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Research article

SPATIAL-DYNAMIC HETEROGENEITY OF THE COVID-19 EPIDEMIC PROCESS IN THE RUSSIAN FEDERATION REGIONS (2020–2023)

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The coronavirus pandemic has produced considerable effects on medical and demographic processes worldwide and in Russia in particular. The epidemic process involved a sequence of circulating SARS-CoV-2 virus strains with different mutations and this reflected in registered levels of incidence and mortality against spatial heterogeneity of socioeconomic factors in different RF regions.

The aim of this study was to analyze spatial-dynamic heterogeneity of the COVID-19 epidemic process in the RF regions in 2020–2023.

We performed retrospective analysis of incidence and mortality at the national and regional levels. The analysis relied on departmental statistical data provided by Rospotrebnadzor as well as public data that described the intensive indicators of the COVID-19 epidemic process and results obtained by sequencing of biomaterial samples to identify COVID-19 in them in 2020–2023.

In 2020–2023 we identified five 'waves' of the COVID-19 epidemic processes that interchanged sequentially. Within these waves, RF regions reached local peaks in incidence with different speed. According to available data, the highest primary incidence among all the RF regions in 2021–2022 was established in Saint Petersburg (12,821.8 cases and 17,341.2 cases per 100 thousand people); the highest mortality in 2021 was detected in the Tver region (427 cases per 100 thousand people) and in the Arkhangelsk region in 2022 (350.9 cases per 100 thousand people).The greatest number of the RF regions where the incidence due to the disease was higher than its average annual level was established in October, November, December 2021 and February 2022 (51, 68, 51 and 82 RF regions accordingly).

The established spatial-dynamic heterogeneity of the epidemic process may indicate that this process can be largely determined by differences in the initial socioeconomic, medical and demographic characteristics of the RF religions.

Limitations of the study are related to the used statistical data on registered incidence and mortality as well as the concept of the epidemiological 'wave' accepted in it.

The identified territorial differences in the COVID-19 epidemic process should be considered when developing optimal regulatory impacts including those aimed at predicting probable emergent infections.

Keywords: *epidemiological process, COVID-19, epidemiological waves, incidence, mortality, RF regions, epidemiological analysis.*

According to the WHO statistics, 763,740,140 confirmed COVID-19 cases and 6,908,554 deaths caused by the disease were registered worldwide as of April 2023[1]. In absolute values, Europe accounts for 36.1 % of all the disease cases (the first rank place) and 32.2 % of all the deaths caused by it (the second rank place). The Russian Federation holds the

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[1] The data cover the whole COVID-19 pandemic by April 2023.

31st rank place in Europe (the 55th in the world) for incidence (5,021.1 cases per 100 thousand people) and the 19th rank place in Europe (the 32nd in the world) for mortality (90.7 cases per 100 thousand people) over 2020–2022 [1].

The WHO classification [2] states that at present (April 2023) no variants of the virus circulating now could raise some concern. Only two variants of *Omicron* line are circulating at the moment that could be of some interest, *XBB.1.5* (so called *Kraken*) and *XBB.1.16* (so called *Arcturus*). They are potentially able to induce new epidemic waves due to their greater capability to effectively escape any immune response of the human body [3, 4]. Still, according to the available estimates [3, 4], these sub-variants are not prone to induce more severe disease than other *Omicron* lines and have smaller virulence against the previously dominating strains that induced the first epidemiological 'waves'.

While the infections agent (*SARS-CoV-2*) as well as its mutations and variants were actively spreading all over the world, it was deemed necessary to make reliable predictions how an epidemic situation would develop. These predictions should consider not only some peculiar features of the new infection (the basic reproduction number, incubation, virus mutation, etc.) but also relevant healthcare measures (vaccination, social isolation, face mask wearing etc.) [5, 6]. The general decline in the epidemic process motivates researchers to accomplish retrospective assessments of its active phases, relevance and timeliness of accomplished measures aimed at the disease control within epidemiological 'waves'. All this is done to identify the most effective strategies for fighting against similar threats in future [7]. Despite there is no clear unambiguous definition of a 'wave'[2], six COVID-19 waves have already been identified in Russia[3] and each of them has mostly been caused by specific variants of the virus and had its specific peaks in incidence and mortality.

The analysis of the research in the field has revealed that in Russia the COVID-19 epidemic process was estimated as per specific 'waves' / periods during which incidence and mortality were growing. However, such studies and analysis often focused either at the national level [8–10] or on just one or several RF regions / Federal Districts [11–13]. Some studies addressed identification and comparative analysis of *SARS-CoV-2* genetic variants that were detected in Russia during different periods of the COVID-19 epidemic process [14, 15]. Some studies established regional peculiarities and regularities lying in differences associated with multiple environmental factors able to modify the epidemic process, its intensity and duration [16, 17].

Despite some relevant studies in the field, only limited data are available in scientific literature that describe peculiarities of the COVID-19 epidemic process in RF regions or provide comparative inter-region assessments of it relying on the concept of epidemiological waves caused by consistent changes between several dominating *SARS-CoV-2* strains.

The aim of this study was to analyze spatial-dynamic heterogeneity of the COVID-19 epidemic process in the RF regions in 2020–2023.

Materials and methods. We have conducted retrospective epidemiological analysis of indicators related to the COVID-19 epidemic process (confirmed disease cases and deaths) over 2020–2023 at the national (the RF) and regional (RF regions) levels relying on open information sources[4] as well as departmental statistical reports issued by Rospotrebnadzor. We analyzed indicators that

[2] WHO Coronavirus (COVID-19) Dashboard. Geneva, World Health Organization, 2020. Available at: https://covid19.who.int/ (April 20, 2023).

[3] Virusolog Chepurnov predupredil o nastuplenii novoi volny koronavirusa [Chepurnov, a virologist, warns a new coronavirus wave is possible]. *URA.RU: Informatsionnoe agentstvo [Information Agency]*. Available at: https://ura.news/news/1052624187 (April 20, 2023) (in Russian).

[4] Daily new confirmed COVID-19 cases per million people. *Our World In Data: COVID-19 Data Explorer*. Available at: https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&facet=none&country=~RUS&pickerSort=asc&pickerMetric=location&Metric=Confirmed+cases&Interval=7-day+rolling+average&Relative+to+Population=true&Color+by+test+positivity=false (April 20, 2023).

were directly associated with the epidemic process, namely, the results of sequencing of COVID-19 genetic samples. Our information sources were open data taken from the *Our World In Data*[4], a web-site specializing in aggregating official statistical data provided by different countries. Our analysis of regional data on the COVID-19 incidence and mortality over 2021–2022 relied on using the Federal Statistical Report Forms No.2 Data on Infectious and Parasitic Diseases[5].

In this study, we have taken on a concept that describes the COVID-19 epidemiological process in dynamics of consistent interchanges between epidemiological waves. The term 'wave' means a period when a certain strain circulating among infected people accounted for more than 50 % in sequenced biomaterial samples; each wave usually involves a rise in incidence and / or mortality. Intra-wave dynamics of COVID-19 incidence as per specific RF regions was analyzed by establishing incidence peaks in weekly averaging and calculating a number of weeks necessary to reach them. RF regions were divided into separate groups relative to the mode value of the number of weeks necessary to reach an incidence peak within the analyzed wave at the regional level (in specific regions). RF regions where the number of weeks necessary to reach a peak in incidence was below the mode value were considered areas with 'extensive' (rapid) growth in incidence; in case this number was above the mode value, a region was considered an area with 'slowed' growth in incidence. RF regions where this number was equal to the mode value were considered areas with 'steady' growth in incidence. RF regions were divided into separate groups during the second wave, which involved two sequential rises in COVID-19 incidence, on the basis of specific dynamics of these two rises: regions with a plateau-like curve of the first rise, regions where the first rise in incidence was higher than the second one, and regions where the second rise was higher than the first one. Intensive indicators were calculated using data on population numbers provided by the RF Federal State Statistics Service.

This study did not require any approval by a committee on biomedical ethics (the study used only open population data taken from official statistical reports).

Results and discussion. According to available data[4,5, 6] over 2020–2022, in general, the COVID-19 (ICD-10 code U07.1) incidence grew in the RF by 282.4 % (from 2,157.1 cases to 8,248.7 cases per 100 thousand people); the COVID-19 mortality also grew by 59.0 % (from 0.39 cases to 0.62 cases per 1 thousand people) (Table 1). Among the first diagnosed diseases, COVID-19 accounted for 2.8 % in 2020 and for 7.2 % in 2021; the disease accounted for 2.7 % in 2020, 9.9 % in 2021 and 4.8 % in 2022 in the all-cause mortality in the country,

In 2021–2022, the highest incidence of the first diagnosed COVID-19 was in Saint Petersburg (12,821.8 cases and 17,341.2 cases per 100 thousand people); the highest mortality due to COVID-19 in 2021 was in the Tver region (427 cases per 100 thousand people), and in 2022 in the Arkhangelsk region (350.9 cases per 100 thousand people) (Figure 1, 2).

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[5] Ob utverzhdenii form federal'nogo statisticheskogo nablyudeniya s ukazaniyami po ikh zapolneniyu dlya organizatsii Federal'noi sluzhboi po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka federal'nogo statisticheskogo nablyudeniya za sanitarnym sostoyaniem sub"ekta Rossiiskoi Federatsii: Prikaz Rosstata ot 30.12.2020 № 867 [On Approval of federal statistical report forms with recommendations on how to fill in them to facilitate federal statistical monitoring of the sanitary situation in RF regions by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing: the Order by Rosstat issued on December 30, 2020 No. 867]. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/573324768 (April 21, 2023) (in Russian).

[6] Demografiya [Demography]. *Federal State Statistics Service*. Available at: https://rosstat.gov.ru/folder/12781 (April 19, 2023) (in Russian); Raspredelenie umershikh po polu, vozrastnym gruppam i prichinam smerti: Statisticheskaya forma № 5 (tablitsa 51) [Distribution of the deceased as per sex, age groups and causes of death: Statistical Form No. 5 (Table 51)] (in Russian); Zabolevaemost' vsego naseleniya Rossii s diagnozom, ustanovlennym vpervye v zhizni: statisticheskie materialy za 2019–2021 gg. [Incidence of the first diagnosed diseases among the whole RF population: statistical data collected in 2019–2021]. Moscow, the RF Ministry of Health (in Russian).

Table 1

Some statistical indicators of public health in the Russian Federation in 2019–2022

Indicator / Year	2019	2020	2021	2022
Average annual population of the RF[6], abs.	146,764,655	146,459,795	146,575,531	146,713,743
Deceased due to all causes, total[7], abs.	1,798,307	2,138 ,86	2,441,594	1,905,778*
The number of patients with the first diagnosed diseases as per all the nosologies[8], abs.	114,512,153	111,294,314	125,022,382	–**
All-cause mortality among the whole population, cases per 1 thousand people	12.25	14.6	16.7	12.9
The first diagnosed diseases among the whole population as per all the nosologies, cases per 100 thousand people	78,024.3	75,989.7	85,295.5	–**
The number of infected[9] with COVID-19, abs.	–	3,159,297***	9,054,041	12,102,028
The number of deceased[9] due to COVID-19, abs.	–	57,019***	240,586	90,836
COVID-19 Incidence, cases per 100 thousand people	–	2,157.1 (2.8 %)****	6,177.1 (7.2 %)	8,248.7 (–)
COVID-19-caused mortality, cases per 1 thousand people	–	0.39 (2.7 %)	1.64 (9.9 %)	0.62 (4.8 %)

N o t e: * preliminary data provided by Rosstat; ** data unavailable; *** according to the web-site *Our World In Data*; **** the share in the total incidence / mortality is given in brackets.

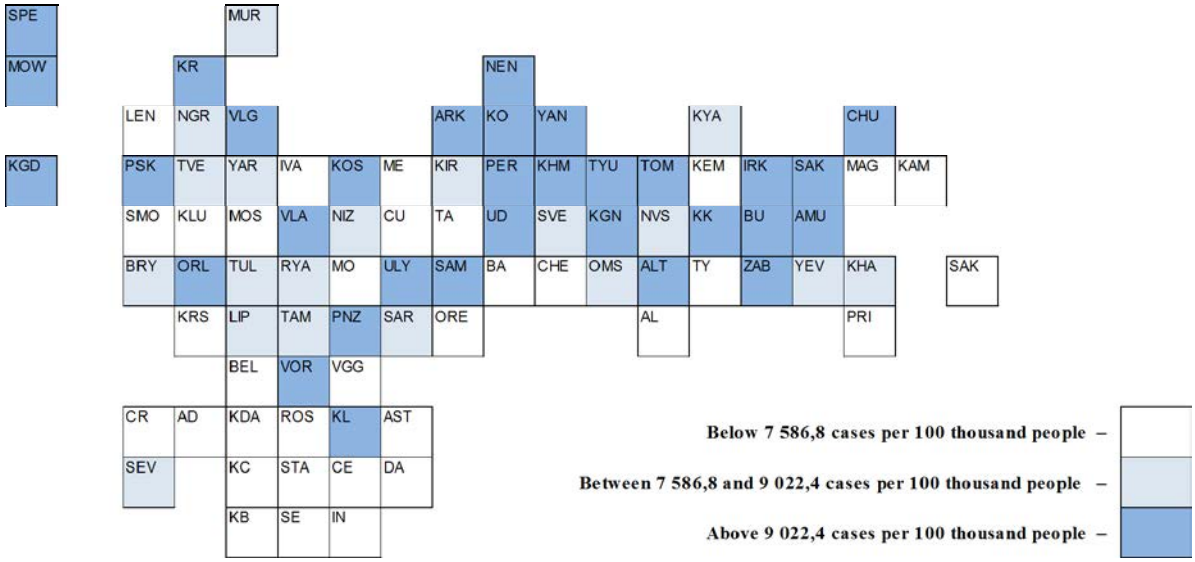


Figure 1. Spatial distribution of COVID-19 incidence among the RF regions in 2021, cases per 100 thousand people

[7] Raspredelenie umershikh po polu, vozrastnym gruppam i prichinam smerti: Statisticheskaya forma № 5 (tablitsa 51) [Distribution of the deceased as per sex, age groups and causes of death: Statistical Form No. 5 (Table 51)] (in Russian).

[8] Zabolevaemost' vsego naseleniya Rossii s diagnozom, ustanovlennym vpervye v zhizni: statisticheskie materialy za 2019–2021 gg. [Incidence of the first diagnosed diseases among the whole RF population: statistical data collected in 2019–2021]. Moscow, the RF Ministry of Health (in Russian).

[9] Daily new confirmed COVID-19 cases per million people. *Our World In Data: COVID-19 Data Explorer*. Available at: https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&facet=none&country=~RUS&pickerSort=asc&pickerMetric=location&Metric=Confirmed+cases&Interval=7-day+rolling+average&Relative+to+Population=true&Color+by+test+positivity=false (April 20, 2023).

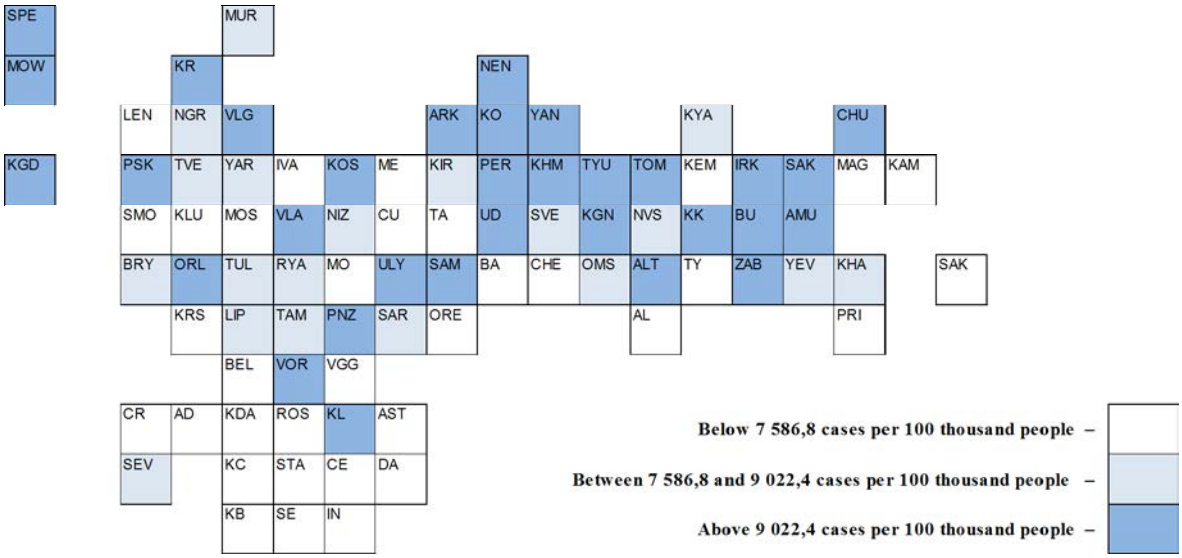


Figure 2. Spatial distribution of COVID-19 incidence among the RF regions in 2022, cases per 100 thousand people

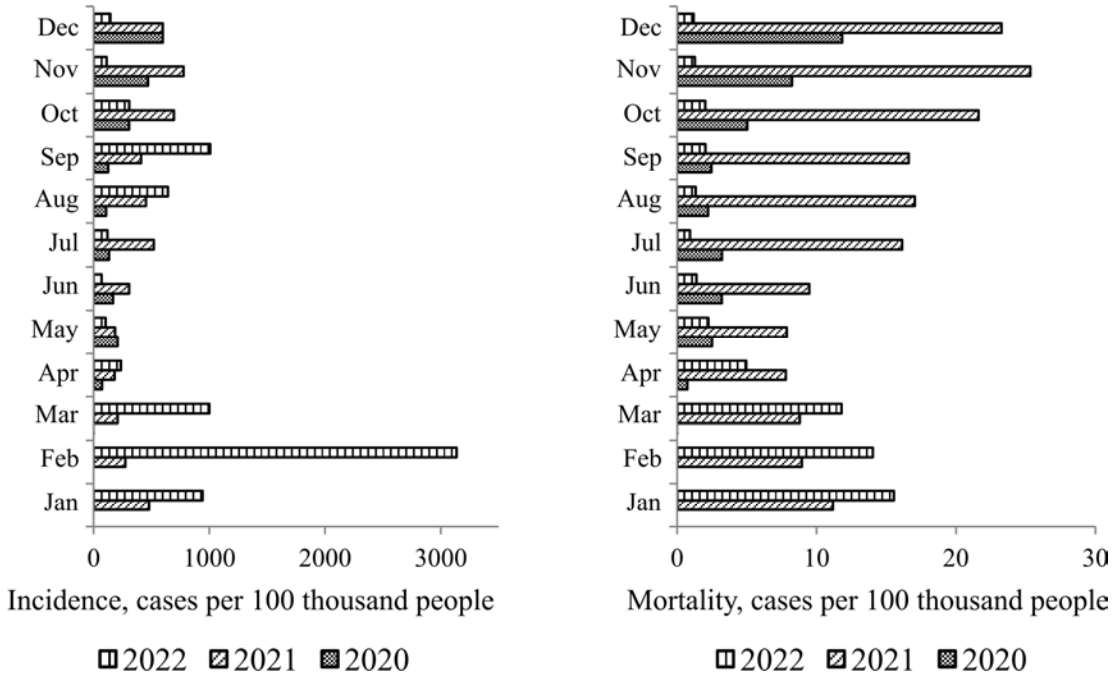
Dynamics of the COVID-19 incidence and mortality varied within substantial ranges at the regional level in 2021–2022: between -54.5 % (growth rates) in Dagestan to 222.2 % in the Novosibirsk region for incidence (the regional average is 43.4 %); between -98.9 % in the Nenets Autonomous Area and 168.2 % in the Nizhniy Novgorod region (the regional average is -57.1 %) for mortality.

In the RF as a whole, children (≤ 17 years) accounted for 10.1 % among all the infected in 2021 and 15.7 % in 2022; at the regional level, the share of children in the total infected population ranged between 1.8 % (Tatarstan) and 22.5 % (Buryatia) in 2021, the regional average was 10.5 %; in 2022, the share ranged between 8.3 % (the Belgorod region) and 30.0 % (the Yamal Nenets Autonomous Area), the regional average was 16.2 %.

In the RF, incidence was 1.5–1.8 times higher in urban areas than in rural ones both in 2021 (6,759.8 cases and 4,448.6 cases per 100 thousand people accordingly) and in 2022 (9,264.3 cases and 5,225.8 cases per 100 thousand people accordingly). At the national level (RF), cases of carrying the COVID-19 infectious agent equaled 6.8 % in 2021 and 6.9 % in 2022; the share of COVID-19-induced pneumonia went down considerably over the same period, from 18.3 to 3.7 %.

