference groups: *A* is a production worker, concentration is 1.98 μg/l; *B* is a reference sample, concentration is 0.28 μg/l

We tested the suggested GC-MS method for determining 1-OHPyr contents in urine and revealed the following methodical peculiarities. First, we established optimal conditions and parameters for sample preparation that facilitated a significant decrease in its duration. This was achieved due to a shorter time required for enzymatic hydrolysis with β-glucuronidaze and derivatization of 1-OHPyr with BSTFA silylating reagent. Second, we managed to make the analysis highly precise due to using the isotope-labeled internal standard 1-OHPyr-d9 and noted higher sensitivity of determination due to greater extraction of analyte from a biomaterial by liquid-liquid extraction with hexane. The limit of detection and the limit of quantification for 1-OHPyr equaled 0.02 and 0.1 mg/ml accordingly and this is significantly lower than the limit of detection established by foreign procedures for measuring this metabolite in urine (0.1–0.5 mg/ml) [12, 18].

We identified and analyzed contents of 1-OHPyr in urine of 142 workers employed at electrolysis workshops and 14 people who did not work at the analyzed production. They were divided into three groups: workers who had occupational contacts with PAH depending on an occupation and employed technology for aluminum electrolysis (two test groups) and the reference group. The first test group was made of 112 workers with basic occupations in workshops where self-baking anodes were used: electrolysis operators, anode handlers and crane operators (their average age was 37.5 ± 0.8 years and their average work records, 9.0 ± 0.5 years). The second group included 30 workers from workshops where prebake anodes were used: operators of automated production responsible for handling new high-performance electrolyzers (electrolysis operators), anode frame operators responsible for its maintenance and EOT (bridge) crane operators. Average age of workers in this group was 37.4 ± 1.2 years; average work records, 6.7 ± 0.7 years. The third or reference group was made up of 14 people who were not employed at the analyzed enterprise and did not have any occupational contacts with PAH.

To assess 1-OHPyr contents objectively, urine samples were taken during a periodical medical examination provided for workers at the enterprise polyclinic. All the samples were taken in the morning before the next morning shift started. The results of 1-OHPyr measur-

ing in worker's urine were compared with the median level detected in the reference group (0.17 μg/l) and the maximum permissible BEI value in urine (ACGIH) that equaled 2.5 μg/l [1].

All the results were statistically analyzed in Jamovi statistical software package (version 2.3.2) with the non-parametric Kruscal – Wallis test and Mann – Whitney test with the Bonferroni correction and without it. The results are given as the median value (*Me*), interquartile range (Q_{25}–Q_{75}) and a range of concentrations, μg/l.

Results and discussion. We established that contents of volatile components typical for coal-tar pitch sublimes and benz(a)pyrene were 0.2–0.36 mg/m^3 and 0.21–3.9 μg/m^3 accordingly in workplace air inside the analyzed electrolysis workshops where safe-baking anodes were used. This was higher than permissible levels (0.2 mg/m^3 and 0.15 μg/m^3 accordingly) on average by 1.8 and 26 times accordingly. The highest average shift concentrations of tarry matter and benz(a)pyrene that exceeded MPC by up to 1.8 and 26 times accordingly were detected at workplaces of anode handlers and electrolysis operators. At the same time, average concentrations of coal-tar pitch sublimes were within their permissible ranges (0.2 mg/m^3) in workshops where prebake anodes were used; benz(a)-pyrene concentrations varied from 0.5 to 1.4 MPC in those workshops [21, 22]. According to some foreign authors, contents of benz(a)-pyrene varied from 0.19 to 2.8 μg/m^3 in workplace air inside electrolysis workshops at European aluminum-producing enterprises. They could reach 48 μg/m^3 at a workplace of an anode handler in close proximity to Soderberg self-baking anodes [17, 23]. Therefore, if we want to optimize working conditions in electrolysis workshops to make them conform to hygienic standards, obviously, we have to update production equipment and replace a conventional technology with updated one that employs prebake anodes.

We analyzed 1-OHPyr contents in urine of workers employed at workshops with either conventional or updated aluminum production technology by using GC-MS. The results are provided in the Table and Figure 2.

According to the research results, 1-OHPyr was detected in urine of all the examined workers employed at electrolysis workshops as well as people from the reference group who did not have any occupational contacts with PAH. The metabolite contents varied within quite a wide range, from 0.17 to 267.0 μg/l and from 0.08 to 0.9 μg/l accordingly.

We established significant differences in 1-OHPyr contents in urine of workers employed at electrolysis workshops. The differences were established both between basic occupational groups and between the test groups and the reference one as well as the maximum permissible BEI value recommended by the ACGIH. Thus, median 1-OHPyr concentrations

Table

Concentrations of 1-hydroxypyrene in urine of workers with basic occupations in electrolysis workshops where aluminum is produced

An employed technology, occupation	*n*	*Me* (Q_{25}–Q_{75}), μg/l	Min–Max, μg/l
Self-baking anodes. All occupations	112	11.0 (2.4–39.3)*	0.17–267.0
Electrolysis operator	49	3.6 (1.5–13.3)▲	0.17–98.0
Anode handler	26	75.2 (16.5–138.5)▲, ■, ♦	0.87–267.0
Crane operator	37	11.8 (2.7–30.0)■	0.18–57.7
Prebake anodes. All occupations	30	3.5 (1.4–7.3)*	0.61–14.7
Electrolysis operator	16	3.5 (1.3–7.7)	0.61–14.7
Anode frame operator	6	2.2 (1.6–3.4)♦	1.1–7.3
EOT (bridge) crane operator	8	6.8 (2.4–7.8)	0.81–10.9
The reference group	14	0.17 (0.10 – 0.30)	0.08–0.9

Note: *, ♦, ▲, ■ mean there are differences in compared indicators between the groups; the statistical significance is taken as $p < 0.05$.

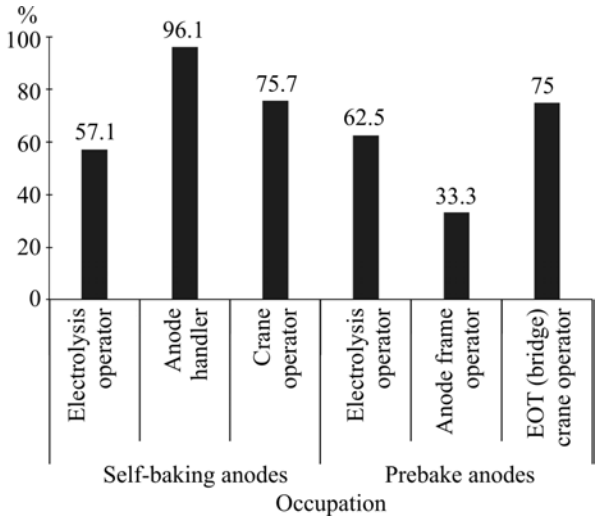

Figure 2. A share of samples (%) with 1-OHPyr contents in urine higher than the maximum permissible BEI value in basic occupational groups in workshops where either self-baking or prebake anodes are applied

in urine of workers employed at workshops (all there occupational groups) where self-baking anodes were used were higher than the same indicator in the reference group as well as the BEI value by 21–442 and 1.4–30 times accordingly ($p < 0.05$). The highest shares of samples with 1-OHPyr contents being higher than the recommended BEI value were detected among anode handlers and crane operators, 96.1 and 75.7 % accordingly, whereas this share was only 57.1 % among electrolysis operators. Anode handlers who maintained and replaced self-baking charcoal anodes in electrolyzers had the highest 1-OHPyr contents in urine, on average by 30 times higher than the recommended BEI value. 1-OHPyr contents in urine were by 20 times higher than this value in electrolysis operators and by 6.3 in crane operators ($p < 0.05$). This indicates that exposure to PAH was predominantly work-related at workplaces of anode handlers and that these workers had high health risks due to it.

Median 1-OHPyr contents in urine varied within the 2.2–6.8 μg/l range in workers with basic occupations in workshops where the updated aluminum production technology (with prebake anodes) was applied. This was on average by 1.4–2.7 times higher than the maximum permissible BEI value and was detected predominantly in electrolysis operators and EOT (bridge) crane operators ($p < 0.05$). The lowest 1-OHPyr concentrations in urine, which were within the permissible BEI range, were detected in anode frame operators (2.2 μg/l) who had to replace anodes in frames and to repair anode installation units in electrolyzers. A share of samples with 1-OHPyr contents being higher than the maximum permissible BEI value was also higher among electrolysis operators (62.5 %) and EOT (bridge) crane operators (75.0 %) against anode frame operators (33.3 %).

We measured 1-OHPyr excretion with urine in exposed workers depending on an aluminum production technology applied in a given workshop and compared the results. We established that median concentrations of the metabolite in urine were authentically lower among anode frame operators as well as the whole group of workers with basic occupations in workshops with the updated technology (prebake anodes) than among the same occupational groups in workshops where the conventional technology (self-baking anodes) was employed (by 34.2 and 3.1 times accordingly). This might be associated with a substantial decrease in volumes in which PAH components occur and enter workplace air due to prebake anodes used in up-to-date electrolyzers as confirmed by monitoring data on contents of tarry matter and benz(a)pyrene in workplace air [21, 22].

We should note that in general the research results are in line with data obtained in foreign studies and fully reflect occupational peculiarities of 1-OHPyr excretion with urine in workers who deal with electrolyzer maintenance [12, 17, 24]. It is especially noteworthy that elevated 1-OHPyr contents in urine were established in anode handlers in workshops with self-baking anodes as well as EOT (bridge) crane operators. The latter worked on cranes located in the upper zone of electrolysis workshops where hazardous dust and gas mixtures were brought to by ascending airflows. Several researchers revealed that exposure to

PAH at a level when 1-OHPyr contents in urine is 4.4 μg/l can correspond to a relative risk of lung cancer being equal to approximately 1.3; the metabolite contents in urine that exceeds 7.7 μg/l can already be considered the highest risk of lung carcinoma for workers [25, 26]. Therefore, high 1-OHPyr contents in urine that we have established in workers from basic occupational groups employed in aluminum production can indicate there are serious threats for their health since these contents are substantially higher than the maximum permissible BEI value. The GC-MS method, which we have applied to identify and quantify contents of 1-OHPyr as a marker PAH metabolite in urine of exposed workers, allows performing objective assessment of effects produced by exposure to PAH on the body within biomonitoring studies. The most effective and radical way to prevent occupational and work-related incidence (oncologic one included) among workers is to implement new technologies of aluminum electrolysis. Such technologies should employ prebake charcoal and inert anodes and up-to-date pressurized electrolyzers; dust collection should be fully automated and modernized since in this case it removes toxic and carcinogenic substances from the occupational environment much more effectively.

Conclusions. Therefore, the results obtained by the accomplished biomonitoring study indicate that workers employed in electrolysis workshops at the analyzed aluminum production enterprise have high contents of 1-OHPyr, a marker PAH metabolite, in their urine. These contents depend on a level of exposure to PAH components, a technology applied in a given workshop and a worker's occupation. The highest PAH burdens as per 1-OHPyr contents in urine and associated health risks were determined for anode handlers and crane operators in workshops that employed the conventional technology with self-baking anodes. The lowest ones were established for electrolyzer operators and anode frame operators in workshops that employed the updated technology with prebake anodes. In this study, we tested the GC-MS method for identifying the PAH metabolite 1-OHPyr in urine as a biomarker. This method is quite adequate for assessing occupational exposure to PAH compounds, benz(a)pyrene included. Our research results allow us to recommend the inclusion of biological monitoring of 1-OHPyr contents in urine of workers employed in electrolysis workshops at aluminum productions into profound periodical medical examinations. This is necessary for developing activities aimed at primary and secondary prevention of occupational and work-related diseases.

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Competing interests. The authors declare no competing interests.

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Research article

LIFE EXPECTANCY AT BIRTH FOR THE RF POPULATION: PREDICTION BASED ON MODELING INFLUENCE EXERTED BY A SET OF SOCIO-HYGIENIC DETERMINANTS ON AGE-SPECIFIC MORTALITY RATES EXEMPLIFIED BY DISEASES OF THE CIRCULATORY SYSTEM

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The article dwells on cause-effect relations between certain socio-hygienic factors and age-specific mortality rates due to cardiovascular diseases. New research trends in hygiene, a multidisciplinary approach to studies in the field and the current state policy make the present work topical.

Our methodical approach to predicting probable age-specific mortality rates due to cardiovascular diseases relied on applying artificial neural networks. We analyzed a set of indicators that described the public healthcare system, sanitary-epidemiological welfare on a given territory, lifestyle, economic conditions, sociodemographic conditions, and primary incidence.

Overall, we obtained 18 models (as per 5-year age-specific periods) of a relationship between socio-hygienic determinants and mortality rates due to cardiovascular diseases. The determination coefficients fell within 0.01–0.75 range and the greatest explanatory power occurred when the age period "30 years and older" was analyzed. We detected comparability of variational series obtained for mortality due to cardiovascular diseases among the whole population and the determination coefficients of the created models. We established predictive estimates of life expectancy at birth (LEB) in case there were changes in the analyzed socio-hygienic determinants by 2024 set within a certain scenario. Thus, changes in the whole set of determinants would result in 514 days added to LEB; lifestyle-related indicators, 205 days; indicators describing sanitary-epidemiological welfare, 126 days; economic indicators, 102 days; sociodemographic indicators, 101 days; primary incidence rates, 40 days; indicators describing the public healthcare system, 19 days. Several determinants were shown to be the most significant for reducing mortality due to cardiovascular diseases among working age population and older age groups. They are indicators describing people's physical and motor activity, income levels, consumption of vegetables, education, and working conditions. Our research results are consistent with those obtained by other studies with their focus on establishing cause-effect relations between environmental factors and public health.

Keywords: *life expectancy at birth, mortality, cardiovascular diseases, socio-hygienic determinants, environmental factors, lifestyle factors, artificial neural networks, factor analysis, prediction of medical-demographic situation.*

The new profile of the academic specialty 3.2.1 "Hygiene" clarifies several research trends[1] in the sphere that concentrate on life expectancy and quality of life. They correspond to the national goals outlined in the strategy for the RF development for the period

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[1] The Profiles of academic specialties within which academic degrees are granted, approved by the Order of the RF Ministry for Science and Higher Education; Nomenklatura nauchnykh spetsial'nostei, po kotorym prisuzhdayutsya uchenye stepeni (s izmeneniyami na 11 maya 2022 goda) (utv. prikazom Ministerstva nauki i vysshego obrazovaniya Rossiiskoi Federatsii ot 24 fevralya 2021 g. № 118) [The Nomenclature of academic specialties within which academic degrees are granted (last edited on May 11, 2022), approved by the Order of the RF Ministry for Science and Higher Education on February 24, 2021 No. 118]. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/573956750 (August 15, 2022) (in Russian).

up to 2030, which is "preservation of population, people's health and wellbeing" [2]. A key component in many of them is identifying priority socio-hygienic factors that determine current mortality rates and life expectancy at birth (hereinafter LEB).

These trends can provide a certain ground for preventive medicine (hygiene) to be able to form a unified complex with such fields of knowledge as sociology, demography, informatics (mathematics) and some others. They can expand analytical potential of hygiene but still preserve its traditional connections with physiology, toxicology, and clinical medicine and its capacity to find solutions to purely hygienic tasks. Besides, these trends are extremely topical now [1, 2], given the current project activities[3] accomplished by the state and concerning multiple spheres in people's lives. The document[4] has initiated changes in the nomenclature of academic specialties. It highlights the necessity to make appropriate effort to perform research studies on the interdisciplinary basis since it corresponds to the context (essence) of contemporary science accepting the complexity of this world, its objects, phenomena and processes and relying on a complex interdisciplinary approach [3].

Over the last decades and at present as well, mortality due to cardiovascular diseases (CVD for short) has been and still is the basic reason for population decline. This mortality, together with that caused by malignant neoplasms, produces substantial effects on public health losses in most countries worldwide [4]. Elevated blood pressure is the leading risk factor[5] that causes CVD and diseases with elevated blood pressure being their typical clinical sign are considered socially significant in Russia[6].

Contemporary concepts regarding these diseases consider them multi-factorial ones with additive-polygenic inheritance with a threshold effect [5]. With this in mind, we face a rather difficult task, which is to establish exact contributions (the size of an effect) made by each component (genetic or environmental one) to CVD development. Still, it is a very promising research trend. Any results achieved within it will make it possible to develop the most effective strategies to minimize harm (risk) to public health caused by priority socially significant diseases[5].

LEB as an integral indicator of public health is relatively easy to calculate and use in assessments, including those of an existing medical and demographic situation within a specific population cohort at a fixed moment. Still, it has certain drawbacks that arise from its origin [6].

Artificial neural networks (hereinafter ANN) are quite an effective and precise analytical procedure that is applied to predict LEB levels and to analyze associations between this

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[2] O natsional'nykh tselyakh razvitiya Rossiiskoi Federatsii na period do 2030 goda: Ukaz Prezidenta ot 21.07.2020 № 474 [On the national goals of the Russian federation development for the period up to 2030: the Order by the RF President issued on July 21, 2020 No. 474]. *The official Internet portal for legal information*. Available at: http://publication.pravo.gov.ru/Document/View/0001202007210012 (August 15, 2022) (in Russian).

[3] Edinyi plan po dostizheniyu natsional'nykh tselei razvitiya Rossiiskoi Federatsii na period do 2024 goda i na planovyi period do 2030 goda; utv. rasporyazheniem Pravitel'stva RF ot 01.10.2021 № 2765-r (s izm. ot 24.12.2021) [The unified action plan on achieving national goals of the Russian Federation development for the period up to 2024 and plans for the period up to 2030; approved by the RF Government Order dated October 01, 2021 No. 2765-r (with alterations made on December 24, 2021)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_398015/ (August 15, 2022) (in Russian).

[4] Perechen' poruchenii po itogam sovmestnogo rasshirennogo zasedaniya prezidiuma Gossoveta i Soveta po nauke i obrazovaniyu. Pr-589, p.1zh-2 [The list of order following the joint extended meeting of the Presidium of the State Council and the Council on Science and Education. Pr-589, p.1zh-2]. *Prezident Rossii*. Available at: http://www.kremlin.ru/acts/assignments/orders/63083 (August 15, 2022) (in Russian).

[5] GBD cause and risk summaries. *The Lancet*. Available at: https://www.thelancet.com/gbd/summaries (August 15, 2022).

[6] Ob utverzhdenii perechnya sotsial'no znachimykh zabolevanii i perechnya zabolevanii, predstavlyayushchikh opasnost' dlya okruzhayushchikh: Postanovlenie Pravitel'stva RF ot 01.12.2004 № 715 (red. ot 31.01.2020) [On approval of the list of socially significant diseases and the list of diseases that pose hazard for people: The RF Government Order issued on December 01, 2004 No. 715 (last edited on January 31, 2020)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_50559/49feaa28d1c4631a481c33187e7a693e879fb051/ (August 15, 2022) (in Russian).

indicator and environmental and lifestyle-related factors [7–9].

Latest works that concentrate on identifying reasons for incidence and mortality among population, CVD-related included, rely on the concept of social determinants of health[7]. These determinants are multiple factors variable in their origin including education; food quality; quality of ambient air and drinking water; socioeconomic status; etc. [10–13].

The project activities that are being accomplished by the state now are aimed at reducing mortality, including that caused by CVD; achieving growth in LEB; mitigating negative effects produced by health risk factors (creating favorable conditions for people to improve their lifestyle); improving socioeconomic conditions. Many studies address risk factors for specific population groups; however, a population as a whole is extremely heterogeneous and exposed to multiple heterogeneous factors with different compatibility and influence. Therefore, it is quite relevant to make an effort to identify cause-effect relations between influence exerted by environmental factors and public health indicators, including those determined for age-specific groups, and to predict a future medical and demographic situation.

Our research goal was to estimate a potential growth in LEB for the RF population by 2024 based on modeling cause-effect relations between environmental and lifestyle-related factors (socio-hygienic determinants) and age-specific mortality rates due to cardiovascular diseases.

Materials and methods. The task was to examine common regularities of cause-effect relations between the analyzed socio-hygienic determinants and LEB in detail and to predict effects on the indicator considering managerial decisions being implemented at present. To achieve this, we modeled relationships between a set of socio-hygienic determinants and age-specific mortality rates due to cardiovascular diseases as a priority cause of death.

The present study relies on principles and methodical approaches to predicting LEB that were described in our previous article [14] and stipulated in the Methodical guidelines MR 2.1.10.0269–21[8]. In accordance with the MR 2.1.10.0269–21, we took a dataset that consisted of 148 indicators based on official state statistical data collected in 2010-2018 in all the RF regions. These data were taken from statistical reports and collections issued by Rospotrebnadzor, the RF Public Healthcare Ministry, and the Federal Statistic Service. The dataset covered the following: sanitary-epidemiological welfare (53 indicators), lifestyle (30 indicators), economy (14 indicators), public healthcare (9 indicators), a social and demographic situation (34 indicators), weather and climate (8 indicators). Besides, to solve tasks outlined within the present study, we added data collected in 2019. We also introduced ten new indicators describing a sanitary-epidemiological profile and 48 indicators describing primary incidence of basic nosologic categories as per age groups (children, working age population, and people older than working age). The ultimate dataset was made of 206 indicators that described the environment, lifestyle and incidence among the RF population over 2010–2019.

We applied an artificial neural network (ANN) to create models of the analyzed cause-effect relations. The ANN structure was based on a four-layer perceptron with two internal layers. A process for accomplishing predictive estimates of changes in mortality rates due to CVD was iterative in its essence since we examined 5-year intervals in age-specific mortality. Values of the analyzed indicators first un-

[7] According to the WHO, Social Determinants of Health (SDoH) are non-medical factors that influence health status.

[8] MR 2.1.10.0269-21. Opredelenie sotsial'no-gigienicheskikh determinant i prognoz potentsiala rosta ozhidaemoi prodolzhitel'nosti zhizni naseleniya Rossiiskoi Federatsii s uchetom regional'noi differentsiatsii (utv. Glavnym gosudarstvennym sanitarnym vrachom RF A.Yu. Popovoi 14 dekabrya 2021 g.) [MR 2.1.10.0269-21. Identification of socio-hygienic determinants and prediction of a potential growth in life expectancy at birth for the RF population, regional differentiation taken into account (approved by A.Yu Popova, the RF Chief Sanitary Inspector on December 14, 2021)]. Moscow, 2021, 113 p. (in Russian).

derwent factor transformation and then were fed into the ANN input layer; age-specific mortality rates were the ANN output layer. The ultimate predictive LEB level was calculated by using tables with ages of survival based on predicted and actual mortality rates. The calculations were based on scenario changes in socio-hygienic determinants. Therefore, predictive LEB levels were determined by effects produced by the analyzed socio-hygienic determinants on age-specific mortality rates due to CVD.

To obtain predictive estimates of age-specific mortality rates due to CVD, we applied an approach similar to that described in our previous work [14] and the Methodical guidelines MR 2.1.10.0269-21[8]. It involves accomplishing several consequent stages: creating a baseline and a target scenario of changes in 206 analyzed indicators; calculating model age-specific mortality rates due to CVD according to both scenarios; calculating predictive mortality rates as a difference between model mortality rates within the baseline and target scenario. Values of socio-hygienic indicators obtained for the last year (2019) in the analyzed period (2010–2019) were taken as a baseline scenario. The target scenario included indicator and target values of indicators fixed in the National and Federal projects ("Clean Air", "Clean Water", "Sport is the standard of living", "Public health improvement", etc.) as well as registered tendencies of changes in other indicators as per a logarithmic or a linear trend by 2024 depending on the determination coefficient (R^2). We applied the same scenario conditions to predict all age-specific mortality rates in this study. We used standard software packages for statistical analysis (Statistica 10, RStudio, MS Excel 2010) to create a data matrix, to perform statistical analysis of the data and to visualize the results.

Results and discussion. Having modeled effects produced by the analyzed socio-hygienic determinants on age-specific mortality rates due to CVD, we obtained 18 neural network models with the determination coefficient (R^2) falling within the range from 0.01 to 0.75 (Table 1).

Table 1

Determination coefficients (R^2) and correlation coefficients (r) of ANN models within the "socio-hygienic indicators – age-specific mortality rates due to CVD" system

Model No.	Age group of mortality due to CVD, years	Determination coefficient (R^2)	Pearson correlation coefficient (r)	Qualitative evaluation of correlation intensity *
15	70–74	0.75	0.87	High
11	50–54	0.71	0.84	High
13	60–64	0.70	0.84	High
14	65–69	0.69	0.83	High
12	55–59	0.69	0.83	High
17	80–84	0.69	0.83	High
16	75–79	0.60	0.77	High
7	30–34	0.60	0.77	High
10	45–49	0.56	0.75	High
18	85 and older	0.55	0.74	High
8	35–39	0.49	0.70	Notable
9	40–44	0.46	0.68	Notable
6	25–29	0.44	0.66	Notable
2	5–9	0.22	0.47	Moderate
5	20–24	0.20	0.45	Moderate
1	0–4	0.16	0.41	Moderate
4	15–19	0.03	0.18	Low
3	10–14	0.01	0.12	Low

N o t e : * qualitative evaluations of correlation intensity are given as per the Chaddock scale. Further analysis concentrates on age groups 30 years and older.

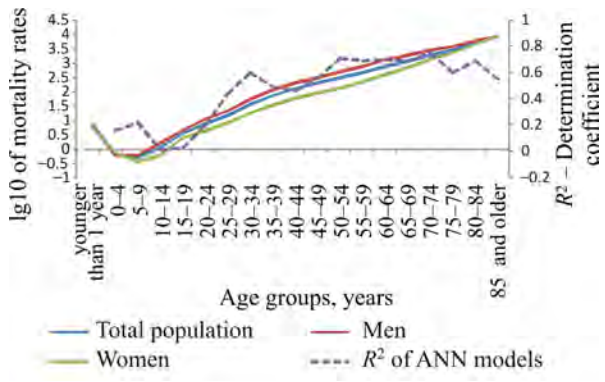

Figure 1. Age-specific mortality rates due to CVD in 2019 (per 100 thousand people in the relevant age group) with the model determination coefficients

We established that the determination coefficient had low values in models that described relations between the analyzed determinants and age-specific mortality rates within the range from 0 to 29 years ($R < 0.5$). The coefficient exceeded 0.5 starting from the age group "30 years and older", except the age groups 35–39 years and 40–44 years. At the next stages, the analysis covered only models created for age groups 30 years and older considering the determination coefficient values and qualitative evaluations of correlation intensities. They meant that the applied dataset had rather weak explanatory force in the models created for age groups younger than 30 years.

We analyzed how mortality rates due to CVD were distributed as per age groups. The analysis revealed that mortality due to this cause grew exponentially with age; this trend was more apparent for men than for women but sex-related differences smoothed over with age (Figure 1).

We comparatively analyzed the model determination coefficients and mortality rates. The analysis revealed that the determination coefficients in the models that described relations between socio-hygienic indicators and primary incidence rates and age-specific mortality rates due to CVD among the RF population were similar to actual distribution of mortality rates due to this cause as per age groups.

According to the target scenario of changes in the analyzed socio-hygienic determinants and without considering impacts exerted by COVID-related processes and the current socioeconomic conditions (economic sanctions), the ultimate LEB level should increase by 1.41 years (514 days) by 2024 solely due to changes in modified age-specific mortality rates due to CVD (Table 2).

Table 2

Comparative assessments of the results obtained by modeling a potential change in LEB (years / days) within scenarios of modifying influence exerted by the whole set of socio-hygienic determinants / specific groups of such determinants

A group of socio-economic determinants	"SHD – LEB" model*		18 "SHD – CVD – LEB" models**		A share of predictive values as per "SHD – CVD – LEB" models relative to "SHD – LEB", %
	Years	Days	Years	Days	
The whole set of determinants (all the analyzed SHD together with primary incidence rates)	–	–	1.41	514	–
The whole set of determinants (without primary incidence rates)	3.0	1095	1.3	473	43.3
Lifestyle-related indicators	1.26	461	0.56	205	44.4
Sanitary-epidemiological welfare on a given territory	0.58	212	0.34	126	58.6
Economic indicators	0.36	131	0.28	102	77.8
Socio-demographic indicators	0.54	196	0.28	101	51.8
Public healthcare system	0.19	70	0.05	19	26.3
Primary incidence	–	–	0.11	40	–

Note: * is the model showing LEB dependence on socio-hygienic determinants (SHD), which we described in our previous study [11]; ** is the set of models showing dependence of age-specific mortality rates on socio-hygienic determinants, which is analyzed in the present work with the following LEB calculation.

If we use scenarios without primary incidence in the models showing a relation between the analyzed factors and age-specific mortality rates due to CVD, then the ultimate potential growth in LEB amounts to 1.3 years (473 days). This equals 43.3 % of the effect on LEB obtained due to modeling a direct relation between socio-hygienic factors and LEB (Table 2). An actual contribution made by mortality due to CVD to the total mortality is comparable and amounts to approximately 47.7 %[9]. This means our estimates are quite correct.

Scenario modeling of changes in socio-hygienic factors that included age-specific mortality rates due to CVD discovered several most significant areas with substantial reserves for LEB growth that were not used properly. They were lifestyle-related indicators (205 days) and sanitary-epidemiological indicators (126 days).

We estimated a decline in age-specific mortality rates due to CVD within the analyzed scenarios and established that all the groups of the analyzed determinants had their peculiar effects regarding larger age groups, such as "from 30 to 59 years" and "60 years and older" (Figures 2 and 3).

We analyzed the results obtained for the larger age groups. The analysis showed that the aggregated modifying influence exerted by the analyzed determinants on mortality due to CVD was more apparent among middle-aged and older people of working age (30–59 years) than among those who were older than working age (60 years and older). A predicted decline in age-specific mortality rates would be equal to 24.8 % (within the range from 17.6 to 34.1 %) and 22.3 % (within the range from 12.8 to 30.2 %) accordingly (Figures 2 and 3). The

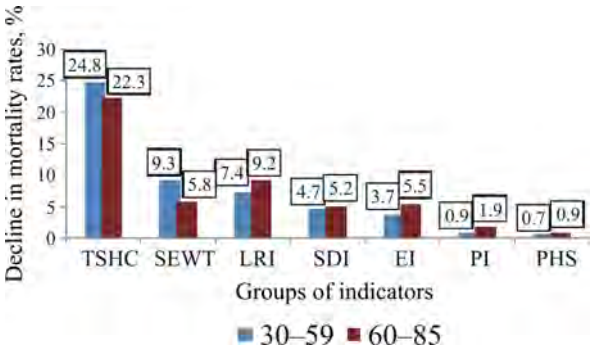

Figure 2. A percent of decline in age-specific mortality rates due to CVD among the whole RF population (average rates as per the age groups 30–59 years, 60 years and older) under scenario changes in the analyzed socio-hygienic determinants as per their conventional groups by 2024, (%): TSHC is the whole set of the determinants; SEWT is sanitary-epidemiological welfare of a given territory; LRI is lifestyle-related indicators; SDI is sociodemographic indicators; EI is economic indicators; PI is primary incidence; PHS is public healthcare system

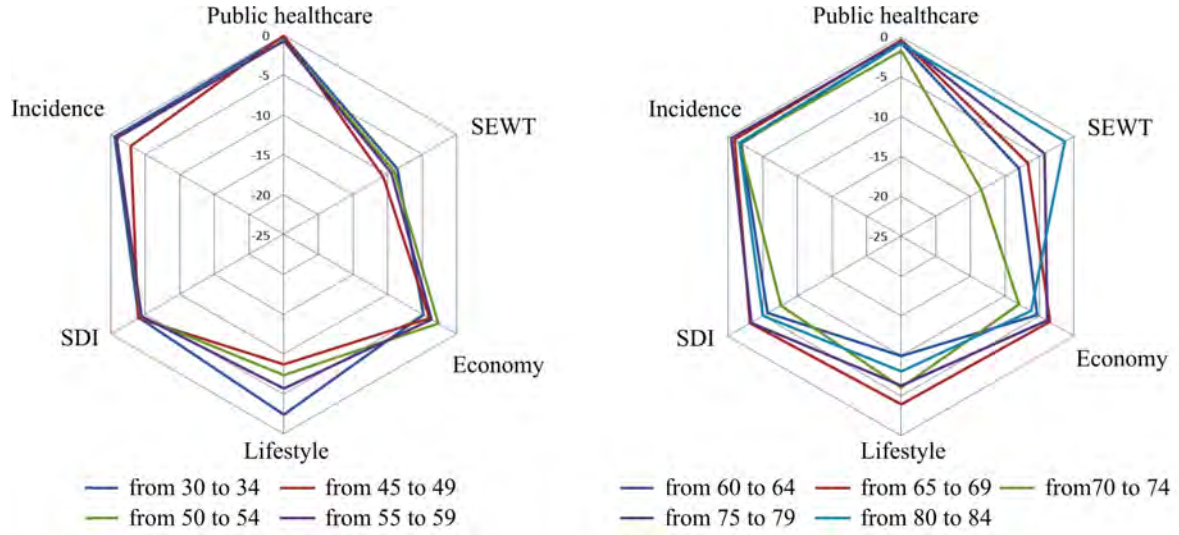

Figure 3. A decline in age-specific mortality rates due to CVD among the RF population as per groups of the determinants given their scenario changes by 2024, (%): SEWT is sanitary-epidemiological welfare on a given territory; SDI is socio-demographic indicators

[9] Actual mortality rates due to CVD accounted for 47.0 % in the total mortality in 2019.

discovered differences between the analyzed age groups were largely due to influence exerted by indicators of sanitary-epidemiological welfare on the age group "30–59 years". It was by 1.6 times higher in this age group than among older people (a decline in mortality rates equaled 9.3 and 5.8 % accordingly).

The group of indicators that characterized lifestyle also turned out to be significant for a predicted decline in mortality rates due to CVD. An averaged decline in the analyzed mortality rates amounted to 9.2 % in the age group "60 years and older" within the set scenario. It was by 1.24 times higher than in the age group "30–59 years". Changes in socio-demographic indicators and indicators of the public healthcare system had comparable capacities to facilitate a potential decline in age-specific mortality rates due to CVD under the set scenarios. This decline would reach 4.7 % and 0.7 % accordingly in the age group "30–59 years" and 5.2 % and 0.9 % in the age group "60 years and older". Primary incidence rates are both factors that result from impacts exerted by all the analyzed socio-hygienic determinants and the initial basis under modifying influence by the analyzed SHD (they describe the initial health status). Their role in a decline in age-specific mortality rates due to CVD was more apparent in the age group "60 years and older" (by 2.1 times higher) than among people aged 30–59 years under the set scenarios (Figure 2).

We analyzed isolated effects produced by specific socio-hygienic factors on age-specific mortality rates due to CVD and calculated potential LEB levels. This enabled us to determine priority determinants for the analyzed age groups (Table 3).

Physical activity is the most significant factor in the analyzed larger age groups (30–59 years and 60 years and older). In case the indicator reaches its target value 55.0 %[10], LEB grows by 21 and 106 days accordingly. We detected a significant effect produced by growing economic welfare of households in the analyzed age groups (growing consumer expenses provided additional 9 and 41 days; growing average incomes per capita, 4 and 22 days accordingly). We also established another significant factor with comparable priority. It characterized diets, namely, consumption of vegetables and melons growing by 34.0 % against the current levels up to the recommended standards[11]. This target achieved, effects produced on LEB would be positive in both larger age groups, resulting in its growth by 6 and 25 days accordingly. "A share of employed people with higher education" was important for both analyzed groups as it would facilitate LEB growth by 5 and 17 days accordingly if it increased by 11.9 % against its current level.

A decrease (from 34.0 to 83.0 %) in a share of workers exposed to harmful occupational factors was a priority in the age group "30–59 years". This concerns a decline in such exposures as work intensity (5 days), harmful microclimate at a workplace (3 days), dust and aerosols in workplace air (3 days), and electromagnetic fields at workplaces (3 days).

Several factors were established to have high priority in the age group "60 years and older". They include a rise by 11 % in shares of expenses on social policies within consolidated budgets (11 days); a decline by 23 % in ethanol consumption per capita (adult population) (8 days); a growth by 46.0 % in gross regional product (6 days); a decline by 7.0 % in primary incidence of diseases of the musculoskeletal system and connective tissue among people older than working age (4 days).

[10] A share of people who do sports or physical exercises. Federal'nyi proekt «Sport – norma zhizni» ["Sport is the standard of living" Federal project]; Pasport natsional'nogo proekta «Demografiya» (utv. prezidiumom Soveta pri Prezidente RF po strategicheskomu razvitiyu i natsional'nym proektam, protokol ot 24.12.2018 № 16) [The profile of the "Demography" National project (approved by the Presidium of the RF Presidential Council on strategic development and national projects, the meeting report issued on December 24, 2018 No. 16)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_317388/4e8c28415c3cabb0f45fa6ed843c85bd7dbee4b9/ (August 15, 2022) (in Russian).

[11] Ob utverzhdenii Rekomendatsii po ratsional'nym normam potrebleniya pishchevykh produktov, otvechayushchikh sovremennym trebovaniyam zdorovogo pitaniya: Prikaz Ministerstva zdravookhraneniya RF ot 19 avgusta 2016 g. № 614 [On approval of the Recommendations on rational consumption of foods that correspond to up-to-date standards of a healthy diet: The Order by the RF Public Healthcare Ministry dated August 19, 2016 No. 614]. *GARANT: information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/71385784/ (August 15, 2022) (in Russian).

Table 3

Priority socio-hygienic factors that separately modify age-specific mortality rates due to CVD with calculated LEB levels as per larger age groups, days

30–59 years		60 and more years	
Socio-hygienic factor	Effect on LEB, days	Socio-hygienic factor	Effect on LEB, days
A share of people who do sports or physical exercises, %	21	A share of people who do sports or physical exercises, %	106
Consumer expenses per capita, rubles per month	9	Consumer expenses per capita, rubles per month	43
Consumption of basic foods in households (vegetables and melons), kg/year/consumer	6	Consumption of basic foods in households (vegetables and melons), kg/year/consumer	25
A share of employed people with higher education aged 15–72 years, %	5	Average incomes per capita, rubles per month	22
A specific weight of workers with working conditions at their workplaces not conforming to hygienic standards (work intensity), %	5	A share of employed people with higher education aged 15–72 years, %	17
Average incomes per capita, rubles per month	4	A share of expenses on social policies within consolidated budgets, %	11
A percent of soil samples not conforming to sanitary-hygienic requirements (microbiological indicators), %	3	Ethanol per capita (adult population)*, liters per capita	8
A share of workplaces at industrial enterprises not conforming to sanitary-hygienic requirements (microclimate at a workplace), %	3	A percent of soil samples not conforming to sanitary-hygienic requirements (microbiological indicators), %	6
A share of air samples with admixtures exceeding MPC at industrial enterprises (dust and aerosols at workplaces), %	3	Gross regional product per capita, rubles	6
A share of workplaces at industrial enterprises not conforming to sanitary-hygienic requirements (EMF at a workplace), %	3	Primary incidence of diseases of the musculoskeletal system and connective tissue among people older than working age, ‰	4

Note: * means the calculation was based on retail sales of alcohols. A share of ethanol was taken according to the values stated in the State Standards (GOST) for relevant types of alcohol products.

Discussion. As we were modeling relations between the analyzed socio-hygienic determinants and age-specific mortality rates due to CVD, we established low explained variance of the analyzed factors in age groups younger than 30 years and, in addition, declining values of the determination coefficient in age groups 70 years and older although it still remained higher than 0.55. This may indicate some additional effects produced by other factors on mortality rates due to CVD in these age groups that were not included in the analyzed set of socio-hygienic determinants. Children mortality due to CVD most often occurs in case there are congenital malformations and cardiomyopathy that are largely caused by genetic factors or improper healthcare (poor prenatal diagnostics, surgical treatment or pediatric care not being effective) [15, 16]. Meanwhile, adverse effects produced by socio-hygienic factors on children due to allostatic loads or chronic stress may create elevated risks of cardiovascular diseases developing at adulthood [17, 18].

We established that the models of relations between the analyzed socio-hygienic determinants and age-specific mortality rates due to CVD predicted 43.3 % of the effects on LEB obtained by direct modeling of relations between socio-hygienic factors and LEB [14]. Actual contribution made by mortality due to CVD to the total population mortality equals 47.0 % and this indicates that the created models allow quite precise predictions.

In addition, we compared the results of modeling accomplished in the present research

work with those obtained in our previous work [14] and found out they were quite consistent as regards identified priority determinants or their groups. This may indicate the perceptron truly has an optimal structure and there is continuity of the modeling results.

The authors of the work [19] applied hierarchical linear regression to examine 35 indicators. They established that modifiable health determinates accounted for 54.0 % of explained variance of public health at the national level in the USA. Relative contributions made by each groups of determinants were as follows: socioeconomic factors, 47.0 %; behavioral factors, 34.0 %; factors related to public healthcare, 16.0 %; environmental factors, 3.0 %. In this study, lifestyle-related indicators and sanitary-epidemiological welfare on a given territory were established to be the most significant groups of determinants that produced the greatest effects on LEB through age-specific mortality rates due to CVD.

Certain socio-hygienic determinants, such as people's physical activity, incomes, education, and consumption of vegetables, had more apparent effects on LEB. It was shown in multiple relevant studies that aimed to determine cause-effect relations between environmental factors and lifestyle-related ones and incidence of / mortality due to cardiovascular diseases [20–22].

Our estimates of priority regarding influence of the analyzed factors on LEB in older age groups are similar to the results obtained in the study [23]. The authors examined remaining life expectancy[12] in various administrative districts in Germany by using two-dimensional analysis. They showed that "a share of employees with academic degrees" was the most reliable predictor of this indicator; RLE was also influenced significantly by "a share of elderly people provided with financial support", "household incomes", and "unemployment". In addition, the authors of the work [23] showed that factors related to public healthcare had only insignificant influence and this is well in line with our results, which, as we'd like to point out, were obtained by using multi-dimensional analysis (factor analysis, ANN) of heterogeneous factors.

The study [24] showed that life expectancy at birth could be determined by socio-economic differences between population groups. Thus, 13.0 % of women and 27.0 % of men with low incomes were established to die before they reach 65 years; differences in LEB between people with low and high incomes amounted to 4.4 years for women and 8.6 years for men. In this study, we revealed that "consumer expenses" and "incomes per capita" were also significant factors able to modify LEB levels as it was shown in other relevant studies [25–27]. In addition, such factors as "expenses on social policies" and "gross regional product" turned out to be significant for the age group "60 years and older". This might be due to compensatory influence exerted by these factors on retired people who have to face a substantial decline in incomes (loss of their major source).

Overall, we can conclude that studies with their aim to examine influence exerted by a multi-component environment on public health are a promising trend in preventive medicine (hygiene). However, finding solutions to tasks set within such studies and achieving their goals should rely on multi-level and interdisciplinary approaches [28].

This study has certain limitations. First, only a limited list of indicators has been examined (206 overall) that characterize a multi-component complex environment in the RF; second, a time range is rather short (2010–2019); and finally, a research territory (the Russian Federation). The study results are largely able to give an insight into cause-effect relations between environmental and lifestyle-related factors and age-specific mortality rates due to CVD in the age group "30 years and older" together with providing a predictive estimate of potential changes in LEB. If we want to establish such relations in age groups younger than 30, we will

[12] Remaining life expectancy (RLE) is applied since the study focuses on calculating LEB for people aged 60 years (e_{60}).

need to adjust our initial datasets and, probably, to develop our mathematical approach.

Conclusions:

1. Our examination of cause-effect relations between socio-hygienic factors and age-specific mortality rates due to CVD revealed that the greatest share of explained variance ($R^2 > 0.5$) is in the age groups "30 years and older".

2. A predicted growth in LEB determined by using scenario modeling of relations between the analyzed socio-hygienic factors and age-specific mortality rates due to CVD amounted to 514 days (1.3 years). The greatest aggregated effect on a potential growth in LEB would be produced by lifestyle-related factors (0.56 years or 205 days) and sanitary-epidemiological welfare on a given territory (0.34 years or 126 days). We established that a probable decline in mortality due to CVD within the analyzed models amounted to 24.8 % in the age group "30–59 years" and 22.3 % in the age group "60 years and older".

3. "A share of population doing sports or physical exercises", "Consumer expenses per capita", "Average incomes per capita", "Consumption of vegetables and melons", "A share of population with higher education" and some other determinants are priority ones as regards a decline in mortality rates due to CVD in the age groups "30 years and older".

4. Indicators that described working conditions also had quite a high priority among influencing socio-hygienic determinants in the age group "30–59 years". These indicators included work intensity (5 days), microclimate at workplaces (3 days), dust and aerosols in workplace air (3 days), electromagnetic fields at workplaces (3 days) etc.

5. Age-specific mortality rates due to CVD in the age group "60 years and older" were mostly determined by such indicators as a share of expenses on social policies within consolidated budgets (11 days); ethanol consumption per capita (adult population) (8 days); gross regional product (6 days); primary incidence of diseases of the musculoskeletal system and connective tissue among people older than working age (4 days).

6. The suggested methodical approach to predicting a potential growth in LEB is based on modeling cause-effect relations between environmental factors and age-specific mortality rates due to CVD. It can be helpful for making relevant managerial decisions regarding prevention of cardiovascular diseases among population as well as within examining influence exerted by environmental factors and lifestyle-related ones on other priority reasons for population mortality.

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Research article

FIVE-YEAR EXPERIENCE IN PROVIDING INFECTIOUS SAFETY OF DONOR BLOOD AND ITS COMPONENTS GAINED BY THE BLOOD CENTER OF THE RF FEDERAL MEDICAL-BIOLOGICAL AGENCY

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Screening technologies aimed at identifying such transfusion transmissible infections (TTI) as hepatitis B and C, HIV-1,2 and syphilis have been developing and this has resulted in increased safety of applied hemotherapy.

Our research goal was to analyze detection of infectious markers in donors of the FMBA Blood Center over five years.

We examined 167,389 samples of donor blood taken from 53,093 donors of blood and its components by the FMBA Blood Center over the period from 2015 to 2019.

Over the whole analyzed period, we detected 1453 infectious-positive samples taken from 1235 donors. Average long-term quantity of detected hepatitis C markers equaled 78.6 ± 9.4; hepatitis B, 49.8 ± 8.2; syphilis, 66.2 ± 16.8; HIV, 52.8 ± 13.2. We also analyzed detected TTI markers in long-term dynamics and established an ascending trend in a number of syphilis markers (the growth rate was 3.2), hepatitis B (the growth rate was 2.5), and a descending trend in hepatitis C markers (the decrease rate was 3.3) as well as HIV markers (the decrease rate was 1.7). This decrease rate in detection of HIV markers (fall by 1.7) occurred both among first-time and regular donors. At the same time, we revealed growing detection of syphilis markers both among first-time donors where it grew by 3.6 and among regular ones, by 1.4. Frequency of infection markers was higher among first-time donors than among regular ones as per syphilis markers, 2.351 (95 % CI: 1.862–2.938), $p < 0.00001$; hepatitis B markers, 2.111 (95 % CI: 1.622–2.763), $p < 0.00001$; hepatitis C markers, 2.107 (95 % CI: 1.708–2.609), $p < 0.00001$; and HIV, 2.471 (95 % CI: 1.9–3.238), $p < 0.00001$.

Over the last 5 years, there was a descending trend in detection of transfusion transmissible infections among donors regarding HIV and viral hepatitis C excluding tests aimed at detecting syphilis and viral hepatitis B markers.

Keywords: *Blood service, blood donors, transfusion transmissible infections, HIV, hepatitis, syphilis, viral hepatitis B, viral hepatitis C, infections markers screening, infectious safety of blood transfusions.*

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The Blood service is a key branch of the public healthcare in Russia. It secures storage and use of safe blood components necessary for rendering high-technology and specialized medical assistance. A priority safety issue in the field is to prevent transfusion transmissible infections (TTI). The Blood service applies three basic tools to resolve it. The first one is temporary or permanent rejection of a donor based on questioning or a medical examination that includes epidemiological control. The second tool is laboratory blood screening aimed at detecting leading infection markers and the third one is additional treatment of donated blood components (quarantine, leukodepletion, pathogen-inactivating technologies, etc.).

Donor blood was first screened to detect any infection markers in it as far back as in 1940ties; the first screening involved testing to detect syphilis in donor blood [1]. Notably, the first case when syphilis was transmitted with transfused blood was detected in 1915 and already by 1941 there were 138 such cases registered in literature sources [2, 3]. *Treponema pallidum* bacteremia is more often detected at the first or second stage of the disease and often persists for a short period even if a donor has become infected quite recently [4]. At the same time, Treponemas are relatively fragile and sensitive to cold; therefore, there is a very low risk that the infection is transmitted with transfused blood that was kept under a temperature below 20 °C for more than 72 hours [3]. There is a direct relationship between a number of organisms in blood and a period of their viability (potential infectivity) [5, 6]. A retrospective study involved examining 98 blood units which were donated by syphilis-positive people, underwent a 7-day quarantine period under 4 °C and then were transfused to 90 recipients. As a result, no transmissions were detected and none of the tested recipients had seroconversion [7]. The same study did not reveal any passively transfused antibodies in recipients when their initial titer was lower than 1:8; passively transmitted antibodies were not further detected after 10 days in those recipients who received blood component units with their titer varying from 1:8 to 1:64. In many developed countries, transfusion transmissible syphilis is no longer detected and this leads to questions why blood donors are still tested to reveal the disease [8]; however, sometimes syphilis is still transmitted with blood components in the southern Asia [9].

In early 1970ties testing to detect hepatitis B surface antigen (HBsAg) was introduced [10]. Data obtained by initial HBsAg screening revealed greater infection prevalence among paid donors; this made the Blood service switch to completely unpaid donation in the USA and many other countries by middle 1970ties [11, 12]. Only 10 % of all the post-transfusion viral hepatitis cases that were still detected in 1970ties were caused by the hepatitis B virus (HBV). The remains cases were first assumed to be caused by the hepatitis A virus [13]. However, typical hepatitis A is an acute disease without tendency to become chronic and due to it the disease is quite easy to diagnose. Therefore, donor banks are able to detect it by simply questioning a donor [11]. Further studies aimed at examining other hepatitis types did not find any evidence of antibodies to hepatitis A [14] and this resulted in Doctor Harvey Alter spotting out the third hepatitis type which he called “human non-A, non-B hepatitis”. Large-scale multi-centered prospect studies accomplished in late 1980ties and early 1990ties revealed epidemiological associations between surrogate markers, namely elevated alanine aminotransferase (ALT) levels, in donors and developing post-transfusion hepatitis in recipients [14]. At the same time, some data proved that anti-HBc-positive blood was associated with residual cases of post-transfusion hepatitis B that was not detected by HBsAg screening [15]. In 1986, after the US National Institute of Health (NIH) issued a report on anti-HBc, blood banks in the USA introduced additional testing to establishing ALT levels and anti-HBc-testing [16]. In 1989 Michael Houghton with colleagues from the US Center for Disease Control (CDC) and the US National Institute of Health (NIH) discovered the hepatitis C virus (HCV) and this put an end to the searching

for reasons of developing "human non-A, non-B hepatitis" [17]. These experts also developed laboratory testing procedures for detecting antibodies to this virus.

The first official discussion on whether it was possible to transmit HIV with blood and its components started in December 1982 in the weekly report on incidence and mortality issued by the US Center for Disease Control [18]. The human immunodeficiency virus (HIV) itself was detected in spring 1984 and detection of antibodies was very high in homosexual males. Several studies identified this virus as the one that caused AIDS [19, 20]. The first certified test to detect antibodies to HIV became available only in 1985 and this made it possible to reduce risks of becoming infected via blood transfusion by 86 % [21]. Some retrospective studies established that more than 30 % of donors who were HIV-positive also had some reactions to anti-HBc just like 90 % of recipients who received blood donated by HIV-infected people or people who were assumed to have the acquired infection [15]. At the same time the very concept that it was acceptable to use surrogate markers in blood donation was very often criticized [22, 23].

In 1990ties, a model was developed to assess risks of incidence. This showed that an antibody-negative window preceding to the development of serological markers as a patient's response made the greatest contribution to residual risks for the established transfusion transmissible viruses [24]. An antibody-negative window for the first generation of tests aimed at detecting antibodies to HIV equaled 56 days [25]. In 1999 NAT (Nucleic acid testing) was introduced to detect HIV and this allowed reducing a residual infection window down to one week [26]. Up-to-date testing to detect primary transfusion transmissible viruses relies on simultaneous use of molecular-biological and immunological studies thereby reducing risks of becoming infected with HIV, hepatitis B and C down to one case per 2,000,000 [10].

The FMBA Blood Center in Russia acts in accordance with the existing regulatory documents and selects blood donors either from permanent residents or from people who were registered in Moscow and the Moscow region at least half a year ago and have been living here ever since. Given that, it is especially interesting to examine prevalence of infectious markers among blood donors and to compare the results with the official statistical data on incidence of these diseases among population in this region.

Our research goal was to analyze detection of infectious markers in donors of the FMBA Blood Center over the period from 2015 to 2019.

Materials and methods. We performed a retrospective observation study of donors who were accepted by the FMBA Blood Center (hereinafter FMBA BC for short) from 2015 to 2019. Over the analyzed period, 53,093 donors visited the FMBA BC, 162,099 blood units and blood components were donated, and 5290 donors were examined. All the donated blood units and components were tested to detect HIV, hepatitis B and C, and syphilis markers. Over the whole analyzed period, 1452 samples were established to be positive regarding transfusion transmissible infections; these samples were taken from 1235 donors.

Testing to detect syphilis was accomplished by precipitation to reveal non-specific antibodies to cardiolipin antigen and by Chemiluminescence Immunoassay (CLIA). If either of the tests was positive, testing was repeated twice under the same conditions as in the first tests, reagents included. If at least one of this repeated testing was positive after either of selected methods was applied, a donor blood sample was considered syphilis-positive. We used several reagent kits including "LUIS-TEST" to detect syphilis-associated reaginic antibodies ("NPO "Diagnostic systems"" LLC, Russia) and ARCHITECT Syphilis Reagents 8D06-35 (Abbott Laboratories, USA). CLIA tests were performed with ARCHITECT i2000SR analyzer (Abbott Laboratories, USA).

Hepatitis B and C markers and HIV markers were detected by CLIA and by molecular-biological techniques, namely multiplex NAT-tests by PCR using COBAS S 201 system (Roche Diagnostics GmbH, Germany)

and transcriptional amplification using Procleix Panther system (Gen-probe Inc, USA). Several reagent kits were used, including ARCHITECT HIV Ag/Ab Combo Reagent, ARCHITECT Ab HCV Reagent, ARCHITECT HBsAg Qualitative II Reagent (Abbott Laboratories, USA) for CLIA and Cobas TaqScreen MPX Test, v 2.0 (Roche Diagnostics GmbH, Germany), Procleix Ultrio Elite Assay (Gen-probe Inc, USA) for molecular-biological techniques.

In our analysis, people who donated blood or its components at the FMBA BC for the first time were considered first-time donors. A medical examination of a donor at the FMBA BC prior to donation included establishing ALT activity and clinical blood tests with total leukocyte count. In case any deviations were detected in these indicators, a donor was rejected to donate blood or its components.

Statistical analysis focused on growth rates, average long-term numbers, and odds ratio for independent samplings. The results were statistically analyzed using Microsoft Office Excel 2016 and SPSS v. 23.

Results. Table 1 shows the total targets regarding donor acceptance and the number of examined donor blood samples.

Over the period from 2015 to 2019, the number of donors accepted by the FMBA BC grew by 7.5 % and donation of blood and its components increased by 13 %. The absolute number of regular donors went up by 14 % whereas the number of first-time donors remained steady.

Over the last five years, the share of samples with detected TTI markers was lower than 1.0 % (0.73–0.92 % of the total donations) or 1.5 % (1.22–1.44 % of the total number of donors). Table 2 shows the total quantity of TTI markers detected in donors from 2015 to 2019.

The average long-term number of TTI markers detected from 2015 to 2019 at the FMBA BC equaled 290.4 ± 40.5 (or 8.67 ± 1.21 per 1000 donor blood samples). Tables 3–6 show occurrence of syphilis, hepatitis B, hepatitis C and HIV in blood donors accepted by the FMBA BC in 2015–2019.

The number of detected VHC markers amounted to 393 (0.74 % of the total number of donors in 2015–2019); syphilis markers, 331 (0.62 % of the total number of donors in 2015–2019); HIV markers, 264 (0.5 % of the total number of donors in 2015–2019); VHB markers, 249 (0.47 % of the total number of donors in 2015–2019).

The average long-term number of detected VHC markers equaled 78.6 ± 9.4; VHB markers, 49.8 ± 8.2; syphilis markers, 66.2 ± 16.8; HIV markers, 52.8 ± 13.2. We analyzed TTI markers in long-term dynamics and revealed an ascending trend in the number of syphilis markers (the growth rate equaled 3.2) and VHB markers (the growth rate was 2.5) whereas the number of VHC markers went down (the decrease arte was 3.3) as well as the number of HIV markers (the decrease rate was 1.7) (Table 7).

Over five years, from 2015 to 2019, there was an increase in the growth rate of the VHB markers detected in donors; despite that, the number of detected markers went down in

Table 1

Target donor acceptance and the number of examined blood samples at the FBMA BC from 2015 to 2019

Period	2015	2016	2017	2018	2019	Over the whole period
Number of donors	18,399	17,687	17,294	18,961	19,793	53,093
First-time donors	7847	7398	6920	7358	7730	
Regular donors	10,552	10,289	10,374	11,603	12,063	
% of first-time donors	42.6 %	41.8 %	40.0 %	38.8 %	39.1 %	
Donations	32,587	30,417	30,192	32,074	36,829	162,099
Tests	723	246	371	2145	1805	5290
A number of samples	33,310	30,663	30,563	34,219	38,634	167,389
% of samples form first-time donors	24.1 %	24.3 %	22.9 %	22.9 %	21.0 %	

Table 2

Prevalence of TTI markers detected by the FMBA BC from 2015 to 2019

Period	2015	2016	2017	2018	2019
The total number of donor blood samples	33,310	30,663	30,563	34,219	38,634
The number of samples with detected TTI markers, abs.	245	285	291	326	305
The number of samples with detected TTI markers, %	0.73	0.92	0.95	0.95	0.79
The total number of donors	18,399	17,687	17,294	18,961	19,793
The number of donors with detected TTI markers, abs.	238	254	247	256	242
The number of donors with detected TTI markers, %	1.29	1.44	1.43	1.35	1.22

Table 3

Occurrence of syphilis in blood donors accepted by the FMBA BC in 2015–2019

Indicator	2015	2016	2017	2018	2019	TOTAL
Total detection	60	57	57	74	83	331
% of occurrence	0.33 %	0.32 %	0.33 %	0.39 %	0.42 %	0.62 %
First-time donors	41	40	42	54	54	231
Regular donors	19	17	15	20	29	100
Men	46	45	36	51	56	234
Women	14	12	19	23	27	95
Average age	35.7	35.3	36.9	35.5	34.8	35.6

Table 4

Occurrence of hepatitis B in blood donors accepted by the FMBA BC in 2015–2019

Indicator	2015	2016	2017	2018	2019	TOTAL
Total detection	43	57	41	50	58	249
% of occurrence	0.23 %	0.32 %	0.24 %	0.26 %	0.29 %	0.47 %
First-time donors	29	43	30	35	31	168
Regular donors	14	14	11	15	27	81
Men	24	30	22	33	37	146
Women	19	27	19	17	21	103
Average age	30.2	33.5	31.0	30.3	33.0	31.6

Table 5

Occurrence of hepatitis C in blood donors accepted by the FMBA BC in 2015–2019

Indicator	2015	2016	2017	2018	2019	TOTAL
Total detection	74	88	83	78	70	393
% of occurrence	0.40 %	0.50 %	0.48 %	0.41 %	0.35 %	0.74 %
First-time donors	51	70	46	58	40	265
Regular donors	23	18	37	20	30	128
Men	41	50	53	46	41	231
Women	33	38	30	30	29	160
Average age	34.5	33.7	32.2	32.3	31.5	32.8

Table 6

Occurrence of HIV in blood donors accepted by the FMBA BC in 2015–2019

Indicator	2015	2016	2017	2018	2019	TOTAL
Total detection	61	52	66	54	31	264
% of occurrence	0.33 %	0.29 %	0.38 %	0.28 %	0.16 %	0.50 %
First-time donors	40	35	46	45	21	187
Regular donors	21	17	20	9	10	77
Men	35	27	42	32	19	155
Women	26	25	24	22	12	109
Average age	33.6	32.9	29.4	31.3	30.0	31.4

Table 7

Average long-term number and growth / decrease rate of the detected TTI markers

TTI markers	Average long-term number	Growth arte	Decrease rate
VHC	78.6 ± 9.4	-	3.3
VHB	49.8 ± 8.2	2.5	-
Syphilis	66.2 ± 16.8	3.2	-
HIV	52.8 ± 13.2	-	1.7

first-time donors (2.8 cases, whereas the growth rate equaled 0.9 among regular donors). As for VHC markers, the decrease rate amounted to 2.0 among first-time donors and the growth rate amounted to 0.9 among regular donors. The number of detected HIV markers went down by 1.7 both among first-time and regular donors. At the same time, the number of detected syphilis makers increased both among first-time donors, by 3.6, and among regular ones, by 1.4. Overall, over the analyzed years, frequency of the TTI markers was higher among first-time donors than among regular ones as per syphilis, 2.351 (95 % CI: 1.862–2.938), $p < 0.00001$; hepatitis B, 2.111 (95 % CI: 1.622–2.763), $p < 0.00001$; hepatitis C, 2.107 (95 % CI: 1.708–2.609), $p < 0.00001$; and HIV, 2.471 (95 % CI: 1.9–3.238), $p < 0.00001$.

A probability to detect TTI markers was higher among donors in 2019 than in 2015 regarding syphilis, $OR = 1.286$ (95 % CI: 0.9227–1.8), $p = 0.1383$, and hepatitis B, $OR = 1.254$ (95 % CI: 0.8453–1.871), $p = 0.2627$. Yet, it was lower for hepatitis C and HIV, $OR = 0.8793$ (95 % CI: 0.6328–1.221), $p = 0.4425$, and $OR = 0.4724$ (95 % CI: 0.3032–0.7248), $p = 0.0005$ accordingly. The total probability of detecting any TTI markers was slightly lower for donors in 2019 than in 2015, $OR = 0.9452$ (95 % CI: 0.78–1.132), $p = 0.5397$.