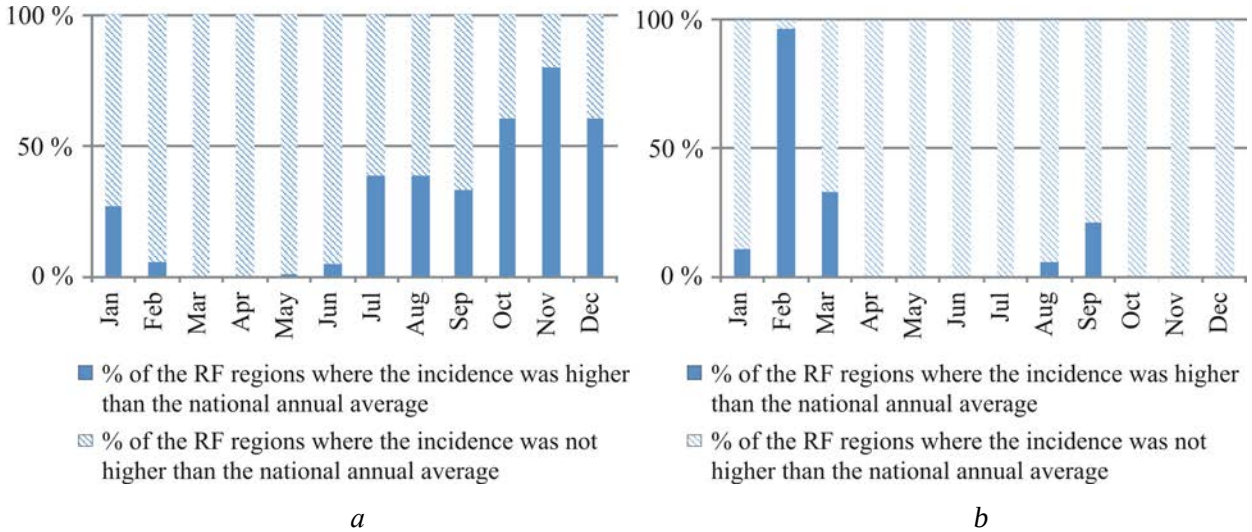
It is difficult to analyze the COVID-19 incidence and mortality within one year due to the epidemic process being rather short, anti-epidemic activities being distributed unevenly both in the world and in the country, and frequent interchanges between dominant strains. That is, social, natural and biological factors are not stable and this does not make it possible to discuss any seasonality within one year and even more so any long-term cyclicity. Still, we were able to establish incidence and mortality levels higher than the annual average in October – December 2020–2021, as well as in July – September 2021 and January – March 2022 due to more virulent (*Delta*) and contagious (*Omicron*) strains circulating at that moment (Figure 3).

We assessed monthly dynamics of the COVID-19 incidence in the RF regions in 2021; as a result, levels of this incidence higher than the national annual average (considering two standard errors $M + 2m$) were identified in all the months except from March and April (Figure 4a); in 2022, except from the periods April – July and October – December (Figure 4b). The greatest number of the RF regions where the COVID-19 incidence was higher than the national annual average (considering two standard errors $M + 2m$) was established in October (51 regions), November (68), and December (51) 2021 and February (82 regions) 2022.



a *b*

Figure 3. Monthly dynamics of the COIVID-19 incidence (*a*) and mortality (*b*) in 2020–2022 in the RF, cases per 100 thousand of the total population



a *b*

Figure 4. The share of the RF regions with the COVID-19 incidence being higher than the national annual average in 2021 (*a*) and 2022 (*b*), %

According to the concept of epidemiological waves accepted in this study and based on the analyzed data, we established five 'waves' of the COVID-19 epidemic process that sequentially changed one another over 2020–2023. These waves are characterized by a change in prevalence of the most contagious *SARS-CoV-2* strains with relevant rises in the COVID-19 incidence (Figure 5).

The first wave was 73-week long; it started in the first decade of March 2020 and ended in late May 2021. It was accompanied with genetic diversity of the virus, wide prevalence (up to 30 %) of the *Alpha* strain at the end (Figure 5, 6). The second wave was 32-week long, from late May 2021 and till the beginning of January 2022; it was characterized with the dominating *Delta* strain (Figure 5, 6).

This wave had the highest weekly COVID-19 mortality levels (up to 6 ‰) among the total (Figure 6). The third wave lasted 24 weeks, from early January 2022 till early June 2022, and was characterized with two dominant sub-variants of the *Omicron* strain changing each other, *BA.1* and *BA.2* (Figures 5, 6). The *BA.1* sub-variant of the *Omicron* strain induced a 'drastic' growth in the COVID-19 incidence and the beginning of a decline in the COVID-19 mortality (Figures 5, 6). The fourth COVID-19 wave lasted from early June 2023 till the beginning of January 2023, 27 weeks overall (Figures 5, 6). During this wave, the prevailing *BA.5* sub-variant of the *Omicron* strain induced another rise in the weekly COVID-19 incidence (up to 240 ‰) together with a slight growth in the COVID-19 mortality (up to 0.5 ‰). The fifth wave started after one of the *Omicron* strain variants, *XBB,* had become prevalent. It has been lasting from middle January 2023 up to now (April 2023) and is characterized with relatively low levels of the COVID-19 incidence and mortality due to the prevailing strain being even less contagious and virulent (Figure 5, 6).

The epidemic process had its peculiarities in different RF regions within the aforementioned waves. We analyzed Rospotrebnadzor's department statistical reports on the weekly incidence in the RF regions (starting from September 2020). As a result, three different groups of the RF regions were identified; the maximum COVID-19 incidence was reached with a different speed during the **first** wave: regions with slowly growing incidence (18 regions); regions with steadily growing incidence (19 regions); regions with extensively growing incidence (47 regions) (Figure 7). There were some regions in all three groups where the COVID-19 incidence was not higher than the national average (12, 21 and 16 regions accordingly). The maximum incidence was identified on the 52nd week (late December) of 2020, 136.4 cases per 100 thousand people.

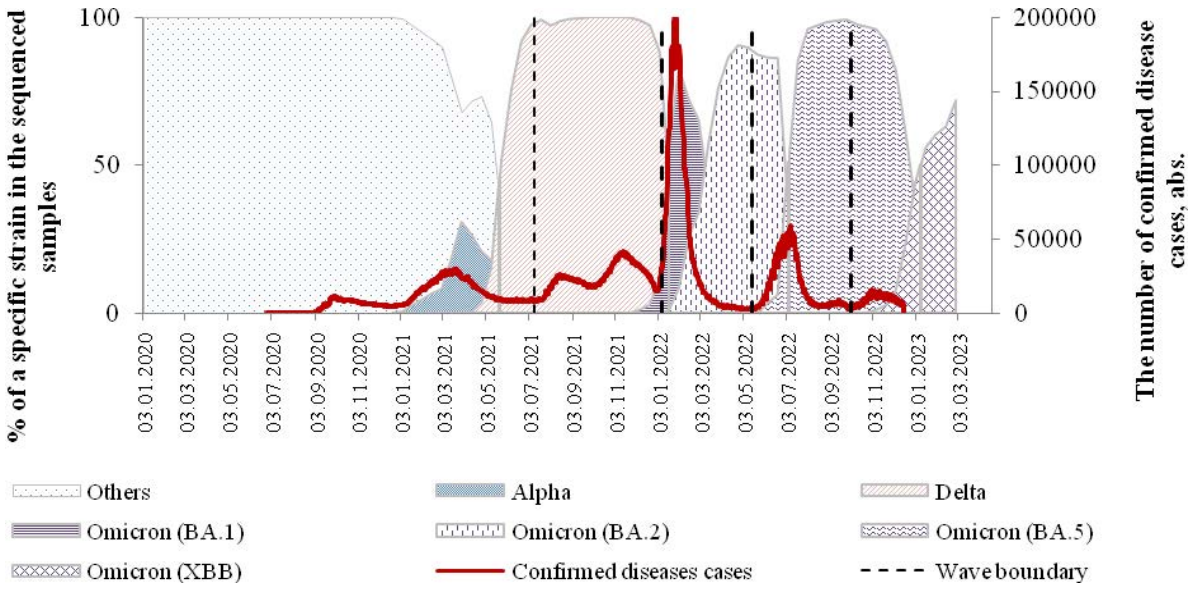


Figure 5. Dynamics of the confirmed COVID-19 cases[10] and the share of dominant SARS-CoV-2 strains among the sequenced[11] samples in 2020–2023

[10] Daily new confirmed COVID-19 cases per million people. *Our World In Data: COVID-19 Data Explorer*. Available at: https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&facet=none&country=~RUS&pickerSort=asc&pickerMetric=location&Metric=Confirmed+cases&Interval=7-day+rolling+average&Relative+to+Population=true&Color+by+test+positivity=false (April 20, 2023).

[11] SARS-CoV-2 sequences by variant, Russia, Apr 24, 2023. *Our World In Data: COVID-19 Data Explorer*. Available at: https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&facet=none&country=~RUS&pickerSort=asc&pickerMetric=location&Metric=Variants&Interval=7-day+rolling+average&Relative+to+Population=true&Color+by+test+positivity=false (April 20, 2023).

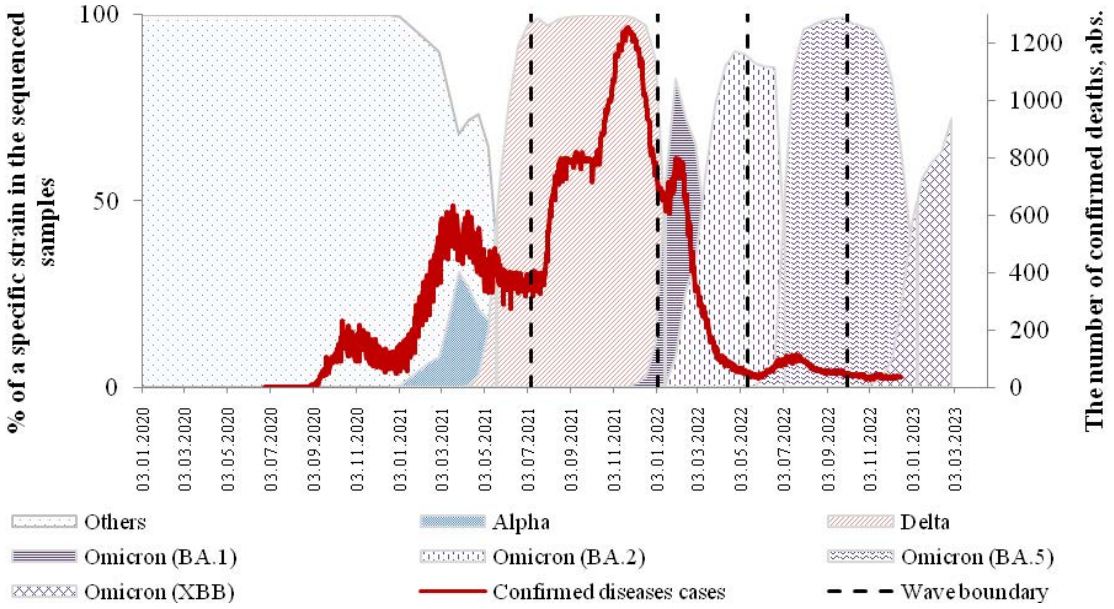


Figure 6. Dynamics of the confirmed COVID-19 deaths and the share of dominant SARS-CoV-2 strains among the sequenced [11] samples in 2020–2023

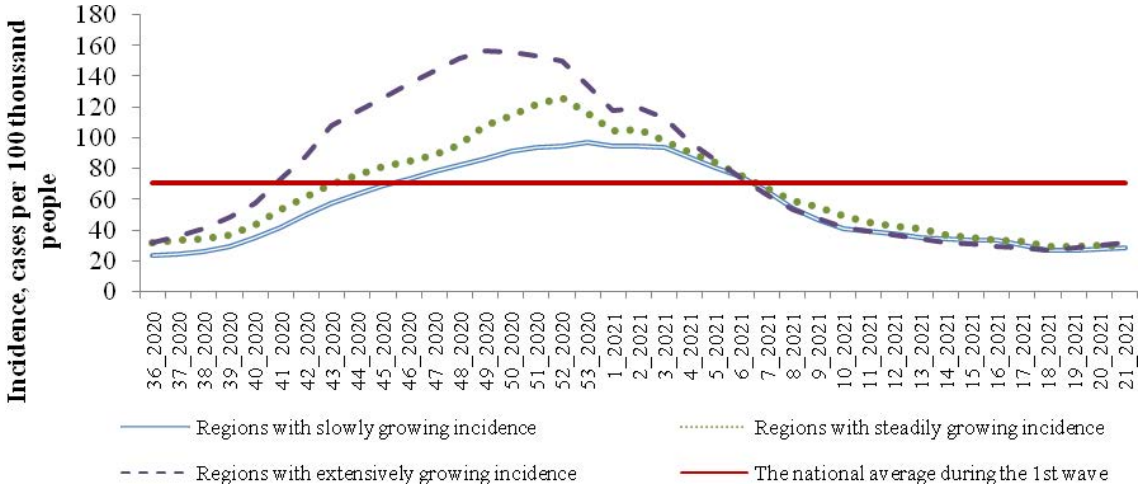


Figure 7. Dynamics of the weekly COVID-19 incidence in three groups of the RF regions during the first wave

The second COVID-19 epidemiological wave had two subsequent rises in incidence caused by the *Delta* strain (Figure 8). Differentiated analysis of the period also made it possible to identify three groups of the RF regions as per the character of the incidence growth during its first rise: regions with a plateau-like curve during the first rise in incidence (52 regions); regions with a fast growth and decline in the incidence with its level not exceeding the second rise (21 regions); regions with rapidly growing and declining incidence with its level being higher during the first rise than the second one (12 regions). There were some regions in all three groups where the COVID-19 incidence was not higher than the national average during the second wave (32, 9 and 3 regions accordingly). The highest incidence for the *Delta* strain prevalence was identified on the 44th week of 2021 (early November) when it equaled 191.0 cases per 100 thousand people.

The *Omicron* strain prevailed during the **third** wave with the highest incidence and its most rapid growth. We did not identify any ap-

parent asynchronicity among the RF regions as regards reaching the incidence peak during this wave. It had a rather short (6 weeks) period during which the incidence was higher than the national average and the incidence peak was achieved quite rapidly during this wave (6–7 weeks) in most RF regions (68). The third wave was characterized with apparent differences between the RF regions as per the value by which a regional incidence level was higher than the national average (Figure 9). The maximum incidence in the third wave was identified on the 6th week of 2022 (middle February) and was equal to 907.6 cases per 100 thousand people.

The fourth COVID-19 wave occurred due to the *BA.5* sub-variant of the *Omicron* strain; it involved relatively higher incidence than the first two waves but at the same time mortality was relatively low during it (Figures 5, 6). This wave was similar to the first one as per the epidemic process during it since there was similar asynchronicity in the speed at which different RF regions reached the incidence peak (Figure 10). Within the wave, three different groups of the RF regions were identified: regions with slowly growing incidence (5 regions); regions with steadily growing incidence (52 regions); regions with extensively growing incidence (28 regions). During this wave, the incidence peak was reached on the 37th week of 2022 (late September), 253.1 cases per 100 thousand people.

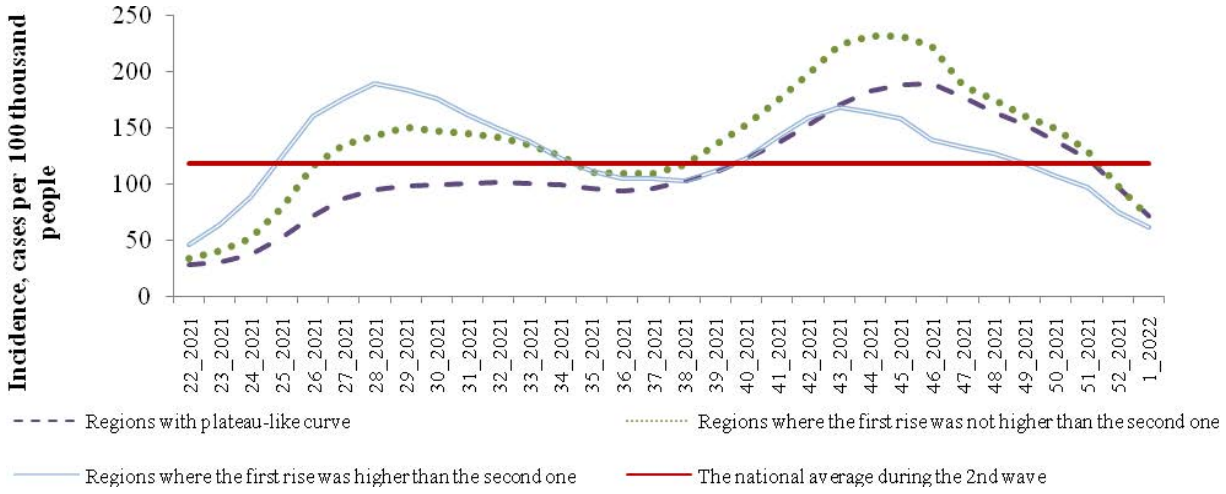


Figure 8. Dynamics of the weekly COVID-19 incidence in three groups of the RF regions during the second wave

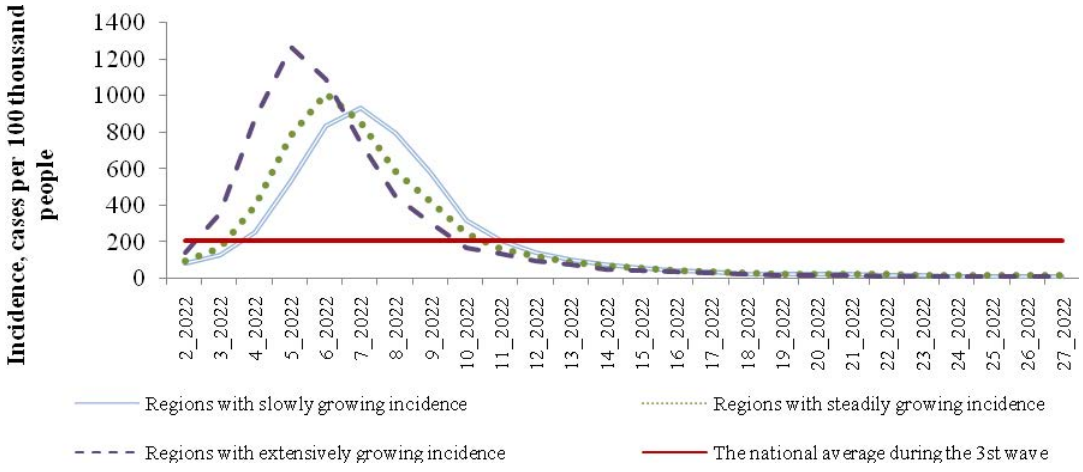


Figure 9. Dynamics of the weekly COVID-19 incidence in three groups of the RF regions during the third wave

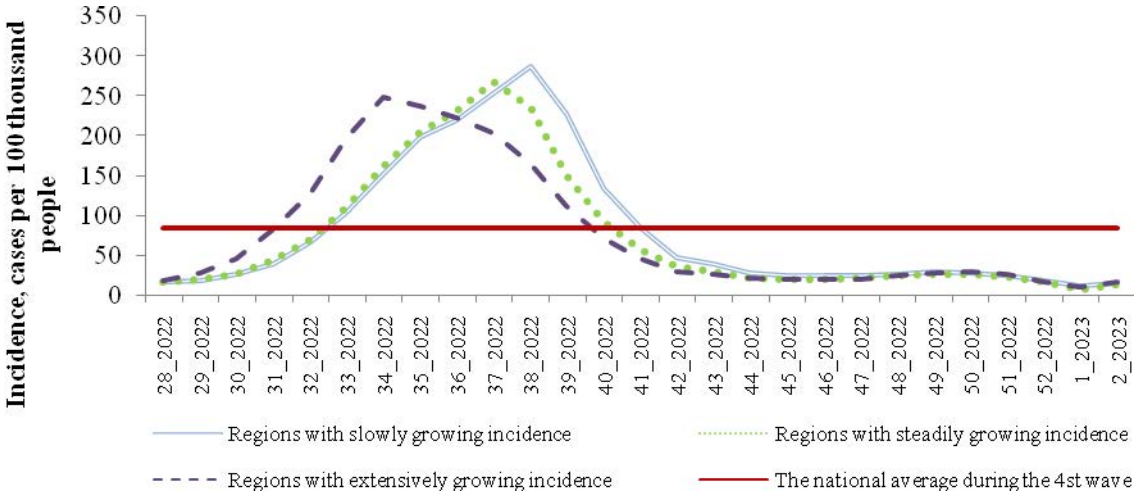


Figure 10. Dynamics of the weekly COVID-19 incidence in three groups of the RF regions during the fourth wave

It was hardly advisable to have full-scale analysis of the **fifth** COVID-19 epidemiological wave at the moment this study was being conducted (April 2023). Although we can see an obviously prevailing strain (*Omicron* subvariant *XBB*) and an already reached peak in the incidence, the epidemic process is still ongoing.

Therefore, we have established spatial-dynamic heterogeneity of the epidemic process over the whole pandemic period. This indicates that intensity of the process depends not only on unstable biological factors (strains changing each other) and introduced restrictive measures but also on initial socioeconomic conditions and medical-demographic features of the RF regions. Some studies have established that levels of the COVID-19 incidence tend to differ depending on age and sex structure of population and socioeconomic conditions. This also includes differences identified between different epidemiological waves of incidence accompanied with implemented non-medical activities that could be also different in their intensity [18, 19].

Initially, working age population and elderly people prevailed among COVID-19-infected people in the RF regions; however, the COVID-19 incidence among children started to grow gradually over 2021–2022 and in 2022 its share reached 16 % in the total COVID-19 incidence. These changes in the structure of incidence are possibly due to a change in prevailing *SARS-CoV-2* strains with better ability to 'escape' an immune response of the human body [3, 4, 20].

When it comes down to territorial differences, the COVID-19 incidence was 1.5–1.8 times (2021–2022) higher among urban residents than among rural population over the whole epidemiological process observed up to the present moment. Some studies report that such factors as high population density, frequent social contacts, and available tourist attractions are more typical for urban areas and they can make the COVID-19 epidemic process more intense regardless of any introduced restrictions [21–24].

The COVID-19 incidence and mortality had the greatest influence on public health indicators (the total incidence and mortality) at the end of 2021 and the beginning of 2022 despite all the introduced restrictive measures and high vaccination scales. The prevailing *Delta* and *Omicron* strains had high infectivity and virulence [20] and easily promoted wide spread of the infection all over the country. In addition, the highest share of COVID-19-induced pneumonia among all the infected people (18.3 %) was also identified in 2021 and this confirms high virulence of the *Delta* strain [25]. Still, the number of cases of carrying the COVID-19 infectious agent was approximately the same both in 2021 and 2022, about 7.0 %.

We have not been able to establish any apparent regularities of the incidence within one year due to the epidemic process being relatively short, anti-epidemic activities being distributed unevenly and different in different regions, and frequent changes between dominant strains. At the same time, the research results allow tracing some trends of elevated incidence levels in autumn and winter. Thus, the greatest number with the RF regions where the COVID-19 incidence was higher than the national average was established in October (51 region), November (68 regions), and December (51 region) 2021 and February (82 regions) 2022, that is, during a period with autumn-winter weather, which meant lower air temperatures, and a growth in seasonal incidence of other airborne infections [23, 26].

In literature, analysis of COVID-19 epidemiological waves frequently relies on using compartmental models that are run with ordinary differential equations to describe how fast people move between groups participating in an epidemic process (susceptible, infected, and recovered) [5, 27]. In the present study, regional peculiarities of the COVID-19 epidemic process were established with retrospective assessments of incidence growth rates within the established time boundaries of the beginning and end of each epidemiological wave together with analyzing prevalence of this or that particular strain.

Limitations of the study. Among limitations of the present study, we should mention the statistical data used in it as regards results of sequencing and the graphs showing how the prevailing coronavirus strains replaced each other that were built on their basis. The actual structure of strain prevalence could be distorted either by volumes of conducted sequencing when laboratory diagnostics was focusing on specific strains during certain periods or by sensitivity of test-systems applied in the process. Some uncertainty also occurs due to the concept of a 'wave' upon which epidemiologists and healthcare experts have not reached a consensus yet. Given that, the waves that are investigated in this study are rather tentative and this might have influenced the ultimate results of assessing incidence growth rates in the RF religions. To get a better insight into differences in the epidemic process among RF regions, in future it would be necessary to perform additional assessment of influence exerted by various factors on registered incidence and mortality.

Conclusion. This study has made it possible to identify some regional peculiarities of the COVID-19 epidemic process among the RF regions over 2020–2023. We have established that peaks of the COVID-19 incidence were reached at different speed in different RF regions within each epidemic wave; this might be due to heterogeneity of environmental factors that influence the epidemic process. The identified territorial differences in the COVID-19 epidemic process should be considered when developing optimal regulatory impacts including those aimed at predicting probable emergent infections.

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Research article

ALCOHOL CONSUMPTION AS HEALTH RISK FACTOR FOR THE POPULATION IN THE RF REGIONS IN THE 'BEFORE CRISIS' AND 'AFTER CRISIS' PERIODS (2017–2022)

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In this study, we have estimated alcohol consumption and alcohol-associated incidence in the RF regions in the 'before crisis' (2017–2019) and 'crisis' (2020–2022) periods. We identified types of the RF regions using hierarchical cluster analysis (Ward's method) and relying on indirect indicators of alcohol consumption. As a result, we established considerable differences between the macro-regions (the Federal Districts) and RF regions as per alcohol consumption and severity of its outcomes. Poles in this differentiation are represented by 'favorable' regions in the Southern Russia where alcohol sales, alcohol-associated crime and incidence are low and 'unfavorable' regions located in the Far East and southern Siberia where alcohol-associated crime and incidence are high. We have shown in this study that retail alcohol sales cannot be considered a sufficient indicator to describe alcohol use in a given region. Thus, considerable volumes of alcohol sales involve severe socially significant outcomes in some regions (for example, the Khabarovsk region and Primorye) whereas such outcomes do not occur in other regions with similarly high alcohol sales (Moscow, Saint Petersburg, the Moscow region and the Leningrad region). The level of socioeconomic welfare on a given territory is confirmed as a significant determinant of alcohol consumption.

We have also analyzed a correlation between economic vulnerability of RF regions during the 'pandemic' and 'sanction' crises and levels of alcohol consumption. The analysis revealed that large industrial regions, though expected to be vulnerable, turned out to be quite stable (it is probably due to delayed macroeconomic effects). We have not been able to identify any resources of improving a tense situation with alcohol consumption in economically unfavorable but less vulnerable subsidized agricultural regions. In general, the crisis period of 2020–2022 can be considered a source of additional health risks for the population in the RF regions where the situation with alcohol consumption was rather unfavorable in the 'before crisis' period.

Keywords: *alcohol consumption, crimes, alcohol intoxication, incidence, alcoholism, alcoholic psychoses, RF regions.*

Alcohol consumption remains a leading behavioral health risk factor worldwide. It makes a significant contribution to incidence [1, 2] and preventable mortality [3, 4] as per many nosologies. According to the Global Strategy to Reduce the Harmful Use of Alcohol issued by the World Health Organization (WHO) as far back as in 2010, prevention and reductions of harmful use of alcohol should become a top priority of public healthcare both in developed and developing countries[1]. In 2018, average world alcohol consumption per capita (people aged 15 years and older) equaled 6.2 liters (9.7 liters for males aged 15 years and older) according to the data provided by the WHO and World Bank[2]. Russia

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[1] Global strategy to reduce the harmful use of alcohol. *WHO*. Available at: http://apps.who.int/iris/bitstream/handle/10665/44395/9789241599931_eng.pdf?sequence=1 (March 01, 2023).

[2] Total alcohol consumption per capita (liters of pure alcohol, projected estimates, 15+ years of age). *The World Bank*. Available at: https://data.worldbank.org/indicator/SH.ALC.PCAP.LI (March 01, 2023).

belonged to the group of countries where alcohol consumption was higher than the world average and equaled 11.19 liters per capita (this group also included Poland, Greece, Romania, Great Britain, Australia, and some other countries). However, alcohol consumption in Russia typically follows a specific ('northern') pattern with high shares of strong spirits in its structure [5] (there was a slight shift in it towards a 'mixed' style by the end of 2010ties [6]) and 'alcohol burden' is typically distributed unevenly in the country with the prevailing share of middle-aged man among consumers of strong alcohols [7]. Besides, regional differentiation in alcohol consumption also tends to be typical for Russia [8]; it determines substantial differences in alcohol-associated incidence and mortality between RF regions [9].

Alcohol consumption has been declining steadily in Russia since the early 2000ties; the trend is confirmed both by data on alcohol sales and results of social surveys among population [10]. However, the COVID-19 pandemic started in 2020 and involved introducing various prohibitions and restrictions (including those limiting free travel and social contacts), growing social tensions, and inability of the public healthcare to perform its functions properly. All this raised a sound concern whether this favorable trend was likely to persist (and not only in Russia). Already at the end of 2020, American experts established a growth in alcohol consumption by the US population [11]; a systemic review by British experts that covered 45 studies on consumption of psychoactive substances (PAS) during the pandemic revealed a growth in consumption of not only alcohol but also drugs and other nonnarcotic PAS [12]. At the same time, an opposite trend was identified in some countries where alcohol consumption declined due to its decreasing physical availability [13].

Indirect indicators of alcohol consumption in Russia were estimated for a period between January and November 2020; they indicated a growth in it including a growth in consumption of strong alcohols and related outcomes becoming more severe [14]. Retail alcohol sales also grew in Russia between 2019 and 2021 [15]. Results of social surveys performed during the first months of the pandemic established multidirectional changes in frequency and volumes of alcohol consumption [16]. It is noteworthy that such an indirect indicator as 'spending on purchases in alcohol-selling outlets', which is widely used by the Public Opinion Foundation to describe alcohol consumption, reveals a rather positive trend[3].

Considerable stressors in the environment and growing uncertainty are key reasons for growing alcohol consumption during crises (including pandemics or world economic crises) as well as increasing alcohol-related health problems and alcohol psychoses. These harmful factors make people perceive a situation subjectively as unsafe, unstable and hardly predictable [18, 19]. The epidemiological crisis associated with the COVID-19 pandemic in 2020–2021 was followed by a socioeconomic one in Russia, the latter being called 'system crisis' [20], 'sanction crisis' [21], or 'economic crisis of non-economic nature' [22]. Probably, the whole period from 2020 and up to now can be described as 'a permanent crisis' in Russia and we can assume that the current level of stressors in the environment is fundamentally different from that observed over several previous years.

Little attention has been given by experts to regional peculiarities of alcohol consumption by Russians during the COVID-19 pandemic (2020–2021) and after it (2022). There is some evidence of fundamentally different dynamics of alcohol consumption estimated on the basis of retail alcohol sales in RF regions in 2020 against 2019, from a growth by several dozen percent in some regions to a similar

[3] Potreblenie na fone pandemii. Kak epidemiya koronavirusa menyaet potrebitel'skie praktiki rossiyan [Consumption against the pandemic. How the coronavirus epidemics changes consumer practices in Russia]. *Fond Obshchestvennoe Mnenie [Public Opinion Fund]: official web-site*. Available at: https://covid19.fom.ru/post/potreblenie-na-fone-pandemii (March 03, 2023) (in Russian).

decline in others [17]. However, experts have not yet come up with a convincing model able to explain these data. Differences in vulnerability of RF regions to the 2022 socioeconomic crisis imply that heterogeneous dynamics of alcohol consumption in them is quite likely.

In this study, our aim was to identify different types of the RF regions as per alcohol consumption and dynamics of alcohol-associated incidence in Russia over the period between 2017 and 2022 and to suggest a model able to explain the detected regional differences.

Material and methods. In this study, we relied on data (both the whole country and as per specific regions) taken from the Unified Interdepartmental Informational Statistical System (UIISS); the data were collected from 2017 to 2022 and covered two indirect indicators of alcohol consumption[4], retail alcohol sales (per 100 thousand people) and the number of crimes (from preliminarily investigated ones) committed under alcohol intoxication (per 100 thousand people). Alcohol-associated incidence was described based on the following indicator: 'Incidence of the first diagnosed alcoholism and alcoholic psychosis (per 100 thousand people)'[5].

To identify specific types of RF regions (overall, 85 RF regions were included in the study) as per alcohol consumption and alcohol-associated incidence, we applied hierarchical cluster analysis (Ward's method). Clusterization was performed separately for two periods, 'before crisis' (2017–2019) and 'crisis' (2020–2022) as per all the selected indicators. We used SPSS Statistics v. 23 for statistical analysis.

Results and discussion. Analysis of the situation on the country level established different dynamics of the selected indicators that described alcohol consumption. Thus, retail alcohol sales grew steadily in Russia between 2017 and 2020. In 2021, a slight decline occurred in this indicator; however, alcohol sales grew again in 2022. A drastic growth in alcohol sales occurred in 2018 (by 8.5 % against 2017). Regions with the maximum growth in alcohol sales in 2018 include Ingushetia (+47.8 %), the Altai Republic (+32.5 %), the Amur region and Khakassia (+28.7 % and +27.3 % accordingly). Ingushetia remained the leader as per a growth in alcohol sales in 2022 against 2021 (+28.8 %). Alcohol sales also grew in the Altai Republic (+9.5 %), Khakassia (+9.2 %), the Belgorod region (+12 %) and the Karachai-Cherkess Republic (+14.1 %).

The number of people who committed crimes under alcohol intoxication declined annually in Russia between 2017 and 2022. In 2017 the country 'number of crimes (from preliminarily investigated) committed under alcohol intoxication per 100 thousand people' equaled 257.5 cases; in 2022, this number fell to 173.9 cases. However, the level of 'alcohol-related crime' in 2022 is rather alerting since the share of people who committed crimes under alcohol intoxication is rather significant and accounts for almost one third of the whole number of people who committed crimes. Several RF regions had high numbers of crimes committed under alcohol intoxication between 2017 and 2019 including Transbaikalia, Chukotka, the Altai Republic and Tyva. It is typical that no significant changes in the number and structure of leader (and anti-leader) regions as per the number of crimes committed under alcohol intoxication per 100 thousand people were identified between 2020 and 2022.

Incidence of the first diagnosed alcohol and alcoholic psychosis (per 100 thousand people) had non-linear dynamics in the RF. Its level decreased from 55.7 to 40.3 (by 27.6 %) between 2017 and 2020. However,

[4] Data on alcohol consumption based on direct indicators are not collected continually in Russia, either in the country as a whole or in specific regions.

[5] Another important indicator to analyze outcomes of alcohol consumption is mortality caused by accidental alcohol poisonings; unfortunately, these data are not available in the UIISS for 2022 as per specific regions.

this incidence grew again after 2020 and equaled 46.3 and 46.5 cases in 2021 and 2022 accordingly. The Khabarovsk region, the Magadan region and the Nenets Autonomous Area had stably high levels of alcohol-associated incidence between 2017 and 2019; these levels were significantly higher than the national average. In 2021, the situation changed and new regional leaders appeared including the Mari El Republic (364.6 cases per 100 thousand people), the Khabarovsk region (143.3 cases), and Mordovia (151.4 cases). Chukotka raised special concern between 2017 and 2022 as regards alcohol-associated incidence.

The clusterization of the RF regions between 2017 and 2019 allowed identifying seven different clusters (Figure 1). Table 1 provides average indicator values as per all the clusters.

The first cluster has the smallest number of regions and the situation there is the worst. The regions in these clusters are the Magadan region, the Nenets Autonomous Area, the Komi Republic and Chukotka. Retail alcohol sales are typically high in this cluster (the average cluster value is 238.8 thousand deciliters per 100 thousand people) and the number of crimes committed under alcohol intoxication is considerably higher than the national average (the average cluster value is 566.2 crimes per 100 thousand people). Alcohol-associated incidence is also critical in these regions (the average cluster value is 159.9 cases per 100 thousand people).

The second cluster has relatively low retail alcohol sales (the average cluster value is 86.5 thousand deciliters per 100 thousand people) but the critically high number of crimes committed under alcohol intoxication (the average cluster value is 626.6 crimes per 100 thousand people). Alcohol-associated

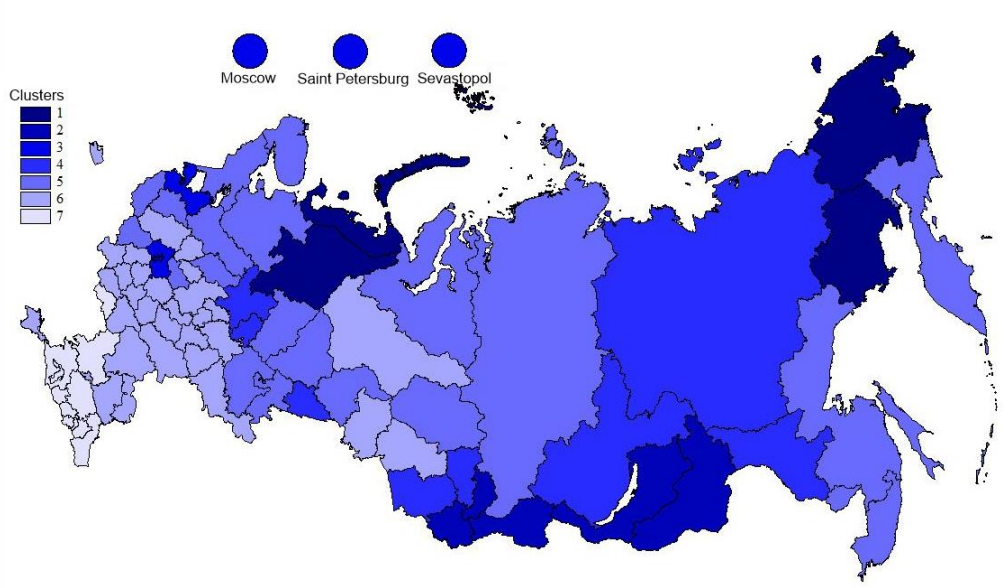

Figure 1. Clusterization of the RF regions as per indirect indicators of alcohol consumption and alcohol-associated incidence in 2017–2019

Table 1

Average indicator values as per the identified clusters of the RF regions (2017–2019)

Indicator	Cluster No.						
	1	2	3	4	5	6	7
Retail alcohol sales (thousand deciliter per 100 thousand people)	**238.8**	86.5	205.3	132.6	180.1	131.2	46.9
The number of crimes committed under alcohol intoxication (cases per 100 thousand people)	566.2	**626.6**	108.0	455.5	335.3	229.3	96.2
Incidence of the first diagnosed alcoholism and alcoholic psychosis (cases per 100 thousand people)	**159.9**	70.7	36.3	78.7	77.8	64.9	27.5

incidence in the cluster is close to the national average (the average cluster value is 70.7 cases per 100 thousand people). This cluster includes Transbaikalia, the Altai Republic, Buryatia, Tyva, and Khakassia.

The third cluster is rather peculiar as per its characteristics; it includes the Leningrad region, the Moscow region, Moscow, Saint Petersburg, and Sevastopol. Although retail alcohol sales are relatively high in the cluster (the average cluster value is 205.3 thousand deciliters per 100 thousand people), the number of crimes committed under alcohol intoxication (the average cluster value is 108 crimes per 100 thousand people) as well as alcohol-associated incidence (the average cluster value is 36.3 cases per 100 thousand people) are relatively low.

The clusters from the *fourth to sixth* were combined in one provisional group based on values of the indicators being predominantly similar to the national average. Retail alcohol sales (the average cluster value is 132.6 thousand deciliters per 100 thousand people) and alcohol-associated incidence (the average cluster value is 78.7 cases per 100 thousand people) similar to the national average are a peculiarity of the *fourth* cluster; but the number of crimes committed under alcohol intoxication is higher in this cluster than the national average (the average cluster value is 455.5 crimes per 100 thousand people). This cluster includes the Altai region, the Amur region, the Irkutsk region, the Kemerovo region, the Kirov region, the Kurgan region, Yakutia, and Udmurtia.

The *fifth* cluster includes 22 RF regions located in the Central Federal District (the Vladimir region and the Kostroma region), the North-West Federal District (the Vologda region and the Murmansk region), the Volga Federal District (the Perm region and the Sverdlovsk region), the Siberian Federal District (the Krasnoyarsk region and the Tomsk region), and the Far East Federal District (Primorye and the Khabarovsk region). All the analyzed indicators have values similar to the national average in this cluster including retail alcohol sales (the average cluster value is 180 thousand deciliters per 100 thousand people), the number of crimes committed under alcohol intoxication (the average cluster value is 335.3 crimes per 100 thousand people), and primary incidence of alcohol and alcoholic psychosis (the average cluster value is 77.8 cases per 100 thousand people).

The sixth cluster includes the greatest number of regions, namely 30, where the situation with retail alcohol sales (the average cluster value is 131.2 thousand deciliters per 100 thousand people) and alcohol-associated incidence (the average cluster value is 64.9 cases per 100 thousand people) is relatively good. This cluster also has a relatively low level of 'alcohol-associated crime' (the average cluster value is 229.3 crimes per 100 thousand people). Tatarstan, Mari El, Mordovia, the Astrakhan region, the Bryansk region, the Orel region, the Orenburg region as well as some other RF regions are included into the sixth cluster.

The most favorable situation is in the *seventh* cluster, which differs significantly from all the other RF regions due to low levels of the analyzed indirect indicators describing alcohol consumption. This cluster includes all seven regions in the North Caucasian Federal District, Adygei, the Krasnodar region, the Rostov region, and the Belgorod region. The cluster has the lowest number of crimes committed under alcohol intoxication, 96.2 cases per 100 thousand people. Retail alcohol sales and alcohol-associated incidence are also lower in this cluster than the national average (the average cluster values are 46.9 thousand deciliters and 27.5 cases accordingly).

The clusterization of the RF regions between 2020 and 2022 allowed identifying ten different clusters. Some clusters retained the same regions in this period and their structure did not change significantly. Such clusters are those from the *first* to *fourth* and the *seventh*. The *fifth* and *sixth* clusters redistributed and regions that were included into them created three relatively new clusters. In addition, two new groups of RF regions with similar indicators were identified (Figure 2). Table 2 provides average cluster values as per all the analyzed indicators.

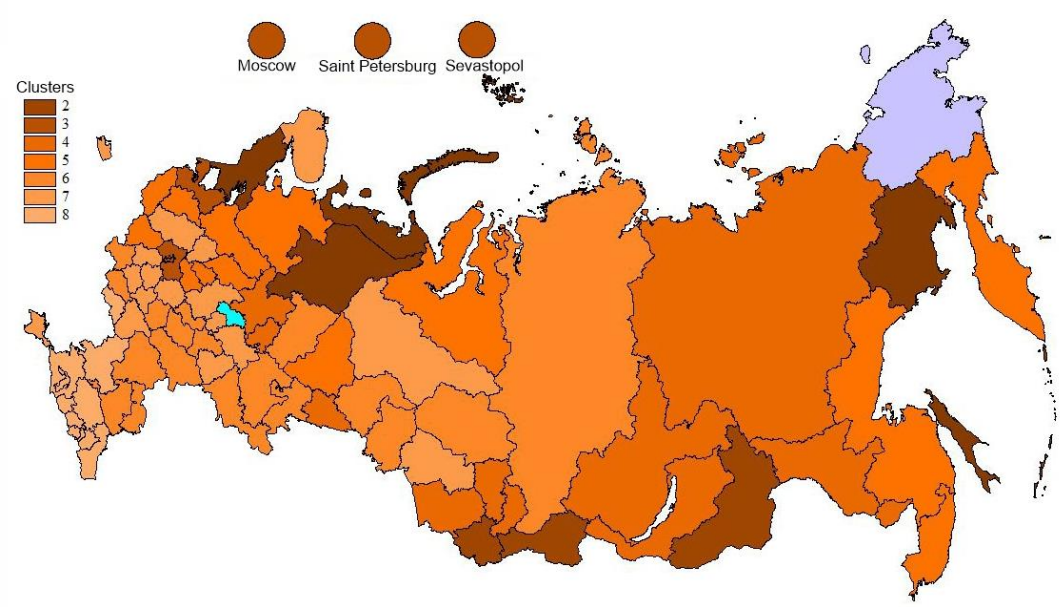

Figure 2. Clusterization of the RF regions as per indirect indicators of alcohol consumption and alcohol-associated incidence in 2020–2022

Table 2

Average indicator values as per the identified clusters of the RF regions (2020–2022)

Indicator	Cluster No.*									
	1	2	3	4	5	6	7	8	9	10
Retail alcohol sales (thousand deciliter per 100 thousand people)	**256.4**	87.5	216.1	136.6	191.5	119.8	160.4	54.0	150.9	178.1
The number of crimes committed under alcohol intoxication (cases per 100 thousand people)	395.3	**597.3**	101.1	378.1	259.0	243.4	173.6	81.3	210.3	514.4
Incidence of the first diagnosed alcoholism and alcoholic psychosis (cases per 100 thousand people)	93.5	58.6	18.1	69.0	72.0	52.2	47.5	19.1	219.3	**287.7**

N o t e : * cluster No. 9 is Mari El; cluster No. 10 is Chukotka.