Syphilis markers were more frequent among male donors than among female ones, $OR = 2.121$ (95 % CI: 1.674–2.703), $p < 0.00001$. The same was true for hepatitis C, $OR = 1.24$ (95 % CI: 1.013–1.52), $p = 0.037$. As for the other two infections, we did not detect any statistically significant differences for them: hepatitis B markers, 1.216 (95 % CI: 0.9454–1.569), $p = 0.13$; HIV markers, 1.22 (95 % CI: 0.9553–1.563), $p = 0.11$.

Discussion. Donors who are accepted by the FMBA BC account for a rather small share of the total donors who donate blood and its components in Russia, from 1.218 to 1.477 % [27, 28].

According to the documents that regulate donation of blood and its components, only a healthy adult person who voluntarily consents to donate blood or its components can be a blood donor. Additional medical examination prior to blood donation makes it possible to refuse potential donors with clinical signs of certain diseases (skin rush, fever, etc.). Yet, symptomless infections are the most dangerous ones and the same goes for infections that can persist in spite of additional treatment provided for blood components after donation (leukofiltration, pathogen inactivation) and proper storage conditions.

To provide infectious safety of donor blood and its components, all the stored products (including those under quarantine) taken from donors with occurring TTI markers (in case a positive or a doubtful sample was detected by the first testing) were rejected and destroyed.

In the analyzed period, there was a stable ascending trend in the number of detected TTI markers in first-time donors and a descending trend in the number of such markers among regular donors. Frequency of TTI markers is known to be significantly lower among regular donors of blood and its components than among first-time ones [29].

Overall, over the last five years, frequency of infectious markers regarding such

infections as hepatitis B and C as well as human immune deficiency virus tends to decrease among blood donors and this is in line with the general statistical data collected in the country[1]. This remarkable success in fighting against viral hepatitis B was achieved due to mass immunization of the RF population against the disease. Incidence with acute hepatitis B went down by 4.9 times over the last ten years (from 2011 to 2020)[1]. Incidence with acute viral hepatitis C in the RF has also been declining steadily and annually since 2014. Over the last 10 years HIV detection among the RF population has also been decreasing steadily although coverage of the population with HIV testing has grown by 43.7 % over the same period[1]. This fully coincides with our statistical data on donors accepted by the FMBA BC; however, the epidemiological situation as per HIV remains rather tense in the Russian Federation.

In our study, we detected a certain growth in frequency of syphilis markers in blood donors over the last five years. The population group with this indicator growing is males aged 30–39 and this is fully in line with the statistical picture of incidence in Russia [30]. Growing incidence of late and unspecified types of syphilis is predominantly due to an increasing number of cases detected among foreign citizens, workers employed by transport companies, banks and educational institutions.

World studies based on clinical and experimental data estimate a residual risk of infection as being equal to 3–14 %; this risk is associated with testing potential donors who are infected with hepatitis B but still have negative test results obtained by immunological and molecular-biological tests to detect HBsAg [31]. Given that, in 2021 the Blood Service introduced additional testing to detect anti-HBcore[2].

It is noteworthy that occurrence of positive TTI markers detected by the Blood service does not always indicate that a donor has an infection and requires additional examination by a specialized medical organization. Still, their detection is an important step towards increasing infectious safety of donor blood and its components.

Conclusions. Our study indicates that over the last five years frequency of TTI markers has tended to decrease among donors accepted by the FBMA Blood Center, syphilis markers excluded. The total frequency of syphilis markers equals 0.62 %; viral hepatitis B markers, 0.47 %; viral hepatitis C markers, 0.74 %; and HIV markers, 0.5 % of the total number of blood donors accepted by the RF FMBA Blood Center over the last five years. Markers of infections were more frequently detected among first-time donors than among regular ones and among male donors than among female ones.

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Competing interests. The authors declare no competing interests.

[1] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2020 godu: Gosudarstvennyi doklad [On sanitary-epidemiological welfare of the population in the Russian Federation in 2020: the state report]. Moscow, the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2021, 256 p. (in Russian).

[2] Ob utverzhdenii poryadka prokhozhdeniya donorami meditsinskogo obsledovaniya i perechnya meditsinskikh protivopokazanii (vremennykh i postoyannykh) dlya sdachi krovi i (ili) ee komponentov i srokov otvoda, kotoromu podlezhit litso pri nalichii vremennykh meditsinskikh pokazanii, ot donorstva krovi i (ili) ee komponentov: Prikaz Ministerstva zdravookhraneniya RF ot 28.10.2020 № 1166n [On approval of the procedure for medical examination of donors and the list of medical contraindications (temporary and permanent) to donating blood and (or) its components and the period of rejection in case a potential donor has temporary medical contraindications donating blood and (or) its components: The Order by the RF Public Healthcare Ministry dated October 28, 2020 No. 1166n]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/566420621 (December 16, 2021) (in Russian).

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Research article

SUBSTANTIATION OF STATISTICAL MODEL TO DESCRIBE AND PREDICT RISKS OF TICK BITES FOR POPULATION

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Incidence of tick-borne encephalitis and other tick-borne infections correlates with a number of people applying for medical aid due to tick bites. Obviously, the number of registered tick bites is proportionate to people's economic and recreational activities on an endemic territory and the quantity of hungry ticks. In its turn, the quantity of ticks depends on abundance of main hosts for blood-feeding stages but with a certain time lag caused by their life cycle parameters such as molting to the next stage, diapauses, and apparent seasonality in a continental boreal climate zone.

Our research goal was to analyze and synthesize an adequate formalized/parameterized statistical model to describe and predict risks of tick bites for population.

To describe dynamics and to predict a number of people bitten by ticks exemplified by the Sverdlovsk region, we used several linear (by parameters) logistic regression models. We applied a multimodel inference framework to assess whether the observed dynamics was described adequately. Long-tern dynamics of the number of people bitten by ticks in the Sverdlovsk region is characterized with an occurring high-amplitude slow long-wave oscillation (circadecadal one, with a quasi-period being approximately 10 years) and a short-wave 2–3-year cyclicity. The former may be associated with climatic rhythm and socioeconomic trends; the latter may be caused by biotic factors.

By using the logit-regression model, we showed that the number of small mammals, both in the previous year and at the beginning of the current tick activity season can be a valuable predictor of a risk for population to be bitten by ticks.

Predictive values of the created statistical model adequately describe an initial time series of chances / probabilities of tick bites.

Keywords: *ticks, small mammals, affected by tick bites, pathogen transmission, population dynamics, population cycles, odds ratio, time series.*

Tick-borne encephalitis (TBE) is an endemic disease typical for the Central and Eastern Europe, some parts of the Northern Europe as well as for the Northern and Central Asia. Annually, 10 to 12 thousand TBE cases are registered on these territories [1].

The Urals Federal District (UFD) is highly endemic in terms of tick-borne encephalitis; within its boundaries, the greatest number of bitten people and the highest incidence rates are usually registered in the Sverdlovsk and Kurgan regions [2, 3]. Registered TBE incidence correlates with a number of people who apply for medical aid due to tick bites. Typically, there are periodical changes in incidence of tick-borne encephalitis. They have been detected over many decades and are associated with such factors as demography, changes in land use and relevant density of organisms (population) in wilderness, and

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people's recreational behavior. We should also remember that the climate change makes a significant contribution to the process as a possible driving force for cyclicity of TBE-related processes [4].

In Western Europe, virus of tick-borne encephalitis (TBE) is mostly transmitted by *Ixodes ricinus* whereas Siberian and Far Eastern strains are carried by *I. persulcatus* [5]. Ticks usually have several stages in their life cycle. Each stage in tick life cycle lasts from several months to a year, therefore, the whole cycle usually takes from two to three years. However, it may last longer, from two to six years, depending on a geographical location and sustenance. A transfer between stages in tick development is directly linked to changes related to populations of small mammals (SM) since they are basic feeders for larvae and nymphs and (though, to a lesser extent) for imago [6]. Apparent drastic changes in density of small mammal populations with the 2–3 order amplitude and a quasi-period from 3 to 5 years are well known as an example of so called population cycles [7, 8]. Abundance of small animals is assumed to have a positive effect (with certain lags) on quantities in which subsequent stages of ticks (basically, larvae and nymphs) are generated. There is a direct relation between a number of free and hungry ticks that failed to find a usual feeder and risks for people to get bitten by them [9].

Our research goal was to analyze and synthesize an adequate formalized/parameterized statistical model to describe and predict risks of tick bites for population.

Materials and methods. We took initial data (a number of bitten people in the Sverdlovsk region) from the federal statistical report form No. 2 "Data on communicable and parasitic diseases" (Section 1) (issued in 2017–2021) and from the materials provided by the Sverdlovsk Regional Center for Hygiene and Epidemiology (data collected in 1992–2006).

SM quantities were calculated at stationary spots by using break-back traps and wooden live traps [10] in spring and fall over the period from 1992 to 2021.

We calculated odds of tick bites in order to quantify influence exerted by SM density on number of people who applied for medical aid due to tick bites. *Odds* are a ratio of a number of bitten people (N_1) to the whole population of Sverdlovsk region, bitten people excluded (N_0).

There is a possible way from odds to a self-explanatory scale of likelihood or risks (1):

$$P(X) = \frac{\exp(LogOdds)}{1+\exp(LogOdds)} = \frac{Odds}{1+Odds}. \quad (1)$$

We applied logit regression, a conventional apparatus of the generalized linear models theory[1] (2):

$$Ln\left(\frac{N_1}{N_0}\right) = b_0 + \sum b_i X_i. \quad (2)$$

We estimated effects produced by the following (exogenous) predictors of (X_i): SM density in spring and fall in the previous year (SMspr(t–1) and SMfall(t–1)) and in spring in the current year (SMspr(t)). A time series (a trend) of the dependable variable Log odds ticks attacks, or LOTA, was apparently non-stationary. To consider it, we used several approaches (some strict, some heuristic to a certain extent):

1) an autoregression member of the first order being included into the model: AR(1)X where the LOTA(t–1) values observed in the previous year served as an additional predictor;

2) preliminary LOTA time series smoothing (and subsequent inclusion into the model as an additional predictor) by using local regression (*loess*); the optimal value of the smoothing parameter (*span* = 0.427) was identified with 10-fold cross-validation;

3) preliminary STL (Seasonal and Trend decomposition) of LOTA time series by using Loess and identification of the trend by smoothing it with local regression.

The initial time series and its smoothed variants are shown in Figure 1.

[1] McCullagh P., Nelder J.A. Generalized linear models. London, Chapman and Hall, 1989, 511 p.

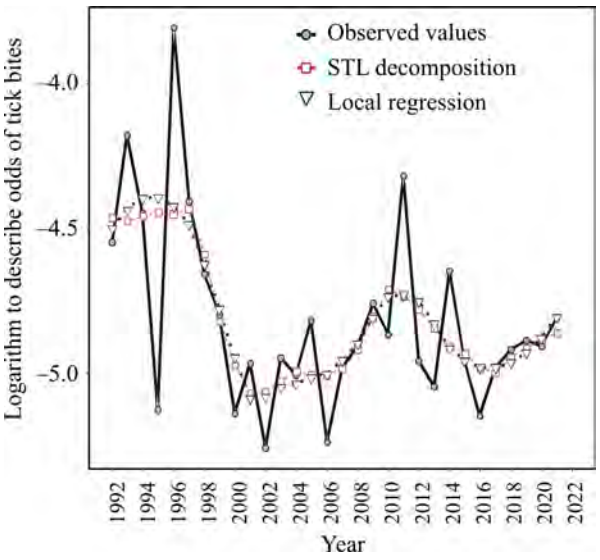

Figure 1. Dynamics of the logarithm describing odds of tick bites and smoothed variants of the rime series used to identify the trend. Sverdlovsk region, 1992–2021

Odds ratios (*OR*) and their confidence intervals (95 % CI) are given after the transformation: $OR = \exp(b_i)$ or $OR^{-1} = 1/\exp(b_i)$, where b_i are the logit regression parameters (odds ratio logarithms). Odds ratios for rare events (frequency < 10^{-1}) approach relative risk levels and it simplifies the interpretation.

We applied *Akaike information criterion or AIC* to compare and rank our logit regression models. This criterion determines optimality as a compromise between a model accuracy and complexity. A model with greater statistical adequacy corresponds to the smallest *AIC* value. The models were compared based on the modification of the initial *AIC*, *consistent Akaike information criterion (CAIC)*, calculated as per the formula (3):

$$CAIC = -2LL + k\left[1 + \ln(m)\right], \qquad (3)$$

where *LL* is the logarithm of the likelihood function maximum, *k* is the number of parameters, and *m* is the number of observations. This modification, in comparison with *AIC*, imposes stricter "penalties" for additional parameters[2].

"Weight" (relative plausibility) of each model calculated as per the formula (4) was applied to rank and compare competing models:

$$w_i = \frac{\exp\left(-0.5\Delta CAIC_i\right)}{\sum \exp\left(-0.5\Delta CAIC_i\right)}. \qquad (4)$$

This "weight" can be interpreted as a posterior probability that the *i*-th model is the best given the examined multiplicity of other candidate models. If the "weight" differed from w_{max} by less than 10 %, we considered these models to be identical as per the quality of the best one [11].

The results were statistically analyzed and visualized with Statistica v. 10.0 applied software package (StatSoft, Inc) and the R (v. 3.4.4) system for statistical computation and graphics [12].

Results and discussion. The observed long-term dynamics of odds for people to be bitten by ticks is obviously a non-stationary (not as per the mean value, or amplitude, or a period) time series (Figure 1). We can spot out the following in it:

– a trend as a long-term drift of mean values, relatively slow changes over time;

– a quasi-periodical component that is repeated relatively fast;

– remains as an irregular component in the series, relatively high-frequency noise.

The trend is probably an "echo" of both 1) a long circadecadal weather and climate cycle associated with large-scale phenomena (formation and duration/stability of atmospheric circulations and such phenomena as anticyclones that block the transfers from west) responsible for typical long-term temperature fluctuations and precipitations in a given region [13, 14]; and 2) a peculiar socioeconomic situation that existed in the Russian Federation in 90ties last century and its following improvement [15].

Quasi three-year cycles (T = 2–3 years) might be associated both with parameters of tick lifecycle and dynamics of SM numbers

[2] Akaike H. A new look at the statistical model identification. *IEEE Transactions on Automatic Control*, 1974, vol. 19, pp. 716–723.

[16], such periods being quite typical for the latter [17]. SM and tick populations are interrelated as years when ticks are highly active (their activity is estimated as per number of bitten people) follow years with maximum density of small rodents [18]. Larvae and nymphs mostly feed on small mammals and this leads to natural TBE transmission.

Dynamics of the logarithm for odds of tick bites is described optimally ($w \approx 1$, $CAIC = 13005588$) with a model that contains a trend obtained by STL-decomposition. Autoregression and local smoothing models are at a "significant disadvantage" in comparison to it: $w \sim 0$, $CAIC = 13009459$ and $w \sim 0$, $CAIC = 13072412$, accordingly.

The optimal model includes five parameters: the trend that was isolated from the LOTA time series by STL-decomposition (trend-STL); SM density: in spring in the current year, in spring and fall of the previous year; a free term b_0 (Table 1).

We included a trend estimate as an additional component into the list of predictors in the logit regression model. This made it possible to consider, though only heuristically, non-stationarity of the time series and estimate certain effects which we thought were interesting (Figure 2A).

A growth in SM density in spring last year will lead to ($p < 0.01$) odds of tick bites (to the Sverdlovsk region population) growing by 1.04 times (by 3.53 % higher, Figure 2B). A growth in the number of ticks at different stages (nymphs or imago) that are out from the diapause is very likely in the current year due to abundance of feeders that occurred last spring.

Greater SM density this spring will lead to a statistically significant decrease by 1.06 times in odds of tick bites (by 5.87 % lower, Figure 2C). Therefore, SM population in its growing phase "intercepts" tick nymphs and imago since sufficient quantities of feeders make tick bites less likely for large mammals and people.

Growing SM density last fall will lead to a statistically significant growth by 1.02 times in odds of tick bites (by 1.98 % higher, Figure 1D). SM population in fall is a projection of its density (quantity) in spring and summer. Therefore, we can expect a growing number of ticks at different stages in this tick season and it makes for growing likelihood of people being bitten during it.

Figure 3 shows the current risks of tick bites and risks (likelihood) expected (predicted) by the model for the Sverdlovsk region population.

Obviously, levels predicted by the model are quite consistent with the initial time series: both the trend and the periodical component are similar both for actual levels and those predicted by the statistical model (the correlation is strong and direct: Spearman's correlation coefficient $r_S = 0.70$; $p < 0.0001$). The determination coefficient is quite high: $R^2 = 0.66$, therefore, the model is able to explain 66 % of dispersion regarding dynamics of the logarithm for a risk (or likelihood) of tick bites. If we include additional predictors into our model, for example, those associated with dynamics of tick populations and their feeders' ones, climatic changes and socioeconomic factors, this is expected to improve its predictive capabilities.

Table 1

Parameters of the optimal model to describe long-term dynamics of the logarithm for odds of tick bites. Sverdlovsk region, 1992–2021 ("the best" logit regression model: LR (4) = 99827; $p < 0.0001$; $R^2 = 0.66$)

Parameters	b	SE(b)	Wald test (Z)	p	Odds ratio		
					OR	*95 % CI*	
b_0	1.10	0.02	47.72	< 0.0001	–	–	–
trend-STL	1.24	0.004	272.10	< 0.0001	3.45	3.42	3.48
SMspr(t–1)	0.03	0.001	41.04	< 0.0001	1.04	1.03	1.04
SMspr(t)	-0.06	0.001	-80.81	< 0.0001	1.06^{-1}	1.057^{-1}	1.061^{-1}
SMfall(t–1)	0.02	0.001	20.83	< 0.0001	1.02	1.017	1.021

Note: b_0 is a free term; *OR* is odds ratio; *LR(df)* is the test of ratios between likelihood and a number of degrees of freedom; *trend-STL* is the trend isolated from LOTA time series by STL-decomposition; SM density is: *spr(t–1)* last spring, *spr(t)* this spring, *fall(t–1)* last fall; -1 – $OR^{-1} = 1/\exp(b_i)$.

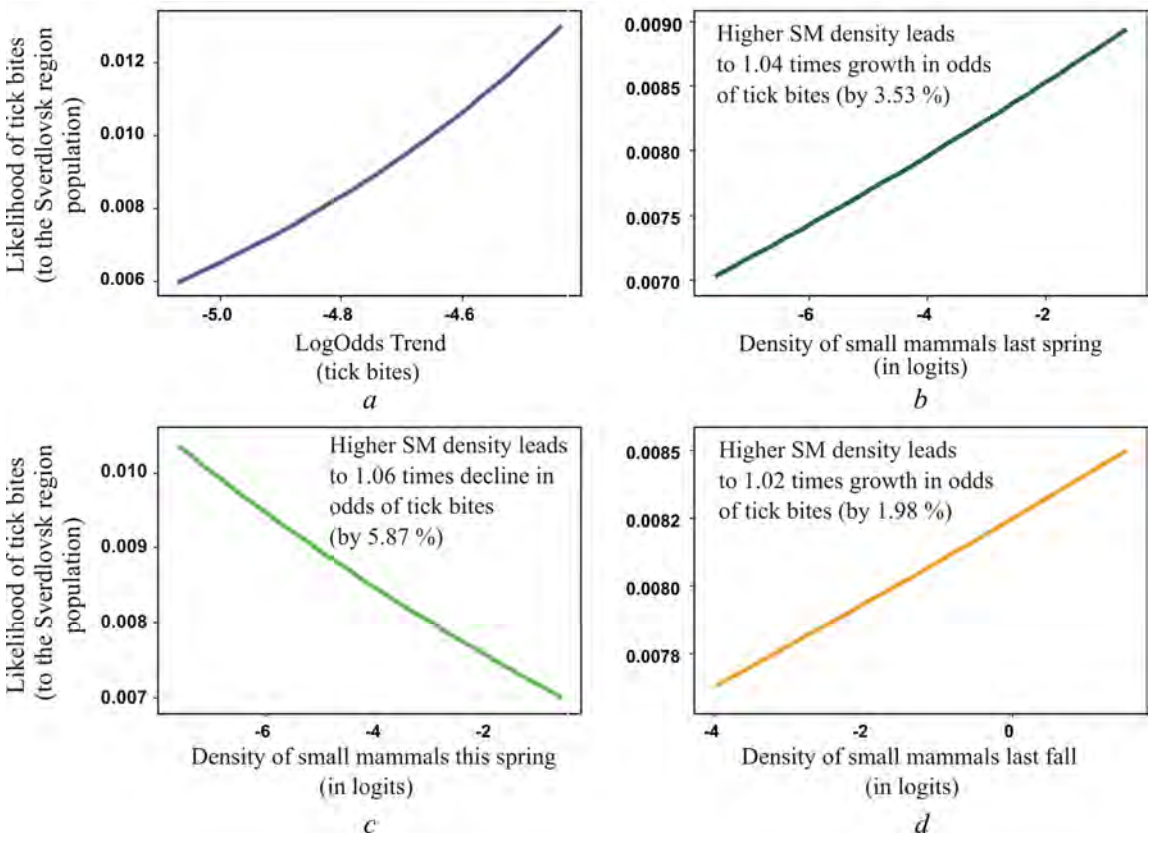

Figure 2. Dependence between likelihood of tick bites and density of small mammals: **A** is dependence on the logarithm for odds of tick bites; dependence on density of small mammals: **B** is last spring, **C** is this spring; **D** is last fall

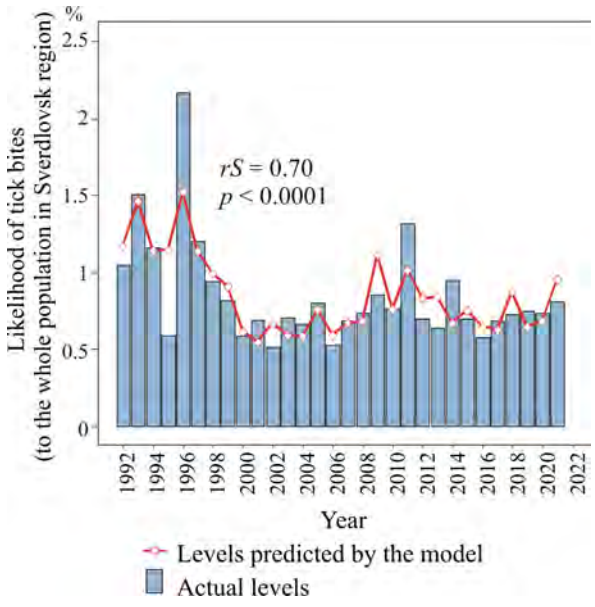

Figure 3. Actual and predicted likelihood of tick bites for the Sverdlovsk region population, 1992–2021

Conclusions:

1. Long-term dynamics of the number of people bitten by ticks can be adequately described with a model of a non-stationary time series that contains the trend and the quasi non-periodical component.

2. The logit regression model clearly showed that numbers of small mammals in the previous year and at the beginning of the current epidemiologic season when ticks are especially active can serve as a risk predictor for population warning them tick bites are quite possible. High density of small mammals in spring in the current tick activity season leads to the established "interception" effect and quantitatively estimated decline in likelihood of people being bitten by ticks. However, if density of small mammals was high in spring and fall of the year prior to the current tick activity season, then we should expect a growth in numbers of ticks at different stages in their lifecycle that have molted and survived winter (nymphs, imago) and growing risks for people to be bitten by ticks.

3. Levels predicted by the created statistical model adequately describe the initial time series of odds / likelihood of tick bites. Addi-

tional parameters included into the model will probably improve its predictive capabilities.

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Competing interests. The authors declare no competing interests.

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Research article

RISK FACTORS OF HEALTHCARE-ASSOCIATED INFECTIONS IN RECIPIENTS OF BONE MARROW TRANSPLANT

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Bone marrow recipients are the most immunocompromizied patients who are susceptible to multiple infections. It is especially true for long-term episodes of drug-associated granulocytopenia.

Our research goal was to identify risk factors of healthcare-associated infections (HAIs) in patients after bone marrow transplantation (BMT).

Risk factors of developing HAIs were identified by accomplishing an analytical epidemiological "case – control" study with 973 patients participating in it. They all underwent BMT in the Hematology, Chemotherapy and Bone Marrow Transplantation Department of the Pirogov National Medical and Surgical Center on a period from 2015 to 2018. The following diseases were diagnosed in them: lymphoma (n = 158), multiple myeloma (n = 96), and multiple sclerosis (n = 719). HAIs cases were selected based on the standard (epidemiological) case definition in accordance with the Federal Clinical Recommendations on Epidemiological Surveillance over HAIs approved by the National Association of Experts responsible for Control over Healthcare-Associated Infections.

Retrospective analysis established 75 HAIs cases or 7.7 % of the total number of the analyzed patients after BMT. Catheter-related bloodstream infections took the leading place among all the HAIs accounting for 52.0 ± 2.4 %. They were followed by bloodstream infections, 28.0 ± 3.1 %; lower respiratory tracts infections, 17.0 ± 3.2 %; and post-injection complications, 3.0 ± 0.6 %. Oncological diseases were established to cause HAIs in bone marrow recipients more frequently (OR = 5.603; 95 % CI = 3.422–9.174) than multiple sclerosis (OR = 0.178; 95 % CI = 0.109–0.292). This indicates that an underlying disease has its influence on a risk of infectious complications. We established a direct correlation between HAIs frequency and contamination with opportunistic microorganisms detected in objects in the hospital environment (r = 0.79, p = 0.01). This calls for implementing up-to-date disinfection provided for such objects.

Keywords: *bone marrow transplantation, healthcare-associated infections, febrile neutropenia, mucositis, risk factors.*

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Healthcare-associated infections (HAIs) are among the most pressing multidisciplinary issues in contemporary healthcare. This is due to their wide prevalence and their grave negative outcomes for patients' health, health workers and a country economy[1] [1–4].

A medical organization examines HAIs-related issues within the risk-based approach [5, 6] depending on its profile and applied technologies. The approach highlights the necessity to determine patient groups that are the most susceptible to risks of HAIs. Bone marrow recipients (BMR) are among patients with high risks of HAIs considering their long-term in-hospital treatment and long-term episodes of drug-associated granulocytopenia[2] [7]. According to the latest research, cumulative infectious incidence among BMR equals 10.5 % (95 % CI: 12.0–25.8 %) after allogeneic transplantation. Fifty-seven percents of these infection cases occur during a period when a patient suffers from severe neutropenia (neutrophils contents are $< 0.1 \cdot 10^6$ units/l) or pancytopenia [8]. Lethality can reach 60 % in case of developing infectious complications [9–11].

Most frequently, HAIs as well as bacteremia are induced by opportunistic microorganisms. They occur everywhere and are well-known representatives of skin, mucosa and GUT microflora[1]. At present, microorganisms from ESCAPE-pathogen[3] group are more and more frequently identified as HAIs agents.

Up-to-date infection diagnostic procedures and use of broad-spectrum antibacterial drugs make development of severe infectious complications as well as a fatal outcome much less likely [11]. However, cellular and humoral immunity in bone marrow recipients with neutropenia is not able to react adequately when an infectious agent penetrates the body. Given that, a septic shock can develop quite rapidly in such patients skipping all the previous stages in sepsis development [10].

Therefore, patients after bone marrow transplantation (BMT) have elevated risks of HAIs [10, 12, 13]. At the same time, studies that focus on determining risk factors that cause HAIs in such patients are scarce and rather contradictory.

Our research goal was to determine risk factors of healthcare-associated infections in patients after bone marrow transplantation.

Materials and methods. HAIs cases were detected by using a diagnostic card, which we developed ourselves. It was done based on retrospective active searching for purulent septic infections in 973 patients. They were treated in the Hematology, Chemotherapy and Bone Marrow Transplantation Department of the Pirogov National Medical and Surgical Center (the Hematology Department) in a period from 2015 to 2018. All the examined patients underwent bone marrow transplantation due to the following diagnosed diseases: lymphoma (n = 158), multiple myeloma (n = 96), and multiple sclerosis (n = 719). In our study, we applied the standard epidemiological case definition in accordance with the Federal Clinical Recommendations on Epidemiological Surveillance over HAIs approved by the National Association of Experts respon-

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sible for Control over Healthcare-Associated Infections[4].

Risk factors of HAIs were established by accomplishing an analytical epidemiological "case – control" study.

Our test group was made up of 75 patients who had signs of various HAIs during their in-hospital treatment. The reference group included 898 patients without any registered HAIs during one month after bone marrow transplantation.

Influence exerted by contamination of objects in the hospital environment on HAIs occurrence and development was accomplished in dynamics by analyzing correlations between incidence of HAIs among patients and contamination of external objects surrounding them in a hospital. Contamination levels were established as per results produced by scheduled sanitary-bacteriological examinations that were accomplished in the Hematology Department in 2015–2018.

All the data were statistically analyzed with parametric and non-parametric statistical procedures. Initial data were accumulated, corrected and systematized and the obtained results were visualized with Microsoft Office Excel 2016 and Medstatistic.ru calculator.

In case quantitative characteristics were distributed normally, we applied Student's t-test for two independent samplings to analyze them and the results were given as a simple mean (M) ± standard error of mean (m).

We calculated odds ratio (OR) of HAIs depending on whether risk factors were present or absent as per results of building up a fourfold table according to the formula $A \cdot D/B \cdot C$. The indicator was considered positive if its value was > 1. Differences were considered authentic if a confidence interval for this indicator did not include unity.

We applied Pearson's χ^2 test to reveal statistical significance of differences in qualitative characteristics. In this study, the critical significance level was taken as equal to 0.05 ($p \leq 0.05$).

Results and discussion. The analysis revealed 75 HAIs cases; the quantity equaled 7.7 % of the overall number of bone marrow recipients over the analyzed period.

Catheter-related bloodstream infections took the leading place among the detected HAIs accounting for 52.0 ± 2.4 %. They were followed by bloodstream infections, 28.0 ± 3.1 %; lower respiratory tract infections, 17.0 ± 3.2 %; and post-injection complications, 3.0 ± 0.6 %. These data are consistent with results produced by some Russian and foreign studies[3, 5] [7, 11, 12].

We estimated cause-effect relations between a supposed risk factor and HAIs development in a patient. Our estimates established certain differences from previously published data (Table).

Therefore, we did not establish any statistically authentic correlation between a patient's age and HAIs frequency; although, it seems only logical that, considering how physiological immune deficiencies tend to develop, the older a patient is, the higher likelihood of severe complications after BMT is. We did not establish any sex-dependent difference in HAIs development either.