The situation with alcohol consumption estimated as per indirect indicators was the worst in the *first* cluster in the previous period and remained so in the second one. The cluster added new regions between 2020 and 2022 such as Karelia and the Sakhalin region that were previously included into the fifth cluster with a relatively good situation. The 'crisis' period did not involve any significant or drastic deterioration of indicators describing either alcohol consumption or alcohol-related incidence. It was rather absence of any positive dynamics of these indicators that moved these RF regions into the group with the lowest wellbeing[6]. Chukotka that was also included in this cluster was assigned into another separate cluster. Just as in the period between 2017 and 2019, the regions included in this cluster have considerable retail alcohol sales (the average cluster value is 256.4 thou-

[6] For reference, the Murmansk region was included in the same fifth cluster as Karelia and the Sakhalin region in 2017–2019 but in 2020–2022 there was a significant decline in this region in both the number of crimes committed under alcohol intoxication and alcohol-associated incidence (but retail alcohol sales remained at the same level). This allowed us to assign the Murmansk region into a group of regions with relatively normal wellbeing in the 'crisis' period included into the seventh cluster.

sand deciliters per 100 thousand people) and concerning numbers of crimes committed under alcohol intoxication and high levels of alcohol-associated incidence (the average cluster values are 395.3 crimes per 100 thousand people and 93 disease cases per 100 thousand people).

The number of regions included into the *second* cluster went down to three. Only Transbaikalia, the Altai Republic and Tyva remained in it. This cluster still has relatively low retail alcohol sales (the average cluster value is 87.5 thousand deciliters per 100 thousand people) and excessively high levels of 'alcohol crime' (the average cluster value is 597.3 crimes per 100 thousand people). Primary incidence of alcoholism and alcoholic psychosis is similar to the national average in this cluster (the average cluster value is 58.6 cases per 100 thousand people). It is noteworthy that retail alcohol sales are three times lower in Tyva against the other regions in this cluster; however, alcohol-associated incidence and crime correspond to the average cluster values[7].

The *third* cluster retained the same regions as in the previous period, namely, the Leningrad region, the Moscow region, Moscow, Saint-Petersburg, and Sevastopol. Retail alcohol sales grew insignificantly over the analyzed period against the previous one (the average cluster value grew from 205.3 to 216.1 thousand deciliters per 100 thousand people); this trend is in line with the national dynamics. Other indirect indicators describing alcohol consumption by people living in these regions still have relatively low values and negative dynamics. Thus, there was a slight decrease in the number of crimes committed under alcohol intoxication (the average cluster value went down from 108 cases to 101.1 cases per 100 thousand people). Primary incidence of alcoholism decreased considerably (the average cluster value went down by two times).

The *fourth* cluster retained all the regions included into it over the previous period and 'added' the Jewish Autonomous Area, Buryatia, and Khakassia[8]. Even with this new structure, the cluster still has retail alcohol sales (the average cluster value is 136.6 thousand deciliters per 100 thousand people) and alcohol-associated incidence (the average cluster value is 69 cases per 100 thousand people) that are similar to the national average. The number of crimes committed by people living in these regions under alcohol intoxication raises considerable concern (the average cluster value is 378.1 cases per 100 thousand people).

The *fifth* cluster has lost a lot of RF regions previously included into it. Between 2017 and 2019, it had 22 regions but only 13 remained in it in the period between 2020 and 2022. Ten regions left the cluster but the Ivanovo region was included into it[9]. The analyzed indirect indicators of alcohol consumption are very similar to the national average in the Arkhangelsk region, the Vologda region, the Nizhniy Novgorod region, the Smolensk region, and other RF regions in the fifth cluster. Thus, the average retail alcohol sales equaled 191.5 thousand deciliters per 100 thousand people in the cluster. Alcohol-associated incidence and crime were also close to the national average (the average cluster value is 72 cases per 100 thousand people and 259 cases per 100 thousand people accordingly).

The *sixth* and *seventh* clusters include the greatest number of regions in the period

[7] Tyva and Transbaikalia also typically have high levels of mortality caused by accidental alcohol poisonings. In 2021, 17.2 cases per 100 thousand people were registered in Tyva and 15.6 cases per 100 thousand people were registered in Transbaikalia (the national average is 6.36 cases per 100 thousand people). Mortality due to accidental alcohol poisoning was also high in the Altai Republic in 2020 (16.3 cases per 100 thousand people); in 2021, the level went down to 4.52 cases per 100 thousand people.

[8] Buryatia and Khakassia moved to the fourth cluster from the second 'before crisis' one with a less favorable situation since alcohol-associated crime went down during the 'crisis' period in both regions and alcohol-associated incidence also decreased in Khakassia. The Jewish Autonomous Area, on the contrary, faced a decrease in its wellbeing due to growing levels of alcohol-associated crime and relatively high alcohol consumption.

[9] The Ivanovo region was included into the six cluster with relatively favorable conditions in the 'before crisis' period; in the 'crisis' period, retail alcohol sales grew in the region although alcohol-associated crime an incidence went down.

between 2020 and 2022. The *sixth* cluster includes 18 RF regions: seven regions located in the Volga Federal District[10], such as the Perm region, the Saratov region, Bashkortostan and others; three regions located in the South Federal District (the Astrakhan region, the Volgograd region, and the Kalmyk Republic) and the Central Federal District (the Bryansk region, the Kursk region, and the Tambov region); two regions located in the Ural Federal District (the Tyumen region and the Chelyabinsk region) and the Siberia Federal District (the Omsk region and the Tomsk region). Retail alcohol sales are slightly lower than the national average (the average cluster value is 119.8 thousand deciliters per 100 thousand people). Alcohol-associated incidence and crime are within the national trends. The average cluster number of crimes committed under alcohol intoxication equals 243.4 cases per 100 thousand people; the average cluster primary incidence of alcoholism and alcoholic psychosis is 52.2 cases per 100 thousand people.

The *seventh* cluster includes 17 RF regions. The hierarchical clusterization allowed including eight regions located in the Central Federal District (the Voronezh region, the Lipetsk region, the Yaroslavl region and others), four regions from the Volga Federal District, two regions from the North-West Federal District (the Murmansk region and the Kaliningrad region), one region from the Ural (the Khanty – Mansi Autonomous Area), Siberia (the Novosibirsk region) and South (Crimea) Federal Districts. Retail alcohol sales are slightly higher than the national average in the cluster (the average cluster value is 160.3 thousand deciliters per 100 thousand people). On the contrary, alcohol-associated incidence and crime are slightly lower than the national average. The average cluster number of crimes committed under alcohol intoxication is 173.6 cases per 100 thousand people; average primary incidence of alcohol and alcoholic psychosis is 47.5 cases per 100 thousand people.

The *eighth* cluster with the most favorable conditions is similar to the seventh cluster identified as per the clusterization over the period between 2017 and 2019. It includes all the regions located in the North Caucasian Federal District, the Belgorod region, the Rostov region, Adygei, and the Krasnodar region. Retail alcohol sales remained low between 2020 and 2022 in comparison with the previous period (the average cluster value grew insignificantly from 46.9 thousand to 54 thousand deciliters per 100 thousand people); the average cluster number of crimes committed under alcohol intoxication went down slightly from 96.2 to 81.3 cases per 100 thousand people; alcohol-associated incidence also decreased (the average cluster value declined from 27.5 to 19.1 cases per 100 thousand people).

And finally, Chukotka and Mari El were assigned into two separate clusters. In Chukotka, retail alcohol sales are relatively higher than the national average. The levels of other indirect indicators also raise considerable concern. Thus, the number of crimes committed under alcohol intoxication is more than two times higher than the national average; alcohol-associated incidence is more than five times higher (the average cluster values are 514.4 crimes per 100 thousand people and 287.7 disease cases per 100 thousand people accordingly). In Mari El, the poorest situation is with alcohol-associated incidence (the average cluster value is 219.3 cases per 100 thousand people). It is noteworthy that primary incidence of alcoholism grew by more than five times between 2020 and 2021 (from 66.5 to 364.6 cases per 100 thousand people) and then decreased slightly by 2022 (down to 226.67 cases per 100 thousand people). The other analyzed indirect indicators that describe alcohol consumption are similar to the national average in Mari El.

[10] Out of 14 RF regions included into the Volga Federal District (the second biggest in the RF as per its population after the Central Federal District), the overwhelming majority were included into clusters with favorable conditions in the 'crisis' period; seven regions were in the sixth cluster, the other four (the Nizhniy Novgorod region, Tatarstan, and Chuvashia) were in the seventh cluster. Out of the remaining three, two regions (the Kirov region and Udmurtia) were included in the fourth cluster and only Mari El, which creates its own separate cluster, has an extremely poor situation as regards alcohol consumption.

At present, the socioeconomic situation in the country is rather unstable and this creates elevated public health risks [23] including those caused by harmful use of alcohol. Patterns of alcohol intake mediated by effects of social contexts become especially apparent mediators of public health deterioration during economic crises. Moreover, negative health outcomes are often delayed and appear after a certain time lag.

This study describes RF regions over the periods between 2017 and 2019 and between 2020 and 2022. They are combined in clusters as per similarity in the markers of alcohol consumption and therefore regions in different clusters are different from each other as per these markers. The results indicate there is regional specificity and considerable differences in the analyzed indirect indicators of alcohol consumption.

The most alerting situation as regards alcoholization of population occurred in the period between 2017 and 2022 in Chukotka. Thus, primary incidence of alcoholism and alcoholic psychosis per capita is stably high in this RF region (in 2021, 306.9 cases per 100 thousand people were diagnosed in Chukotka and this level is more than 6.5 times higher than the national average over the analyzed period). Experts conventionally explain this situation by a low living standard, high unemployment rates, and other socioeconomic factors affecting the indigenous people of the Far North who live under harsh natural and climatic conditions [24]. In addition, the most burning issue is a growth in primary incidence of alcoholism and alcoholic psychoses among children and adolescents in Chukotka; this is largely due to substantial sales of illegal alcohol [25].

The stably unfavorable situation with alcohol consumption, alcohol-associated crime and incidence is observed in the Magadan region, the Nenets Autonomous Area and the Komi Republic. This is an apparent marker indicating that the socioeconomic situation is rather poor in these regions [26]. Overall, life quality in a region is associated with alcohol consumption (especially with alcohol-associated crime and incidence). In 2021, the top 20 RF regions as per life quality were identified by the Agency for Strategic Initiatives[11]; among them, 18 regions were assigned by our analysis into the ‘top’ or the most favorable clusters in the ‘crisis’ period. The only exceptions were Moscow with high retail alcohol sales (but low levels of alcohol-associated crime and incidence) and Udmurtia where retail alcohol sales were similar to those in Moscow but alcohol-associated crime and incidence were substantially higher than in the capital.

High levels of alcohol consumption with negative outcomes persist in the Southern Siberia in such regions as Transbaikalia, the Altai Republic[12], Buryatia, Tyva, and Khakassia. This is also due to extremely unfavorable socioeconomic situation in these regions both in the ‘before crisis’ and ‘crisis’ periods [27]. Thus, for example, according to the data provided by Rospotrebnadzor, 26 % of all the alcohol poisonings in the Altai Republic in 2022 were caused by unspecified alcohol; 4.5 % of cases, methyl alcohol. In these RF regions, the human development index tends to be low [28] and risky behavior is widespread [29]. In addition, levels of unregistered alcohol consumption also tend to be high in these regions[13] [8].

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[11] Reiting kachestva zhizni [Life quality rating]. *Agency for Strategic Initiatives: official web-site*. Available at: https://asi.ru/government_officials/quality-of-life-ranking/ (March 21, 2023) (in Russian).

[12] Po itogam 2022 goda otravleniya alkogolem zanimayut vedushchee mesto v strukture otravlenii khimicheskoi etiologii v Respublike Altai: press-reliz [As per the results of 2022, alcohol poisonings occupy the leading place among chemical poisonings in the Altai Republic: press-release]. *Rospotrebnadzor's Regional Office in the Altai Republic*. Available at: http://www.04.rospotrebnadzor.ru/index.php/san-nadzor/2015-10-01-05-48-10/17906-16012023.html (March 21, 2023) (in Russian).

[13] Alkogolizm i narkomaniya v regionakh RF. Otsenka masshtaba problemy na osnove dostupnykh statisticheskikh dannykh, 2019 g. [Alcoholism and drug addiction in RF regions. Assessment of the problem scope based on available statistical data, 2019]. *Esli byt' tochnym: the informational platform*. Available at: https://static.tochno.st/files/analytical/a95ec80f72d0a36b08753a9e6484a644.pdf (March 21, 2023) (in Russian).

Regions included in the North Caucasian Federal District (Dagestan, Ingushetia, Chechnya, North Ossetia, the Karachai-Cherkess Republic and others) are predominantly populated with Muslims and are constantly assigned into the so called 'light-drinking' category [30]. Religion as a social factor thus compensates for the low level of socioeconomic development in these regions as a factor able to stimulate higher alcohol consumption. In our opinion, an insignificant growth in retail alcohol sales can be due to intensified interregional migration and is caused, in particular, by sporadic alcohol purchases by tourists[14].

High retail alcohol sales in some large and wealthy RF regions (Moscow, Saint Petersburg, the Moscow region, and the Leningrad region) do not have severe social outcomes (high alcohol-associated incidence and crime). This is probably due to low consumption of unregistered alcohol (homemade drinks, illegal alcohol, and various surrogates) in these regions since consumption of alcohol surrogates is usually determined by such factors as a social status, education, and incomes [31].

We put forward a hypothesis in this study in an effort to explain dynamics of alcohol consumption in RF regions. This hypothesis emphasizes different influence exerted by the factors related to the pandemic and 'sanction' crisis on the socioeconomic situation in different regions, different levels of stressors in the environment and different social tension. Studies that addressed economic resistance to the COVID-19 pandemic reported greater vulnerability of developed and large economies and mining regions and greater resistance of poorly developed predominantly agricultural regions with substantial governmental support [32]. Sanctions have affected the industrially developed RF regions most seriously since their economies have tight connections with the global market and their predominant branches are extraction of hydrocarbons and metals and civil engineering [21]. Therefore, it was in these regions where we could expect a growth in alcohol consumption in the 'crisis' period. The study results confirm this only partially. Thus, in 2022, the greatest decline in industrial production among all the RF regions was observed in the Sakhalin region (it dropped by 38 % against its level in 2021) and there was also a significant drop in tax payments of the income tax (by 11 % in May 2022 against May 2021) [21]. In addition, retail alcohol sales in the Sakhalin region were among the highest in the country in 2022, 258.4 thousand deciliters per 100 thousand people (comparably high retail alcohol sales were also registered in Karelia, 258.9 thousand deciliters per 100 thousand people, and in the Magadan region, 257.6 thousand deciliters per 100 thousand people). In 2022, a significant decline in industrial production was also detected in the Tula region, Kaliningrad region, Samara region, and Ulyanovsk region; however, none of these regions were included into the clusters unfavorable as per alcohol consumption in the 'crisis' period.

Conclusions. The analysis has revealed that the regional differentiation as per indirect indicators describing alcohol consumption identified in the 'before crisis' period persists also in the 'crisis' one. We have not established any fundamental trends either in 'unfavorable' or 'favorable' groups of regions. We can identify three separate sub-groups of RF regions where the situation with alcohol consumption is rather poor. The first sub-group includes regions with high retail alcohol sales, high levels of alcohol-associated incidence and crime (the Magadan region, the Nenets Autonomous Area, the Komi Republic, and Chukotka). The second sub-group includes regions with relatively low retail alcohol sales but high levels of alcohol-associated crimes and incidence (Transbaikalia, the Altai Republic, Tyva, and Khakassia). The third sub-group is made of regions with high retail alcohol sales but relatively low levels of alcohol-associated crime and incidence (Moscow and Saint Petersburg, the Moscow region and the Lenin-

[14] The greatest growth in retail alcohol sales between 2017 and 2022 was identified in Dagestan, from 12.6 thousand deciliters to 20.7 thousand deciliter per 100 thousand people.

grad region). Relatively high retail alcohol sales as well as their positive dynamics can be evidence of both intensive alcohol consumption by population and a small share of illegal or surrogate alcohol and homemade drinks in the structure of alcohol consumption.

Crisis processes related to the tense epidemiological (2020–2021) and socioeconomic (2022) situation have not had any substantial influence on alcohol consumption in most regions that were considered the most vulnerable to pandemic and sanction-related challenges. This might be due to a delayed effect produced by macroeconomic factors. Those RF regions where the socioeconomic situation was rather poor in the 'before crisis' period have not gained any additional sources of resistance that would allow improving the situation with alcohol consumption including its most severe negative outcomes.

Some additional factors able to influence alcohol consumption and associated health risks include availability and prevalence of moonshining and production of other homemade alcohol in a region; prevalence of strong alcohols in the structure of consumption; sex, age, national and occupational structure of population in a region (a share of male population, a share of young people and working age people, a share of people with physical labor, etc.). Institutional factors also have their importance, for example, how effectively regional authorities fight against surrogate alcohol, how successful the anti-alcohol policy is in a region, how well organs and authorities responsible for prevention of alcohol-associated incidence cope with their functional tasks.

The development of the contemporary Russian society is non-linear in its essence; it is rather difficult to predict dynamics of the social, political and economic situation; the level of social tension is still high. All this requires constant monitoring of various health risk factors including alcohol consumption at the regional and national level for timely decision-making in the sphere of public health protection.

The study limitations. The study relies only on indirect indicators of alcohol consumption and does not consider illegal alcohol sales. Since there are no sufficient statistical data available in the UIISS on specific regions, alcohol consumption is not described using such indicators as 'mortality caused by accidental alcohol poisonings' or 'incidence of poisoning with ethanol and alcohol surrogates'.

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Research article

ALCOHOL CONSUMPTION IN A RUSSIAN METROPOLIS: FACTORS AND RISK GROUPS

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In recent years, Russia has seen a considerable decrease in the number of consumers of alcoholic beverages. However, mortality from alcohol-related causes is still quite high. In the context of the Concept for lowering alcohol use in the Russian Federation up to 2030, it is promising to assess the risks of alcohol involvement of Muscovites as residents of a certain metropolitan region. The purpose of the study is to identify the characteristics of alcohol intake by Moscow residents, including factors and risk groups. An empirical sociological survey (CATI, randomized sample, N = 1002) was conducted in October 2022 among adult residents of Moscow. The study has showed that 78 % of Muscovites have consumed alcohol over the past year; the rate of heavy drinking is 14 % among male drinkers and 7 % among female drinkers, which is consistent with data from previous studies conducted on a nationwide sample. Also, 16 % of Muscovites note that they have consumed homemade alcohol over the past month, which means that they represent a potential risk group for poisoning. The study identified the structure of alcohol consumption, which served as the foundation for consumer classification: "bar type" (24 %), "homemade alcohol of various strengths" (21 %), "strong alcohol and homemade wine" (20 %), "wine" (18 %), "only vodka" (17 %). Alcohol abuse is uncommon among young individuals. Involvement in drinking alcohol is frequently influenced by relatives (including parents), colleagues and friends, highlighting the need to address alcoholism's social components. Respondents evaluate the current anti-alcohol measures in Moscow rather positively.

Keywords: *alcohol, alcoholization, anti-alcohol policy, abuse, Moscow, unregistered alcohol, mortality, reduction in alcohol consumption.*

The Ministry of Health of the Russian Federation has developed a draft Concept for lowering alcohol use in the Russian Federation up to 2030, which is currently undergoing public expertise. The draft proposes that by 2030 alcohol use per capita should decrease to 7.7 liters (9.1 liters in 2020), the death rate from alcohol abuse should be reduced to 23.3 people per 100,000 (32.5 persons in 2020)[1]. This document should contribute to the downward trend in the number of alcohol-addicted Russians that has been observed since the second half of the 2000s.

Thus, Russia is no longer listed among the countries with the highest rates of alcohol consumption. Also, according to the Higher School of Economics, the share of heavy alcohol-addicted is steadily decreasing: in 2017 it

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amounted to 14.8 % among male drinkers and 7.8 % among female drinkers, which is about 12–14 % of the total number of current alcohol consumers [1]. 46.8 % of Russians do not drink alcohol at all or have not done it for a year [1].

These data represent not only the current decline in the number of alcohol consumers, but also fundamental changes in consumption patterns. Today, Russia has a "post-Soviet" model of alcohol consumption with lower consumption of vodka and liquor beverages (less than 5 liters per capita, adults, per year) and higher beer consumption (up to 4 liters per year) [2]. Today Russia is transitioning from the so-called "northern" alcohol consumption pattern to the "Central European" pattern where vodka competes with beer [3]. Subsequently, there is an increase in consumption of low-alcohol drinks and more expensive drinks [4]. Changes in patterns of alcohol consumption are also reflected in the socio-demographic changes of the alcohol-consuming population, and various studies reveal similar types of alcohol consumers [4, 5].

However, the current situation concerning alcohol consumption in the country is still far from ideal. Russia has a high rate of alcohol intake among drinkers, with alcohol contributing roughly 12 % of all premature deaths (alcohol-addicted are 25.5 times more likely to die prematurely [6]), and alcohol consumption costs the Russian economy at least 1.7 trillion rubles each year [7]. Due to excessive drinking, holidays represent a significant risk. The peak of alcohol mortality is registered on January 1, 7 and 14, February 23, March 8, May 1 and 9, June 12 and November 4 [8]. From 2011 to 2019, excess deaths from alcohol on birthdays amounted to 78,000 cases [8].

The official statistics of alcohol consumption do not include unregistered sales of homemade (illicit, unregistered, counterfeit, surrogate, etc.)[2] alcohol, which may significantly differ from official data, as it is hard to evaluate it due to little knowledge about the gray market. The principal methodological challenge of researching homemade alcohol may be related to the fact that respondents tend to conceal the real amount of alcohol consumed due to its social unacceptability in Russia.

In this regard, expert assessments may be used along with survey data. In general, the World Health Organization estimates the consumption of unregistered alcohol in Russia at 3.2 liters of pure alcohol per capita[3]. According to the head of Federal Service for Alcohol Market Regulation (Rosalkogolregulirovanie), the share of unregistered vodka turnover in Russia is about 22 %; budget losses at all levels total more than 31 billion rubles [7]. Experts estimate that unregistered alcohol market accounts for between 28 and 45 % of all alcoholic beverages consumed [7, 9].

Consumption of illicit alcohol is dangerous to human health. People drinking moonshine (Russian home-distilled spirit called "samogon") consume alcohol much more often than those who prefer legally produced beverages (1.5–2.5 times) [10, 11]. People who have relatives, neighbors, or acquaintances producing homemade alcoholic beverages tend to drink homemade alcohol 4–6 times more frequently than other consumers, depending on the type of alcohol [10]. Binge drinkers make a significant contribution not only to mortality rate due to alcohol poisoning, but also to total consumption indicators [11]. Nonetheless, a general decrease in binge alcohol intake was observed among consumers of homemade alcohol, specifically moonshine [12].

From this perspective, it is worthwhile to investigate the state of alcohol use in Moscow. Firstly, Moscow is the capital city with a sizable solvent population, so strictly economic measures, such as price increases, may be effective only to a certain extent. Thus, there is an urgent need to find alternate measures to reduce

[2] Please note that these concepts are not identical in their meaning, as illicit alcohol, such as stolen from manufacturing facility and sold later, does not have the same meaning as homemade alcohol beverages consumed by its producer. In our article, we will use these concepts in the context of alcohol distributed beyond state regulations.

[3] Alcohol, unrecorded per capita (15+) consumption (in litres of pure alcohol) with 95 % CI. *WHO*. Available at: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/alcohol-unrecorded-per-capita-(15-)-consumption-(in-litres-of-pure-alcohol)-with-95-ci (March 22, 2023).

alcohol consumption. Secondly, acceptable levels of alcohol consumption among Moscow residents can be adopted by other regions, just as certain anti-alcohol measures in the capital can influence alcohol consumption in other regions (for example, drinking tours).

The **purpose** of the study is to identify the main characteristics of alcohol consumption by Moscow residents. Thus, it is necessary to analyze the general structure and places of alcohol drinking, consumer groups and their motivation, specific aspects of homemade spirits consumption. The study aims to identify main factors of alcohol abuse and risk groups, quantify those elements, and, in general, to create points of references in the execution of Moscow's anti-alcohol policy.

Materials and methods. From October 11 to October 19, 2022, an empirical sociological study with participation of adult citizens permanently residing in Moscow was carried out. The survey was conducted using a random stratified dual-frame sampling method of Moscow mobile and landline phone numbers (CATI). A total number of respondents was 1002. The sample is representative by sex and age based on the Federal State Statistics Service (Rosstat) data.

Respondents were interviewed using two versions of questionnaire. The short version included questions assessing general attitudes towards alcohol use, while the expanded version focused on personal binge drinking experiences. The expanded questionnaire was filled in by a limited number of respondents, however, there was enough information to conduct a quantitative data analysis. This approach allowed us to evaluate two research aspects at the same time: quantitative assessment and a deeper study of alcohol risk groups. Subsample sizes are mentioned in the text when the question was asked only to a certain group of respondents.

Data analysis was performed using IBM SPSS Statistics version 26.0. χ-square test and z-test were used. Confidence interval was selected at 95 % for all cases. Hierarchical clustering (Ward's method, Euclidean metric) was carried out. Verification of statistical criteria (links, comparison of shares, etc.) was performed on unweighted data.

Results and discussion. The results of our study performed by using the projective technique (sentence completion method) showed that the absolute majority (68 %) of Moscow residents considers questions about alcohol in terms of its consumption prevalence, and often there are statements that support the myths about rampant alcoholism in Russia. At the same time, many answers are formal and clichéd, which indicates a poor reflection on this issue.

The most common belief is that excessive alcohol intake is a global problem. Nonetheless, 13 % of Moscow citizens note that alcohol abuse is a national problem in Russia. Other vulnerable groups include young people, low-income households, male population, as well as residents from small settlements and certain regions of the country.

People think that society (13 %), an individual (7 %), government and authorities (5 %), family/relatives (4 %) are primarily responsible for presence and prevalence of this problem. Alcohol addiction is considered not only as a social problem (including education, 13 %), but also a biomedical (addiction as a disease, medicine-related problem, 7 %) and a psychological one (personal qualities and background, 5 %). Therefore, the collective consciousness to a certain extent has some ideas about the complex nature of the disease.

Dichotomous questions (Figure 1) allowed us to understand some ideas about socially accepted alcohol intake and situations that trigger alcohol use. For example, there is a popular opinion that it helps to build relationships. In particular, the impact of external conditions (economic, social and political agenda) is more often claimed by people with higher education (63 % vs. 43 % without higher education, $p < 0.001$) and young people under 35 compared to people over 50 (65 % vs. 51 %, respectively, $p < 0.05$).

The survey shows more than 3/4 of respondents have consumed alcohol beverages over the past year (78 %). Older people who describe their health as “poor” and “very poor” (42 % compared to 20 % as “fine” and 19 % as “good, excellent”, $p < 0.05$) tend to deny drinking more often than other age groups (31 %, the second place is 22 % for the group aged 35–49, $p < 0.05$).

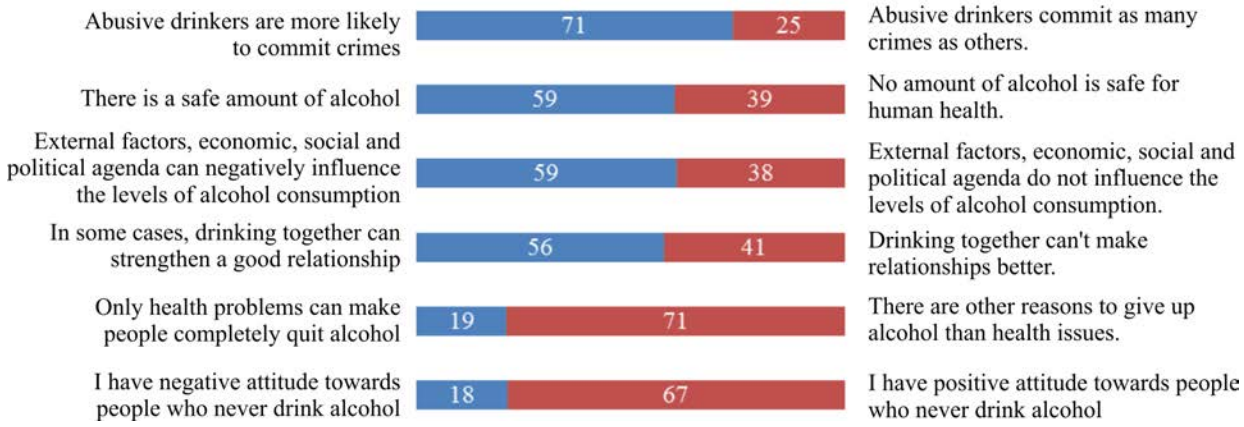

Figure 1. Dichotomous questions, % (N = 1002). The answer "Undecided" is not presented

Excessive alcohol consumption is a significant challenge for modern medicine. Alcohol intake is defined as excessive when the total consumption in grams per month is estimated to be more than moderate. The norm is differentiated by sex and amounts up to 800 grams of pure alcohol[4] per month for men and up to 400 grams of pure alcohol for women [1]. The survey reveals that 14 % of male drinkers and 7 % of female drinkers are excessive alcohol consumers, which corresponds to the monitoring data from the all-Russian survey RLMS-HSE (The Russia Longitudinal Monitoring Survey, Higher School of Economics).

In the study, the respondents were also asked to make an individual assessment of excessive alcohol consumption, considering as excessive intake for a man of 5 or more servings of alcohol per day once a week or more, and 3 or more servings of alcohol for a woman (one serving of alcohol equals a shot of vodka or a can of beer or one glass of wine or champagne). 19 % of respondents have personal experience of excessive alcohol consumption, 58 % have alcohol abusers among relatives or acquaintances, 34 % admitted that they have never experienced alcohol abuse, and 1 % remained undecided. Thus, 19 % of respondents are in the risk group of alcohol consumption.

Alcohol consumption highly depends on a social circle. For example, men who drink alcohol excessively (67 %) are more aware of alcohol abuse among close friends than those who drink moderately (38 %).

One of the most common reasons for taking alcoholic beverages is to improve the emotional climate in a team (friendly communication, easy talk, relationship strengthening) or the emotional state of an individual in distressing circumstances (moral stress, bad mood) (Figure 2). Thus, alcohol becomes a temporary and illusionary way to escape from everyday problems. Such way of emotional and physical stress relief is more common among men (13 % for emotional stress relief and 6 % for physical stress in men compared to 7 % and 1 % in women, respectively, $p < 0.01$).

Speaking about the causes of alcoholism prevalence, the respondents point out a significant role of personal factors both more objective, such as stress or life dissatisfaction, and judgmental, such as "self-indulgence", "social parasitism", and "desire to have fun", which may be an indicator of a certain stigmatization of alcohol drinkers (67 %) as "immoral".

Almost equal attention is paid to biomedical (hereditary factor or a disease – 24 %) and social factors (low quality of life, the current socio-political situation, no hobbies, unemployment, poor public awareness campaign – 19 %). Among social factors, respondents specifically mentioned bad company (8 %) or cultural influences related to traditions or holidays (4 %).

[4] We used such parameters as: 40 % ABV for liquor and vodka beverages, 40 % – cognac, brandy, whiskey, rum and tequila, 40 % – moonshine, 5 % – industrial beer, 3 % – homemade beer and brew, 12 % – dry and sparkling wine, 18 % – fortified wine, 10 % – alcoholic cocktails, 40 % – others (various beverages from bitters to absinthe).

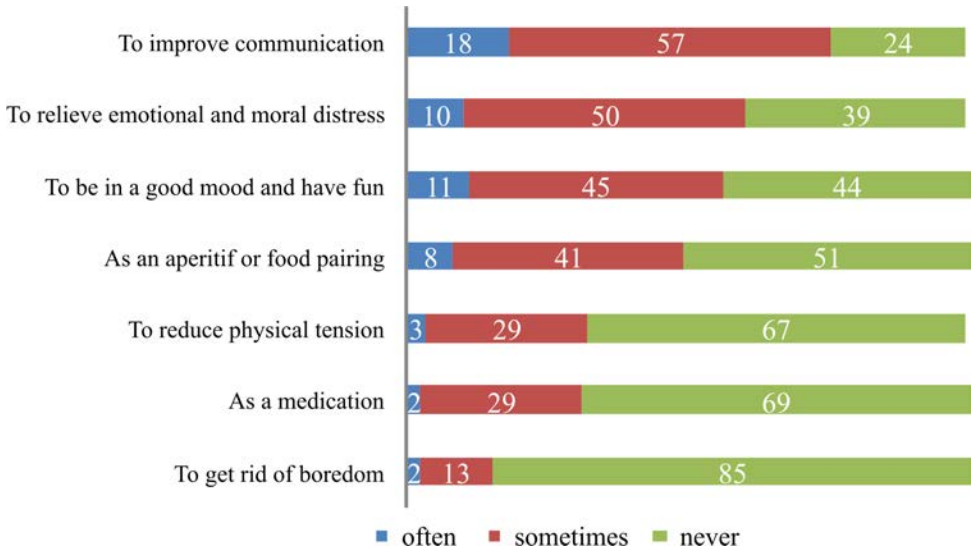

Figure 2. Distribution of answers to the question: "Now I will give you several situations when some people drink alcohol. Do you drink alcohol in these situations? If so, does it happen often or rarely?" (in % of those who consumed alcohol over the past 12 months or previously gave no answer, $N = 781$). The answer "Undecided" is not presented

Table 1

Structure of alcohol consumption by Muscovites

Alcohol type	Share of drinkers over the past 30 days, %	Average volume per day (ml/g)	Average number of days when alcohol consumption took place per month	Average volume of alcohol beverage consumed over the past month (ml/g)
Wine, sparkling wine (industrial)	45	286	3	858
Beer (industrial)	38	812	4.7	3816
Cognac, whiskey, liquor	25	163	2.5	408
Vodka	22	197	4.4	867
All kinds of homemade wine	11	230	2.6	598
Alcoholic cocktails	9	387	2.9	1122
Fortified wine (industrial)	6	248	1.5	372
Moonshine	6	229	2	458
Non-alcoholic beer	5	524	1.9	996
Other (40–70 % beverages)	3	145	3.3	479
Homemade beer	1	1469	3.3	4848
Brew	0	225	2.5	563

Note: A number of questions with additions / changes from the Monitoring of the health and economic welfare of households and individuals in the Russian Federation RLMS-HSE were used.

Table 1 shows the structure of alcohol consumption. In terms of consumption prevalence, wine and industrial beer are in the first and second places and were consumed by 45 and 38 % of drinkers over the past month. Strong alcohol beverages (vodka, cognac, whiskey, liquor and other strong drinks) are in the third place, in the past month they were consumed by about a quarter of drinkers among our respondents.

Certain circumstances can also influence the choice of alcoholic beverage. For example, those who tend to use alcohol to relieve emotional stress are more likely to choose beer or strong alcohol (vodka – 23 %, cognac, liquor – 19 %), rather than wine (9 %). Moreover, the choice of drinks is gender-dependent. Also moonshine is more commonly preferred as food pairing (25 %), rather than beer or wine (10 % and 9 %, respectively).

To determine the types of alcohol consumption and identify socio-demographic risk groups, a cluster analysis was carried out. It allowed us to identify the following clusters:

1. "Bar type" cluster (24 % of alcohol consumers over the past month), which includes beer, alcoholic cocktails, non-alcoholic beer. It is mainly presented by young people under 35 (42 %), a bit less often by people aged 35–49 (33 %). They characterize their health mainly as positive (55 % as "good" and "very good", another 40 % as "fine");

2. "Homemade alcohol of various strengths" (21 % of alcohol consumers over the past month). This cluster represents both homemade beer and moonshine consumers. 44 % of all respondents with school education belong to this group, while the share of people with higher education is significantly less – 19 % ($p < 0.05$);

3. "Strong alcohol and homemade wine" (20 % of alcohol consumers over the past month). Compared to other consumers, this cluster is characterized by more frequent alcohol intake. It includes cognac, whiskey, liquor, tequila, absinthe, rum, as well as homemade wine. It is a socially diverse group without prevalence of any particular socio-demographic group ($p > 0.05$);

4. "Wine" (18 % of alcohol consumers over the past month), including fortified wines. This group is mainly presented by women (in this group 72 % of women and 28 % of men);

5. "Only vodka" (17 % of alcohol consumers over the past month). This group is mainly presented by men (75 %) and people over 50 (65 %).

All these clusters represent certain risk groups.

In our sample, 16 % of respondents have consumed homemade alcohol over the past month, which means that they represent a potential risk group for poisoning. Among Muscovites, intake of homemade wine (11 % have consumed it over the past month), beer and moonshine (6 % each) is quite common. Speaking of the main reasons for alcohol consumption, many respondents mentioned "company", its "natural" ingredients and "quality" (Figure 3).

In general, the most popular places for alcohol consumption are homes (79 %), parties (64 %), cafes and restaurants (47 %) and bars (18 %) (more than one answer could be given, the resulting percentage of answers can exceed 100 %).

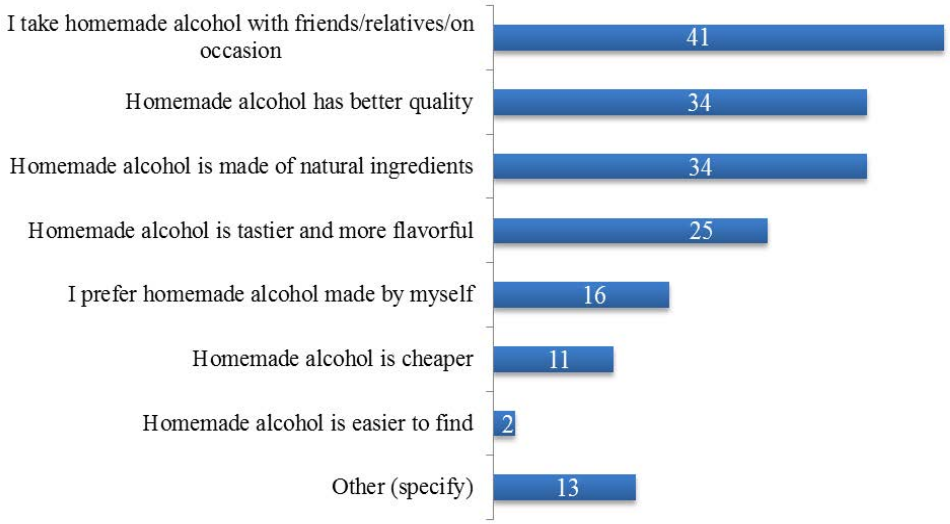

Figure 3. Distribution of answers to the question "You have mentioned earlier that you take homemade nonindustrial alcohol. What is the reason? Why do you prefer homemade alcohol?" (in % of those who consumed nonindustrial alcohol (homemade beer, wine, moonshine) over the past month $N = 124$. Multiple-choice questions, the resulting percentage of answers can exceed 100 %)

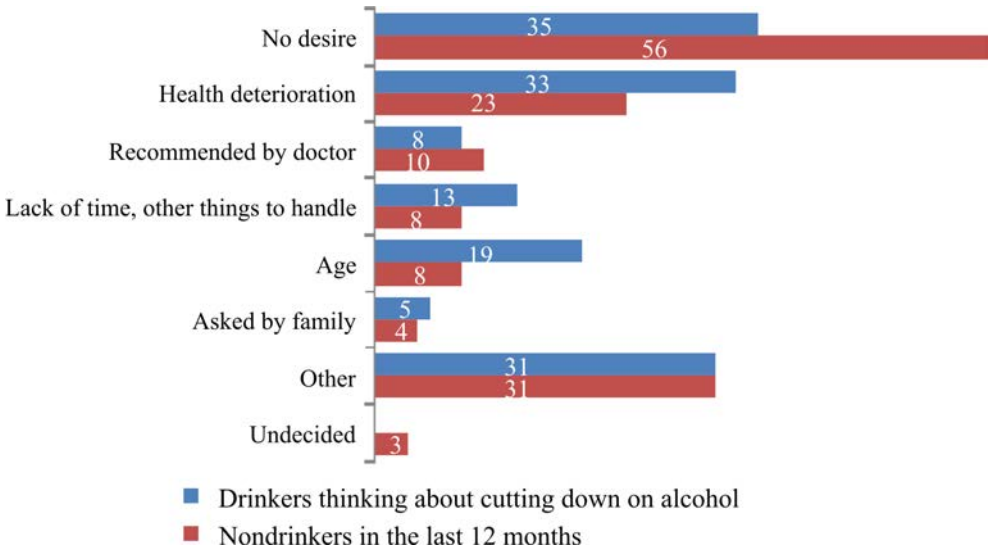

Figure 4. Distribution of answers to the question "Why do you think about cutting down on alcohol or stop drinking?" (N = 505. Multiple-choice questions, the resulting percentage of answers can exceed 100 %)

Young people under 35 prefer to drink alcohol in bars (39 % compared to 21 % aged 35–49 (the second highest value), $p < 0.001$). Women tend to meet at home or visit cafes and restaurants (68 % vs. 58 % for men, $p < 0.01$). As for home feasts, there is no typical group. It is the most common place of alcohol consumption for all population groups ($p > 0.05$).

Excessive drinking often leads to withdrawal syndrome. 19 % of Moscow drinkers use alcohol to relieve hangover symptoms. This indicator is observed significantly more often than in average sampling among men who consume excessive alcohol (48 %, $p < 0.05$). Alcohol intake as a way to manage hangover symptoms is unsafe as it creates a risk of further intoxication and episodes of heavy drinking.

Those Muscovites who do not plan to reduce alcohol consumption are more likely to face withdrawal syndrome. The majority of the respondents (61 %) have never thought about stopping drinking alcohol, therefore, they do not think that it might be a problem. 38 % of drinkers had thoughts about stopping drinking or reducing the amount of alcoholic beverages. A third of them explained it by health deterioration, and another third as the lack of desire to take alcohol.

The reasons that motivate people to give up alcohol are shown in Figure 4. As we can see, health deterioration and age are predominant in the group of respondents thinking to stop alcohol intake compared to the group who stopped alcohol consumption over the past 12 months.

Among "Other" reasons, the most common are "I'm tired of drinking", "I drink too much", "My attitude have changed", i.e. the desire to stop drinking is related to personal transformation and does not reflect external factors. There is also a religious factor. Also, it is interesting that some respondents who have had an experience of communication with alcohol addicts don't want to resemble them. At the same time, respondents note that an increase in prices or changes in alcohol quality are not significant reasons for refusing it, which may indicate either certain limitation of strict economic and legal measures to reduce alcohol consumption or low public awareness of their effectiveness.

According to public opinion, the problem of excessive alcohol consumption in Moscow is not very relevant: the average assessment of its severity is 3.71 points out of 10. The attitude of Muscovites towards policy for reducing alcohol consumption can be described as "consistently positive". 37 % said that the situation remained the same, 32 % think that it improved, 17 % observed some degradation, and 14 % could not answer the question.

The respondents positively (46 %) perceive the measures taken, usually because they

can observe real results such as restrictions on alcohol consumption, a decrease in number of alcohol consumers, relevant anti-alcohol advertising, etc. 28 % of Muscovites were negative towards the current alcohol consumption rates, 26 % found it difficult to answer.