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Risk factors of HAIs in bone marrow recipients

Risk factor	Likelihood		Odds ratio	95 % CI	χ^2
	in the test group	in the reference group			
Sex:					
male	0.829	0.666	1.245	0.775–2.000	0.825
female	1.206	1.501	0.803	0.500–1.290	0.825
Age, years:					
younger than 20	0.014	0.015	0.920	0.119–7.130	0.006
20–30	0.190	0.166	1.146	0.601–2.184	0.171
30–40	0.364	0.439	0.828	0.487–1.409	0.485
older than 40	1.273	1.164	1.094	0.680–1.757	0.137
Underlying disease:					
oncological	1.679	0.300	5.603	3.422–9.174	56.314
multiple sclerosis	0.596	3.338	0.178	0.109–0.292	56.314
BMT complications:					
mucositis	0.563	0.244	2.308	1.400– 3.802	11.800
febrile neutropenia	4.357	0.691	6.304	3.474–11.440	46.001

We analyzed frequency of HAIs depending on an underlying disease and established that complications were much more likely in patients with oncological diseases (lymphoma and multiple myeloma): 1.679 (*OR* = 5.603; 95 % CI: 3.422–9.174) against 0.596 (*OR* = 0.178; 95 % CI: 0.109–0.292) in patients with multiple sclerosis.

Infectious complications develop after transplantation largely depending on how inhibited the hematopoietic and immune systems are in a given patient[6] [14, 15] when he or she is being prepared for transplantation with cytostatic therapy. This therapy often induces mucositis (necrotic lesions in GUT mucosas) [16–18] and this is a predisposing factor of developing infections. We established that HAIs frequency amounted to 0.563 among patients with mucositis whereas it equaled 0.244 in the reference group (patients without this pathology) (*OR* = 2.308, 95 % CI: 1.400–3.802). This indicates that endogenous infection often acts as an inducer of developing complications in patients after BMT.

Results produced by multiple research works indicate that febrile neutropenia rather frequently develops in an early post-transplantation period. It can be viewed as a marker of subsequent HAIs development [19–21] as it was confirmed by the results produced by the present study. Thus, frequency of febrile neutropenia equaled 4.357 in the test group against 0.691 in the reference one (*OR* = 6.304, 95 % CI: 3.474–11.440). This makes it possible to consider this clinical sign a criterion of early HAIs diagnostics in patients after BMT.

High contamination with infectious agents detected in objects in the hospital environment is a well-known risk factor that can cause HAIs in patients [21, 22].

We estimated results produced by sanitary-bacteriological control of external objects in the Hematology Department (816 wash-offs); samples were established positive in 12.5 % of the cases. Several groups of microorganisms were detected the most frequently including coagulase-negative staphylococcus (80.4 %), Pseudomonas aeruginosa

[6] Poddubnaya I.V., Babicheva L.G. Vtorichnye immunodefitsity v onkogematologii: uch. posobie [Secondary immune deficiencies in oncohematology: manual]. Moscow, “Econ-Inform” Publ., 2019, 63 p. (in Russian).

(8.8 %), Staphylococcus aureus (3.9 %), and Enterococcus faecalis (3.9 %).

We established a direct correlation between a growing number of HAIs cases in patients after BMT and levels of contamination with opportunistic microorganisms detected in objects in the hospital environment. The correlation coefficient was equal to 0.79 ($p = 0.01$). This indicated that HAIs agents were spread in the Hematology Department through communal contacts, common items and objects in the hospital environment being the leading transmission factors.

Therefore, effective management of infection risks for patients aimed at reducing them down to their acceptable levels requires constant epidemiological prospect surveillance over bone marrow recipients. This surveillance should involve monitoring of all the aforementioned risk factors.

Conclusions:

1. We established that infectious complications developed in bone marrow recipients in 7.7 % of the cases and that catheter-related bloodstream infections prevailed in the incidence of HAIs accounting for 52.0 ± 2.4 %.

2. Age- and sex-dependent differences are not among risk factors of developing HAIs among bone marrow recipients.

3. An oncological disease in bone marrow recipients as an underlying one is the most significant risk factor of HAIs for bone marrow recipients (*OR* = 5.603; 95 % CI: 3.422–9.174) in comparison with multiple sclerosis (*OR* = 0.178; 95 % CI: 0.109–0.292).

4. Febrile neutropenia in bone marrow recipients should be considered a marker of subsequent HAIs development (*OR* = 6.304; 95 % CI: 3.474–11.440).

5. HAIs agents are actively spread in hematology departments through communal contacts, which is confirmed by the detected correlation between frequency of such infections and microbial contamination of objects in the hospital environment ($r = 0.79$, $p = 0.01$).

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Research article

FORECASTING RISK ANALYSIS OF DETECTION FOR CAROTID ARTERY STENOSIS BASED ON SERUM LEVELS GRADING OF LIPOPROTEIN (A)

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Aim of the study: to assess the relationship between Lp(a) serum levels grading and carotid artery stenosis (CAS).

The Duplex Registry database was used for this study. CAS was verified by duplex scanning in the presence of an atherosclerotic plaque (AP), stenosing the lumen of the carotid artery (CA) by 20 % or more. Patients who underwent a blood test for Lp(a) and the results were entered into the registry database were selected for this study. The immunoturbidimetric method was used to determine the serum level of Lp(a) (mg/dl).

Data from 51 patients (66.6 % men) were included in the final analysis: median age 49.0 [46.0; 59], total cholesterol (TC) 5.93 [5.13; 6.56], Lp(a) 26.5 [14.2; 76.0]. Spearman rank correlation analysis showed the presence of significant relationships ($p < 0.05$) between Lp(a) and age ($r = 0.3$), gender ($r = 0.3$), the presence of AP in the right ICA ($r = 0.5$), HDL ($r = 0.3$). OR and 95 % CI were calculated to determine the effect of Lp(a) grades on the probability of CAS detection: Lp(a) < 30 mg/dl OR 0.36 [0.11; 1.14] $p = 0.04$; Lp(a) > 30 mg/dl OR 1.42 [0.44; 4.58] $p = 0.27$. The prevalence of CAS in the group with Lp(a) level < 30 mg/dl was 33.3 %, 30–50 mg/dl – 50 %, 50–100 mg/dl – 40 %, > 100 mg/dl – 37.5 %. The model of multiple regression analysis for Lp(a) with TC in relation to the right ICA stenosis predicting showed $R = 0.51$, $F = 8.4$, $p = 0.0007$. The statistics of 3M model of the logistic regression function for CAS predicting based on the Lp(a) and TC data showed: $-2 \cdot \log(\text{likelihood}) = 57.16$, Chi-square = 8.17 (cc = 2), $p = 0.016$.

The present study confirmed the relationship between the Lp(a) level and the CAS detection and the presence of an additive effect of total cholesterol on this. The reference role of Lp(a) gradation at the level of 30 mg/dl was determined as significant in relation to predicting CAS detection.

Keywords: *lipoprotein(a), grading, risk analysis, carotid atherosclerosis, stenosis, duplex scanning, prediction.*

Despite the fact that the role of lipid factors in the formation and development of atherosclerosis is well known, the scientific medical community continues to actively pay attention to the study of lipoprotein (a) (Lp(a)) [1, 2]. A high level of Lp(a) is an independent risk factor for the early development of atherosclerosis and related cardiovascular diseases, which is initiated through mechanisms associated with its proatherogenic, proinflammatory, and prothrombotic properties. Lp(a) is a predominantly genetic determinant of cardiovascular risk that is inherited [3]. Therefore, medical scientific associations call for close attention to this risk factor, its stratification and analysis in clinical practice [3–6].

The National Lipid Association guidelines for clinical practice recommend measuring Lp(a) to identify patients with very high Lp(a) levels who have a family history of premature cardiovascular disease or elevated Lp(a) levels [6]. The genetic predisposition to elevated levels of Lp(a) [7] and its correlation with the early development of carotid atherosclerosis [8] was convincingly confirmed in studies performed back in the 90s of the last century. A significant relationship was noted between the joint influence of an elevated level of total cholesterol and Lp(a) in the early manifestation of CVD [9]. At the same time, subsequent studies questioned the role of Lp(a) in the development of early carotid atherosclerosis in young patients

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[10]. A possible role in this could be played by the stratification of the value of Lp(a), which was defined as the limit of the norm.

Despite the fact that the previously noted Lp(a) level > 50 mg/dl was considered a reference [11, 12], other studies have noted that the gradation of the Lp(a) level, starting from 30 mg/dl, has the greatest importance [13].

Aim of the study: to assess the relationship between Lp(a) levels and carotid atherosclerosis, verified on the basis of duplex scanning of the carotid arteries within the local registry.

Materials and methods. Duplex Registry database was used for this study. Detailed methodology for this registry was described earlier in previous publications [14, 15]. Carotid atherosclerosis was verified on the basis of duplex scanning data in the presence of an atherosclerotic plaque that stenosed the lumen of the carotid artery by 20 % or more. Duplex scanning was performed on Vivid 7 (GE) devices according to the standard technique using multi-frequency linear sensors (L9 / L12, 9–12 MHz). Both common carotid arteries and their bifurcations, internal and external carotid arteries were studied in order to determine the section where the atherosclerotic plaque had the largest size. The percentage of stenosis was determined in the zone of maximum narrowing of the arterial lumen in % by the diameter and area of the vessel lumen according to the ECST criteria in accordance with the guidelines for DS performing[1] [16, 17]. The formalized minimum value of stenosis associated with atherosclerotic plaque, which can be correctly expressed as a percentage in accordance with these protocols and recommendations, was taken as 20 % when describing the results of duplex scanning.

For inclusion in the present study, patients were selected who underwent a blood test for Lp(a) and its results were entered into the registry database. The Lp(a) level was determined by the immunoturbodimetric method using a Beckman Coulter 5800 biochemical analyzer.

The referral of patients for this study by a cardiologist and / or lipidologist of the clinic was initially based on strict indications: an early family or own cardiovascular history in combination with confirmed hyperlipidemia, which made it possible to suspect a hereditary predisposition to this pathology.

Statistical analysis. Statistical data processing was performed using the Statistica 10.0 software package (StatSoft). Group data are presented as mean and standard deviation, median, 25 % and 75 % percentile, or as absolute numbers and percentages. Spearman correlation analysis was used to determine the presence of significant relationships between the studied characteristics. The chi-square test was applied to compare groups on a qualitative sign. The extended Mantel – Haenszel chi-square for a linear trend with a p-value for one degree of freedom was used as a model for the analysis of interlevel interactions depending on the gradation of a qualitative sign[2]. Odds ratio (OR) and 95 % confidence interval (95 % CI) were calculated to determine the effect of different gradations of Lp(a) on the probability of detecting carotid atherosclerosis. Multiple regression analysis for a quantitative sign was applied to build models that included Lp(a) in relation to predicting the degree of ICA stenosis. Logistic regression analysis using a Quasi-Newtonian method of estimation was applied to construct a model of the predictive function for the detection of stenosing carotid atherosclerosis based on Lp(a) and TC data (3M function model). ROC-analysis (Receiver Operator Characteristic) with ROC-curve construction and area under curve estimation (Area Under Curve) was applied to evaluate the CAS prediction classifier as a diagnostic test based on the obtained classification logistic function formula. Differences were considered statistically significant at $p < 0.05$.

Results. Data from 51 patients were included in the final analysis. The mean age of the patients was 50.2 + 6.5 years; 2/3 of them

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[2] Rosner B. Fundamentals of Biostatistics, 5th ed. Belmont, CA, Duxbury Press, 2000, 606 p.

belonged to the male sex (n = 34). Arterial hypertension was registered in 37 % of patients (n = 19), in 4 of them the diagnosis of coronary artery disease was also verified (one of them had a history of MI). Carotid atherosclerosis (according to the AP criterion > 20 %) was detected in 19 patients (37.3 %) from the study group (n = 51).

The distribution of patients in the study group by Lp(a) level is shown in Figure 1. Detailed descriptive clinical, laboratory and ultrasound characteristics of the patients included in this study are presented in Table 1.

Spearman rank correlation analysis showed the presence of significant relationships (p < 0.05) between the following signs. Age correlated with IMT (r = 0.3), the presence of AP in the bifurcation of the CA, ICA and RSA (r = 0.3), with CAS gradation (r = 0.45), lipid-lowering therapy (LLT) (r = -0.12), Lp(a) (r = 0.3). AP of the right ICA showed correlations with age (r = 0.34), sex (r = -0.12), total cholesterol level in dynamics (TC2) (r = -0.13), LDL level in dynamics (LDL2) (r = -0.12), Lp(a) level (r = 0.5); while AP of the left ICA - with age (r = 0.33), sex (r = -0.12), TC2 (r = -0.15), LDL2 (r = -0.16). The gradation of CAS severity correlated with age (r = 0.45), sex (r = -0.13), TC2 (r = -0.13), LDL2 (r = -0.14), LLT (r = -0.08). Lp(a) correlated with age (r = 0.3), sex (r = 0.3), presence of AP in the right ICA (r = 0.5), HDL (r = 0.3) and HDL2 (r = 0.4).

The extended Mantel – Haenszel chi-square for linear trend was applied as a model for the analysis of interlevel interactions depending on the gradation of serum levels of Lp(a) and carotid atherosclerosis. The data obtained are presented in Table 2.

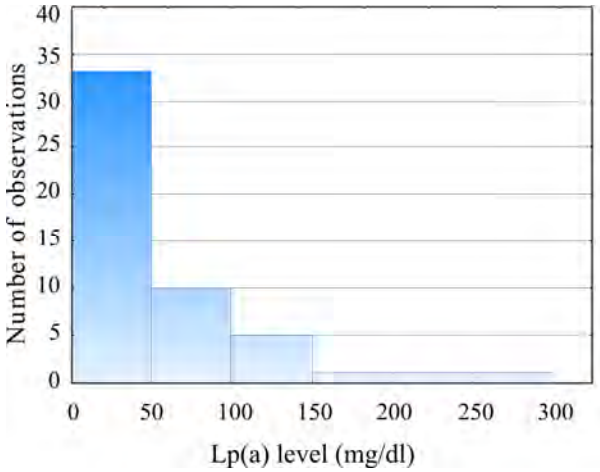

Figure 1. Distribution of patients in the study group by Lp(a) level

Table 1

Clinical, laboratory and ultrasound characteristics of patients included in this study

Sign	Mean ± SD	Med. [Q_{25}; Q_{75} %]	Min; Max
Age (years)	50.2 ± 6.5	49.0 [46.0; 59.0]	37.0; 60.0
TC (mmol/l)	5.93 ± 0.2	5.93 [5.13; 6.56]	3.5; 10.1
HDL (mmol/L)	1.55 ± 0.47	1.47 [1.18; 1.95]	0.84; 2.52
TG (mmol/l)	1.58 ± 0.9	1.42 [0.91; 1.84]	0.56; 4.79
LDL (mmol/l)	3.65 ± 1.03	3.53 [3.02; 4.17]	1.7; 7.22
Lp(a) (mg/dl)	52.8 ± 61.4	26.5 [14.2; 76.0]	0.1; 298.4
IMT right OCA (mm)	1.04 ± 0.2	1.0 [0.9; 1.2]	0.7; 1.5
IMT left OCA (mm)	1.06 ± 0.2	1.0 [0.9; 1.2]	0.7; 1.5
IMT bifurcation of the right CCA (mm)	1.35 ± 0.2	1.4 [1.2; 1.7]	0.9; 1.7
IMT of bifurcation of the left CCA (mm)	1.39 ± 0.3	1.4 [1.2; 1.6]	0.7; 2.1
IMT RSA (mm)	1.46 ± 0.2	1.5 [1.3; 1.6]	0.7; 1.9
AP bifurcation of the right CCA > 20 % (%) (7/51)	4.16 ± 11.5	0.0 [0.0; 0.0]	0.0; 59.0
AP bifurcation of the left CCA > 20 % (%) (7/51)	4.37 ± 11.8	0.0 [0.0; 0.0]	0.0; 48.0
AP right ICA > 20 % (%) (3/51)	1.56 ± 6.4	0.0 [0.0; 0.0]	0.0; 30.0
AP left ICA > 20 % (%) (3/51)	1.96 ± 8.2	0.0 [0.0; 0.0]	0.0; 46.0
AP RSA > 20 % (%) (11/51)	5.74 ± 11.2	0.0 [0.0; 0.0]	0.0; 45.0

N o t e : TC – total cholesterol, HDL – high-density lipoprotein, TG – triglycerides, LDL – low-density lipoprotein, Lp(a) – lipoprotein(a), IMT – intima-media thickness, CCA – common carotid artery, AP – atherosclerotic plaque, ICA – internal carotid artery, RSA – right subclavian artery, CAS – carotid atherosclerosis.

Table 2

Analysis of CAS associations and Lp(a) level gradations in comparison with the normal level (extended Mantel – Haenszel chi-square for a linear trend)

Gradation of levels	Lp(a) value for level	Cases	Controls	Total	Intergroup ratio	Odds ratio	Interlevel comparisons
0	< 30	9	18	27	0.5	1.0	0 vs 0
1	30–50	3	3	6	1	2.0	1 vs 0
2	50–100	4	6	10	0.67	1.3	2 vs 0
3	> 100	3	5	8	0.6	1.2	3 vs 0
Total		19	32	51			

Table 3

Analysis of multiple regression analysis models with Lp(a) and lipid factors in relation to predicting the degree of right ICA stenosis

Model	R	R2	Adjusted R2	F	B	*p*-level
LP(a)	0.50	0.25	0.23	16.7		0.0001
					0.504895	0.0001
LP(a) + TC	0.51	0.26	0.23	8.4		0.0007
	Lp(a)				0.495155	0.0002
	TC				-0.101269	0.42
LP(a) + LDL	0.52	0.27	0.24	8.5		0.0007
	Lp(a)				0.502232	0.0004
	LDL				-0.086074	0.51
Lp(a) + TC + TC2 + LDL + LDL2	0.66	0.44	0.35	4.7		0.002
	Lp(a)				0.617684	0.0002
	TC				-0.380122	0.33
	TC2				-0.145181	0.77
	LDL				0.281620	0.47
	LDL2				-0.014816	0.97

Table 4

Predicting CAS detection depending on Lp(a)

Lp(a) level	Odds ratio	95 % CI	*p*-level
< 30 mg/dl	0.36	[0.11; 1.14]	0.04
> 30 mg/dl	1.42	[0.44; 4.58]	0.27
> 50 mg/dl	1.11	[0.32; 3.70]	0.48

Given the strong correlation found between Lp(a) and the presence of right ICA stenosis, multiple regression analysis was applied to build models that included Lp(a) in predicting the degree of ICA stenosis, with stepwise inclusion of lipid factors in the models. The results of multiple regression analysis are presented in Table 3.

Odds ratio (OR) and 95 % confidence interval (95 % CI) were calculated to determine the effect of different gradations of Lp(a) on the probability of detecting carotid atherosclerosis. Models with different gradations of Lp(a) were analyzed: less than 30 mg/dl, more than 30 mg/dl and more than 50 mg/dl (see Table 4). Lp(a) level less than 30 mg/dl significantly reduced the probability of CAS detection. Lp(a) of more than 30 mg/dl in this model increased the chances of detecting CAS by 1.4 times, but did not reach the level of statistical significance. The use of Lp(a) level more than 50 mg/dl as a reference did not improve the statistics of the model. Thus, the data obtained support the use of 30 mg/dl as the reference level of Lp(a).

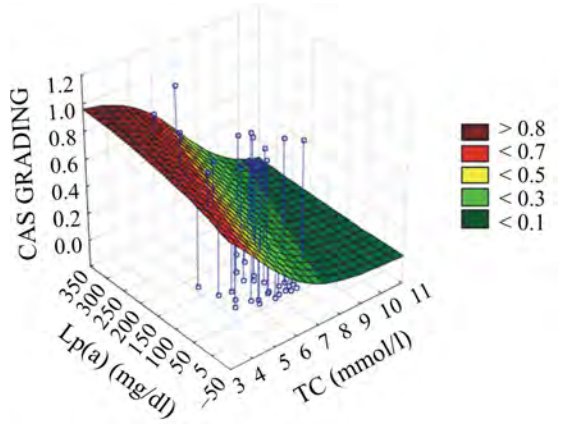

Figure 2. 3D model of the CAS prediction function based on the Lp(a) and TC data

Taking into account the fact that in previous studies a significant relationship was noted between the combined effect of elevated levels of TC and Lp(a) in relation to the development of atherosclerosis [9], TC and Lp(a) were included in the logistic regression model. Logistic regression analysis using the Quasi-Newtonian method of estimation was applied to build a 3D model of the CAS prediction function based on Lp(a) and TC data (Figure 2). As a result of the analysis, the following formula for the classification of logistic function was obtained:

$$\text{Presence of } \mathbf{CAS} = \exp(3.4922341454018 + (-0.7584332031152) \cdot \mathbf{TC} + (0.00571548810893) \cdot \mathbf{Lp(a)}) / (1 + \exp(3.4922341454018 + (-0.7584332031152) \cdot \mathbf{TC} + (0.00571548810893) \cdot \mathbf{Lp(a)})$$

Model statistics: -2·log (likelihood) for this model = 57.16 (only with intercept = 65.34), Chi-squared = 8.17 (cc = 2), $p = 0.016$. Model evaluation parameters are presented in Table 5.

ROC-analysis (Receiver Operator Characteristic) with the construction of the ROC-curve and the estimation of the Area Under Curve indicator (AUC) was applied to evaluate the CAS prediction classifier as a diagnostic test, using the obtained formula of the logistic function classification based on Lp(a) and TC data. An AUC value of 0.7 was obtained in this assay (Figure 3).

Discussion. It is worth discussing the interesting aspects and limitations of the present study. While in a previous Finnish study the role of Lp(a) in the development of early carotid atherosclerosis in young patients was questioned [10], their associations were confirmed in the present study. Although previously reported Lp(a) > 50 mg/dl was considered the reference level [11, 12], most recent studies have noted that Lp(a) levels starting at 30 mg/dl are of greatest importance [18], which was also confirmed in our study. However, the median Lp(a) value in our study group was recorded at a higher level (26.5 [14.2; 76.0]), compared with other recent studies on Lp(a) in patients with isolated stenosing carotid atherosclerosis (N.A. Tmoyan et al. – 20 [8; 55]; J.E. Jun et al. – 14 [3; 35]) [18, 19]. This may be due to differences in the clinical characteristics of the patients included in the studies. N.A. Tmoyan et al. determined that in their study the average age of patients was 60 ± 14 years (60 [47; 74]), men – 53 %, the prevalence of hypertension (AH) – 57 % [17]. In our study, the average age of patients was 50.2 + 6.5 years (49 [46; 59]), men – 66 %, prevalence of AH – 37 %. The present study was

Table 5

Estimation parameters of the logistic regression model of the CAS based on LP(a) and TC data (OR for the model 2.7)

	Estimate	Standard Error	Odds ratio	95 % CI	Wald criterion	p-level
Intercept	-3.49224	1.964310			3.160730	0.07
Lp(a)	-0.00572	0.005164	0.99	[0.98; 1.00]	1.224867	0.26
TC	0.75843	0.338744	2.13	[1.09; 4.14]	5.012934	0.02

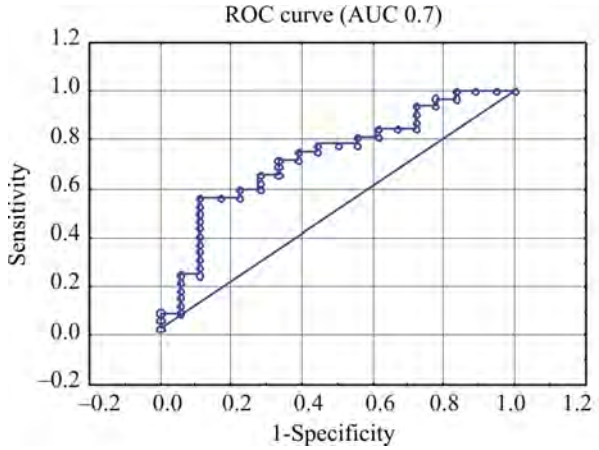

Figure 3. ROC analysis results

closer in clinical characteristics to the work of N. Nasr et al. [20], in which the average age of patients was 44.3 ± 8.6 years, male gender was 60.7 %, and the prevalence of AH was 28 %. But the mean Lp(a) level in the Nasr N et al study was also lower than in our study (35.0 + 38.0 vs 52.8 + 61.4). This may also be explained by the purposeful prescription of Lp(a) analysis by the doctor in the present study if the patient is suspected of having a hereditary (family) predisposition to this pathology (early family or own cardiovascular history in combination with confirmed hyperlipidemia), which is regulated by existing clinical guidelines [3, 4, 6, 21]. At the same time, an analysis of the data of patients included in this study showed a similar distribution of their Lp(a) levels, as in the classic Copenhagen study (Figure 1) [22].

More attention should be paid to early screening for hereditary forms of hyperlipidemia (including hyperLp(a)emia) not only among adults, but also among adolescents, which is reflected in current clinical guidelines [21], which note that the target level of LDL for children older than 10 years is < 3.5 mmol/l (this is of particular importance with a very high level of LDL, elevated levels of Lp (a) and / or a family history of premature development of coronary artery disease or other cardiovascular diseases).

The additive effect of high Lp(a) levels in combination with other lipid factors on the early development of atherosclerosis and the association of Lp(a) with the degree of carotid stenosis has been noted in previous studies [9, 19, 23] and confirmed in the present study. A clear clinical example from the cohort of this study is a 47-year-old patient without history of arterial hypertension and tobacco smoking, who was diagnosed with vertebral-subclavian steal syndrome due to 94 % stenosis of the right subclavian artery, eliminated by percutaneous transluminal angioplasty with stenting. The initial indicators of his lipid profile were follows: TC – 7.17 mmol/l, HDL – 1.02 mmol/l, LDL – 5.22 mmol/l, TG – 2.03 mmol/l, Lp (a) – 48.5 mg/dl [24].

Interesting parallels can be drawn with the study by van Buuren F et al., who analyzed the prevalence of carotid atherosclerosis depending on Lp(a) levels [25]. In the group with Lp(a) values < 2 mg/dl, the prevalence of CAS was 2.8 %, in the group with Lp(a) 23–29 mg/dl – 6.1 %, 30–60 mg/dl – 8.3 %, 60–91 mg/dl – 7.9 %, 91–110 mg/dl – 6.0 %, and > 110 mg/dl – 10.9 %. In our study, the prevalence of CAS in the group with Lp(a) values < 30 mg/dl was 33.3 %, 30–50 mg/dl – 50 %, 50–100 mg/dl – 40 %, > 100 mg/dl – 37.5 %.

It is worth paying attention to the features of the Lp(a) diagnostics by turbidimetry. The immunoturbidimetric method is a high-precision diagnostic technique designed to measure protein concentration by changing the intensity of light scattering of the test solution (serum) when a light flux passes through it[3]. The method is based on determining the concentration of the studied protein during the formation of an antigen-antibody complex with it, which leads to an increase in the turbidity of the solution. The construction of a calibration plot using several concentrations of the calibrator (from three to five) is performed to avoid inaccuracies of obtained results. This

[3] Dolgov V.V., Shevchenko O.P., Sharyshev A.A., Bondar' V.A. Turbidimetriya v laboratornoi praktike [Turbidimetry in laboratory practice]. Moscow, Reafarm, 2007, 175 p. (in Russian).

may be related to obtaining different results when examining the same blood serum using different diagnostic systems. Current commercial immunological assays for measuring Lp(a) concentrations are calibrated differently and their errors vary significantly over the clinically relevant concentration range in a nonlinear manner. This was the purpose of the study by H. Scharnagl et al. [26] to compare different commercial immunochemical analyzers to determine more reliable Lp(a) quantification methods for clinical practice. The investigators determined serum Lp(a) concentrations using six major commercial analyzers, presenting Lp(a) results in mg/dL (Denka Seiken, Abbott Quantia, Beckman, Diasys 21FS, Siemens N Latex) or nmol/L (Roche TinaQuant, Diasys 21FS). All analyzes were performed using the five-point calibration method on calibrators provided by the manufacturers. The study showed that compared to the established reference sample, the results of various analyzers differed from the target values (43.3 mg/dl or 96.6 nmol/l): from -8 % (Siemens N Latex) to +22 % (Abbott Quantia). Dividing the samples into five groups with increasing Lp(a) concentrations and plotting the differences showed that the differences between the analyzes depended on the Lp(a) concentration. Some analyzers overestimated the Lp(a) value at high serum concentrations compared to the Denka Seiken analyzer. Lp(a) levels in our study were determined using a Beckman analyzer, which was not compromised in research performed by H. Scharnagl et al. [26]. However, when conducting future studies on Lp(a), their authors should take into account this fact. Further international studies are needed to standardize the interpretation of Lp(a) analysis results to address these issues.

In conclusion, we would like to note the limitations of this study, which are typical for observational registries and all studies based on the analysis of electronic medical databases [27]. The main limitation of this study is the small sample size and a small percentage of patients with confirmed carotid atherosclerosis, which could affect the results of the statistical analysis. The regression coefficients for Lp(a) and lipid factors in the presented regression models have the opposite sign, which is reversed when the data are logarithmically transformed when performing logistic regression analysis. This can be explained by the different distribution type of signs on the one hand (the Poisson distribution for Lp(a); the Gaussian distribution for TC and LDL); and on the other hand, a more significant negative predictive value for normal Lp(a) level (less than 30 mg/dl) in relation to the probability of CAS detecting. However, it should be noted that this combination of predictors did not weaken the obtained models and led to an increase in the R correlation coefficients in the multiple regression models from 0.5 to 0.66 while maintaining a high level of significance ($p = 0.002$), as well as an increase in the chances of CAS detecting in building a logistic regression model with Lp(a) and total cholesterol (OR = 2.76, $p = 0.016$).

Conclusions. The present study confirmed the relationship between Lp(a) levels and stenosing carotid atherosclerosis and its additive effect in combination with other lipid factors on the development of carotid atherosclerosis. The Lp(a) gradation at the level of 30 mg/dl was defined as a reference in relation to predicting carotid atherosclerosis detection. Despite the fact that Lp(a) is an established risk factor for the development of cardiovascular diseases (CVD), unexplored questions remain regarding its use in real clinical practice [28]. There is a need for reliable methods for the quantitative determination of Lp(a) in clinical laboratory practice [26], which should be aimed at harmonization in the interpretation of its results in laboratory studies. More attention should be paid to early screening for hereditary forms of hyperlipidemia (including hyperLp(a)emia) not only among adults, but also among adolescents, which is reflected in current clinical guidelines [3, 4, 6, 21].

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Research article

MATERNAL RISK FACTORS FOR A CHILD'S HEALTH PRIOR TO AND DURING PREGNANCY (RESULTS OF LONG-TERM COHORT MONITORING IN VOLOGDA REGION)

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The work presents the results of the 26-year monitoring with its focus on children's health. Pre-school children living in the Vologda region were selected as a research object. The aim was to assess health risks for children caused by certain maternal factors and conditions. The study was accomplished as an intra-cohort analysis of data on 1454 children from five cohorts (born in 1998, 2001, 2004, 2014 and 2020) by calculating a relative risk rate.