The survey showed that, despite the experience of other countries, the increased price on alcoholic drinks did not seem to be a significant factor to stop drinking. Its effectiveness is estimated at 2.5 points out of 5. It does not mean that such measures are totally ineffective, but it should be taken into account when initiating anti-alcohol campaigns. Population thinks that anti–alcohol education (3.7 points) and certain legal restrictions (better control over drinking establishments – 3.7; ban on trade spots selling alcohol near schools, hospitals, parking lots – 3.5; prohibition on sale of alcohol drinks to intoxicated person – 3.4, increased minimum legal age for the sale of alcohol – 3.1) to be the most effective measures.

We would like to emphasize the following contradiction: Muscovites consider the alcoholization of population as a broad-scale phenomenon and at the same time believe that it is outside of their scope of interest. Such self-distancing reveals misjudgment of possible health risks. It could be explained by the current social stereotype about alcohol drinkers. They are presented as excluded from the society, declassed persons or people with low intelligence ("fools", "boozers"): this image shows the negative stigmatization among population. But, in fact, such stereotypical thinking is harmful, because it can be interpreted as "Since I am not a part of mentioned population group, there are no negative consequences of alcohol drinking for me". In general, the public mind has the concept of comprehensive nature of alcoholism. However, there are a lot of myths and an irrational attitude towards alcohol drinking as a social and health issue among many Muscovites.

Meanwhile, alcohol abuse is stigmatized and associated with abnormal behavior (criminality) and negative consequences. A large part of population positively views alcohol abstinence. Young people under 35 more often than older people (over 50) say that they don't know any situation when alcohol helps to communicate more confidently, and admit the inability to define a safe dose of drink. The fact that youth is better informed about the harm of alcohol and avoids the circumstances for its drinking is definitely a good trend that we need to support.

According to the cluster analysis, Moscow has developed a post-Soviet model of alcohol drinking described by the decrease in heavy drinking and the increase of beer drinking, which is consistent with the early received data [2, 13]. The structure of drinking in Moscow corresponds to the national one, which means that the types of heavy drinkers' behavior are common. It is worth to use the knowledge about these types for elaborating public health policies in the city.

The identified causes of alcohol drinking point out the contribution of social and psychological factors to alcoholism. Therefore, it is crucial to conduct psychological work with the population, to broaden and extend the psychological support programs as well as to present a clear logic of social and political movement which will lessen public anxiety.

The average age of starting to drink alcohol in the sample is 16. On the one hand, this proves that the law which stipulates not to sell alcohol to persons under 18 can be violated. On the other hand, the first drink often happens at home with own family, under the parents' control. However, the side effect in this case is the involvement of children into alcohol drinking by the example of parents. Unfortunately, the scope of the study doesn't allow us to estimate the potential harm or benefit of this decision for people's lives.

About one sixth of Muscovites (16 %) admits to drinking homemade alcohol. Although this percentage should be considered as lowered in comparison with a real number due to the topic's sensitivity, we regard this estimate of prevalence as primary due to the lack of other data.

The main reasons of drinking homemade alcohol are "for company", "organic nature" and "quality". However, this raises the question

if Muscovites are capable to adequately assess the quality of alcohol and its ingredients. In that context, people will more deeply understand potential risks and give reason for not "taste testing" if we share the information about the possible health risks of someone else's homemade alcohol, explain the impossibility to control the alcohol quality "to the taste" emphasize the prevalence of poisoning cases, etc.

Men constitute the risk group of alcohol abuse and poisoning: the volume of consumed homemade alcohol is 1.6 times higher (2394 g/month) among heavy drinkers of strong alcohol. It could be explained by the cheapness and accessibility of homemade drinks.

"Drinking in company" (41 %) is one of the most common reasons for choosing alcohol, which potentially creates a danger of consuming homemade alcohol. In this case, it is quite difficult to keep oneself within limits and it is very easy to overdrink and to get the alcohol withdrawal syndrome.

The following result is worrying too: one third of those who are thinking about reducing the alcohol consumption explains this decision by deteriorating health, and another third by not wanting to drink alcohol at all. Regarding alcohol abuse prevention, the fact that a large part of drinking citizens think about not consuming alcohol only after a decline of their health is absolutely a bad trend. Drinking alcohol could significantly harm health without external evidence for a very long time. The survey shows that there is no difference between the self-estimate of health status by abusive drinkers and by population overall: 11 % of Muscovites describe their health as "bad" or "very bad", the same is relevant for 7 % of abusive male drinkers and 6 % of abusive female drinkers ($p < 0.05$).

The negative effects of alcohol consumption are associated with the impact of the closest social environment (friends, older relatives, parents and colleagues). In this context, alcohol-related diseases and poisonings are the socially induced events linked with the low level of health literacy among some social groups.

Drinking of illicit strong alcohol is also influenced by certain social group. A study on shadow alcohol market emphasizes that the illicit alcohol is bought almost only by the members of a specific social environment where drinking of illicit alcohol is common and the information about points of sale is generally accessible [9]. A significant portion of the alcohol sold in stores is counterfeit, thus there is a very high risk of consuming alcohol that has not been registered [14]. Therefore, it is important to enforce control and audit operations toward alcohol manufacturers in order to decrease the amount of illicit alcohol consumed.

Theoretically, we assume that the anti-alcohol policy should not be oriented at the total consumption model of S. Ledermann and K. Bruun [15, 16] which says that any alcohol consumer is potentially an alcohol dependent person, so it is critical to reduce even light drinking of alcohol among the whole population. Instead, we would rather use the concept of social and cultural dependence of alcohol consumption formulated by O.-J. Skog [17]. It says that binge drinking of alcohol, including illicit drinks, is done collectively, spreads one by one and concerns specific social groups in the first place.

Moscow is generally characterized by the low level of alcohol abuse and the low rate of mortality from external causes and cardiovascular diseases while mentioned indicators are usually higher in the regions with frequent purchase of strong alcohol [18].

As a result, we would like to suggest some measures which could be useful in Moscow and regions under the Concept for lowering alcohol use in the Russian Federation up to 2030.

In terms of restrictions, the availability of strong alcohol could be temporarily limited during official Russian holidays in order to prevent the harm from binge drinking: at the end of December (before New Year), in the first part of January (after New Year), in the middle of February (on the Saint-Valentine Day and Defender of the Fatherland Day), in the first part of May (on the Workers' Day and Victory Day), in the beginning of November (on National Unity Day). This measure could include 1) prohibiting to place alcohol near the cashiers' area; 2) restricting the working hours of shops selling

strong alcohol; 3) closing the displays with strong alcohol products till shop's closing time; 4) prohibiting to sell alcohol to intoxicated persons [19, 20]. At the same time, some studies show that the temporary restrictions on selling alcohol for individual consumption reduce the purchase of legal and unregistered alcohol ("I have no possibility to buy alcohol, so I won't drink it") [21]. It is also crucial to fight with counterfeit alcohol sold as legal products, which could additionally decrease the consumption of homemade alcohol.

Unfortunately, the results of our survey show that alcohol drinking is still supported by some cultural attitudes. There are the patterns of alcohol consumption for "Russians", "normal people", "men", etc. [3]. That's the reason why the bureaucratic socio-economic and legal arrangements for fighting with binge drinking should be accompanied by creating a universal healthy lifestyle. It could eliminate the successive involvement in heavy drinking, for example, through the promotion of practices for family recreation and raising healthy children. Socio-economic and legal arrangements give primary, but limited outcomes; for example, the problem of higher prices of alcohol could be solved by the high level of income and the problem of legal restrictions by corruption. Therefore, the potential reduction of alcohol consumption is connected with elaborating the culture of drinking alcohol.

It is promising to introduce classes like Life Skills Training for avoiding the pressure of collectivity in the primary and secondary schools and the programs of drug use literacy in the high school and universities as well as to implement projects on healthy lifestyle, like Healthy Moscow pavilions, in collaboration with nonprofit organizations. In addition, we should agree that these educational activities should not be nominal, because academic lessons could raise the interest of young people in drugs and alcohol instead of eliminating it.

Limitations. Since this study is a large-scale standardized quantitative research conducted with the means of telephone survey, its nature limits the reliability of conclusions on the sensitive topics like consumption of illicit alcohol, and doesn't fully cover certain social groups: alcohol dependent people, persons with alcohol-induced psychotic disorders and poisonings.

Conclusion. The study enables to define the following features of alcohol consumption in the Moscow metropolis.

General characteristics of alcohol consumption:

– the study demonstrates a relatively low level of alcohol involvement among population, although the greater part of people has had the experience of drinking alcohol for the last year;

– the structure of alcohol consumption in Moscow is quite similar to the structure in most Russian regions. There is difference in the amount of drunk alcohol, and not in the set of drinks or the social and demographic characteristics of consumers;

– Muscovites give a high enough evaluation to the current anti-alcohol measures in the city and define the situation of alcohol involvement as rather positive.

Important risk groups:

– Muscovites who have an experience of heavy drinking constitute a risk group for having alcohol-related diseases and / or poisonings. The current rate of heavy drinkers is 14 % among male drinkers and 7 % among female drinkers;

– About 16 % of Muscovites consume unregistered alcohol, including those who made it at home. Also, they are a part of risk group for alcohol poisoning;

– 19 % of drinkers have an elevated risk for having an episode of heavy drinking due to the use of alcohol for eliminating the alcohol withdrawal syndrome;

– Elderly Muscovites are more exposed to the risk of alcoholization, for example, in the study, we have identified a cluster of men aged 50+ consuming only vodka. At the same time, people under 35 elaborate a negative attitude towards alcohol.

Important factors of alcohol involvement:

– a general neutrality towards alcohol as a social issue and self-distancing from the problem;

– stress conditions of environment, sensitivity to experiencing certain social and personal events;

– lack of necessary criticism. The prevention of alcohol abuse is complicated by the fact that a great part of drinking citizens thinks about stopping to consume alcohol only after they subjectively perceive that their health has deteriorated;

– the main reasons of alcohol consumption are generally social, i.e. communication in a group. Firstly, we should emphasize the impact of the closest social environment – relatives, friends and colleagues. Some people are not capable to withstand peer pressure. Therefore, they are involved in alcohol consumption or perceive a collective consumption of alcohol as the norm. Besides that, parents often involve their children in drinking alcohol even before the majority age, so they create a model of alcohol consumer behavior.

As a result, when developing an anti-alcohol policy, a priority should be put on the social aspects of alcoholization and the measures for preventing the involvement in collective consumption of alcohol.

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Research article

EFFECTIVENESS OF COMPLEX PLANS FOR AIR PROTECTION ACTIVITIES AT HEAT AND POWER ENTERPRISES AS PER RISK MITIGATION AND HEALTH HARM INDICATORS

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The whole complex of air protection activities has been planned in the RF with its aim to reduce levels of ambient air pollution. It is being implemented actively now and as a result the quality of the environment should improve for more than 7 million people.

In this study, an algorithm has been suggested for assessing effectiveness of air protection activities. It includes six subsequent stages. The algorithm was tested at heat and power enterprises located in a region participating in the Clean Air Federal project. As a result, it was established that these enterprises were sources of potential public health risks; 70 % of them belonged to high risk categories. Until air protection activities are implemented, heat and power enterprises pollute ambient air in some areas in the city (up to 29.9 single maximum MPC; up to 6.9 average daily MPC; up to 19.0 average annual MPC), create unacceptable health risks (up to 25.8 HI for acute exposure, 22.7 HI for chronic exposure, CR_T is up to $3.28 \cdot 10^{-4}$), and cause more than 87 thousand additional disease cases. Implementation of air protection activities at heat and power enterprises will reduce local levels of ambient air pollution but we still expect hygienic standards to be violated for 10 chemicals up to 3–22 MPC and high health risks are likely to persist (up to 6.5–25.5 HI for acute exposure, 11.9–22.4 HI for chronic exposure, CR_T will be up to $3.28 \cdot 10^{-4}$). Effectiveness of the air protection activities planned at heat and power enterprises corresponds to the target levels of the gross pollutant emissions (reduction by 20.56 % by 2024) set within the Clean Air Federal project but it is estimated as 'unacceptable' as per the health harm indicator, which is additional disease cases associated with activities of these enterprises (< 20 %). It is necessary to implement additional air protection activities with respect to 12 pollutants (nitrogen dioxide, particulate matter, carbon (soot), carbon oxide, sulfur dioxide, dihydrosulfide, inorganic dust containing silicon dioxide in %: 70–20, dimethyl benzene, ethyl benzene, benzene, formaldehyde, and kerosene); to use the best available technologies with respect to the most hazardous chemicals; to monitor public health in areas with elevated health risks; to implement complex medical and preventive activities.

Keywords: *heat and power enterprises, emissions, ambient air quality, public health risk, fine-dispersed particles, non-carcinogenic hazard, health disorders.*

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At present, thermal power generation is a leading branch of the world power engineering. Thermal power generation accounts for 90 % of all the produced electricity worldwide. In Russia, a substantial share of electric energy (almost 40 %) is also produced by thermal power stations, which not only generate power but also participate in centralized heat supply[1] [1]. Thermal power stations are often located in close proximity to residential areas and this may have negative influence on ambient air quality and consequently on health of exposed population[2] [2].

In the Russian Federation, thermal power stations basically use coal, heavy oil or natural gas; oil, benzine, diesel oil, peat, shale or firewood is used rarer.

According to the State reports issued by the RF Ministry of Natural Resources and the Environment, fuel and energy enterprises emit approximately 3 million tons of pollutants every year. More than 50 % of these emissions are concentrated in the eastern part of the country (the Siberian and Far East Federal Districts)[3].

Apart from thermal power stations, a lot of private coal-fueled boiler houses and autonomous heat sources (AHS) function in Russia; in 2018 more than 74.8 thousand such objects were registered in the country. Private boiler houses tend to have rather low chimneys (6–8 meters high) and consequently they pollute the bottom layers of the atmosphere, that is, the layers from which people breathe air[4].

The greatest number of autonomous heat sources that use solid fuels is also located in the Siberian and Far East Federal Districts (the Krasnoyarsk region, Transbaikalia, Kemerovo region, Irkutsk region, Novosibirsk region, etc.). The basic advantage of boiler houses that use solid fuel is their high autonomy, which is a significant component in the technological process able to ensure uninterrupted heat and hot water supply to private houses and industrial facilities in harsh winter typical for Siberia and the Far East.

Combustion of solid fuel (coal) has substantial influence on ambient air quality due to high levels (about 90 %) of mineral noncombustible substances in coal. Thus, some studies have established that heat and power objects with predominant use of solid fuels emit both solid noncombustible particles (ash, soot, dust, particulate matter $PM_{2.5}$ and PM_{10} that contain various metal compounds) and various gases (carbon dioxide and monoxide, hydrocarbons, sulfur compounds, nitrogen oxides etc.) into ambient air [3–5]. When compounds of such metals as lead, mercury, chromium, zinc, copper, manganese, and some others penetrate the bottom layers of the atmosphere, they are able to have significant adverse influence on human health affecting the respiratory organs, central nervous system, liver, and kidneys; they can also produce mutagenic and carcinogenic effects. In addition, fine-dispersed particulate matter sized 2.5 μm or smaller is hazardous for human health [6].

According to the data provided by the World Health Organization (WHO), each eighth death in the world is caused by ambient air pollution. Fine-dispersed solid particles ($PM_{2.5}$) pose the greatest threat since they are able to penetrate deep into the human airways, enter the blood flow and affect the heart, cerebral vessels and the respiratory system. Black carbon (soot) is the most hazardous type of fine-dispersed particulate matter as per its chemical compositions. The international team of experts has established that if the level of such particles in ambient air grows by 0.1 μm/m^3, this leads to a 12 % growth in incidence of lung diseases. In 2013, the Inter-

[1] Bystritskii G.F., Gasangadzhiev G.G., Kozhichenkov V.S. Obshchaya energetika (Proizvodstvo teplovoi i elektricheskoi energii) [Total energy production (thermal and electric energy generation)]: manual, 2nd ed. Moscow, KNORUS, 2014, 408 p. (in Russian); Rynok elektroenergetiki Rossii i osnovnye igroki otrasli [The market for electric power engineering in Russia and the branch leaders]: Analytical report. *Analytic Research Group (ARG)*, 2018, 487 p. (in Russian).

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national Agency for Research on Cancer (IARC) classified solid particles sized less than 10 and 2.5 μm as carcinogens able to cause lung cancer. Their levels in ambient air are also one of the most important indicators applied for assessing exposure to ambient air pollution and its influence on human health. Poor ambient air quality can have negative effects on the brain and central nervous system and double a risk of anxiety and depression. In addition, the smallest toxicant particles penetrate the airways, injure artery walls and induce chronic inflammation [7–10].

Since 2018, the experiment on setting quotas for emissions has been conducted in Russia; its main aim is to reduce levels of ambient air pollution all over the country and it is planned to be completed by 2030. The procedure for setting emission quotas involves introducing certain quotas of emissions for enterprises participating in the experiment. These quotas are introduced for priority ambient air pollutants on the basis of aggregated calculations[5] and this will make it possible to improve ambient air quality in cities with high pollution levels.

In addition, the Clean Air Federal project has been implemented in the Russian Federation since 2018 in accordance with the RF President Order 'On State Tasks and Strategic Goals of the Russian Federation Development for the Period up to 2026'. Twelve cities participate in this project and half of them are located in Siberia. In 2023, 29 cities and urban districts with high and extremely high levels of ambient air pollution are going to be included into the experiment on setting quotas for pollutant emissions[6]. Eighty percent of these cities are located in the Siberian and Far East Federal Districts where heat and power objects are mostly fueled by coal.

The aforementioned state project, in particular the experiment on setting quotas for emission of harmful pollutants into ambient air, have one basic aim, which is to reduce the total pollutant emissions by 20 % by the end of 2024 against the levels identified in 2017; another aim is to reduce emissions of harmful pollutants from industrial facilities, including thermal power stations and AHS as well as communal and transport infrastructure, by two times by 2030 against the levels identified in 2020. Implementation of these projects is expected to improve quality of the environment for more than seven million people. According to the Complex plans of air protection activities aimed at reducing pollutant emissions into ambient air (approved within the Clean Air Federal project), a whole set of activities is to be implemented at heat and power objects that involves installing new technical and technological equipment at large thermal power stations, relocating people from dilapidated housing with stove heating, replacing ineffective coal-fueled boiler houses with heat and power provided by large thermal power stations.

All the aforementioned highlights the relevance of assessing influence exerted by heat and power objects on ambient air quality and public health.

The aim of this study was to assess sufficiency and effectiveness of air protection activities aimed at reducing emissions into ambient air by heat and power objects as per conformity with the existing hygienic standards, mitigation of health risks and health harm.

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[5] Ob utverzhdenii pravil kvotirovaniya vybrosov zagryaznyayushchikh veshchestv (za isklyucheniem radioaktivnykh veshchestv) v atmosfernyi vozdukh: Prikaz Minprirody Rossii ot 29.11.2019 № 814 [On Approval of the procedure for setting quotas of pollutant emissions (excluding radioactive substances) into ambient air: the Order by the RF Ministry of Natural Resources and Environment issued on November 29, 2019 No. 814]. *Ofitsial'nyi internet-portal pravovoi informatsii [The Official Internet-portal for legal information]*. Available at: http://publication.pravo.gov.ru/Document/View/0001201912260045 (January 15, 2023) (in Russian).

[6] Ob utverzhdenii perechnya gorodskikh poselenii i gorodskikh okrugov s vysokim i ochen' vysokim zagryazneniem atmosfernogo vozdukha, dopolnitel'no otnosyashchikhsya k territoriyam eksperimenta po kvotirovaniyu vybrosov zagryaznyayushchikh veshchestv (za isklyucheniem radioaktivnykh veshchestv) v atmosfernyi vozdukh na osnove svodnykh raschetov zagryazneniya atmosfernogo vozdukha: Rasporyazhenie Pravitel'stva RF ot 7 iyulya 2022 g. № 1852-r [On Approval of the list of urban settlements and urban districts with high and extremely high ambient air pollution that are to be added to the list of territories participating in the experiment of setting quotas for pollutant emissions (excluding radioactive substances) into ambient air on the bases of aggregated calculation of ambient air pollution: the RF Government Order issued on July 7, 2022 No. 1852-r] (the document has not come into force yet). *GARANT: information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/404867269/ (April 10, 2023) (in Russian).

Materials and methods. We used exposure levels, inhalation risks and incidence associated with ambient air quality influenced by operations of heat and power objects and AHS as our initial data for assessing sufficiency and effectiveness of investment programs and the Complex plans of air protection activities.

Effectiveness of activities included into the Complex plan was estimated considering a necessary decrease in effects produced on ambient air by operating heat and power objects and AHS by 2024 against 2018; conformity with the existing hygienic standards; declining inhalation risks together with calculation of residual risks and a decrease in additional incidence associated with ambient air quality.

We have developed a methodical algorithm for assessing how effective the Complex plans of air protection activities were with respect to mitigation of health risks and health harm caused by operating heat and power objects against the background influence exerted by other sources of ambient air pollution. The algorithm consists of six sequential stages:

– analysis of a potential health risk caused by heat and power objects and analysis of complex air protection plans at these objects;

– creation of aggregated databases on all the stationary and mobile sources of ambient air pollution, identification of their parameters with spotting out fuel and energy complex (FEC) objects and AHS prior to implementation of air protection activities and after it;

– identification of spatially differentiated levels of ambient air pollution in residential areas considering contributions made to them by FEC objects and AHS prior to implementation of air protection activities and after it; assessment of conformity to the existing hygienic standards and identification of priority pollutants;

– health risk assessment, identification of risk rates prior to implementation of air protection activities at FEC objects and AHS and after it;

– calculation of associated disease cases caused by exposure to pollution created by FEC objects and AHS prior to implementation of air protection activities and after it;

– assessment of effectiveness of implemented / planned activities at FEC objects and AHS as per conformity to the existing hygienic standards, health risk and health harm indicators represented by additional incidence associated with ambient air pollution.