Negative effects produced by sociodemographic, socioeconomic and environmental conditions as well as maternal harmful occupational factors during pregnancy are significant health risk factors for a child. It is true not only for the neonatal period but also during pre-school years. Such health-related factors as stillbirths in case history, complications of a present pregnancy (up-to-date reproductive technologies being applied to achieve it, eclampsia, multiple pregnancy, dangerous fetus position, prematurity, postmaturity, anemia, edemas, protein in urine) and birth (rapid labor, use of vacuum extraction) do the most severe damage to a child's health at birth and their influence persists as a child grows. Other significant risk factors that influence children's health in their pre-school years include diseases of the genitourinary and endocrine systems diagnosed in a mother prior to pregnancy; a mother being single; low incomes; electromagnetic radiation at a place where a family lives; harmful working conditions at a mother's workplace (gases in workplace air, work on a conveyor belt, radiation exposure). A mother's young age is also a health risk factor for a fetus during the prenatal period but its influence reduces as a child grows. In contrast, if a mother is older than 40, this factor protects a child's health during pregnancy but increases likelihood of retarded neuropsychic development by the school age (due to a mother's low health potential).

Overwhelming majority of health risk factors we detected in this study are quite manageable. Our results can be used in creating programs aimed at preserving health of a mother and a child at any level, from individual to national one.

Keywords: *health risks for children, biomedical, sociodemographic, socioeconomic, and environmental factors and conditions, harmful working conditions, a child's health group, prevalence of diseases, dispensary observation and record keeping.*

According to the Global Burden of Disease Study 2019 (GBD 2019), fertility has been declining steadily worldwide over the last two decades whereas life expectancy has been growing in most regions. This leads to a reduction in labor force and in population ageing, which, in their turn, lead to grave socioeconomic and political problems in the contemporary society [1].

Reproductive behavior of the RF population is also changing as families without children or with only one or two children are becoming more widely spread [2]. An outbreak of the new coronavirus infection, among other negative outcomes, has also led to an additional decline in a number of people who want to have children (including those who still do not have them) [3].

The UN predicts that the world population will reach 9.7 billion by 2050. And a share of elderly people will be higher than a share of adolescents and youth (aged from

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15 to 24 years) combined. A share of children younger than 5 years will be lower than a share of people older than 65 years[1].

In Russia, the most substantial loss in children population occurred in 1990–2011 when it decreased by 14 million people; this was followed by a growth in this population group. However, we can well expect another decline in the nearest future. According to average estimates given by Rosstat[2], by 2035 a number of children younger than 14 years will go down by almost 5 million. The most substantial loss is expected in the youngest age group, children aged from 0 to 3 years (by 1.7 million) and those aged from 4 to 6 years (by 1.8 million).

At present, enormous effort is being made in Russia to improve the demographic situation in the country, to support parenthood and childhood, to protect and improve children's health. However, despite all this effort taken both by the state and the society, there is considerable concern about children's health and we should remember that this population group is declining as it is. Health of future generations is a major component in the reproductive and labor potential as well as human potential in general and its preservation has specific economic significance. Given that, it is becoming extremely vital to search for and develop mechanisms able to manage factors that can deteriorate it[3].

Research data indicate that health of a an infant or a preschool child is largely affected by maternal risk factors such as mother's health, biomedical factors including course of a pregnancy, the ordinal number of a birth and abortions in case history, occupational hazards, and mother's age. Obstetric and extragenital pathologies result in complications during the antenatal period and various fetal pathologies; they also create risks of pathologies developing in a child in the neonatal period or at an older age [4].

Our research goal was to assess health risks for a child during the prenatal and preschool period created by exposure to variable maternal factors and conditions prior to and during pregnancy.

To achieve that, the following tasks were set:

1. To analyze studies on maternal health risk factors for a child.

2. To assess a relative health risk for a child caused by certain maternal factors in the prenatal period.

3. To assess a relative health risk for a child caused by certain maternal factors in the preschool period.

4. To suggest targeted recommendations how to develop activities aimed at health preservation and neutralization of adverse health risk factors for preschool children, which we identified in this study.

Our research object was health of children living in the Vologda region. The study focused on examining risk factors for newborns as well as children aged 1–2, 3–4 and 6–7 years.

The research methodology. The study relied on data obtained by five waves of the cohort medical and social monitoring accomplished by the Vologda Research Center of the Russian Academy of Sciences. The monitoring was accomplished within the scientific research project entitled "The study on conditions for raising a healthy generation" [5]. We applied several criteria to include a child into each cohort. First, a child should be born in a specific period (in 1995, May 15–21; 1998, March 01–07; 2001, March 01–25; 2004, March 01–25; 2014, March 01–21; 2020, March 16–April 10)[4]; a maternity

[1] Shifting Demographics. *The UN*. Available at: https://www.un.org/en/un75/shifting-demographics (April 04, 2022).

[2] Edinaya mezhvedomstvennaya informatsionno–statisticheskaya sistema [The Unified interdepartmental information and statistical system]. Available at: https://fedstat.ru (April 04, 2022) (in Russian); Predpolozhitel'naya chislennost' naseleniya Rossiiskoi Federatsii: stat. sb. [Expected population of the Russian Federation: statistical data collection]. *Federal State Statistics Service*. Available at: https://rosstat.gov.ru/compendium/document/13285 (April 04, 2022) (in Russian).

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[4] Each stage was accomplished in 5 settlements in the Vologda region, namely Vologda, Cherepovets, Velikii Ustyug, Kirillov and Vozhega. These settlements were selected randomly.

patient gave her consent to fill in the questionnaire and to participate in further stages of the prospective study; health workers at a maternity hospital had all the necessary documents on a peculiar course of a given pregnancy and respondent's health. Families with children who took part in at least one stage in the monitoring until a child reached 7 years (n = 1037) were selected from the overall data array (n = 1464) to be analyzed in this study (Table 1).

We applied a relative risk (*RR*) as an indicator to estimate influence that was exerted by the analyzed risk factors on a child's health[5].

We identified and classified several maternal risk factors based on the analyzed literature sources (the results of this analysis are given below) and available biomedical and sociological monitoring data. Use of this exact classification allows correcting the existing system for mother and child protection and supplementing it with targeted activities that have solid scientific basis.

(1) medical and demographic factors: age, marital status of a mother, relationships between spouses;

(2) socioeconomic factors: financial conditions, a possibility to satisfy family needs given the total available family income; estimation of living conditions including absence of own housing;

(3) environmental conditions on a territory where a mother lived: poor quality of water, ambient air pollution, soil pollution (dump, wastes), elevated noise levels, no green spaces or parks, and electromagnetic radiation.

(4) harmful working conditions at a mother's workplace: chemicals and toxicants, dustiness, gas pollution, vibration, noise, humidity, radiation and effects produced by SHF, substantial physical loads, working on a conveyor, working in 2 or 3 shifts, exposure to high and low temperatures, biological hazards, mental strain, night shifts.

(5) biomedical factors: a mother suffering from diabetes mellitus (chronic and gestational); gynecological diseases (chronic noncommunicable ones) and diseases of the urinary tracts (pyelonephritis); hazardous infections (venereal, tuberculosis, hepatitis B/C, HIV, toxoplasmosis); hyper- or hypofunction

Table 1

The profile of the analyzed sampling

Sampling volume	1998 cohort	2001 cohort	2004 cohort	2014 cohort	2020 cohort	Total	
						abs.	%
Initial number of maternity patients	199	250	265	370	380	1464	100.0
Took part in at least one stage in the monitoring (newborns excluded) until a child reached 7 years (inclusively),	166	211	190	243	227	1037	70.8
% of the initial volume	83.4	84.4	71.7	65.7	59.7		
Data base for the study:							
Children aged: younger than 1 year	166	211	190	243	227	1037	100.0
1–2 years	162	196	176	236	227	997	96.1
3–4 years	135	166	160	186	–	647	62.4 (79.9)*
6–7 years	109	144	140	134	–	527	50.8 (65.0)*

N o t e : * analysis for the age periods 3–4 years and 6–7 years was performed as per data obtained by monitoring of the cohorts that included children born in 1998, 2001, 2004 and 2014; % of the initial volume was calculated without considering the 2020 cohort (n = 810).

[5] *RR* was calculated as a ratio of a risk that a disease would developed in an "exposed" group (influenced by a given risk factor) to a risk that a disease would develop (health would deteriorate or an incidence rate would grow) in an "unexposed" group. In this study, we considered only those *RR* values with the lower limit of their confidence interval (CI) being higher than 1.10. Statistical significance of a relative risk was estimated in each case with its value being 95 %.

of the thyroid gland; obesity. We considered a number and outcomes of previous pregnancies and peculiarities of the current one (toxicosis, anemia, edemas, protein in urine, risk of preeclampsia or eclampsia); birth complications (prolonged or rapid labor, cesarean delivery, forceps operation, vacuum extraction, weak birth activity, abnormal (breech) fetus presentation, or multiple pregnancy). A mother's smoking status prior to and during pregnancy was also accounted for.

The estimation was performed in 2 stages:

I. Changes in a child's health during the prenatal period. The estimation criteria included intrauterine growth retardation (IUGR) in a fetus and health disorders (pathologies, diseases, and congenital malformations) in a newborn.

II. Changes in a child's health at an age of 1–2, 3–4 and 6–7 years. These age periods were selected in accordance with the dates of regular medical check-ups that involved examination performed by the greatest number of specialists.

At the second stage, we estimated whether a child was assigned into the health group 2 or higher[6], how frequently a child fell sick, whether a child had any chronic diseases that required mandatory regular medical check-ups. In addition, we estimated RR of specific diseases.

We analyzed biomedical and sociological data by using SPSS statistical software package.

This study makes it possible to identify and classify maternal health risk factors for a child, and to estimate levels and duration of exposure to each of them during the whole preschool period.

Our results and recommendations following them can be used by regional and federal authorities in developing complex programs for providing economic, psychological, pedagogical and medical support to women in their reproductive age. Such support is especially vital during pregnancy. Another important aspect is to ensure additional specific support to risk groups in order to preserve human, intellectual and reproductive potential of children as future generations. Achieving this means that national security of the country has been reinforced.

Analysis of studies and research articles on the subject. Let us consider maternal health risk factors for children, which, in our opinion, are the most significant ones.

A mother's age, an age of marriage and education describe socioeconomic maturity of potential parents and allow judging whether they are ready to take on responsibility to raise a child and to change their life in a drastic way

[6] According to the Order by the RF Pubic Healthcare Ministry dated August 10, 2017 No. 514n "On the procedure for performing regular medical check-ups of minors":

Health group 1 includes minors with proper physical and mental development, without any anatomic defects, functional and morphofucntional disorders;

Health group 2 includes minors who have no chronic diseases (conditions) but have certain functional and morphofucntional disorders; reconvalescents, especially those who have had severe communicable diseases; minors with overall physical retardation without any diseases of the endocrine system (low height, delayed biological development), with body mass deficiency or overweight; minors who often fall sick with respiratory diseases and are sick for a long time; minors with physical malformations, consequences of injuries or operations with functions and systems of the body remaining intact.

Health group 3 are minors who suffer from chronic diseases (conditions) and are in clinical remission, with rare exacerbations, with intact or compensated functions of organs and systems, without any complications of the major diseases (conditions); minors with physical malformations, consequences of injuries or operations provided that functions of organs and systems are compensated and their state does not impose any limitations on minors' abilities to learn or work.

Health group 4 are minors who suffer from chronic diseases (conditions) in their active phase or are in unstable clinical remission with frequent exacerbations, with intact or compensated functions of organs and systems or incomplete functional compensation; minors with chronic diseases (conditions) in remission, with functional disorders of organs and systems that require supporting therapy; minors with physical malformations, consequences of injuries or operations with incomplete compensation of functions performed by organs and systems and resulting limitations imposed on their ability to learn or work.

Health group 5 are minors who suffer from severe chronic diseases (conditions) with rare clinical remissions, frequent exacerbations, continuous recurrent clinical course, apparent functional decompensation of organs and systems, complications that require permanent therapy; minors with physical malformations, consequences of injuries or operations with apparent functional disorders of organs and systems and significant limitations imposed on their ability to learn or to work; minors with chronic diseases and decompensation.

[6]. All over the world, the existing trends indicate that women get pregnant at an older age more and more often. A mother's age that exceeds 40 years has a positive correlation with preterm birth [7], which, in its turn, produces negative effects on a newborn's health. In particular, children born by mothers who are older than 40 years have congenital heart diseases by two times more frequently [8]. However, this correlation between prematurity and a mother's age remains rather disputable since there is a possibility that negative health outcomes in a newborn result from combined exposure to other harmful factors (primary hypertension, obesity, diabetes mellitus, varicose veins, gynecological diseases, complications during labor and use of artificial reproductive technologies).

Acute and chronic diseases of a mother, threat of miscarriage, and alcohol consumption during pregnancy are well-known maternal perinatal risk factors of developmental disorders during the preschool period [9]. Polycystic ovary syndrome (PCOS) is proven to create an elevated risk of certain mental disorders for a child including sleeping disorders, attention deficit hyperactivity disorder (ADHD), autistic disorders, behavioral, tick and anxiety disorders, intellectual disability, and eating disorders. It should be added that a risk of any neuropsychic disorders is significantly higher for offspring of mothers who have both PCOS and class III obesity; when other factors (a mother suffering from gestational diabetes, cesarean delivery, or infertility) were excluded, it did not change the results [10].

Iron deficiency *anemia* is widely spread among women, especially pregnant ones. It leads to negative outcomes for their physical and emotional health. The disease creates elevated risks of a fetus death, preterm birth, and low birthweight[7].

Diabetes mellitus is among the most widely spread chronic diseases diagnosed in fertile women all over the world and its prevalence is only growing [11]. Women who suffer from gestational diabetes have an elevated risk of complications during pregnancy and birth. Such women and their children are exposed to an elevated risk of developing type II diabetes[8]. Epidemiological studies revealed that a pregnancy complicated with a mother having diabetes could result in development disorders of offspring (for example, autistic disorders [12, 13] and ADHD [14, 15]) due to oxidative stress and fetal hypoxia [1, 16]. Data obtained by a study on a children cohort indicated that children born by mothers with any type of diabetes diagnosed during pregnancy had an elevated lifetime risk of schizophrenia, anxiety disorders, intellectual disability, and behavioral disorders [17].

According to data provided by the WHO, approximately 80 % of people who have type II diabetes mellitus are obese. Diabetes develops by seven times more frequently in people with overweight than in those with normal body weight. *A mother being overweight* is a risk factor that can cause obesity in a child, as shown by the data of multiple regression analysis [18]. And this risk is practically proven manageable. Offspring born by obese mothers who were treated for gestational diabetes mellitus (GDM) had better outcomes regarding their BMI than offspring born by mothers who were not treated for the diseases in the last trimester and suffered from developing dysglycemia [19].

Several latest studies disprove any relationship between a mother *smoking* and developing diseases in future offspring. Thus, according to a prospective cohort study accomplished in Japan, active smoking of a mother prior to and during pregnancy as well as living with a smoking person in a family in the postnatal period did not have any relationship with a risk of asthma for a child. In contrast, if mothers who had never smoked were exposed to "passive smoking" at work and/or at home during pregnancy, their children had elevated risks of developing asthma

[7] De Jesús Montoya Romero J., Castelazo Morales E., Castro E.V., Velázquez Cornejo G., Nava Muñoz D.A., Escárcega Preciado J.A., Montoya Cossío J., Pichardo Villalón G.M. [et al.]. Review by expert group in the diagnosis and treatment of anemia in pregnant women. Federación Mexicana de Colegios de Obstetricia y Ginecología. *Ginecol. Obstet. Mex.*, 2012, vol. 80, no. 9, pp. 563–580 (in Spanish).

[8] Diabetes. *WHO*, 2021. Available at: https://www.who.int/news-room/fact-sheets/detail/diabetes (April 07, 2022).

[20, 21]. It is noteworthy that, according to data obtained by some Norwegian researchers, if a mother smoked during pregnancy, it produced negative effects on health of her grandchildren. Thus, each fourth mother with a child suffering from asthma stated that her mother smoked during her pregnancy [22].

A child's health is especially dependent on exposure to *environmental factors*, such as ambient air pollution, harmful chemicals, climate change, and poor quality of water [23]. One third of the total child disease burden is caused by exposure to harmful environmental factors [24]. According to our research, adverse environmental conditions on a territory where a family lives produce negative effects on labor activity (primarily due to an elevated risk of cesarean delivery as obstetric aid) and on health of newborns [25] and preschool children [26].

Harmful working conditions at a woman's workplace can also affect her reproductive health and make for pathologies developing in children during the first year of their life. Chemical pollution was established to produce negative effects on health and reproductive functions of female workers employed at metallurgic plants, textile productions, gas and oil processing enterprises; female model makers and controllers employed in civil engineering; female laboratory workers dealing with chemical analysis; female engineers in chemical industry; female surgeons, gynecologists, obstetricians, and nurses at in-patient surgical hospitals [27]. These female workers are more frequently exposed to threats of abortions, spontaneous miscarriages, complications during pregnancy and birth, and offspring's congenital malformations. These pathological states were shown to have a relationship with elevated contents of sulfur dioxide, phosphor anhydride, lead, nickel, and iron in ambient air. We should remember that pregnancy makes a woman's body more sensitive to harmful environmental factors [28]. As shown in our earlier studies, harmful working conditions at a future mother's workplace are also a risk factor that can cause complications during birth and lead to weak labor activity, necessity to use stimulation or cesarean delivery; or, on the contrary, this factor can cause rapid labor thereby increasing a risk of negative health outcomes in a newborn (pathological states, diseases or congenital malformations) [25].

Pregnancy maintenance and, consequently, fetus development are highly vulnerable and sensitive to any disorders caused by *prenatal stress*. Prevalence of any clinically diagnosed anxiety disorders during pregnancy equals 15 % (reaching 18 % during the first month after birth) [29]. Five percent of mothers in high-income countries suffer from clinical depression in the perinatal period; the share reaches 15–50 % in low- and middle-income countries [30].

Anxiety, depression and stress during pregnancy are risk factors that can have negative outcomes such as threat of miscarriage [31], preterm birth, and necessity to use premedication or cesarean delivery [32]. There are several delayed outcomes, such as an elevated clinically significant level of generalized anxiety (even after the prenatal one has been put under control) half a year after birth [33] and a shorter breastfeeding period [34]. This, in its turn, produces negative effects on a child's health.

It should be noted that an unwanted pregnancy and stress before birth are risk factors that can cause stillbirth [35], fetal hypotrophy [31], developing endocrine and immune reactions during pregnancy. Consequently, a child has an elevated risk of chronic diseases, such as allergy and asthma [36], recurrent respiratory infections [37], more frequent hospital admissions due to all types of communicable diseases (typically among boys) [38]. Maternal stress factors have a remote outcome which is earlier menarche in girls; this is highly undesirable regarding their mental, social and reproductive health and a reason for weaker immunity and overweight [39]. As for boys, this factor is associated with weaker reproductive functions in adulthood [38].

If a mother experiences negative emotions, this has significant influence on formation of a child's mental health [40, 41]. Depression and anxiety during pregnancy can induce emotional disorders in a child, create certain difficulties in mastering pro-social behavior, facilitate disorders of motor (in a child

younger than 2 years), cognitive and speech development [30]. They can also create elevated risks of oppositional defiant disorder (ODD) [42], behavioral disorders, and attention deficit hyperactivity disorder in a child, as well as raise a level of anxiety and dependence on psychoactive drugs [43].

Abortions produce the greatest effects on a woman's reproductive potential. A risk of dangerous infections grows drastically after *surgical abortion* (they account for one third of deaths associated with abortions, predominantly due to infection with Clostridia [44]). Women with artificial abortions in their case history, even after potential distorting factors had been corrected, still had significant risks of preterm birth (prior to the 37th week of pregnancy) and low birthweight (less than 2500 grams). Perinatal outcomes were worse in case of surgical abortion against medical one [45]. In addition, previous abortions create elevated risks of developing placenta previa in future [46], depression, breast neoplasia and cancer [47].

At present, issues related to influence exerted by *cesarean delivery* on a child are becoming especially vital since more and more children are born by this operation (the share reaches 25–30 % across the RF). Cesarean delivery results in elevated risks of negative effects on a child's physical health and neural and cognitive development as opposed to natural birth. The risks persist even after all maternal and obstetric factors have been corrected [48]. Besides, scientists established that women became pregnant less frequently after cesarean delivery. Studies indicate that cesarean delivery can be associated with smaller gestational age at birth and a reduced opportunity to breastfeed a baby, elevated risks of respiratory diseases in the neonatal period, developing asthma [49], type I diabetes and attention deficit hyperactivity disorder [50], autism [51], epilepsy [52], eczema [53], obstructive sleep apnea [54], elevated risks of lower respiratory tract infections [55] and higher body mass index in six month time (but without obesity in future) [56]. A type of delivery was shown to influence development of cognitive abilities in 5-year old children. Children who were born by cesarean delivery turned out to be less successful in doing cognitive tests than their counterparts who were born naturally [57].

Therefore, research articles describe a wide range of harmful maternal risk factors for a child's health. Next, we are making an effort to assess their relative risk within our long-term cohort study.

Results and discussion. ***I stage. Assessment of health risk factors for a child in the prenatal period.*** A young age of a mother during pregnancy creates by 2.2 times higher risk of intrauterine growth retardation (*RR* = 2.22, 95 % CI: 1.23–3.98) and by 70 % higher risks of severe health disorders in a newborn (*RR* = 1.69, 95 % CI: 1.24–2.28). This might be due to the fact that this factor often aggravates a clinical course of a pregnancy by creating an elevated risk of anemia (on average by 48 %) and edemas (by 2.2 times) for a mother thereby producing extremely negative effects on a child's health.

According to our calculations, a more mature age of a mother does not create an elevated health risks for a child in the prenatal period. However, it increases a risk of cesarean delivery (as a mother becomes older: the risk is by 35 % higher among women older than 35 years and by 88 % higher among those older than 40 years). This, in its turn, may have certain negative influence on a child's health in future.

Marital status of a mother produces indirect effects on a child's health, according to our data. Lone mothers (single, divorced or widowed) have by 3 times higher risks of intrauterine growth retardation (*RR* = 2.22, 95 % CI: 1.27–3.68) and consequently giving birth to a child with health disorders (by 1.7 times, *RR* = 1.66, 95 % CI: 1.24–2.21). Probably, lacking support and help provided by a man becomes a long-term stress factor for a pregnant woman who has to rely only on herself during this difficult period in life, financial issues included. Therefore, our study confirms that perinatal stress produces extremely negative effects on a child's health, starting from the embryonic period.

Financial position of a family expecting a child primarily influences health of a fu-

ture mother and if it is poor, a pregnancy is likely to have complications. Thus, low purchasing capacity made for developing anemia and edemas in the respondents (the risk grew by 33 % and 80 % accordingly) and the same was true for living conditions estimated as unsatisfactory by the respondents themselves (by 43 % and by 2 times accordingly). This was probably due to diets not being rich in all the necessary nutrients and not being variable enough, overcrowding, too much stuffiness and humidity in a place of living. We did not establish any effects produced by these factors on fetal development but they still can become apparent later, as children grow.

Pregnant women who live on territories with an *unsatisfactory ecological situation* have greater risks of edemas during pregnancy, especially if water quality (a 58 % increase in the risk) and ambient air quality (a 75 % increase) do not conform to the existing hygienic standards. Polluted ambient air correlates also with likelihood of cesarean delivery (this risk grows by 60 %).

When future parents live under exposure to electromagnetic radiation, this creates higher risks (by 2.7 times) that their newborns will have developmental deviations, congenital malformations and diseases (*RR* = 2.72, 95 % CI: 1.53–4.85).

Harmful occupational factors create health risks for a mother and a child. Women who work under exposure to chemicals and toxicants as well as to biological hazards have higher risks of cesarean delivery (by 76 % and 90 % accordingly).

Such a harmful factor as “dustiness” increases a risk of congenital malformations in future offspring on average by 60 % (*RR* = 1.59, 95 % CI: 1.17–2.16).

A future mother’s health and chronic diseases in her case history is also a health risk factor during pregnancy. Thus, we confirmed that diseases of the urinary tracts naturally increased a risk of edemas during pregnancy (*RR* = 2.64, 95 % CI: 1.85–3.77) and obesity created an elevated risk of cesarean delivery (*RR* = 2.18, 95 % CI: 1.41–3.38). We did not detect any negative effects produced by specific diseases of a mother on intrauterine development.

Another significant risk factor is obstetric complications during previous pregnancies. In particular, preterm birth and stillbirth in case history increase a risk of cesarean delivery in future by 2.4 and 4.3 times accordingly.

We should pay special attention to *peculiarities and complications of a pregnancy* as health risk factors for children. Thus, edemas, protein in urine, eclampsia, abnormal (breech) presentation, prematurity or postmaturity (the latter prevailed in our study), rapid labor and a multiple pregnancy create elevated risks of a newborn having pathologies, congenital malformations, or developmental disorders (Table 2). According to our monitoring data, out of all the biomedical obstetric factors, the greatest harm to a newborn’s health (by 2.9 times higher risks) is done by use of reproductive technologies (occurred exclusively in the 2020 cohort).

Table 2

Obstetric case history as a risk factor during pregnancy and for a child’s health in the prenatal period (relative risk)

Complications during pregnancy	Health disorders in a newborn
Edemas	1.72 (1.32–2.25)
Protein in urine	1.61 (1.24–2.08)
Eclampsia	2.08 (1.37–3.15)
Abnormal (breech) presentation	1.75 (1.19–2.59)
Prematurity / postmaturity	1.41 (1.10–1.79)
Rapid labor	1.73 (1.18–2.53)
Multiple pregnancy	2.07 (1.34–3.20)
IVF (only for the 2020 cohort)	2.87 (1.35–6.08)

Eclampsia, in its turn, increases risks of intrauterine growth retardation by 3.4 times (*RR* = 3.39, 95 % CI: 1.51–7.61)[9].

[9] According to obstetric case histories, eclampsia tended to be diagnosed less and less frequently up to 2014 (it was detected in 6 % of the respondents in 1998; 4 %, in 2001; 2 %, in 2004; and 1.2 %, in 2014). Starting from 2020, there was an increase in the indicator up to 2.2 %, and deaths due to the diagnosis happened in each analyzed year (one stillbirth), 2020 excluded.

II stage. Effects produced by risk factors on children's health in the preschool period. The analysis of socio-demographic factors revealed that *a mother's age* exceeding 40 years created elevated risks of: need in regular medical check-ups already during infancy (*RR* = 2.14, 95 % CI: 1.47–3.11); underweight (*RR* = 4.23, 95 % CI: 1.10–16.23) and anemia (*RR* = 2.43, 95 % CI: 1.17–4.29) in a child aged 1–2 years; diseases of the ENT at the age of 3–4 years (*RR* = 1.77, 95 % CI: 1.13–2.76) and delayed neuropsychic development (NPD) by the age of 6–7 years (*RR* = 7.24, 95 % CI: 2.58–20.30). A mother's rather young age (younger than 20 years) increased risks of intrauterine growth retardation but did not turn out to be a health risk factor for children in future. Its influence was eliminated. This might be associated with high health potential of a younger mother and since this potential gradually declines with age, an impact on a child's health is obvious.

A mother being single is a significant health risk factor not only in the prenatal period but also in later years since it can cause chronic diseases in a child as early as in infancy (*RR* = 1.50, 95 % CI: 1.18–1.91) and at the age of 3–4 years (*RR* = 1.55, 95 % CI: 1.21–1.99). Children born by single mothers have retarded physical and neuropsychic development at the age of 1–2 years (*RR* = 1.45, 95 % CI: 1.15–1.84) with NPD progressing further at the age of 3–4 years (*RR* = 1.64, 95 % CI: 1.10–2.51) and 6–7 years (*RR* = 3.89, 95 % CI: 2.09–7.23). A risk of cardiovascular diseases (*RR* = 1.95, 95 % CI: 1.40–2.70) and diseases of the ENT (*RR* = 1.68, 95 % CI: 1.11–1.54) almost doubles at the age of 3–4 years; the same goes for risks of neurological pathologies at the age of 6-7 years (*RR* = 1.84, 95 % CI: 1.29–2.62).

Previous studies confirmed that a *poor financial position and low purchasing capacity* of a mother during pregnancy and birth had a remote effect on a child's health that became apparent in the preschool period. This resulted in elevated risks of a child needing regular medical check-ups (*RR* = 1.39, 95 % CI: 1.11–1.74) predominantly due to diseases of the gastrointestinal tract (GIT) (*RR* = 1.87, 95 % CI: 1.13–3.09) and neurological pathologies (*RR* = 1.53, 95 % CI: 1.12–2.11).

Environmental factors on a territory where a family lives undoubtedly affect a child's health. Thus, drinking "low-quality water" during pregnancy creates an elevated risk of developing cardiovascular diseases for a child by the age of 1–2 years (*RR* = 1.63, 95 % CI: 1.17–2.94). Exposure to electromagnetic radiation multiplies a number of diseases a child has had by the senior preschool age (*RR* = 1.25, 95 % CI: 1.19–1.30), makes for more children being assigned into the health groups 3–5 (*RR* = 1.16, 95 % CI: 1.12–1.20), creates elevated risks of the ENT diseases (*RR* = 3.39, 95 % CI: 1.50–7.69) and obesity (*RR* = 9.19, 95 % CI: 1.75–48.35).

Harmful working conditions at a mother's workplace one year prior to childbirth deteriorate a child's health. Thus, if a mother worked on a conveyor production, it elevates a risk of neurological disorders in a child at the age of 1–2 years (*RR* = 2.08, 95 % CI: 1.19–3.60); occupational exposure to high temperatures (*RR* = 2.19, 95 % CI: 1.30–3.67) and work in night shifts (*RR* = 1.75, 95 % CI: 1.15–2.67) increases risks of cardiological diseases; exposure to low temperatures creates elevated risks of underweight (*RR* = 3.71, 95 % CI: 1.19–11.46) and lacrimal duct stenosis (*RR* = 5.77, 95 % CI: 1.35–24.56); exposure to vibration raises risks of allergic reactions (*RR* = 1.94, 95 % CI: 1.14–3.29); exposure to gas pollution at a mother's workplace creates elevated risks of retarded physical and neuropsychic development (*RR* = 2.02, 95 % CI: 1.45–2.83).

Gas pollution (*RR* = 1.71, 95 % CI: 1.33–2.21), exposure to radiation and SHF (RR = 1.48, 95 % CI: 1.10–2.08), working at a conveyor production (*RR* = 1.61, 95 % CI: 1.11–2.34), and exposure to high temperatures (*RR* = 1.47, 95 % CI: 1.15–1.87) increase risks of the ENT diseases by 50–60 % in children aged 3–4 years. We should mention that if a future mother works on a conveyor, this creates by 2.5 times higher risks of such diseases in older children as well (*RR* = 2.57, 95 % CI: 1.26–5.25 at the age of 6-7 years)**.** Exposure to

gas pollution (*RR* = 1.16, 95 % CI: 1.12–1.21) and radiation (*RR* = 1.16, 95 % CI: 1.13–1.20) a year prior to childbirth is a risk factor for a child being assigned into a worse health group by the school age.

According to our monitoring data, *a woman's health* did not impose serious threats for a child's health, hereditary diseases being the only exclusion. Such pathologies as hyper- or hypofunction of the thyroid gland increase a risk of an endocrine pathology in a child developing before it reaches the preschool age by 8 tines (*RR* = 8.18, 95 % CI: 2.04–32.88). And if a future mother has diabetes and obesity in her case history, than a number of diseases a child has is likely to multiply at the age of 1–2 years (*RR* = 1.20, 95 % CI: 1.13–1.29) and a child's health is more likely to deteriorate at the age of 3–4 years (*RR* = 1.18, 95 % CI: 1.14–1.22).

A mother smoking during pregnancy creates elevated risks of delayed physical and neuropsychic development at the age of 1 year (*RR* = 1.57, 95 % CI: 1.23–1.97), diseases of the ENT in infancy (*RR* = 1.57, 95 % CI: 1.14–2.17) and delayed NPD by the age of 2 years (*RR* = 2.73, 95 % CI: 1.35–5.50). If a mother smoked prior to a pregnancy, it increases a risk of obesity in a child by 2.8 times by the age of 6–7 years (*RR* = 2.81, 95 % CI: 1.20–6.61). We did not establish any likelihood that asthma would develop in a preschool child in case a mother smoked. Probably, this factor will show itself later.

Such *pregnancy complications* as edemas and anemia made for developing neurological diseases (*RR* = 1.43 and 1.80 accordingly), diseases of the ENT (*RR* = 1.57 and 1.77 accordingly) and GIT pathologies (*RR* = 1.64 and 1.96 accordingly) as well as anemia (*RR* = 1.44 and 1.58 accordingly) in a child at the age of 1–2 years. Cardiovascular diseases become more frequent by the age of 3–4 years (*RR* = 1.60, 95 % CI: 1.15–2.27). We should remember that a young age of a future mother, her low purchasing capacity, unfavorable environmental factors in a place of living and diseases of the genitourinary system in case history create elevated risks of edemas and anemia during pregnancy. Therefore, they indirectly act as health risk factors for a child in future. Protein in urine increases risks of cardiological diseases by the age of 1–2 years (*RR* = 1.59; at the age of 3-4 years, *RR* = 1.50, 95 % CI: 1.10–2.06), neurological diseases (*RR* = 1.85) and the ENT diseases (*RR* = 1.71; by the age of 3–4 years, *RR* = 1.37, 95 % CI: 1.15–1.63).

Let us examine *peculiarities of previous frequencies* as a potential risk health factor for preschool children. Stillbirths in case history do not disrupt intrauterine development (probably due to more profound medical support and timely prophylaxis); nevertheless, they make a number of diseases in infancy multiply and create elevated risks of a child needing regular medical check-ups already in infancy and early preschool age thereby reducing basic health indicators by the age of 7 years (Table 3). A child also has elevated risks of GIT pathologies during the first year of life (*RR* = 5.54, 95 % CI: 1.36–22.47); underweight (*RR* = 22.85, 95 % CI: 9.51–54.92) and anemia (*RR* = 3.94, 95 % CI: 1.75–8.89) at the age of 1–2 years; and by 15 times higher risks of bronchial asthma at the age of 6–7 years (*RR* = 15.88, 95 % CI: 2.89–87.25). We can assume that a previous tragic experience associated with stillbirth is a significant stress factor for a mother during her whole life and it is especially true for another pregnancy. In addition, this diagnosis indicates that a woman's reproductive system is rather weak, she has serious health issues and her health potential is rather low. All this might trigger weaker health of her future children.

Spontaneous miscarriages in a mother's case history make for chronic diseases developing in a child at the age of 6–7 increasing their risks by 1.5 times against children whose mothers do not have miscarriages in their case history (Table 3).

We can also trace a relationship between ectopic pregnancies in a mother's case history and such chronic pathologies developing by the school age as bronchial asthma (*RR* = 11.89, 95 % CI: 1.97–71.57) and obesity (*RR* = 6.88, 95 % CI: 1.19–39.75).

Table 3

Obstetric case history of previous pregnancies as a health risk factor for a child in the neonatal and preschool period (relative risk)

Risk factor	Health group 2 or higher at the age of 6–7 years	Frequency of diseases		Need in regular medical check-ups	
		1–2 years	6–7 years	1–2 years	6–7 years
Stillbirth	1.16 (1.12–1.20)	1.23 (1.19–1.27)	1.25 (1.19–1.30)	2.56 (2.30–2.84)	-
Miscarriages	-	-	-	-	1.45 (1.13–1.86)
Ectopic pregnancy	1.16 (1.12–1.20)	-	-	-	-

Table 4

Peculiarities of a pregnancy as a health risk factor for a future child in the preschool period (relative risk)

Risk factor	Health group 2 and higher		Frequency of diseases at the age of 6–7 years	Need in regular medical check-ups		
	3–4 years	6–7 years		1–2 years	3–4 years	6–7 years
Rapid labor	-	-	-	-	-	1.59 (1.11–2.29)
Multiple pregnancy	-	1.16 (1.12–1.20)	1.25 (1.20–1.31)	-	1.59 (1.11–2.29)	-
Vacuum extraction	1.18 (1.14–1.22)	1.16 (1.12–1.20)	-	2.54 (2.29–2.82)	-	1.91 (1.26–2.89)

Peculiarities and complications of the current pregnancy produce the greatest effects, first of all, on a newborn's health. Still, their negative outcomes can become apparent also as a child grows up. A multiple pregnancy is the most severe complication and the gravest health risk factor for children. It creates elevated risks for children aged 1-2 years regarding neurological deviations (*RR* = 1.76, 95 % CI: 1.12–2.74) and disorders of the GIT (*RR* = 2.79, 95 % CI: 1.55–5.05); for children aged 3–4 years, allergic reactions (*RR* = 3.48, 95 % CI: 1.77–7.02), neurological diseases (*RR* = 3.05, 95 % CI: 1.69–5.52) and diseases of the ENT (*RR* = 1.67, 95 % CI: 1.19–2.33); as a result, children need regular medical check-ups (Table 4). If a woman carries twins[10], it makes health deterioration more likely in children aged 6–7 years creating elevated risks of diseases of the CNS (*RR* = 3.36, 95 % CI: 2.18–5.61), diseases of the visual organs (*RR* = 4.33, 95 % CI: 1.24–15.09) and bronchial asthma (*RR* = 12.98, 95 % CI: 3.37–49.95).

Rapid labor makes for a child needing regular medical check-ups already at the age of 6–7 years (Table 4) and creates an elevated (by 4.6 times higher) risk of obesity at this age (*RR* = 4.63, 95 % CI: 1.66–12.90).

Vacuum extraction[11] correlates with children needing regular medical check-ups due to chronic diseases already at the age of 1–2 years and with their poorer health in future. After vacuum extraction has been applied during labor, children have by 5 times higher risks of GIT diseases (*RR* = 5.54, 95 % CI: 1.36–22.47) and by 6 times higher risks of cardiovascular diseases (*RR* = 6.05, 95 % CI: 1.49–24.58). Children aged 3-4 years have by 8 times higher risks of allergic reactions (*RR* = 8.08, 95 % CI: 6.58–9.91), and children aged 6–7 years have by 25 % higher risks of diseases of the ENT (*RR* = 1.25, 95 % CI: 1.20–1.30).

We should note that research articles mention multiple facts proving negative influence exerted by cesarean delivery on a child's health.

[10] In our cohort study, all cases of multiple pregnancies were diagnosed exclusively when two newborns were born.
[11] We detected one case of vacuum extraction in the 2014 cohort and one more in the 2020 cohort in our cohort study.

We can confirm growing prevalence of this type of delivery (from 10 % in the 1998 cohort up to 27 % in the 2020 cohort) similarly to the global trends. Still, we did not detect any elevated relative health risks for children who were not born naturally in our study. Partially, this can be due to the fact that cognitive disorders in children are determined more reliably by using cognitive tests and longitudinal observations in primary school, and this was beyond the scope of our research tasks and the sampling analyzed in the present research article.

Conclusion. The accomplished study allows making the following conclusions. Overwhelming majority of socio-demographic, socioeconomic, biomedical and environmental maternal risk factors exert their influence on a child's health not only in the prenatal and postnatal periods but also deteriorate it throughout the whole preschool period.

If a woman younger than 20 gave birth to a child with a risk of intrauterine growth retardation, a child's health improved up to its physiological standards by 7 years. But in case the same happened to women being older than 40 years, deviations in neuropsychic development persisted in their children up to the age of 6–7 years. Such children are a risk group regarding behavioral disorders, failure to master school subjects, and difficulties in adapting to school routines. We can assume that the difference occurs due to a younger mother having a higher health potential, which is genetically transferred to a child.

A mother being single also produces negative effects on a child's health starting from the intrauterine period and aggravating issues related to a child's neuropsychic development by the age of 7 years.

Low financial incomes of a family indirectly influence children's health during the preschool period. They, among other factors, are able to cause diseases of the gastrointestinal tract, neurological diseases and need in regular medical check-ups.

Harmful environmental factors produce the most apparent negative effects on how a child's body develops and functions. In our study, we detected a relationship between a family living under exposure to electromagnetic radiation and fetus pathology in the prenatal period. The outcomes usually persist up to the age of 6–7 years (ENT pathologies, more frequent diseases, and increased body mass index).

Despite the scientific and technical progress and new safe technologies being implemented at productions where future mothers are employed, harmful working conditions deteriorate children's health as pediatricians stated when questioned about it. Regular medical check-ups that are usually accomplished at the age of 1–2 and 3–4 years revealed diseases of the nervous and cardiovascular systems, diseases of the ENT and eye. Outcomes occurring due to exposure to such harmful factors as "dustiness", "high temperature", "low temperature", "work in night shifts", and "vibration" are reduced to their minimum by the time children start school and we can state that children recover. But it is rather alerting that effects produced by gas pollution, work on a conveyor and exposure to radiation and SHF persist up to the age of 6–7 years and become apparent due to a child being assigned into a health group with poorer health in general and diseases of the ENT in particular.

If we consider a mother's health a risk factor for a child, we bear in mind a woman's health both prior to pregnancy and during it including diseases in her case history and her bad habits such as smoking. As revealed by our study, a developing endocrine pathology in a child by the end of the preschool period has the most significant relationship with a mother having hyper- or hypofunction of the thyroid gland in her case history and smoking before pregnancy.

When we assess risk rates created by variable maternal health risk factors, we should note that obstetric case history with complications during previous pregnancies, namely stillbirths and ectopic pregnancy, crates by 10 times higher risks of such an autoimmune disease as bronchial asthma in children predominantly by the age of 6–7 years.

Complications of the current pregnancy and birth, such as anemia, edemas, or protein in urine, make for a pathology developing in a child in the prenatal period, at the age of 1–2 years and 3–4 years. A child usually recovers by the time he or she goes to school.

More severe complications including multiple pregnancy, rapid labor, or vacuum extraction have more serious consequences that persist during the whole preschool period. Typically, they are neurological diseases, diseases of the ENT and visual organs, increased BMI, and bronchial asthma.

Given the research results, we believe that it is necessary to improve activities aimed at preventing and treating diseases of children caused by manageable maternal risk factors. Overwhelming majority of maternal health risk factors for a child, which we established in our study, are manageable and can be neutralized by introducing proper state socioeconomic support to future parents, by improving gynecological and obstetric aid, and by developing perinatal centers.

Children who are born by women aged 40 years and older as well as single mothers are to be assigned into a risk group susceptible to deviations in neuropsychic development. Such children require regular medical check-ups to monitor their neuropsychic development up to the age of 18 years. It is necessary to develop a mechanism and a procedure for this monitoring and medical, psychological and pedagogical support that should involve parents, experts at preschool children facilities and polyclinics for children.

When a pregnant woman with low incomes comes to a gynecological clinic to be observed during her pregnancy, it is necessary to provide her with additional social support. Then, it is necessary to provide her child with the same monitoring regarding neuropsychic development and medical, psychological and pedagogical support that should involve parents, experts at preschool children facilities and polyclinics for children and be provided up to the age of 18 years.

We should try to provide families with children with housing located on territories free from any exposure to electromagnetic radiation. It is necessary to provide sanatorium-resort treatment for children who have diseases of the ENT and live on a territory exposed to electromagnetic radiation as well as children born by mothers who have to work under harmful working conditions. We also believe it is necessary to improve the regulatory and legislative base concerning health protection provided for women who work under harmful or hazardous working conditions.

We should communicate the results of scientific studies focusing on negative influences produced by smoking prior to pregnancy on a child's health to mothers, parents and children and motivate them to pursue a healthy lifestyle.

We understand that residual and hardly measurable combinations of all the external and internal risk factors require further investigation. In particular, some attention should be given to impacts exerted on a child's physical and neuropsychic development by a father's age, bad habits among older generations in a family, and cesarean delivery. We also realize the necessity to provide scientific substantiation for targeted recommendations on how to improve strategies aimed at preserving both parents' and children's health in order to increase health potential of next generations.

Limitations of the study. (1) Our study sampling was made of obstetric patients with an initially favorable medical and social situation who gave their consent to participate in the study. It did not include all the women who gave birth to their children during the specific periods when our cohort was sampled. (2) It is rather difficult to keep the same number of participants in the monitoring over the long-term study period. Our sampling reduces every year. (3) Residual and hardly measurable combinations of all the external and internal factors require further investigation.

Prospects of the study. In future, we plan to examine maternal risk factors for a child's health not only in the preschool period but at older ages as well. We realize the necessity to provide scientific substantiation and to develop targeted recommendations on how to improve strategies aimed at preserving both parents' and children's health in order to increase health potential of next generations.

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Research article

INFORMATIVE VALUE OF TWO OBESITY MARKERS, BODY MASS INDEX (BMI) AND LIPID ACCUMULATION PRODUCT (LAP), FOR ASSESSING ATHEROGENIC RISKS IN LIPID PROFILE: COMPARATIVE ANALYSIS

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The obesity epidemic is a global concern nowadays since obesity is a major risk factor that can cause many serious diseases. A high risk of developing diseases in an obese person primarily occurs due to metabolic disorders. As a rule, dyslipidemia acts as an early sign of metabolic disorders in case of obesity.

Our research goal was to compare informative value of body mass index (BMI) and lipid accumulation product (LAP) for assessing atherogenic risks in lipid profile.

Two thousand and four hundred people aged 20–60 years took part in our study. We determined participants' anthropometric and clinical indicators and estimated lipid levels in blood serum.

As expected, LAP values had a strong correlation with BMI values. Spearman's rank correlation coefficient for LAP and BMI values amounted to 0.73 (< 0.001) in men (n = 1168) and 0.77 (< 0.001) in women (n = 1232). However, when we estimated agreement between these two indicators using Cohen's Kappa coefficient, we established that this agreement between LAP and BMI values was rather low (0.35 for men and 0.39 for women). Having compared samplings with quartiles that differed as per LAP and BMI values, we detected that lipid profiles tended to be more atherogenic in people with LAP values being higher than BMI values.

Given this established discordance in the quartiles, higher LAP values are associated with atherogenicity of lipid profile to a greater extent than values of BMI, the conventional obesity indicator. Using solely BMI to diagnose obesity may result in underestimating metabolic disorders in the body. To assess obesity and metabolic health correctly, it is advisable to determine LAP value together with traditional obesity indexes.

Keywords: *lipid accumulation product (LAP), body mass index (BMI), obesity, markers, waist circumference, triglycerides, atherogenicity, metabolism.*

At present, a great variety of indexes is used to assess obesity. These indexes primarily rely on anthropometric parameters and the best examples here are body mass index (BMI) [1], waist-to-height or waist-to-hip ratio [2], conicity index (CI) [3], abdominal volume index (AVI) [4], body adiposity index (BAI) [5], a body shape index (ABSI) [6] and many others. In addition, several combined indexes have been developed recently. Such indexes include not only anthropometric components but also biochemical indicators, primarily those related to lipid metabolism. The most widely spread combined indexes are visceral adiposity index (VAI) [7], cardiometabolic index (CMI) [8] and lipid accumulation product (LAP) [9].

Despite all this variety of indexes, Quetelet index, which is usually called BMI, remains the most widely used one. A for-

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mula to calculate it was developed by Adolphe Quetelet, a Belgian scientist, in 1832. More than a century later, A. Keys with colleagues from the Minnesota University made the index applicable for population studies and gave it a new name, BMI [1]. BMI evaluates a ratio of a person's weight to his or her height thereby giving an opportunity to conclude whether a person has underweight, normal weight or overweight. In 1997, the World Health Organization (WHO) developed the obesity classification as per BMI and recommended using it to assess risks of obesity-related diseases [10]. However, the classification the WHO offers to use has certain drawbacks. Thus, it does not consider sex, age and obesity phenotype. Recently, more research data have become available indicating that BMI does not provide sufficient information to determine health risks properly. This has motivated experts to try developing combined obesity indexes that would include both anthropometric parameters and biochemical indicators. LAP is the simplest to calculate among all combined indexes.

LAP as an obesity index was first introduced in 2005. It combines an anthropometric parameter and a biochemical indicator, namely, waist circumference and triglyceride concentration in blood. They reflect amounts of accumulated fat and circulating fat in the body accordingly [9]. Multiple studies have shown that LAP can be used to predict cardiovascular pathologies and to diagnose metabolic diseases [11–19].

Our research goal was to compare informative value of body mass index (BMI) and lipid accumulation product (LAP) for assessing atherogenic risks in lipid profile.

Materials and methods. There were 2400 participants in our study (1168 men and 1232 women aged 20–60 years). We measured participants' anthropometric parameters (height, weight, and waist circumference). Height and weight were measured with a standard height meter and scales in a standing position; a participant did not wear outer clothing or footwear during measuring. BMI was calculated as per the following formula: BMI (kg/m^2) = weight (kg) / height $(m)^2$. Waist circumference was measured with a centimeter band.

Blood for biochemical analysis was taken from the ulnar vein into vacutainers; it was done in the morning on an empty stomach. We determined triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-C) in blood serum. The test results were used to calculate the following:

♦ atherogenicity coefficient:

AC = (total cholesterol – HDL-C) / HDL-C;

♦ non-HDL-C:

non-HDL-C = total cholesterol – HDL-C;

♦ atherogenic index of plasma (AIP):

AIP = (log [triglycerides / HDL-C]) [20].

LAP index was calculated as per the following formulas:

♦ for men: LAP = (waist circumference – 65) × triglycerides;

♦ for women: LAP = (waist circumference – 58) × triglycerides [9].

All the results were statistically analyzed with MedCalc 19.5.1 software package (MedCalc Software Ltd, Belgium). Quantitative data in the tables are given as median, 25^{th} and 75^{th} percentiles; qualitative data are given as *n* (%). We assessed significance of differences between groups with Mann – Whitney test and used Spearman's rank correlation coefficient to reveal any correlations between indicators. To assess agreement between indicators, we calculated Cohen's Kappa coefficient.

Results and discussion. Overweight and obesity are a threat for health as they create elevated risks of several diseases caused by metabolic disorders. In comparison with traditional anthropometric parameters, LAP has a certain advantage since it simultaneously reflects both anatomic and biochemical outcomes of obesity and provides an opportunity to estimate how fat is distributed in the body and to reflect functional state of fat tissues.

Table 1

Anthropometric parameters and biochemical indicators in participants

Indicator	Men, n = 1168		Women, n = 1232		p
	Median (25 %; 75 %)	Minimum – maximum	Median (25 %; 75 %)	Minimum – maximum	
Age, years	42.0 (32.0; 50.0)	20.0–60.0	41.0 (32.0; 49.0)	20.0–60.0	0.437
Weight, kg	76.0 (69.0; 85.3)	44.0–150.0	66.0 (59.0; 76.0)	43.0–135.0	**<0.001**
Height, cm	175.0 (170.0; 180.0)	140.0–196.0	163.0 (158.0; 166.0)	141.0–184.0	**<0.001**
Waist circumference, cm	84.0 (78.0; 91.0)	66.0–136.0	77.0 (70.0; 88.0)	59.0–138.0	**<0.001**
BMI, kg/m^2	25.1 (22.9; 27.9)	16.4–46.7	25.3 (22.3; 28.8)	16.7–50.0	0.908
LAP, cm·mmol/l	23.0 (12.4; 40.8)	0.5–221.3	20.3 (9.7; 42.3)	0.4–262.2	**0.013**
Total cholesterol, mmol/l	5.41 (4.65; 6.32)	2.36–11.07	5.28 (4.51; 6.14)	1.65–14.24	**0.009**
Triglycerides, mmol/l	1.24 (0.90; 1.72)	0.40–9.50	1.06 (0.77; 1.55)	0.40–9.99	**<0.001**
HDL-C, mmol/l	1.23 (1.10; 1.34)	0.60–1.98	1.27 (1.13; 1.39)	0.58–2.42	**<0.001**
non-HDL-C, mmol/l	4.19 (3.43; 5.09)	1.17–10.11	4.01 (3.29; 4.84)	0.48–12.99	**<0.001**
Atherogenicity coefficient	3.41 (2.78; 4.22)	0.94–10.60	3.19 (2.55; 3.89)	0.41–10.39	**<0.001**
AIP	0.01 (-0.14; 0.16)	-0.52–0.96	-0.07 (-0.21; 0.09)	-0.51–0.83	**<0.001**

We detected significant differences between men and women as per almost all the analyzed indicators, apart from age and BMI (Table 1). All the indicators, HDL-C excluded, were higher in men than in women.

LAP values varied within quite a wide range in both men and women (from 0.5 to 221.3 cm·mmol/l in men and from 0.4 to 262.2 cm·mmol/l in women). However, having analyzed how the data were distributed, we established that the distribution was obviously left-handed (Figure). LAP values in 75 % of both men and women varied within a range from 0.4 to 40 cm·mmol/l. Average LAP values in men and women equaled 23.0 (12.4; 40.8) and 20.3 (9.7; 42.3) cm·mmol/l accordingly (Table 1).

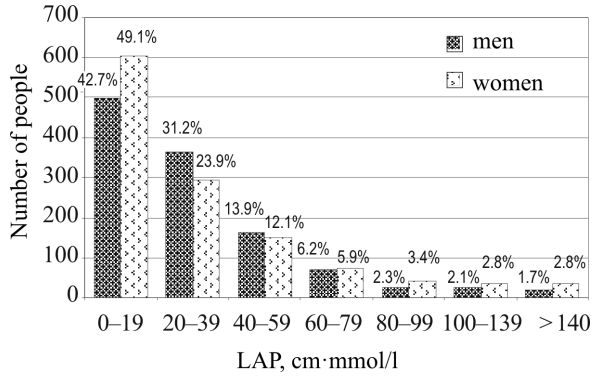

Figure. Distribution of LAP values in men (n = 1168) and women (n = 1232)

The established wide range of LAP values that amounted to 220.8 cm·mmol/l in men and 261.8 cm·mmol/l in women occurs due to its calculation being based on two indicators that have different dimensions (waist circumference and triglyceride concentration). The produced results correspond to data available in literature [16, 21–24]. The greatest range of LAP values was mentioned in a study by M. Bozorgmanesh with colleagues where it amounted to 569.64 cm·mmol/l in men and 619.83 cm·mmol/l in women [16]. Left-handed distribution of LAP values is in line with the data from our previously published study that concentrated on varying peculiarities, sex-related differences and age dynamics of LAP values in practically healthy people [24]. However, boundaries of a range within which LAP values varied turned out to be significantly lower in practically healthy people than the boundaries established in the present research where we did not exclude participants with diseases. The latter was due to the study design aimed at detecting any correlations between obesity indexes and lipid metabolism disorders.

LAP values had strong correlations with BMI values as confirmed by Spearman's rank correlation coefficient between LAP and BMI values. It amounted to 0.73 in men (< 0.001) and 0.77 in women (< 0.001). This strong correlation occurs due to BMI values being dependent on waist circumference value, which is also used to calculate LAP. Obviously, when body weight grows, its circumferences

also increase. According to data available in literature, there is a strong correlation (higher than 0.80) between BMI values and waist circumference. It is especially true for heterogeneous groups including both lean people and patients with obesity [25, 26]. Still, profound data analysis reveals that there can be a wide range of waist circumference values for each specific BMI value. Accordingly, people with the same BMI value but different waist circumference values can face substantially different risks of developing metabolic and cardiovascular disorders [26].

We estimated agreement between LAP and BMI values using Cohen's Kappa test. The estimation indicated that the agreement was rather low between them (Table 2). Quartiles of these two indicators were in agreement only for a half of the examined men and women (52 % and 54 % accordingly). Levels of this agreement in both men and women were higher (16–17 %) in the extreme quartiles and lower (9–11 %) in the middle ones.

Comparison between the samples with quartiles differing as per LAP and BMI values indicated that people with LAP values being higher than BMI values tended to have more atherogenic lipid profile (Table 3). Men who had disproportionately high LAP values against BMI values had significantly higher levels of total cholesterol and non-HDL-C and higher atherogenicity coefficient but HDL-C levels were the same in both groups under comparison. All the cholesterol metabolism indicators were significantly higher among women with LAP values being higher than BMI values. The established differences in triglyceride levels and AIP in the examined people occur due to a specific design used to create the compared groups.

A stronger association between high LAP values and lipid profile atherogenicity in comparison with BMI occurs due to this index is calculated using not only an anthropometric parameter (waist circumference) but also a biochemical indicator (triglyceride concentration). Thus, LAP indicates not only that a person is overweight but also that there is a risk of developing metabolic disorders. According to data available in literature, LAP values have a positive correlation with levels of total cholesterol, apolipoprotein-B and free fatty acids and a negative correlation with HDL-C concentrations. LAP values have also been established to be associated with quantity and size of high and low density lipoproteins [28].

An advantage that LAP has over BMI in predicting risks of metabolic and cardiovascular diseases has been outlined in multiple studies [14, 15, 29–31]. The reason for this advantage is that BMI describes only generalized obesity whereas waist circumference values used to calculate LAP reflect abdominal obesity. Meanwhile, simple measuring of waist circumference does not give a possibility to

Table 2

Agreement between quartiles of LAP and BMI values in men and women

Sex	Indicator	BMI, *n* (%)				Agreement as per Cohen's Kappa test (95 % CI)
	LAP	quartile 1	quartile 2	quartile 3	quartile 4	
Men, *n* = 1168	quartile 1	**192 (16.4)**	74 (6.3)	24 (2.1)	2 (0.2)	low, 0.35 (0.32–0.39)
	quartile 2	77 (6.6)	**108 (9.2)**	72 (6.2)	35 (3.0)	
	quartile 3	21 (1.8)	80 (6.8)	**119 (10.2)**	72 (6.2)	
	quartile 4	2 (0.2)	30 (2.6)	77 (6.6)	**183 (15.7)**	
Women, *n* = 1232	quartile 1	**206 (16.7)**	79 (6.4)	23 (1.9)	0 (0)	low 0.39 (0.35–0.42)
	quartile 2	78 (6.3)	**135 (11.0)**	80 (6.5)	15 (1.2)	
	quartile 3	17 (1.4)	73 (5.9)	**124 (10.1)**	94 (7.6)	
	quartile 4	7 (0.6)	21 (1.7)	81 (6.6)	**199 (16.2)**	

N o t e : Values of Cohen's Kappa test vary from 0 to 1 and show agreement between two variables. Agreement may vary from insignificant (from 0.0 to 0.20), low (from 0.21 to 0.40) and moderate (from 0.41 to 0.60) to significant (from 0.61 to 0.80) and almost ideal (from 0.81 to 1.00), according to J.R. Landis and G.G. Koch [27].

Table 3

Baseline characteristics in men and women with discordant quartiles as per LAP and BMI values

Indicator	Men		*p*	Women		*p*
	BMI quartile > LAP quartile, *n* = 279	BMI quartile < LAP quartile, *n* = 287		BMI quartile > LAP quartile, *n* = 291	BMI quartile < LAP quartile, *n* = 277	
	Median (25 %; 75 %)	Median (25 %; 75 %)		Median (25 %; 75 %)	Median (25 %; 75 %)	
Age, years	44.0 (33.0; 51.0)	42.0 (34.0; 50.0)	0.598	40.0 (31.0; 48.5)	44.0 (37.0; 50.0)	**<0.001**
Weight, kg	79.0 (74.0; 88.0)	74.0 (68.0; 80.0)	**<0.001**	71.0 (64.0; 78.0)	62.0 (56.0; 69.0)	**<0.001**
Height, cm	173.0 (169.0; 178.0)	176.0 (170.0; 180.0)	**<0.001**	162.0 (158.0; 166.0)	163.0 (158.0; 167.0)	0.115
Waist circumference, cm	85.0 (78.0; 91.0)	84.0 (79.0; 88.0)	0.230	79.0 (70.0; 87.0)	77.0 (72.0; 85.0)	0.746
BMI, kg/m^2	26.5 (25.0; 28.6)	24.0 (22.4; 25.4)	**<0.001**	26.9 (24.6; 29.8)	23.7 (21.6; 25.8)	**<0.001**
LAP, cm·mmol/l	17.71 (10.23; 23.58)	31.20 (22.47; 46.69)	**<0.001**	16.0 (8.4; 26.9)	29.6 (18.4; 54.6)	**<0.001**
Total cholesterol, mmol/l	5.23 (4.58; 5.97)	5.78 (4.99; 6.63)	**<0.001**	5.03 (4.36; 5.94)	5.61 (4.93; 6.54)	**<0.001**
Triglycerides, mmol/l	0.89 (0.70; 1.12)	1.72 (1.38; 2.25)	**<0.001**	0.77 (0.61; 0.97)	1.60 (1.15; 2.17)	**<0.001**
HDL-C, mmol/l	1.24 (1.08; 1.34)	1.24 (1.11; 1.34)	0.498	1.25 (1.13; 1.36)	1.30 (1.17; 1.46)	**<0.001**
non-HDL-C, mmol/l	4.00 (3.36; 4.76)	4.49 (3.76; 5.46)	**<0.001**	3.82 (3.12; 4.62)	4.27 (3.59; 5.20)	**<0.001**
Atherogenicity coefficient	3.34 (2.76; 3.99)	3.66 (3.07; 4.47)	**<0.001**	3.02 (2.48; 3.75)	3.26 (2.61; 4.08)	**0.012**
AIP	-0.14 (-0.24; -0.02)	0.15 (0.05; 0.28)	**<0.001**	-0.21 (-0.31; -0.10)	0.08 (-0.04; 0.25)	**<0.001**

differentiate visceral and subcutaneous fats; this drawback, however, is compensated with introducing triglyceride levels into the formula since these levels are associated with visceral fat tissue. It is excessive visceral fat that induces a cascade of metabolic disorders leading to dyslipidemia, hyperglycemia, hyperinsulinemia and insulin resistance [32].

Many researchers admit that BMI is useful in population studies due to being widely recognized as a screening tool to detect obesity. However, its use at an individual level has rather limited prognostic value. BMI is a good diagnostic instrument for revealing obesity when its values are high but as some studies have revealed people with average BMI values are a heterogeneous group regarding fat contents in the body. Another established point is that excessive visceral fat content is associated with metabolic regulation disorders regardless of body mass [33]. In this case, LAP can become a useful tool applied in clinical practice to detect and predict personified risks of metabolic disorders.