Residual pollutant levels, health risks (carcinogenic, acute and chronic) and associated incidence were calculated considering implementation of air protection activities. Effectiveness of these activities was identified as per the formula (23) in the Methodical Guidelines MUK 2.1.10.3675-20[7].

Approaches to assessing effectiveness of air protection activities at heat and power objects were tested on the example of the Complex plan designed for Krasnoyarsk (approved by the Deputy Head of the RF Government on December 28, 2018 (No. 11024p-P6)), a city participating in the Clean Air Federal project, and with specific focus on heat and power objects, AHS included.

Potential health risks were assessed based on data taken from the Federal Register foe Juridical Persons and Private Entrepreneurs subject to sanitary-epidemiological surveillance as of January 2021.

The current and expected exposure in the analyzed residential areas was assessed using the 2020 database covering 6411 sources of pollutant emissions into ambient air from 807 industrial enterprises and organizations (5977 sources), 263 traffic network sections, and 171 sources that could be considered AHS (residential areas with private houses). Ground concentrations of 251 pollutants, including 55 chemicals emitted by FEC objects, were calculated at 13,889 points in the analyzed residential areas (the geometric centers of residential buildings) using the Ekolog-Gorod Unified Software for

[7] MU 2.1.10.3675-20. Otsenka dostatochnosti i effektivnosti planiruemykh meropriyatii po snizheniyu vybrosov zagryaznyayushchikh veshchestv v atmosfernyi vozdukh dlya mitigatsii riskov i vreda zdorov'yu naseleniya: metodicheskie ukazaniya; utv. Glavnym gosudarstvennym sanitarnym vrachom RF 18.12.2020 [MU 2.1.10.3675-20. Assessment of sufficiency and effectiveness of planned activities aimed at reducing pollutant emissions in ambient air to mitigate health risks and health harm: methodical guidelines; approved by the RF Chief Sanitary Inspector on December 18, 2020], item 3.10.7. *KonsultantPlus*. Available at: http://www.consultant.ru/law/hotdocs/68710.html (May 12, 2023) (in Russian).

Calculating Ambient Air Pollution, version 4.60.1. The software relies on the module MR-2017 Methods for Calculating Dispersion of Emissions of Harmful (Polluting) Substances in Ambient Air (approved by the Order of the RF Ministry of Natural Resources and Environment issued on June 06, 2017 No. 273). Based on these calculations, single maximum and average annual levels of pollutants were identified for each calculation point prior to the implementation of planned air protection activities at heat and power objects and after it. Calculated data were verified with instrumental data collected for 34 substances (including 23 chemicals typically emitted by FEC objects) at posts for monitoring of ambient air quality belonging to Rosgidromet, the territorial monitoring network, and the Center for Hygiene and Epidemiology in the Krasnoyarsk region. The instrumental data were collected within social and hygienic monitoring in 2018–2020 in accordance with methodical approaches stipulated in the Methodical guidelines MR 2.1.6.0157-19[8]. We calculated exposure levels created by all sources of ambient air pollution in the city and specifically by FEC objects and AHS and specified contributions made by the latter to the total ambient air pollution.

Public health risks caused by exposure to chemical pollution in ambient air occurring solely due to FEC objects and AHS (55 chemicals) were assessed in accordance with the Guide R 2.1.10.1920-04[9] by sequential completion of all the necessary stages. Ten carcinogenic chemicals were identified in emissions from FEC objects and AHS; in addition, 22 chemicals identified in these emissions were able to produce acute effects and 46 were able to produce chronic non-carcinogenic effects on health.

The next task was to create models of cause-effects relations within the ‘ambient air quality – incidence (as per the data provided by the Fund for Mandatory Medical Insurance)” system with the following calculation of additional associated diseases as an indicator of exposure to airborne chemicals. To do that, we took verified average annual levels of chemicals under chronic exposure established for each calculation point in residential areas on the analyzed territory. Additional diseases associated with ambient air quality were calculated according to the methodical approaches stipulated in the MR 5.1.0095-14[10].

Cause-effect relations within the ‘ambient air quality – incidence’ were established and parameterized using the following multiple regression model:

$$y_j = b_0 + \sum_i b_{1ij} \left\langle x_i - qkp_i \right\rangle,$$

where

y_j is incidence of the j-th disease category among exposed population, cases/1000 people;

x_i is the level of the i-th pollutant, mg/m^3;

qkp_i is the derived no-effect level of the i-th indicator describing ambient air pollution, mg/m^3;

$\left\langle x \right\rangle$ are the Macaulay brackets: $\left\langle x \right\rangle = 0$ at $x < 0$ and $\left\langle x \right\rangle = x$ at $x \geq 0$;

b_0, b_{1ij} are the model parameters.

[8] MR 2.1.6.0157-19. Formirovanie programm nablyudeniya za kachestvom atmosfernogo vozdukha i kolichestvennaya otsenka ekspozitsii naseleniya dlya zadach sotsial'no-gigienicheskogo monitoringa: Metodicheskie rekomendatsii; utv. Glavnym gosudarstvennym sanitarnym vrachom RF 02.12.2019 [MR 2.1.6.0157-19. Creation of programs for monitoring of ambient air quality and quantification of population exposure for solving tasks within social-hygienic monitoring: Methodical guidelines; approved by the RF Chief Sanitary Inspector on December 02, 2019]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/565246542 (April 03, 2023) (in Russian).

[9] Guide R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals; approved and enacted by G.G. Onishchenko, the First Deputy to the RF Minister of Health and the RF Chief Sanitary Inspector on March 5, 2004. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/1200037399 (April 06, 2023) (in Russian).

[10] MR 5.1.0095-14. Raschet fakticheskikh i predotvrashchennykh v rezul'tate kontrol'no-nadzornoi deyatel'nosti ekonomicheskikh poter' ot smertnosti, zabolevaemosti i invalidizatsii naseleniya, assotsiirovannykh s negativnym vozdeistviem faktorov sredy obitaniya: metodicheskie rekomendatsii; utv. rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom RF A.Yu. Popovoi 23 oktyabrya 2014 goda [MR 5.1.0095-14. Calculation of actual economic losses and those prevented due to control and surveillance activities in case such losses are caused by mortality, incidence and disability among population associated with exposure to harmful environmental factors: methodical guidelines; approved by A.Yu. Popova, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing and the RF Chief Sanitary Inspector on October 23, 2014]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200129398 (April 06, 2023) (in Russian).

The derived no-effect level qkp_i was taken as equal to reference concentrations; in case such concentrations were not defined for a certain pollutant, we took average annual maximum permissible levels.

To define the list of chemicals emitted by heat and power objects more precisely, we compared ash created by operations of thermal power stations and ambient air in an area under the strongest influence of a heat and power object. The granulometric structure of ash particles and solid particles in ambient air collected on a filter was established with scanning electron microscopy (the JSM-63090LV scanning electron microscope). The chemical structure of the analyzed particles was investigated by micro-sound x-ray spectral analysis with a SEM analyzer. Image analysis involved quantitative assessment of particle size and shapes using the sphericity coefficient; it was performed with the ImageJ-Fiji software (Analyze Particles Module).

Results and discussion. The fuel and energy complex that operates on the analyzed territory consists of basic heat sources (three thermal power stations) and industrial enterprises with objects being supplied with heat. In addition, a lot of private houses using autonomous heat sources (AHS) are located in the city. According to the updated aggregated database on sources of ambient air pollution (2020), 302 enterprises out of total 807 located in the city belong to the fuel and energy complex or have some heat supply sources on their territory. The total number of emission sources that belong to heat and power objects on the analyzed territory equals 1.2 thousand; in addition, 171 emission sources are classified as AHS.

The overall town planning created a situation when heat and power objects (thermal power stations, boiler houses in city districts, and AHS) are scattered all over the city in close proximity to residential areas (Figure 1). Greatest threats for public health are posed by low emission sources of both heat supply objects and private houses (AHS); such emission sources create local elevated levels of ambient air pollution within a block or a micro-district.

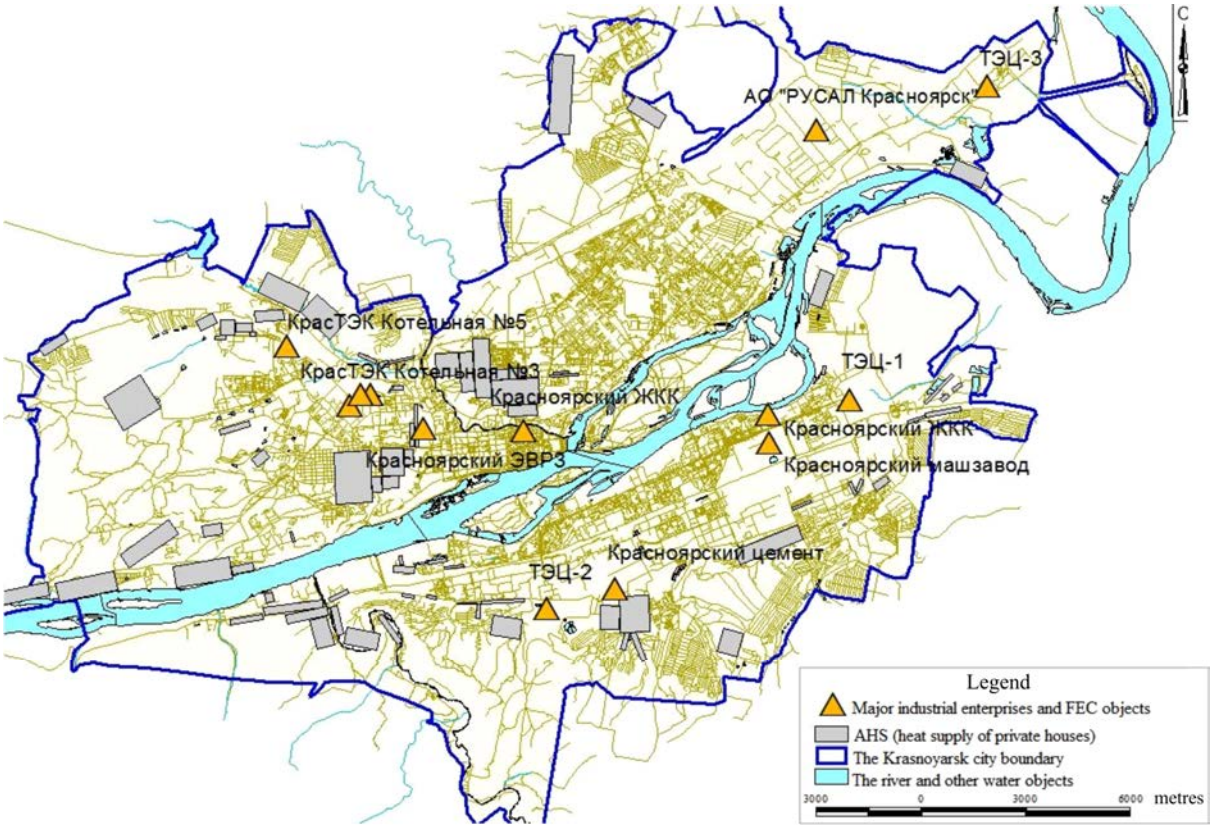

Figure 1. Spatial distribution of major heat and power objects and industrial enterprises with heat and power objects on the analyzed territory

According to the Register of Economic Entities that are subject to sanitary-epidemiologic surveillance, as of January 01, 2021, 70 % (17 units) of the economic entities dealing with 'Provision with Electric Energy, Gas and Steam; Air Conditioning' on the analyzed territory belong to extremely high or high risk category as per potential health harm (the scale of exposure is 0.226–0.518 and 0.00108–0.0065 million people accordingly, the potential health risk (R^l) exceeds $1.98 \cdot 10^{-3}$ and $7.1 \cdot 10^{-4}$–$1.2 \cdot 10^{-4}$ accordingly). The highest potential health risks among all heat and power objects are created by JSC Eniseiskaya TGK (heat generating company) and JSC Krasnoyarskkraygas, both located on the analyzed territory.

The potential health risk (R^l) created by economic entities (heat and power objects) that belong to the extremely high and high risk category is substantially higher in Krasnoyarsk city than in the Krasnoyarsk region as a whole (R^l: $1.11 \cdot 10^{-3}$–0.17 and $1.0 \cdot 10^{-4}$–$9.8 \cdot 10^{-4}$ accordingly), 7.1–50.9 times; it is also higher than potential health risks created by heat and power objects on average in the RF (R^l: $1.0 \cdot 10^{-3}$–0.101 and $1.0 \cdot 10^{-3}$–$1.0 \cdot 10^{-4}$), up to 56.0 times.

Heat and power objects emit more than 50 chemicals into ambient air in the city. Four of them belong to the first hazard category (vanadium pentoxide, lead, chromium, and benz(a)pyrene); 13 chemicals belong to the second hazard category. Only 23 chemicals of the aforementioned 50 are covered by instrumental monitoring of ambient air quality.

Contributions made by heat and power objects into ambient air pollution vary between 1 and 50 % in various areas in the city for chronic exposure and between 12 and 91 % for acute exposure.

Emissions that occur due to technological processes only at heat and power objects create substantial levels of ambient air pollution in residential areas in the analyzed city. Thus, prior to the implementation of Complex activities within the Clean Air Federal project, the existing hygienic standards are violated for acute and / or chronic exposure as per nitrogen oxide, black carbon, sulfur dioxide, dihydrosulfide, inorganic dust with silicon dioxide, in %: 70–20, dimethyl benzene, ethyl benzene, carbon oxide, benzene, formaldehyde, particulate matter and others (up to 1.5–29.9 single MPL; up to 1.4–6.9 average daily MPL; up to 1.4–19.0 average annual MPL). Levels of some chemicals were more than 5-10 times higher than their MPL (Figure 2).

Economic activities of heat supply sources create high acute non-carcinogenic health risks due to carbon oxide (up to 6.5 HQ_{ac}), formaldehyde (up to 19.05 HQ_{ac}), and particulate matter (up to 24.7 HQ_{ac}) in some areas in the city with the population more than 25 thousand people. Acute risks of respiratory diseases, diseases of the eye, disrupted development, cardiovascular diseases as well as systemic effects were ranked as 'high' on the analyzed territory (HI > 6) since the hazard index reached 6.5–25.8 HI_{ac}; the risks were ranked as 'permissible' (HI between 1 and 3) for the reproductive and immune system.

Chronic inhalation exposure creates unacceptable non-carcinogenic chronic health risks related to four chemicals: nitrogen dioxide (up to 2.1 HQ_{ch}), carbon oxide (up to 1.1 HQ_{ch}), formaldehyde (up to 19.04 HQ_{ch}), and particulate matter (up to 11.7 HQ_{ch}). Chronic health risks for respiratory diseases, diseases of the eye, and diseases of the immune system are ranked as 'high' (HI > 6) since the hazard index reaches 14.0–22.7 HI_{ch}, and this is more than 7.5 times higher than its permissible level; health risks for the hematopoietic system are ranked as 'alerting' (HI_{ch} reached 3.47, the hazard index for alerting health risks ranges between 3 and 6); health risks for the central nervous system, cardiovascular system and development processes are ranked as 'permissible' (HI_{ch} reached 1.35–1.67, the hazard index for permissible health risks ranges between 1 and 3) (Figure 3). More than 146 thousand people are exposed to elevated non-carcinogenic chronic health risks (HI > 3).

Heat and power objects, prior to the implementation of the planned air protection activities, create unacceptable carcinogenic health risks caused by exposure to formaldehyde (CR = $3.28 \cdot 10^{-4}$). The total carcinogenic health risk (TCR) ranges between $2.48 \cdot 10^{-6}$ and $3.31 \cdot 10^{-4}$ in the residential areas located on the analyzed territory.

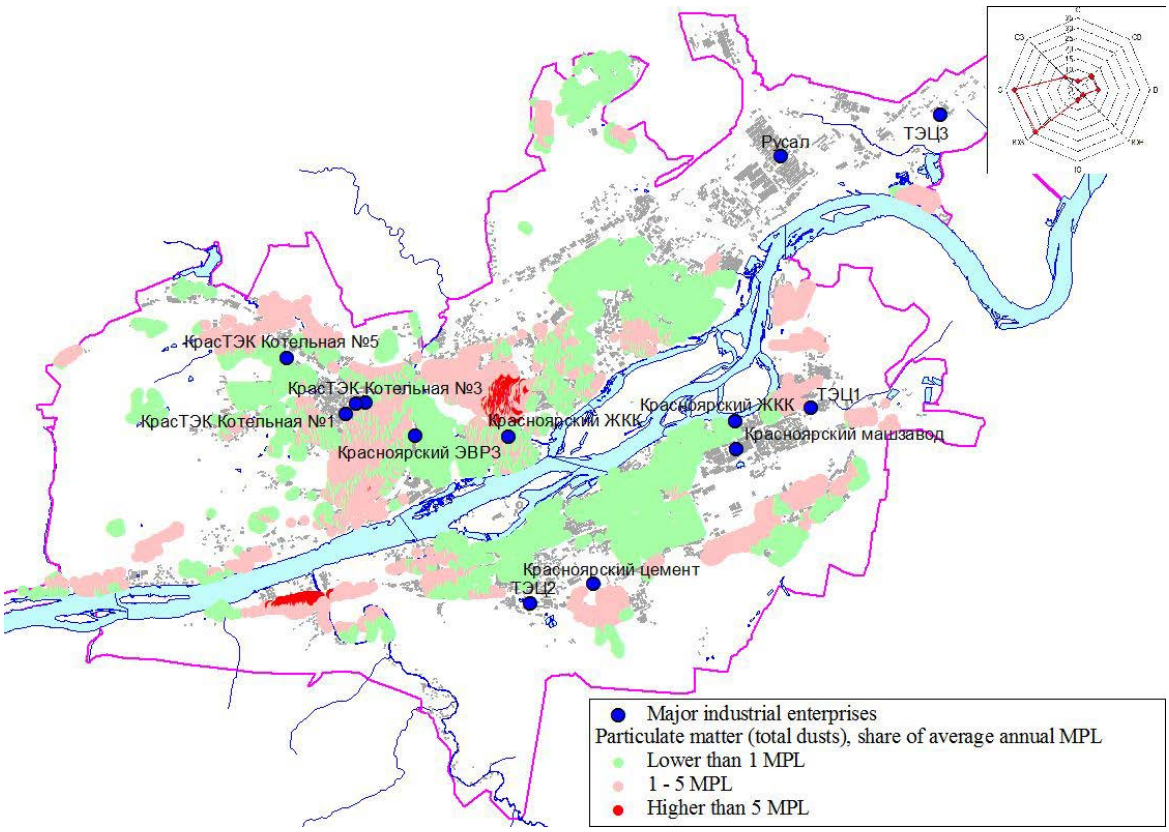

Figure 2. The analyzed territory divided into specific zones as per levels of ambient air pollution with particulate matter (total dusts) created by heat supply sources

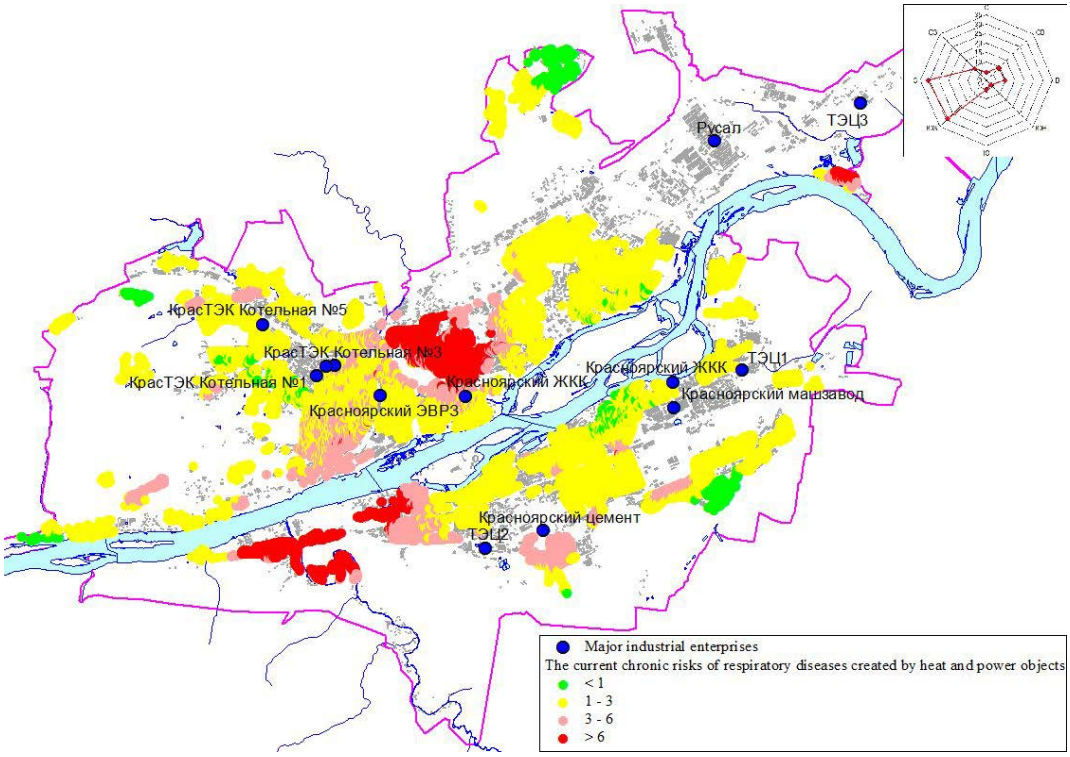

Figure 3. The analyzed territory divided into specific zones as per levels of chronic non-carcinogenic risks of respiratory diseases due to ambient air pollution created by heat supply sources

Table

Example parameters of the cause-effect relations within the 'ambient air quality (chemical levels), mg/m^3 – child incidence, ‰' system, ($p \leq 0.05$)

Disease	Parameter	The coefficient b_i value	F
Diseases of the eye and adnexa	Absolute term	2.61E+04	15.24
	Dimethyl benzene (xylene)	2.29E+05	
	Formaldehyde	1.11E+05	
Diseases of the musculoskeletal system and connective tissue	Absolute term	1.16E+04	24.23
	Gaseous fluorides	6.66E+05	
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Absolute term	1.06E+03	34.66
	Dihydrosulfide	2.04E+05	
Diseases of the genitourinary system	Absolute term	6.93E+03	29.49
	Lead and its inorganic compounds	1.56E+08	
	Dimethyl benzene (xylene)	4.82E+03	
	Tetrachloroethylene	8.95E+04	
Diseases of the nervous system	Absolute term	1.47E+04	39.91
	Lead and its inorganic compounds	1.52E+08	
	Methyl benzene (toluene)	1.07E+05	
	Tetrachloroethylene	4.51E+05	
Diseases of the respiratory system	Absolute term	2.31E+05	41.94
	Dialuminum trioxide	9.01E+07	
	Ozone	3.67E+06	
	Sulfur dioxide	3.27E+06	
	Dihydrosulfide	5.13E+06	
	Dimethyl benzene (xylene)	1.09E+06	
	Tetrachloroethylene	5.41E+05	
	Prop-2-enenitrile	5.39E+06	
	Diiron trioxide	9.50E+07	
Diseases of the digestive system	Absolute term	6.73E+04	38.34
	Dimethyl benzene (xylene)	6.95E+05	
	Trichloroethylene	4.10E+04	
	Hydroxybenzene (Phenol)	1.82E+07	
	Kerosene	8.01E+06	
Diseases of the circulatory system	Absolute term	5.93E+03	41.45
	Benzene	8.29E+03	
	Hydroxybenzene (Phenol)	2.84E+06	
Congenital malformations, deformations and chromosomal abnormalities	Absolute term	3.12E+03	19.17
	Tetrachloroethylene	8.09E+04	
	Lead and its inorganic compounds	8.26E+06	

Having modeled the cause-effect relations within the 'ambient air quality – incidence (according to the data provided by the Fund for Mandatory Medical Insurance)', we built 31 authentic models of such relations that parameterized adverse effects produced by 35 chemicals (Table).