Conclusion. Obesity is a global concern nowadays since it creates elevated risks of many serious diseases. Adverse effects produced by obesity on health are primarily associated with concomitant metabolic diseases. It is necessary to detect metabolic disorders as early as possible and to apply correction therapy in due time in order to prevent negative outcomes of obesity for the body. Our research results indicate that LAP as an up-to-date index to estimate obesity has certain advantages over traditional BMI when it comes to detecting atherogenic changes in lipid profile. Developing atherogenic disorders in case of obesity result from

dysfunction of visceral fat tissue. If LAP is introduced into clinical practice as a complex indicator showing functional state of visceral fat tissue, this will bring about substantial improvements in diagnostics and assessing risks of metabolic disorders associated with obesity.

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Research article

ACE I/D GENETIC POLYMORPHISM AS A RISK FACTOR OF ESSENTIAL HYPERTENSION

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Examining genetic mechanisms of essential hypertension as a cardiovascular risk factor will make it possible to provide monitoring of public health using a personified approach to early diagnostics of cardiovascular pathologies. This will raise effectiveness of preventive activities aimed at reducing population mortality.

Our research goal was to examine features of ACE (the angiotensin-converting enzyme) I/D gene polymorphism (rs4646994) as a risk factor of essential hypertension.

Our test group included 35 people with diagnosed essential hypertension; the reference group was made of 34 relatively healthy people. Lipid spectrum indicators were estimated with an automated or semi-automated analyzer or by calculation. Insulin and cytokines were determined by using the enzyme immunoassay. Genotyping was performed by using the polymerase chain reaction in real time mode.

The research results revealed that the examined patients with essential hypertension had authentic differences from the reference group regarding BMI, lipid spectrum indicators with very low density lipoproteins and triglycerides contents being by 1.3 times higher; insulin contents, by 1.9 times higher; IL-6 contents, by 2.2 times higher; and VEGF, by 1.4 times higher. Genetic analysis revealed 1.3-time higher prevalence of the D-allele of the ACE I/D gene in the patients with essential hypertension (we showed that the dominant inheritance was adequate, P = 0.041). The carriage of this allele was associated with the analyzed disease (OR = 3.16; 95 % CI = 1.08–9.20).

We showed an association between insertion-deletion polymorphisms of the ACE (the angiotensin-converting enzyme) I/D gene and developing essential hypertension in the examined test group (the relative risk was RR = 1.87; 95 % CI =1.07–3.61). This polymorphism can be considered a potential marker of sensitivity to developing essential hypertension.

Keywords: *essential hypertension, angiotensin-converting enzyme, ACE I/D polymorphism, dyslipidemia, proinflammatory cytokines.*

At present, cardiovascular diseases are the major reason for incidence and mortality. Their etiology includes both genetic peculiarities and environmental factors. The renin-angiotensin-aldosterone system (RAAS) is a key regulator of electrolysis balance in the body; SNP-variants of its components are assumed to have substantial influence on cardiovascular homeostasis [1, 2]. Gene examinations and transgenic studies on mice established a crucial role that belongs to *ACE* (the angiotensin-converting enzyme) gene in blood pressure regulation. This resulted in formulating a hypothesis about *ACE* being a probable candidate gene that had an association with essential hypertension [3].

Over the last decades, polymorphisms of *ACE* gene located in the 17q23 chromosome have been examined actively due to developing cardiovascular complications. Insertion/

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deletion (*I/D*) polymorphism of Alu-element with its size being 287 base pairs in the intron 16 of *ACE* gene attracted a lot of attention within the range of cardiovascular phenotypes. It happened due to its correlation with *ACE* activity in blood serum; however, any associations between *ACE I/D* and essential hypertension still remain disputable. Since any associations, as a rule, tend to differ depending on a sex or an ethnic group or under different socio-ecological conditions, it is important to consider potential genetic and genetic-environmental interactions [4, 5].

Our research goal was to examine features of ACE (the angiotensin-converting enzyme) I/D gene polymorphism (rs4646994) as a risk factor of essential hypertension.

Materials and methods. We examined adults who lived in Perm region and were diagnosed with "Essential [primary] hypertension" as per the ICD-10. They were included into the test group, 35 people overall, with their average age being 50.31 ± 1.39 years. Our reference group was made of 34 relatively healthy people with their average age being 48.5 ± 1.36 years. Both groups were comparable in terms of sex, age and lifestyle ($p > 0.05$).

All the examined people gave their voluntary informed written consent to take part in the study. It was accomplished in accordance with the Declaration of Helsinki issued by the World Medical Association (2013 edition) and approved by the Ethical Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies.

Body mass index (BMI) was calculated as per the following formula: BMI = weight (kg) / height $(m)^2$. We took systolic and diastolic blood pressure (SBP and DBP accordingly) by using a sphygmomanometer.

Biochemical indicators of the lipid spectrum (high density lipoproteins or HDLP, low density lipoproteins or LDLP, and triglycerides) were examined with Keylab (BPC+Biosed, Italy) automated clinical chemistry analyzer and Humalyzer 2000 (Human GmbH, Germany) semi-automated one. We calculated levels of very low density lipoproteins as per the following formula: VLDLP = triglycerides $(mmol/dm^3)$ / 2.2. Insulin was examined by ELISA that was performed with Infinite F50 microplate reader (Tecan, Austria) in accordance with the procedure provided by the manufacturer. We calculated insulin resistance index as per the following formula: HOMA-IR = insulin $(\mu IU/cm^3)\cdot$ glucose $(mmol/dm^3)$ / 22.5. We identified markers of immune regulation, namely, interleukins (IL-1beta, IL-6, TNFalfa) and vascular endothelial growth factor (VEGF), by ELISA performed with ELx808 microplate reader (BioTek, USA).

The results were analyzed with "Statistica 6.0" software package (StatSoft, USA). The data are given as the simple mean and standard error of the mean ($M \pm m$). In case distribution was not normal, we applied normalizing log-transformation. Authenticity of differences between mean values determined for different groups was estimated using Student's t-test and differences were considered significant at $p < 0.05$. We applied logistic regression analysis and maximum likelihood estimation to estimate risk factors of essential hypertension, calculated odds ratio *OR* and its 95 % confidence interval (95 % CI) as well as relative risk *RR* and its 95 % confidence interval (95 % CI).

We used biomaterials taken from the oral pharynx mucosa in our genetic analysis. DNA was extracted by using a sorbent. *ACE I/D* (rs4646994) polymorphism was identified with "SNP-screen" kits (Sintol, Russia). We applied the polymerase chain reaction in real time mode using CFX96 thermal cycler (Bio-Rad, USA). The data were analyzed with "Gene Expert" software package. We performed logistic regression analysis that involved building a co-dominant, dominant and recessive inheritance model. Frequencies of alleles and genotypes were calculated according to the Hardy – Weinberg equilibrium based on diagnostics of single nuclear polymorphisms (SNP). We determined whether intergroup dif-

ferences were authentic by using Fischer's exact test and analyzed data on frequency of genotypes and alleles by calculating odds ratio *OR* and 95 % confidence interval (95 % CI). Intergroup differences were considered authentic at $p < 0.05$.

All the tests were accomplished by certified laboratories according to conventional procedures and with certified equipment.

Results. Our examination of patients with essential hypertension established authentic differences ($p = 0.000$) between the test and reference groups as per BMI, SBP and DBP (Table 1). Lipid spectrum indicators were also authentically different between the groups since VLDLP levels were by 1.3 times higher in the test group with a simultaneous decrease in HDLP levels by 13 % ($p = 0.032–0.037$). Triglycerides levels were by 1.3 times higher ($p = 0.036$). We also detected that insulin levels were by 1.9 times higher in the test group than in the reference one and, accordingly, the HOMA-IR index was also higher ($p = 0.022–0.035$).

We examined immune regulation to identify any possible peculiarities and established certain changes in indicators of "the cytokine storm" as IL-6 levels were by 2.2 times higher and VEGF levels by 1.4 times higher in the test group against the reference one ($p = 0.005–0.018$).

Genetic examination identified by 1.3 times more frequent *D* allele of *ACE I/D* gene among the patients with essential hypertension (Table 2); carriage of the allele was associated with the disease ($OR = 3.16$; 95 % CI = 1.08–9.20). We showed that the dominant inheritance model was adequate ($P = 0.041$) and a share of heterozygotes *ID* and variant homozygotes *DD* amounted to 80 % in the test group against 55.9 % in the reference one. Peculiar ratios of frequent genotypes and alleles in the examined groups corresponded to the Hardy – Weinberg equilibrium ($\chi^2 = 0.01–2.32$; $p = 0.13–0.91$).

Logistic regression analysis established risk factors that were independently associated with essential hypertension developing in the examined people (Table 3). Significant intergroup differences were identified for such indicators as VLDLP (by 6.4 times

Table 1

Basic, biochemical and immune indicators in examined patients with essential hypertension and reference group

Indicator	Reference level	Test group	Reference group	*p*
Age, years	-	50.31 ± 1.39	46.5 ± 1.36	0.060
Sex, males/females	-	7/28	4/30	0.513
BMI, kg/m^2	18.5–24.9	33.34 ± 1.59	24.84 ± 1.04	0.000
SBP, mm Hg	120–130	139.41 ± 4.77	119.57 ± 4.06	0.000
DBP, mm Hg	80–85	87.79 ± 3.10	75.86 ± 2.48	0.000
Insulin, μIU/cm^3	2–25	9.61 ± 3.90	5.27 ± 0.80	0.028
HOMA-IR index	0–2.7	2.23 ± 0.99	1.20 ± 0.19	0.041
HDLP, mmol/dm^3	1.42–10	1.63 ± 0.12	1.86 ± 0.15	0.024
LDLP, mmol/dm^3	0–3.9	3.17 ± 0.23	3.12 ± 0.31	0.783
VLDLP, mmol/dm^3	0.26–1.04	0.79 ± 0.14	0.57 ± 0.11	0.014
Triglycerides, mmol/dm^3	0.3–1.7	1.73 ± 0.30	1.24 ± 0.24	0.014
VEGF, pg/cm^3	10–700	327.74 ± 62.39	245.61 ± 45.66	0.039
IL-1beta, pg/cm^3	0–11	1.39 ± 0.31	1.41 ± 0.33	0.917
IL-6, pg/cm^3	0–10	2.56 ± 0.76	1.21 ± 0.56	0.006
TNFalfa, pg/cm^3	0–6	3.14 ± 1.29	3.70 ± 1.09	0.509

N o t e : *p* is the level of significance determined for difference between the test and reference groups.

Table 2

Peculiarities of *ACE I/D* genetic polymorphism in the examined patients with essential hypertension

Genotype, allele	Test group, %	Reference group, %	*P*	*OR* (95 % CI)
Co-dominant model				
II	20	44.1	0.076	0.32 (0.11–0.92)
ID	51.4	29.4		2.54 (0.94–6.85)
DD	28.6	26.5		1.11 (0.39–3.20)
Frequency of alleles				
I	45.7	58.8	0.416	0.59 (0.30–1.16)
D	54.3	41.2		1.70 (0.86–3.33)
Dominant model				
II	20	44.1	0.041	0.32 (0.11–0.92)
ID+DD	80	55.9		3.16 (1.08–9.20)
Recessive model				
II+ID	71.4	73.5	1.0	0.90 (0.31–2.59)
DD	28.6	26.5		1.11 (0.39–3.20)

N o t e : P is Fischer's exact test.

Table 3

Logistic analysis of risk factors that could cause essential hypertension in the examined patients

Indicator	*OR* (95 % CI)	χ^2	*p*
Allele *D ACE I/D*	3.16 (1.06–9.39)	4.70	0.030
BMI	1.29 (1.13–1.47)	28.93	0.000
HDLP	0.24 (0.07–0.85)	5.51	0.019
VLDLP	6.40 (1.27–32.33)	6.62	0.010
Triglycerides	2.35 (1.12–4.95)	6.60	0.010
IL-6	2.51(1.17–5.39)	8.50	0.004

N o t e : *p* is the level of significance determined for intergroup differences; χ^2 is chi-square test adjusted as per likelihood.

higher in the test group), carriage of allele *D ACE I/D* (by 3.16 times), IL-6 levels (by 2.37 times), and triglycerides (by 2.35 times) (p = 0.007–0.030). At the same time, when we assessed risks of essential hypertension in the group associated with allele *D ACE I/D*, this assessment established an authentic probability that the disease would develop as per the relative risk criterion: *RR* = 1.87; 95 % CI =1.07–3.61.

Discussion. The research showed that carriage of allele *D ACE I/D* in the examined group was associated with essential hypertension against developing dyslipidemia and 'the cytokine storm" as risk factors that caused hypertension. *ACE I/D* polymorphism is associated with elevated *ACE* levels in plasma that increase a concentration of angiotensin II, a key factor in regulation of peripheral vascular resistance, and decrease bradykinin levels. All this may act as a risk factor of developing cardiovascular pathology [2, 6].

ACE is the key enzyme in the RAAS. It, together with the kallikrein-kinin system, facilitates physiological functioning of the heart, vessels and kidneys through regulation of blood pressure, blood flow, homeostasis and the vasomotor system. Angiotensin II is a powerful vasoconstrictor agent. It is generated from angiotensin I with help from *ACE*. Angiotensin II influences structures of arterial walls and potentiates atherosclerosis by

stimulating proliferation of smooth muscle cells and synthesis of extracellular matrix. Average *ACE* contents in plasma of people carrying *DD* genotype is approximately by 2 times higher than in *I* genotype carriers. Therefore, allele D indicates that *ACE* is highly active and vice versa. Though *ACE* activity is very different in different people, in general, it remains constant in various tissues or organs in the same person since it is hardly ever influenced by any external factors [7, 8].

There is accumulated evidence that *ACE I/D* gene polymorphism is associated with various cardiovascular diseases including myocardial infarction, heart failure, essential hypertension, atherosclerosis, and endothelial dysfunction [1, 9]. Allele *D* carriage was shown to be associated with elevated blood pressure in patients, susceptibility to hypertensive crises, and authentically more apparent myocardial hypertrophy of the left ventricle. *DD* genotype was more frequent in patients with essential hypertension, ischemic heart disease, diabetes mellitus and their complications and such risk factors as hyperlipidemia, smoking or diseases in family anamnesis [10, 11].

Hypertension-associated genes are grouped together with genes that determine obesity, dyslipidemia and resistance to insulin; however, it is still rather unclear how the RAAS influences lipid metabolism. Some studies show that adipocytes are able to release *ACE* and elevated levels of the enzyme stimulate production of angiotensin II, adhesion molecules and chemokines, LDLP oxidation and formation of foam cells out of macrophages. There is an association between *ACE DD* genotype, developing abdominal obesity and elevated risks of atherosclerosis [6, 12, 13]. Elevated activity of system and fat components in the RAAS is considered a potential way for obesity to result in hypertension and resistance to insulin. It is by this way that *ACE I/D* polymorphism might be associated with these health disorders [14, 15].

A contribution made by cytokines to essential hypertension pathogenesis is primarily associated with their function as inflammation mediators. Research works have shown that patients with essential hypertension tend to have higher levels of IL-6, IL-1 and TNFalfa in their plasma than normotensive people. There is an association between pro-inflammatory markers and systems that regulate blood pressure, the RAAS included. Angiotensin II is able to enhance synthesis of TNFalfa and IL-6 by activating NF-κB nuclear factor. IL-6 was shown to have an important role in developing essential hypertension that was caused by chronic elevated angiotensin II levels. This happened, among other things, due to induced expression of its receptors [16, 17]. IL-6 is able to stimulate production of proteins typical for acute inflammation, to increase cell adhesion in vascular endothelium and ROS concentrations, and to facilitate atherogenesis by disrupting lipoprotein metabolism [18].

Endothelial dysfunction and elevated vascular reactivity are also considered a way for inflammation to contribute to development of essential hypertension. Inflammation can lead to disrupted endothelium-dependent vasodilatation through weakened expression of NO-synthases and lower NO production by such mediators as TNFalfa and C-reactive protein. Besides, activated sections in the immune system can damage endothelial cells and induce remodeling in vascular walls thereby accelerating development of atherosclerosis and ischemic damage in case of essential hypertension [17, 19]. Pathologic angiogenesis develops, among other things, due to VEGF participation which is considered a potential marker of hypertension-induced disorders. VEGF production is initiated by angiotensin II and correlated with blood pressure, cardiovascular risks and early microvascular lesions. However, elevated VEGF levels in patients with essential hypertension are rather a protective mechanism aimed at reducing blood pressure and

are associated with endothelial dysfunction and stimulation of angiogenesis in case vascular walls are damaged [20].

We should note that accumulated data on associations between *ACE I/D* gene polymorphism and essential hypertension are rather controversial. Many studies have established significant differences in distribution of *ACE D/I* gene polymorphism between various ethnic groups and even within the same ethnic group. At the same time, it is necessary to consider possible genetic interactions and a role played by epigenetic changeability, including that occurring under influence of environmental factors, in formation of hereditary predisposition [3, 7, 21–25].

Conclusion. We examined patients with essential hypertension. As a result, insertion-deletion polymorphism of *ACE I/D* gene was established to be associated with a risk of essential hypertension in the examined group (*RR* = 1.87; 95 % CI = 1.07–3.61); in addition, we showed factors related to dyslipidemia and immune inflammation to be also significant (in particular, BMI: OR = 1.29, 95 % CI = 1.13–1.47; IL-6: *OR* = 2.51, 95 % CI = 1.17–5.39; allele *D* of *ACE I/D* gene*: OR* = 3.16, 95 % CI = 1.09–9.39). Therefore, carriage of allele *D* of *ACE* gene can be considered a genetic predictor of essential hypertension; however, the examined sampling was rather small and this calls for further research. This would probably involve examining roles of other RAAS polymorphisms and their interactions that can be applied to solve specific tasks related to prevention and monitoring of essential hypertension.

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Research article

EFFECTS OF GENETIC POLYMORPHISMS OF GSTM1, GSTT1 AND GSTP1 GENES ON BLOOD METAL LEVELS IN NON-FERROUS METAL ALLOY SMELTER OPERATORS

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Heavy metal ions are known to induce generation of a large number of reactive oxygen species (ROS). Glutathione S-transferases (GSTs) play an important role in adaptation and response to oxidative stress. GSTM1, GSTT1, and GSTP1 genes have numerous described polymorphisms, the most significant being GSTM1, GSTT1, and GSTP1 Ile105Val deletion ones.

Our objective was to study the relationship between the genetic polymorphism of GSTM1, GSTT1, GSTP1 genes and blood levels of metals in smelter operators engaged in crude lead refining.

We examined 55 male lead-refining furnace operators working at a non-ferrous metal alloy plant. Blood metal concentrations were measured by inductively coupled plasma mass spectrometry. GSTM1 and GSTT1 deletion polymorphisms were determined using real-time SYBR Green qPCR and that of GSTP1 Ile105Val – using a commercial SNP Screening Kit. Statistical data processing was carried out using the Mann – Whitney U-test.

Blood levels of industry-specific metals were not statistically different between the workers with GSTT1 and GSTP1 genotypes. We established, however, that men with the null genotype of GSTM1 had significantly higher blood arsenic levels.

Our findings indicate that a high blood arsenic level associated with occupational exposure may be attributed to the GSTM1 null genotype. This observation can be used to identify the most vulnerable groups of individuals at risk of overexposure to arsenic.

Keywords: *xenobiotics, GSTM1, GSTT1, GSTP1, glutathione S-transferases, heavy metals, arsenic, polymorphisms.*

Chemical pollution of the environment remains a priority sanitary-epidemiological health risk factor. It is especially true for workers employed at harmful productions.

For example, workplace air in a zone where lead refining takes place contains large quantities of metals that can be found in lead cake such as lead, antimony, cop-

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per, sulfur, bismuth, arsenic, tin and some others.

Heavy metal ions are known to be able to stimulate formation of reactive oxygen species (ROS) in large quantities. These species induce oxidative stress in a cell thereby damaging cellular structures [1, 2].

Glutathione-S-transferases (GST) play an important role in adaptation and response to oxidative stress. Many polymorphisms have been described for GSTM1, GSTT1 and GSTP1 genes; however, the deletions in GSTM1, GSTT1 and Ile105Val for GSTP1 gene are the most significant ones. These polymorphisms lead to either total absence of an enzyme or to a reduction in its activity. As a result, the described mutations can lead to weaker resistance to effects produced by heavy metals [3–6].

Studies with their focus on workers' genetic predisposition provide more data on pathogenesis of a disease and make it possible to identify groups that are more susceptible to exposure to harmful occupational factors. This is vital for developing and implementing activities aimed at managing health risks at a workplace, personified medical and prevention programs included.

Our research goal was to examine an association between genetic polymorphism of GSTM1, GSTT1, and GSTP1 genes and metal contents in blood of smelters dealing with crude lead refining.

Materials and methods. We examined 55 males who worked as smelters in the refining section of a metallurgic (smelting) workshop at an enterprise that produced non-ferrous alloys. Their age was from 28 to 56 years (an average age was 40.94 ± 7.04 years). The sampling was ethnically homogenous. Mass concentrations of metals (Pb, N = 54; Cd, N = 52; Sb, N = 43; As, N = 43) were identified in blood by mass spectrometry with inductively coupled plasma. DNA was extracted from peripheral blood according to conventional procedures and polymorphisms were identified as per the procedure, which we described in our previous studies [7].

Since genotype analysis does not allow distinguishing between the normal homozygote (I/I) and heterozygote (I/D) for GSTT1 and GSTM1 genes, we took a recessive model with using I/* (I/I or I/D) and DD (null allele) variables. We applied a dominant genetic model (Ile/Ile against Val/*) for GSTP1 Ile105Val polymorphism and combined Ile/Val and Val/Val into one group. Differences in the identified indicators were estimated with Mann – Whitney test and χ^2 with Yates's correction. Critical significance in testing the null hypothesis was taken as equal to 0.05. We applied Kolmogorov – Smirnov test to check whether data were normally distributed. The results were statistically analyzed with Statistica 12 software package (StatSoft Inc, USA).

Results and discussion. In the present study, we examined an association between genetic polymorphism of GSTM1, GSTT1, and GSTP1 genes and metal contents in blood of smelters who worked in the refining section of a metallurgic (smelting workshop) at an enterprise that produced non-ferrous alloys. Alleles of the examined genotypes were distributed according to an average pattern typical for a European population (Figure). Therefore, the analyzed sampling was homogeneous. It was then divided into two groups as per presence or absence of predisposition for each genotype: normal genotype/heterozygote and deletion genotype for GSTM1 and GSTT1; normal genotype and mutant genotype / heterozygote for GSTP1.

Metal contents in blood as per genotype frequencies (for better illustration, mean values are used) and authenticity of differences are given in Table.

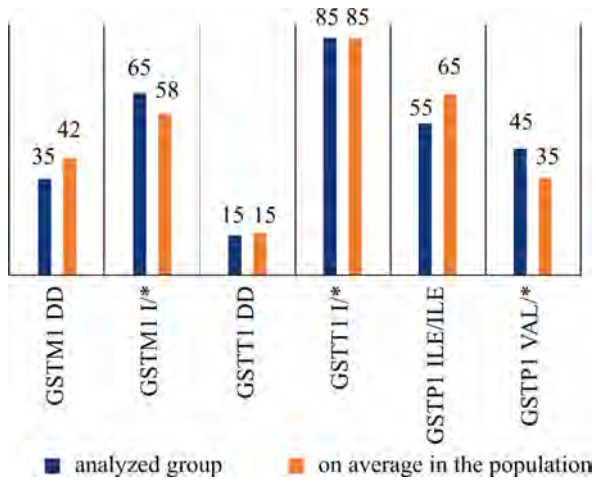

Figure. Distribution of GSTM1, GSTT1, GSTP1 genotype frequencies in smelters working in the refining section of a metallurgic (smelting) workshop at an enterprise that produces non-ferrous alloys and average frequencies in the population: I/* is the normal genotype/heterozygote, DD is the deletion (mutant) genotype, Ile/Ile is the normal genotype, Val/* is the mutant genotype/heterozygote (GSTM1: $\chi^2 = 0.76$, $p = 0.3833$; GSTT1: $\chi^2 = 0.04$, $p = 0.84$; GSTP1: $\chi^2 = 1.69$, $p = 0.1939$)

Overall, we did not detect any statistically authentic differences regarding GSTT1 and GSTP1 genotypes in metal contents in blood of workers under the same exposure. This is probably due to mutant alleles of these genes being less frequent than mutant GSTM1 and since the sampling was rather small, it also prevented us from identifying any significant differences for these two genotypes.

Heavy metals are excreted rapidly from the body due to their hydrophilic properties growing because of enzymatic activity by glutathione-transferases. Probably, compensatory detoxification pathways become involved to excrete lead, antimony and cadmium, and they induce activity of other enzymes.

Although we did not detect any statistically significant differences for all the aforementioned metals, we established an association with the deletion in GSTM1 gene and

Mean metal contents in blood of smelters with different GSTs genotypes

	GSTT			**GSTM**			GSTP		
	I/*	DD	P-value	I/*	DD	P-value	Ile/Ile	Val/*	P-value
Cd, μg/dm^3	0.362 ± 0.06 (N =44)	0.408 ± 0.18 (N = 8)	0.91	0.386 ± 0.07 (N = 34)	0.338 ± 0.1 (N = 18)	0.69	0.4 ± 0.08 (N = 24)	0.342 ± 0.08 (N = 28)	0.56
As, μg/dm^3	7.07 ± 1.78 (N = 36)	4.771 ± 2.67 (N = 7)	0.48	**4.00 ± 0.91 (N = 27)**	**11.24 ± 3.66 (N = 16)**	**0.02**	6.448 ± 3.03 (N = 19)	6.893 ± 1.46 (N = 24)	0.21
Sb, μg/dm^3	8.87 ± 0.71 (N = 36)	8.776 ± 0.87 (N = 7)	0.78	9.15 ± 0.94 (N = 27)	8.34 ± 0.44 (N = 16)	0.66	8.908 ± 1.21 (N = 19)	8.809 ± 0.58 (N = 24)	0.67
Pb, μg/dm^3	369.39 ± 23.8 (N = 46)	416.01 ± 51.6 (N = 8)	0.49	392.04 ± 28.3 (N = 35)	347.33 ± 32.44 (N = 19)	0.55	366.7 ± 37.87 (N = 24)	384 ± 25.02 (N = 30)	0.76

N o t e : I/* is the normal genotype / heterozygote, DD is the deletion (mutant) genotype, Ile/Ile is the normal genotype, Val/* is the mutant genotype / heterozygote. The table contains mean values and error of the mean; statistically authentic differences are given in bold ($p \leq 0.05$).

arsenic contents in blood. People with the mutant genotype had arsenic in their blood in a concentration that was by 3 times higher against the same indicator in people with the normal genotype ($p = 0.02$).

Arsenic metabolism has several ways; binding to certain proteins is one of them [8], and conjugation with glutathione is another [9]. After consequent stages in methylation are completed, this way leads to formation of two end products, methylarsonic acid (MMA) and dimethylarsinic acid (DMA). MMA and DMA metabolites are less toxic than non-organic compounds and are easier to excrete with urine [10, 11]. Such members of the GST family as GSTP1, GSTT1 and GSTM1 can influence an ability to metabolize arsenic depending on their expression and various allele types [12–19]. Thus, González-Martínez with colleagues showed that the deletion variant of GSTM1 produced negative effects on arsenic excretion by the kidneys due to its lower enzymatic activity. Contents of arsenic metabolites in urine went down proportionate to an increase in overall arsenic contents in case the deletion GSTM1 genotype was present. No such regularities were established for GSTT1 and GSTP1 genotypes [20]. This fact indicates that GSTM1 makes a significant contribution to arsenic metabolism and its deletion genotype can lead to high arsenic concentrations in blood due its lower enzymatic activity.

Conclusion. We established in this study that elevated arsenic concentrations in blood detected under exposure to harmful occupational factors might be caused by the deletion GSTM1 genotype. In future, this fact can be used to identify population groups that are the most susceptible to exposure to arsenic in high concentrations as well as to implement prevention activities in due time.

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Competing interests. The authors declare no competing interests.

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Research acticle

MODELING OF ENZYMATIC PROCESSES IN THE DUODENUM TO PREDICT AREAS WITH ELEVATED RISKS OF FUNCTIONAL DISORDERS

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The present work focuses on developing a model of the duodenum considering motility, biochemical reactions occurring under effects produced by secreted digestive juices, and absorption of reaction products in normal conditions and in case of functional disorders. Analysis of literature sources allowed identifying basic bile components and pancreatic and intestinal juice enzymes influencing fats, proteins and carbohydrates that enter the duodenum.

The paper provides a simplified scheme showing how food components are transformed allowing for the neural-humoral mechanism of digestion regulation. Chyme that enters the duodenum is considered a homogenous mixture, which changes its composition during chemical reactions. Mathematical tasking includes mass and momentum conservation equations for a multi-component viscous fluid. The secretion of digestive juices and absorption of components resulting from chemical reactions are described with mass effluents in a pipe in the wall layer. The peristaltic law of the duodenum wall movement was applied to describe the tract motility; the movement characteristics do not depend on the composition of the mixture.

Numeric experiments produced necessary results to describe the hydrolysis of the 5 % starch solution under exposure to pancreatic amylase. Obviously, not all the amount of starch enters a chemical reaction and this is well in line with experimental data. The paper provides data on concentration fields for the components of glucose, amylase, and starch at different moments in time and the fluid velocity field.

The next stage in the model development is expected to consider absorption of food components, functional disorders of secretion / absorption and intestinal motility as well as influence exerted by neural and humoral mechanisms. In future, the developed model can be applied to predict areas with elevated risks of developing functional disorders, ulcer formation, and other defects of the intestinal mucosa. This will help a physician to prescribe personified therapy and diet.

Keywords: *duodenum, multi-component mixture, mathematical modeling, digestive juices, enzymes, secretion, peristalsis, glucose.*

The digestive system is among the most significant parts of the human body. Digestion is a set of biochemical and physiological processes that are involved in physical and chemical processing of consumed food for the subsequent assimilation of nutrients. Physical transformation means that food is reduced to finest particles due to mechanical effects produced by the gastrointestinal tract (GIT) motility. Chemical transformation means that products are transformed under influence exerted by digestive juices[1]. Among the physiological processes, we can spot out secretion of digestive juices and absorption of reaction products.

This paper concentrates on the duodenum as a specific organ in the GIT. It is located between the antral section of the stomach and the small intestine. Its overall length is 25–30 cm and it consists of the superior region (3–6 cm long, the diameter is 3–3.5 cm), descending region (8–10 cm long, the diameter is 4–5 cm), horizontal region (6–8 cm long) and ascending region (the diameter is 4–7 cm)[2]. The major duodenal papilla is located in the descending

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region, 5.5 to 12.8 cm away from the pyloric sphincter; on average, its diameter is 6 mm [1]. The sphincter of Oddi where the common bile duct and the main pancreatic duct open is located in it[3].

Evacuation, motor, secretion and absorption are the basic functions performed by the duodenum. The motor function exists to mix chyme with digestive enzymes. The evacuation function is responsible for transporting chyme to the subsequent sections in the intestines. The secretory function involves secreting digestive juices. Besides, the tract contents are absorbed actively in the duodenum, including elementary food components (amino acids, glycerides, and monosaccharides), water, mineral salts, and vitamins. However, in comparison with the subsequent sections in the GIT, intensity of this absorption is substantially lower in the duodenum, especially when it comes down to food components[4].

The duodenum is a C-shape pipe with typical tonic and pendular peristaltic contractions and non-propulsive segmental activity[5]. Peristalsis plays the leading role in making chyme move into the next section in the tract. Chyme is a pulpy mass that consists of partially digested food, gastric and intestinal juices, secrets of various glands, bile, and microorganisms. Secrets of the intestines and pancreas have an alkaline reaction and this makes for neutralization of the acid medium coming from the stomach. Besides, intestinal and pancreatic juices participate in transforming nutrients into simpler compounds. Secretion of digestive juices is regulated by the neural and humoral mechanism. Hormones make the gall blade contract, induce secretion by the pancreas and bile secretion, and enhance the intestinal motility [2]. Digestion is the most active exactly in this section of the small intestine[6].

Data produced by scientific observations indicate that isolated stomach damage (chronic gastritis) occurs in not more than 10–15 % of patients whereas antral gastritis combined with duodenitis (chronic gastroduodenitis) is the predominant disease [3]. Elevated acidity in the duodenum is among leading factors causing damage to the mucosa [4]. We should note that many aspects associated with proving cause-effect relations between environmental factors and diseases of the duodenum remain unclear so far.

Experimental methods are among those applied to examine digestive processes. They provide an opportunity to obtain data on an organ's shape and size; to examine composition of digestive juices; to determine acidity; to detect digestive diseases etc. These methods have certain drawbacks since they rely on expensive equipment and the necessity to involve highly qualified experts. Another disadvantage is that they do not provide any possibility to make quantitative predictions of functional disorders.

Mathematical modeling techniques applied in medicine allow performing multiple examinations and numeric experiments that are impossible to be performed as full-scale ones due to underdeveloped experimental equipment or probable health hazards for human subjects. Full-scale physiological experiments can be replaced with computational ones. The latter have a certain advantage since they give an opportunity to examine influence exerted by both specific factors (including cases involving great loads) and their combinations on the human body, to obtain high volumes of experimental data over a short pe-

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riod, and to make predictions how a disease would develop based on these data [5].

Mathematical modeling considers conditions of digestion, the geometry of internal organs and their functional disorders. It allows analyzing impacts exerted by specific factors on the digestive organs. At present, experts are concentrating on developing approaches to numeric modeling of the flow in various GIT sections. They predominantly develop two-dimensional models and three-dimensional ones have been introduced into practice mostly over the last decade [6–8]. Researchers have paid more attention to the tract motility and not to digestion in their previously published papers [9–14]. The authors of the work [15] modeled the duodenum as a two-dimensional channel with moving boundaries and with spotting out a boundary layer to describe the permeable tract walls. Chyme was considered a multi-component two-phase mixture; only one reaction, namely hydrolysis of starch under exposure to amylase, was examined. On one hand, development of such models can result in discovering new and previously unknown mechanisms of digestive diseases. On the other hand, this approach is very promising with respect to practical use since it can be applied to develop personified treatment recommendations and a peculiar diet for a given patient. Given that, the authors plan to improve the existing approaches in the model they suggest to consider secretion and absorption of nutrients, their chemical and physical treatment under exposure to digestive juices and the GIT motility, as well as digestive disorders.

The research goal was to develop a mathematical model of the duodenum as a specific section in the gastrointestinal tract; the model would be used for further prediction of areas with elevated risks of functional disorders.

Materials and methods. We consider the duodenum with peristaltic waves typically moving towards the small intestine with considerable contraction of the wall muscles (amplitude) [16]. The duodenum motility is periodic and parameters of peristaltic waves do not depend on food.

A developed mathematical model of the duodenum should describe properties of a fluid; therefore, it is necessary to examine chemical reactions that occur in this section of the intestines and that induce changes in the composition of chyme. The Figure 1 provides a simplified scheme showing how food is transformed due to effects produced by digestive juices and how their secretion is regulated by the neural and humoral mechanism.

According to this simplified scheme, endocrine and exocrine cells start to excrete cholecystokinin and secretin under exposure to introduced fats, proteins and carbohydrates. These two hormones stimulate secretion of bile components and enzymes of intestinal and pancreatic juices. Neural regulation occurs due to irritation of vagal and splanchic nerves that increase or reduce secretion of digestive juices. Therefore, components and enzymes that are necessary to decompose substances into simpler compounds start to be secreted in the duodenum due to neural and humoral regulation. Salts of bile acids and lipase decompose fats into monoglycerides. Hydrolysis of polypeptides down to amino acids occurs due to effects produced by trypsin, chymotrypsin, carcboxypeptidase, and aminopeptidase. Hydrolysis of complex carbohydrates down to monosaccharides occurs due to influence by amylase, maltase, and saccharose. As opposed to pancreatic enzymes, duodenum enzymes influence products of intermediate nutrient hydrolysis.

Therefore, chyme is considered a multicomponent viscous fluid consisting of (the index $i = \overline{0,\mathrm{I}}$) carbohydrates (starch) ($i = 0$), pancreatic amylase ($i = 1$), water ($i = 2$), glucose ($i = 3$), proteins ($i = 4$), polypeptides ($i = 5$), peptides ($i = 6$), aminoacids ($i = 7$), fats ($i = 8$), emulsified fats ($i = 9$), monoglycerides ($i = 10$), lipases ($i = 11$), trypsin ($i = 12$), carboxypeptidase ($i = 13$), salts of bile acids ($i = 14$), amino peptidases ($i = 15$), maltase, saccharose, lactase ($i = 16$). Hormones (cholecystokinin and secretin) are not components in the mixture and produce their effects through the circulatory system. The authors plan to consider their influence on the properties of digestion in further studies.

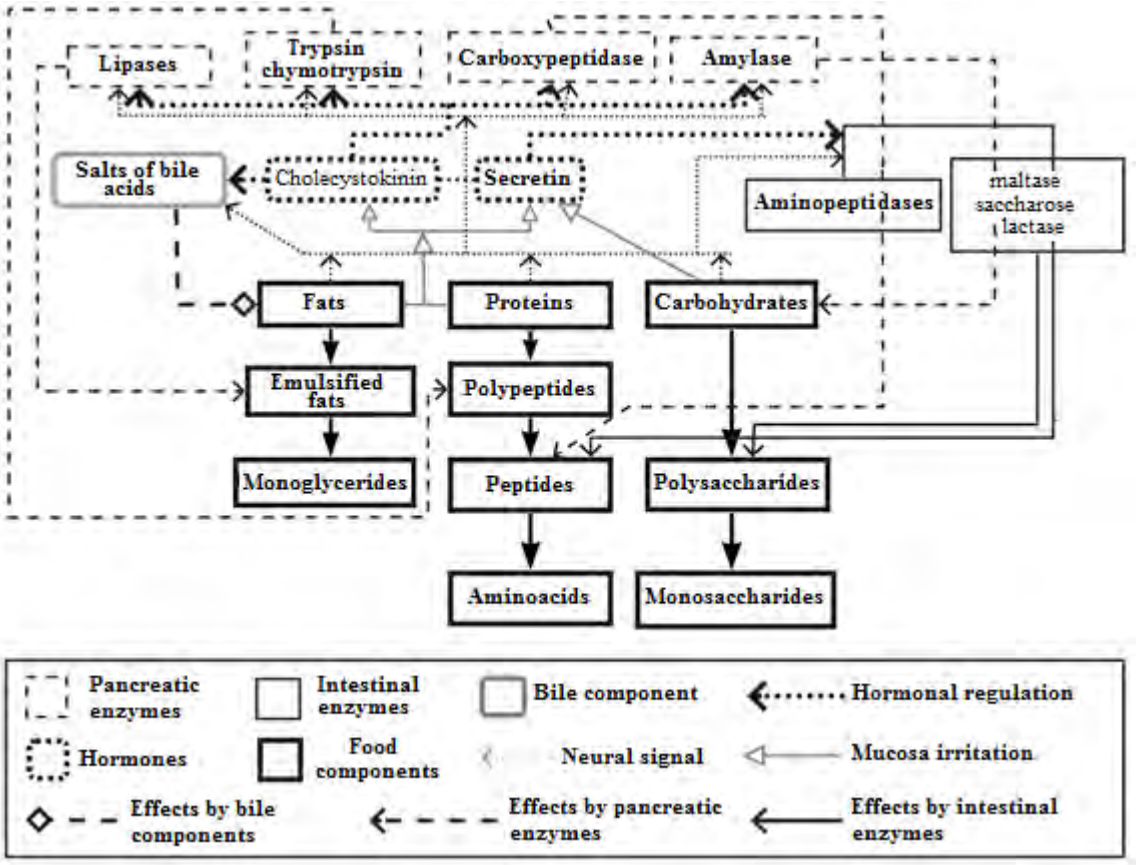

Figure 1. The scheme showing how food components are transformed in the duodenum

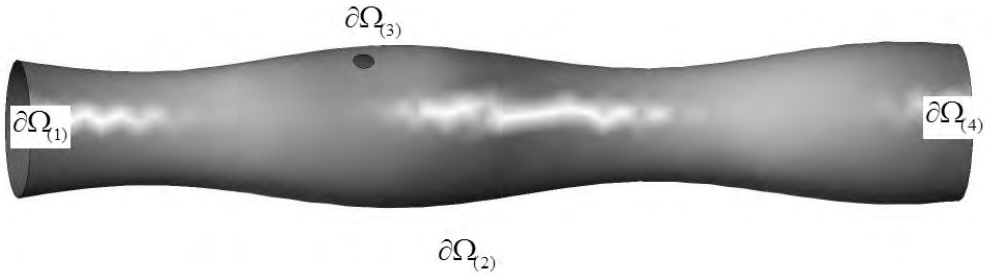

Figure 2. Sub-areas selected as per functional characteristics

The duodenum is divided into L areas where $\partial\Omega_{(1)}$ is the inlet section, $\partial\Omega_{(2)}$ is the area where intestinal juices are secreted and components are absorbed, $\partial\Omega_{(3)}$ is the area where bile and pancreatic juices are secreted (the major duodenum papilla), $\partial\Omega_{(4)}$ is the outlet section where the fluid leaves the duodenum (Figure 2).

Secretion of digestive juices and absorption of chyme components are described with mass effluents in a pipe in the wall layer. Functional disorders of secretion influence the intensity of mass effluents.

Mass conservation equations for various components in the mixture are given as follows considering mass effluents due to secretion and enzymatic reactions:

$$\frac{\partial}{\partial t}(\rho Y_{(i)}) + \nabla \cdot (\rho \mathbf{v} Y_{(i)}) = -\nabla \cdot \mathrm{J}_{(i)} + R_{(i)} + S_{(i)}, \quad (1)$$

$$r \in \overline{\Omega}, \quad t \in [0;T), \quad i = \overline{0,I},$$

where r is the radius vector of spatial points, m;

ρ is medium density, kg/m^3;

Ω is the interior of the whole area;

$\partial\Omega$ is the area boundary;

$\overline{\Omega} = \Omega \cup \partial\Omega$ is the closed area (the area interior and its boundary);

$\partial\Omega_{(l)}$ is the l-th boundary of the area, $l = \overline{1, L}$;

$\Omega_{(l)}$ is the area interior adjacent to the l-th boundary, $l = \overline{1, L}$;

$\mathbf{v}$ is velocity of particles in a medium, m/sec;

$Y_{(i)}$ is the mass fraction of the i-th component;

$\mathrm{J}_{(\mathrm{i})}$ is the intensity vector of the i-th component's mass flow due to diffusion processes, kg/(m^2·sec), $i = \overline{0, I}$;

$R_{(i)}$ is the intensity of the i-th component's mass effluent due to reactions between components, kg/(m^3·sec), $i = \overline{0, I}$;

$S_{(i)}$ is the intensity of the i-th component's mass effluent in the area due to secretion, kg/(m^3·sec), $i = \overline{0, I}$.

In a homogenous mixture, each component occupies its whole volume; a mass fraction (or a percent concentration of a substance) is a ratio of a mass of a dissolved substance to the overall mass of a solution. Its difference from a concentration is that this value is dimensionless and the following condition is met:

$$\sum_i Y_{(i)} = 1, \; i = \overline{0, I}. \qquad (2)$$

An impulse conservation equation for a viscous multi-component liquid is given as follows:

$$\frac{\partial}{\partial t}(\rho\mathbf{v}) + \nabla\cdot(\rho\mathbf{v}\mathbf{v}) = -\nabla p + \nabla\cdot\tau + \rho\mathbf{g},$$

$$\mathbf{r} \in \Omega, \; t \in [0; T), \qquad (3)$$

where p is pressure (Pa); τ is the deviatoric part of Cauchy stress tensor (Pa), which can be given as follows for a viscous incompressible liquid:

$$\tau = \eta(\nabla\mathbf{v} + (\nabla\mathbf{v})^T), \; \mathbf{r} \in \overline{\Omega}, \qquad (4)$$

where η is shear viscosity, Pa·sec.

The intensity vector of the i-th component's mass flow due to diffusion processes can be given as follows:

$$\mathrm{J}_{(\mathrm{i})} = -\rho K_{(i)} \nabla Y_{(i)}, \qquad (5)$$

where $K_{(i)}$ is the diffusion factor of the i-th component in the GIT cavity, m^2/sec, $i = \overline{0, I}$. At a first approximation, $K_{(i)}$ is assumed the same for all the components.

Molar concentration $M_{(i)}$ of the i-th component can be given as:

$$C_{(i)} = Y_{(i)}\rho / M_{(i)}. \qquad (6)$$

Enzyme secretion rate in the area l is determined by the following relation:

$$S_{(i)(l)} = s^0_{(i)(l)} + \frac{s_{(i)(l)}[\rho Y_{(i)}]_{(l)}}{s'_{(i)(l)} + [\rho Y_{(i)}]_{(l)}}, \qquad (7)$$

where

$s^0_{(i)(l)}$ is the baseline level of enzyme secretion (when any food is absent) in the area $\Omega_{(l)}$, kg/(m^3·sec);

$s_{(i)(l)}$ is the constant of the enzyme secretion rate in the area $\Omega_{(l)}$, which is equal to the maximum secretion rate, kg/(m^3·sec);

$s'_{(i)(l)}$ is the second constant of the secretion rate in the area $\Omega_{(l)}$, which is equal to the average mass concentration of those components that intensify secretion of a given enzyme at a moment when the secretion rate reaches a value equal to a half of the maximum secretion rate, kg/m^3;

$[\rho Y_{(i)}]_{(l)}$ is the average mass concentration of those components which enzyme secretion depends on near the tract wall, kg/m^3.

A mass effluent due to an enzymatic reaction is given as:

$$R_{(i)} = \frac{k_{(j)(k)} \rho^2 Y_{(j)} Y_{(k)} / M_{(k)}}{k'_{(j)(k)} + \rho Y_{(j)} / M_{(j)}}, \quad (8)$$

where $k_{(j)(k)}$, $k'_{(j)(k)}$ are the constants of the enzymatic reaction rate, 1/sec, kmol/m^3, $R_{(i)}$ takes a negative value for a reagent and a positive one for a reaction product;

$Y_{(j)}$, $Y_{(k)}$ are mass fractions of a substance and an enzyme;

$M_{(k)}$, $M_{(j)}$ are molar masses.

This formula is a Michaelis – Menten equation for describing the enzymatic reaction rate. The constant $k_{(j)(k)}$ is the limit of this rate; the second constant $k'_{(j)(k)}$ is equal to a concentration of a substance that enters the reaction at a moment when the reaction rate reaches a value equal to a half of its maximum rate.

The absorption rate for components in the mixture is determined as follows:

$$S_{(i)(l)} = -s_{(i)(l)} \left\langle [\rho Y_{(i)}]_{(l)} - h_{(i)} C^b_{(i)} \right\rangle, \quad (9)$$

where $s_{(i)(l)} > 0$ is the constant of the rate at which the *i*-th component is absorbed in the area $\Omega_{(l)}$, 1/sec;

$[\rho Y_{(i)}]_{(l)}$ is the average mass concentration near the tract wall *l*, kg/m^3;

$C^b_{(i)}$ is the mass concentration of the *i*-th chemical in blood, kg/m^3;

$h_{(i)}$ is the factor of proportionality that shows what ratio of concentrations is required to start diffusion.

In the developed model, it is assumed at this stage that particles in the mixture do not stick to the tract walls:

$$\mathbf{v}(t,\mathbf{r}) = \frac{d\mathbf{r}(t)}{dt},$$

$$t \in [0;T),\ \mathbf{r}(t) \in \partial\Omega_{(l)},\ l = 2,3, \quad (10)$$

where $\mathbf{r}(t) \in \partial\Omega_{(l)}$ is the radius vector of a material point on the duodenum wall. Values of mass fractions for components in the mixture $Y_{(i)} = Y^{\partial\Omega}_{(i)}$, the flow rate, and the conditions under which tangent components in the stress vector are equal to zero are set at the boundary $\partial\Omega_{(1)}$:

$$\mathbf{v}(t,\mathbf{r}) = \mathbf{v}_{in},\ \mathbf{t} - (\mathbf{n}\cdot\boldsymbol{\sigma}\cdot\mathbf{n})\mathbf{n} = \mathbf{0},\ \mathbf{t} = \mathbf{n}\cdot\boldsymbol{\sigma},$$
$$t \in [0;T),\ \mathbf{r} \in \partial\Omega_{(l)},\ l = 1,4.$$

The equation system is completed with the following initial conditions:

$$Y_{(i)}(t,\mathbf{r}) = Y^0_{(i)},\ \mathbf{v}(t,\mathbf{r}) = \mathbf{v}^0,\ \mathbf{r} \in \overline{\Omega},\ t = 0.$$

Results and discussion. This study involved performing a numerical experiment to describe hydrolysis of starch under exposure to amylase. The duodenum is considered a pipe, which is 0.28 m long and has a diameter equal to 0.04 m. Peristaltic waves typical for it have the following preset parameters: the period is 20 sec; the amplitude, 0.0035 m; the velocity, $5 \cdot 10^{-3}$ m/sec [17]. In case the motor function is deranged, these parameters may vary.

Chyme is considered a multi-component viscous liquid consisting of (the index $i = \overline{0,I}$) a carbohydrate (starch) (i = 0) and water (i = 2). As the mixture moves along the pipe, its composition starts to change due to effects produced by pancreatic amylase (i = 1); as a result, glucose is formed (i = 3).

The amylase secretion is described with a mass effluent in the pipe in the wall layer at the boundary $\partial\Omega_{(3)}$. The effluent is located 0.1 m away from the inlet section; the diameter of the opening is 0.006 m. The effluent intensity does not change over time.

The reaction rate constants are set as follows: $k_{(0)(1)} = 408$ 1/sec, $k'_{(0)(1)} = 10^{-3}$ kmol/m³ [18]. Molar masses of starch and amylase are taken from literature sources: $M_{(0)}$ = 828.7, $M_{(1)}$ = 54,000 g/mol [19]. The intensity of the

amylase effluent is considered equal to 0.01 kg/(m^3·sec) and it is 0.1 kg/(m^3·sec) for water, which corresponds to an active phase in intestinal digestion. The flow rate for the mixture at the inlet was taken as 0.001 m/sec and the starch molar fraction was considered equal to 0.05.

The previously formulated system of equations to describe digestion in the duodenum was solved using Ansys computation package. A time step was equal to $\Delta t = 0.1$ sec. A mixture of starch and water components was set at the initial moment. Figures 3–5 show how the mixture components are distributed in the pipe.

Figure 3 shows the mass fraction of starch at different moments. Obviously, as time passes, starch is distributed along the pipe, and its maximum concentration does not exceed 0.036; that is, not all the amount of starch enters a chemical reaction. The authors of the work [20] performed an experiment that produced the following results. Not more than 25 % of a 5 %-starch solution was transformed into glucose due to effects produced by amylase over a period equal to 11,000 sec. In our study, the numeric experiment lasted up to 600 sec since our goal was to analyze how the concentration of substances would be distributed allowing for a chemical reaction and components being mixed up due to the moving pipe walls.

Figure 4 shows a situation when glucose is formed due to effects produced by the moving walls that make the components mix and by amylase secreted in the area $\partial\Omega_{(3)}$. It occurs when the reaction time reaches 100 sec and the maximum concentration field for glucose is equal to $9.5\cdot10^{-6}$. Its value grows over time and reaches $2\cdot10^{-5}$ when the reaction time is 600 sec. An area where the concentration of the reaction product is higher is located near to the mass effluent but the concentration of the substance goes down closer to the outlet from the duodenum. This is probably due to time scales of the reaction rate being greater than the scales of the medium transfer; besides, water is pushed back into the pipe due to preset movement of its walls.

Figure 5 shows how amylase is distributed in the pipe. It induces a chemical reaction with glucose being its product. Obviously, as the reaction proceeds, amylase starts to fill in the channel. Its maximum concentration is equal to $3.3\cdot10^{-8}$. This secreted amount is enough to form glucose and its concentration is higher than the amylase concentration in the analyzed area when the reaction time reaches 600 sec.

According to the results shown in Figure 6, we can assume that, given the present peristaltic movement, there are areas where the velocity direction is inverse to the direction of the wave

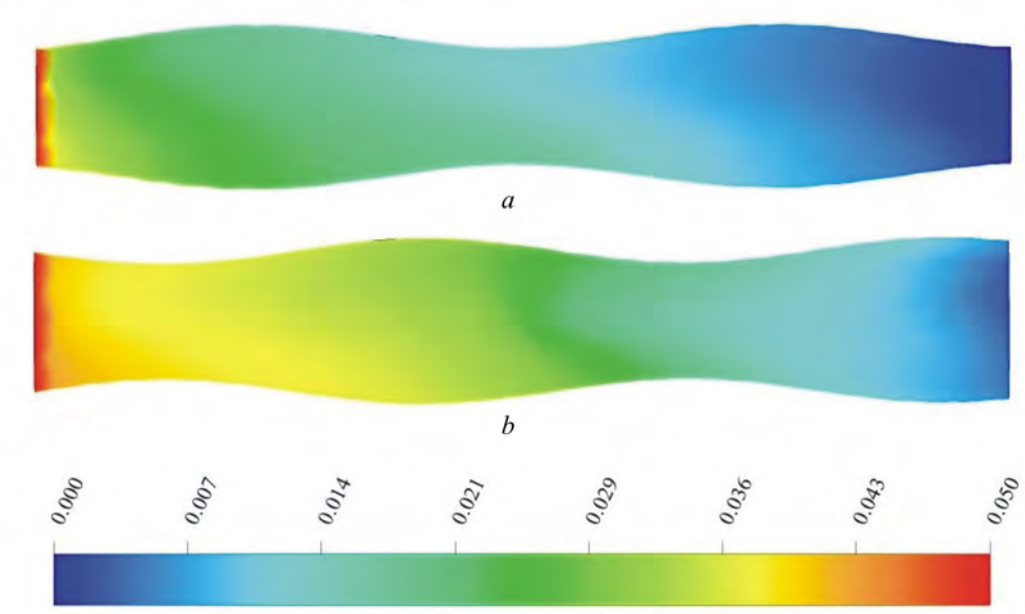

Figure 3. The mass fraction of starch at the moments a) 100 sec, b) 600 sec

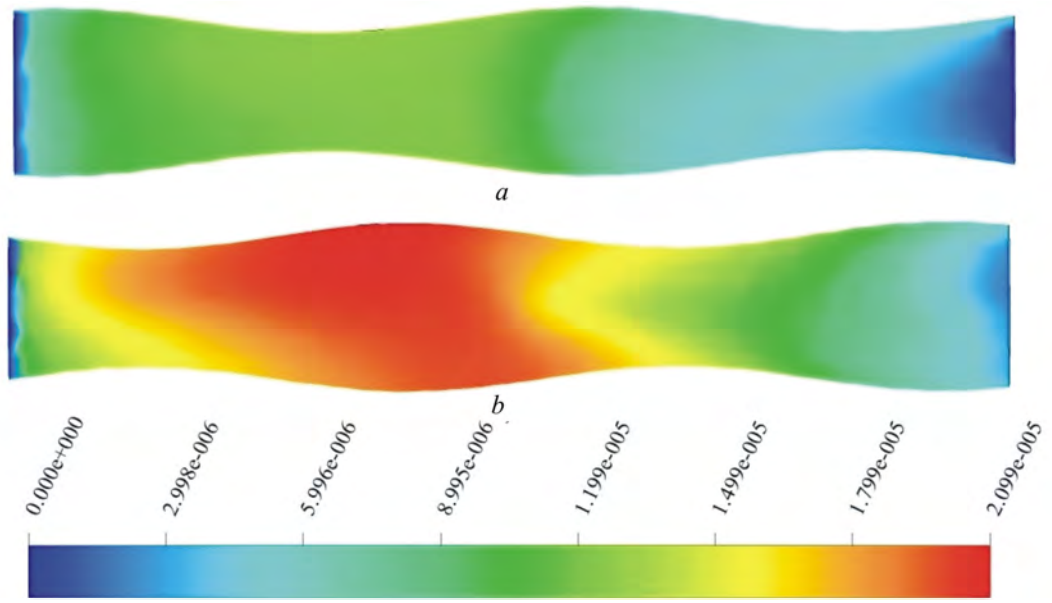

Figure 4. The mass fraction of glucose at the moments a) 200 sec, b) 600 sec

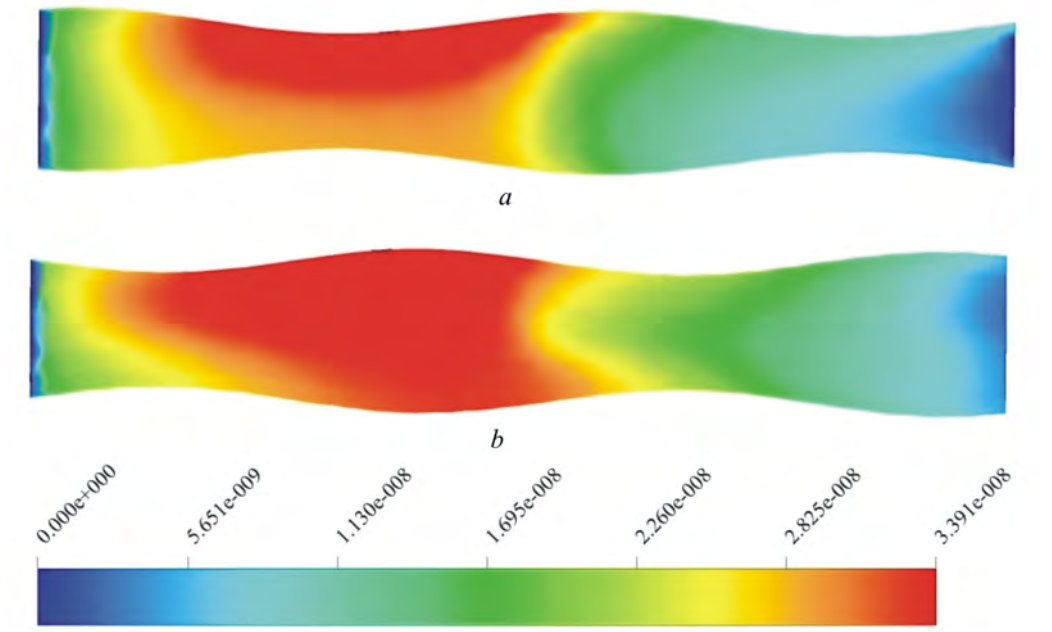

Figure 5. The mass fraction of amylase at the moments a) 200 sec, b) 600 sec

spread (at the points where the pipe contracts). Due to this effect, the components are mixed and the mixture itself is sent back into the pipe at 0.023 m/sec. The maximum flow rate is detected at the area where amylase is secreted (the wall effluent) at the moment when the wall contracts; this rate is equal to 0.07 m/sec. These results are in line with those described in the work [15] where the duodenum was modeled as a two-dimensional channel with moving boundaries; the velocity at the contraction area was the highest and equal to 0.05 m/sec.

Conclusion. The present work focuses on developing a mathematical model to describe the duodenum. The model considers conditions under which substances are being transformed, a shape and a size of an organ, typical features of intestinal peristalsis, and functional disorders in case there are any. It also covers absorption of substances and changes in the composition of a liquid when it moves along a pipe.

By now, mathematical and conceptual tasking has been developed; the section covering

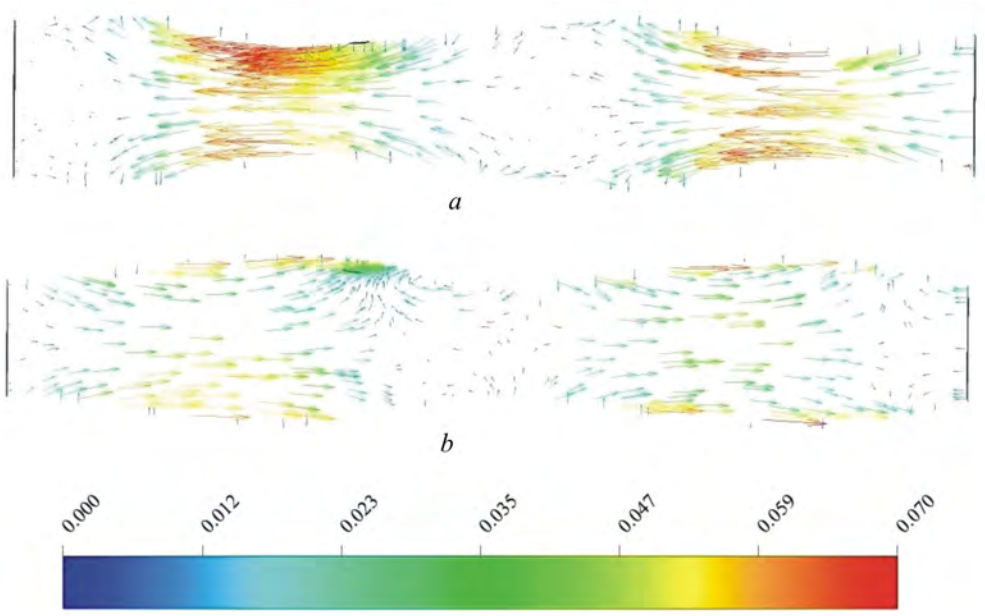

Figure 6. The velocity field (m/sec) at the moments a) 533 sec, b) 550 sec

the results describes an example how the model can be applied in a numeric experiment. To be exact, the experiment involves examining hydrolysis of starch in the duodenum allowing for peristaltic movement of the tract walls that make for the components in the mixture intermingling with incoming amylase. The study provides data on determined concentrations of the substances at different moments as well as the velocity field. As planned, the further studies will consider all the components and chemical reactions shown in Figure 1.

Another vital issue is to examine changes in physical and mechanical properties of a mixture during its flow. The next stage in the model development is expected to consider absorption and examine various scenarios with functional disorders of the secretory / absorption function and intestinal motility. Attention will also be paid to influence exerted by hormonal regulation through such hormones as secretin and cholecystokinin.

Results produced by examining how acidity is distributed in various parts of the duodenum are going to be of primary theoretical and practical importance. In future, the developed model can be applied as a noninvasive diagnostic method in clinical practice. Personal data may be used as a basis for predicting areas with elevated risks of functional disorders, ulcer formation and other defects in the tract mucosa. In addition, results produced by numeric modeling will facilitate detecting what disorders influence abnormal acidity in the duodenum thereby helping a physician to prescribe personified therapy and a diet.

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