Ambient air pollution in Krasnoyarsk due to heat and power objects prior to the implementation of the air protection activities (2020) causes more than 87.5 thousand additional diseases (94.7 cases per 1000 people). More than 44.8 % of these additional diseases occur among children (more than 39 thousand additional diseases or 223.8 cases per 1000 children). Diseases of the respiratory system account for the major part in this additional incidence, namely, for 80.03 % (more than 69 thousand diseases or 7.2 % of the actual incidence of respiratory diseases). They are followed by diseases of the digestive system, 17.9 %; diseases of the eye and adnexa, 1.1 %. Additional child incidence has a similar structure: 80.8 %, 17.9 %, and 1.2 % accordingly.

Heat and power objects and AHS are sources of several harmful environmental factors

creating the highest health losses due to additional incidence among the city population. These factors include black carbon, sulfur dioxide, nitrogen oxides, xylene and other aromatic hydrocarbons, formaldehyde, particulate matter and some other chemicals; their contributions range between 1.1 and 95.2 %. The greatest contributions to health losses among children are made by sulfur dioxide (79.3 %), kerosene (17.5 %), xylene (1 %), and formaldehyde (1 %).

Additional incidence of respiratory diseases among the whole population, which is associated with ambient air pollution created by heat and power objects, is distributed over the whole analyzed territory. Its local peaks are identified in areas influenced by heat and power objects with low or middle-height chimneys (10–50 meters) and AHS (6–8 meters) (Figure 4). Large thermal power stations usually have chimneys 180–270 meters high; they create relatively even ambient air pollution and, consequently, relatively even distribution of additional diseases over the whole city territory.

According to the Complex plan[11] aimed at reducing pollutant emissions into ambient air on the analyzed territory, the total emission volume created by heat and power objects and AHS is expected to fall by 20.56 % against its level identified in 2017. In particular, several activities are to be accomplished at heat and power objects: 25 municipal coal-fueled boiler houses are to be switched to centralized heat supply; a large thermal power station is to be modernized with a new chimney higher than 270 meters to be installed there, a boiler with an electric filter to be reconstructed, ineffective turbines to be removed and new turbines and a new cooling system to be put into

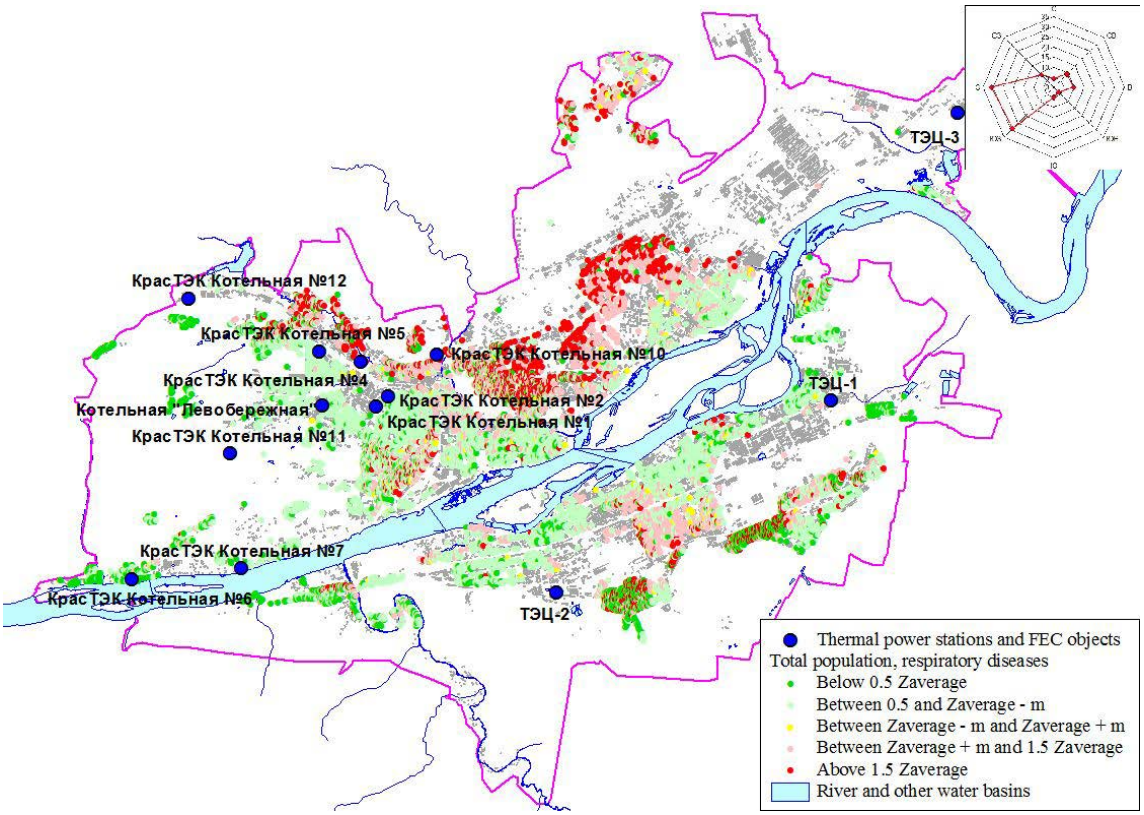

Figure 4. Spatial distribution of additional incidence of respiratory diseases associated with ambient air quality among the total population as a result of activities by heat and power objects, $^{o}/_{oo}$

[11] Kompleksnyi plan meropriyatii po snizheniyu vybrosov zagryaznyayushchikh veshchestv v atmosfernyi vozdukh v g. Krasnoyarske; utv. Zamestitelem Predsedatelya Pravitel'stva RF V. Abramchenko 16 noyabrya 2022 g. № 13424p-P11 [The Complex plan of activities aimed at reducing pollutant emissions into ambient air in Krasnoyarsk; approved by B. Abramchnko, the Deputy to the Head of the RF Government on November 16, 2022 No.13424p-P11]. *the RF Ministry of Natural Resources and the Environment*. Available at: https://www.mnr.gov.ru/upload/medialibrary/db3/%D0%9A%D1%80%D0%B0%D1%81%D0%BD%D0%BE%D1%8F%D1%80%D1%81%D0%BA,%20%D0%BF%D0%BB%D0%B0%D0%BD%20.pdf (April 13, 2023) (in Russian).

operation, automatic sensors for control of pollutant emissions into ambient air to be installed; 35 ineffective coal-fueled boiler houses are to be replaced with capacities of a large thermal power station (closing down ineffective coal-fueled boiler houses on the pilot territory, building new power generating units to balance heat loads related to replacement of ineffective coal-fueled boilers). Implementation of all these air protection activities will make it possible to reduce emissions from heat and power objects and AHS by 10.8 thousand tons by 2024.

Implementation of air protection activities at heat and power objects stipulated by the Complex plan will locally reduce levels of 4 out of 11 chemicals in ambient air, which are now higher than the existing hygienic standards, namely, nitrogen dioxide, carbon oxide, particulate matter, and inorganic dust with silicon dioxide, in %: 70–20, by 1.2–5.5 single MPL, by 1.1–5.8 average daily MPL, by 2.1 average annual MPL. However, hygienic standards are expected to still be violated as per some of these chemicals; thus, only FEC objects and AHS will create elevated levels of particulate matter up to 14.8 single MPL, up to 5.8 average daily MPL, and up to 11.7 average annual MPL. As for sulfur dioxide, operations of FEC objects and AHS, if taken separately, will not create levels higher than the hygienic standards in all the analyzed residential areas. The situation will remain the same for 6 chemicals (lead, ammonia, poorly soluble organic fluorides, benz(a)pyrene, hydroxybenzene, and methyl benzene); their levels will reach up to 22.3 single MPL and up to 3.03 average daily MPL.

Upon implementation of air protection activities aimed at reducing pollutant emissions into ambient air from heat and power objects, positive trends are expected such as a local reduction in acute and chronic risks of diseases of the central nervous, hematopoietic, cardiovascular, reproductive, and immune system, respiratory diseases, development processes, etc. (by 1.1–1.21 times).

Effectiveness of air protection activities was assessed as per residual risks after their implementation. The assessment revealed that carcinogenic risks were expected to still be elevated ($CR > 1 \cdot 10^{-4}$) on the pilot territory for formaldehyde (up to $3.28 \cdot 10^{-4}$). This chemical was also expected to cause high and alerting acute risks of respiratory diseases, diseases of the eye, cardiovascular diseases, development processes, and systemic effects (up to 2.8–25.5 HI_{ac}); high and alerting chronic risks were expected with respect to respiratory diseases, diseases of the eye, diseases of the hematopoietic and immune system (3.5–22.6 HI_{ch}).

The implementation of air protection activities aimed at reducing emissions from heat and power objects should be completed on the analyzed territory by 2024 in accordance with the Complex plan (by 20.56 % against the levels identified in 2017). This will make it possible to move approximately 50 thousand people from a zone with an unacceptable acute risk (HI higher than 3) and more than 120 thousand people from a zone with an unacceptable chronic risk (HI higher than 3) into a zone where risk levels are minimal (target ones). Still, high and alerting risks under acute exposure will persist with respect to diseases of the respiratory system, diseases of the eye, cardiovascular diseases, disrupted development processes and systemic effects (up to 6.5–25.8 HI_{ac}); under chronic exposure, with respect to diseases of the respiratory system, diseases of the eye, diseases of the hematopoietic and immune system (up to 2.96–22.6 HI_{ch}).

After all the planned air protection activities are implemented at heat and power objects, the number of additional diseases associated with ambient air quality will go down by 18.8 % among the total population living on the analyzed territory (by 16.5 thousand additional diseases or 17.8 cases per 1000 people) and will be equal to 70.9 thousand additional diseases. This reduction in additional associated diseases among the total population is largely due to a decrease in incidence among working age population (by 11.8 thousand cases) and children (by 4.5 thousand cases).

The structure of incidence among the total population will remain the same after the implementation of the planned activities at heat and power objects. The first rank place will belong to diseases of the respiratory system

(75.5 %); they will be followed by diseases of the digestive system (21.9 %) and diseases of the eye and adnexa (1.3 %). Diseases of the genitourinary, nervous, and endocrine system will account for 1.2 %. As for child incidence, the first place also belongs to diseases of the respiratory system (78.4 %), which are followed by diseases of the digestive system (20.1 %) and diseases of the eye and adnexa (1.3 %).

According to the submitted inventory lists, heat and power objects emit approximately 55 chemicals with 36 % of them being solid components such as particulate matter including $PM_{2.5}$ and PM_{10}, metal compounds (aluminum, vanadium, wolfram, iron, manganese, copper and others).

Examination of solid ash particles formed as a result of solid fuel combustion (brown coal from the Borodinskoye mine in the Kansko-Achniskiy coal field) established that this ash had several solid components in its structure including sodium, magnesium, iron, silicon, aluminum, potassium, sulfur, phosphor, calcium, and strontium. They are not mentioned in the inventory lists submitted by heat and power objects but we should remember that they are hazardous toxicants able to produce a wide range of adverse effects on human health. Calcium, magnesium, iron, and silicon compounds account for a major part of emitted solid particles with their contributions ranging between 5.8 and 35.5 %.

We analyzed the dispersed structure of solid particles in ash; as a result, particles sized smaller than 10.0 μm were established to prevail in it since their share reached 63.8 % of total particles. Notably, a half of such particles were smaller than 5 μm (30–31 % of total particles) (Figure 5).

Chemical analysis of ash established that particles sized between 0 and 10 μm contained such metals as calcium, aluminum, magnesium, iron, and strontium. Calcium particles (38.9 %) as well as particles of magnesium, iron, and silicon account for the major part in ash (more than 50 %). It is noteworthy that smaller particulate matter (between 2.5 and 10 μm) are not included into the inventory lists of emitted particles by heat and power objects although they are definitely potential risk factors able to produce negative effects on human health.

Several components identified in ash emitted into ambient air by heat and power objects are not covered by monitoring either, for example, iron, silicon, aluminum, sodium, calcium, magnesium compounds and some others.

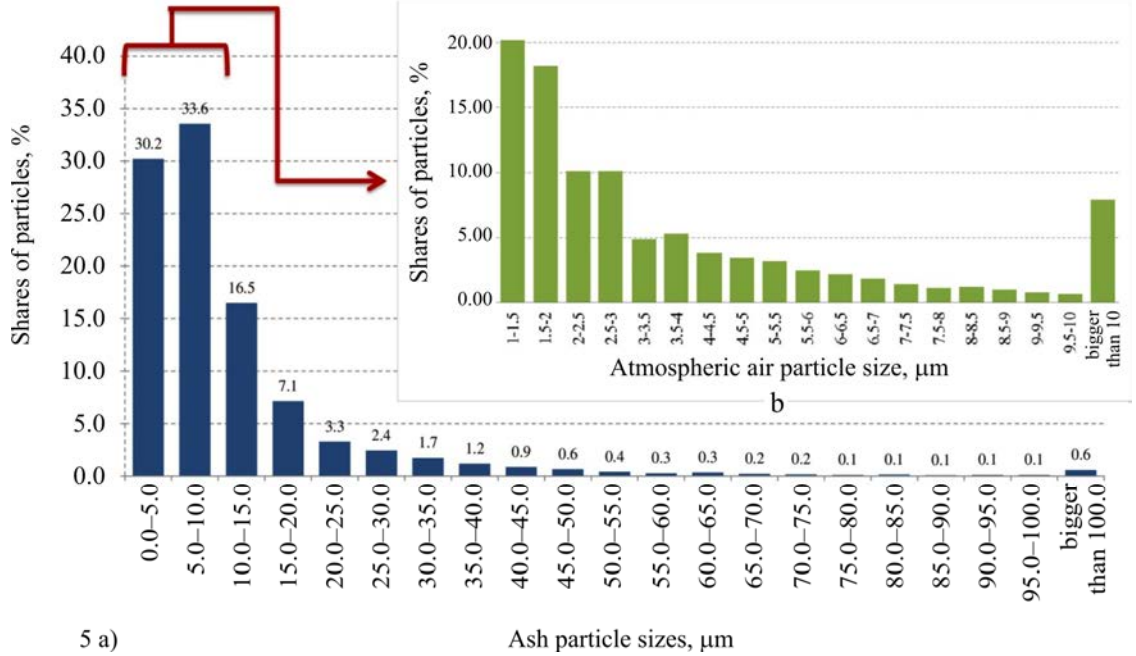

Figure 5. The dispersed structure of particulate matter in ash (5a) and in ambient air (5b) in a zone under maximum influence of FEC objects and AHS, %

It is noteworthy that the chemical structure of ambient air in areas influenced by FEC objects and AHS is similar to that of emitted ash. Sodium, iron, silicon, aluminum, potassium, sulfur, and phosphor accounted for the major part of particles (more than 65 %). The dispersed structure of particulate matter in ambient air and in ash was also quite similar with prevailing smaller particles (up to 10 μm), 88.9 % and 63.8 % accordingly (Figure 5a).

The results obtained by assessing effectiveness of the implemented air protection activities on the example of heat and power objects reveal some positive trends as regards some improvement in ambient air quality. Still, these activities are not sufficient for providing sanitary-epidemiological well-being of the population living on the analyzed territory. We expect the hygienic standards to be violated in areas influenced by heat and power objects and health risks to be higher than their permissible levels as well as resulting additional diseases associated with ambient air quality. Planned reduction in the total emission volume does not consider differentiated effects produced on human health by different chemicals. Effectiveness of the activities to be implemented at heat and power objects is ranked as 'unacceptable'[12] (below 20 %) and insufficient as per health harm mitigation, that is, substantial reduction in additional associated diseases. Technological emissions solely from heat and power objects are expected to cause approximately 70 thousand additional diseases annually.

The suggested approach to assessing effectiveness of health risk and health harm mitigation when planning and implementing air protection activities is an adequate instrument. It makes it possible to assess multicomponent harmful exposures producing multiple negative effects on health, including actual health harm, and sufficiency of implemented activities, which is also confirmed by the research results [11]. In this study, the complex assessment of negative influence exerted by economic entities relied on assessing exposure levels, identifying relationship parameters within the 'dose – effect' system, levels of acceptable and actual health risks, peculiarities of responses by the human body under combined airborne exposures, and plans of air protection activities.

Thus, when all the planned air protection activities are implemented at heat and power objects on the analyzed pilot territory (a city participating in the Clean Air Federal project), we expect some local improvement of ambient air quality, reduction in health risk levels and the number of additional incidence associated with exposure created by such economic entities.

Elevated levels of ambient air pollution created solely by heat and power objects are expected to persist and, consequently, we can expect negative health outcomes in exposed population. In this case, it is advisory to create more precise inventory lists for each source of ambient air pollution at heat and power objects; these lists should cover solid particles, including particulate matter smaller than 2 μm, and ensure conformity with the existing hygienic standards for these pollutants. Another important task is to adjust the complex plans of air protection activities considering their orientation at implementation of the best available technologies and management of priority health risk factors.

The results obtained by examining heat and power objects are comparable with the findings of other relevant studies confirming that long-term persistent pollution of the bottom layers in close proximity to residential areas creates health risks for exposed population and can lead to actual health harm. Thus, the studies [11–16] have established that fine-dispersed dust containing silicon, aluminum, copper, iron, and other metals, which is emitted, among other things, by heat and power objects, is able to produce cumulative effects. Under elevated

[12] MU 2.1.10.3675-20. Otsenka dostatochnosti i effektivnosti planiruemykh meropriyatii po snizheniyu vybrosov zagryaznyayushchikh veshchestv v atmosfernyi vozdukh dlya mitigatsii riskov i vreda zdorov'yu naseleniya: metodicheskie ukazaniya; utv. Glavnym gosudarstvennym sanitarnym vrachom RF 18.12.2020 [MU 2.1.10.3675-20. Assessment of sufficiency and effectiveness of planned activities aimed at reducing pollutant emissions in ambient air to mitigate health risks and health harm: methodical guidelines; approved by the RF Chief Sanitary Inspector on December 18, 2020]. *KonsultantPlus*. Available at: http://www.consultant.ru/law/hotdocs/68710.html (May 12, 2023) (in Russian).

chronic inhalation exposure, such dust leads to negative health outcomes such as respiratory diseases and cardiovascular diseases and influences biochemical processes in the body.

The studies [17–22] have established that any increase in levels of particulate matter smaller than 2.5 μm would have greater influence on mortality under both acute and chronic exposure than an increase in levels of PM_{10} or any other fractions. Major effects produced by micro-sized particles (PM_{10}, $PM_{2.5}$) on the human body are determined by their ability to penetrate deep into the lower airways, to injure lung tissues and to enter the blood flow through damaged cellular membranes of the lung alveoli; they can also produce various toxic effects depending on the their component structure [6–9].

At present, monitoring over ambient air quality is rather limited and does not involve analyzing dispersed structures of micro-sized particles. This requires additional research aimed at assessing effects produced on public health by solid particles with multicomponent structures.

Conclusions:

1. We have suggested an algorithm for assessing effectiveness of air protection activities. It includes six subsequent stages and makes it possible to assess their effectiveness and sufficiency as per conformity with the existing hygienic standards, health risks and actual health harm as additional incidence associated with poor quality of the environment due to activities performed by economic entities.

2. The algorithm has been tested at heat and power objects in a city that was included in the Clean Air Federal project and located in the Siberian Federal District. As a result, it has been established that potential health risks (R^l) created by heat and power objects are ranked as high and extremely high on the analyzed territory and are considerably higher than the regional levels and the national level, 7.1–50.9 times and up to 56.0 time accordingly.

3. Prior to the implementation of the planned air protection activities, heat and power objects emit certain pollutants in some areas in the city in quantities being 5–10 times higher than the maximum permissible levels (up to 29.9 single MPL; up to 6.9 average daily MPL; up to 19.0 average annual MPL). As a result, they create unacceptable (HI > 3) acute health risks (up to 25.8 HI_{ac}) for the respiratory system, eyes, the circulatory system, development processes; unacceptable chronic risks (up to 22.7 HI_{ch}) for the respiratory organs, eyes, and the immune system; unacceptable carcinogenic risks (up to $3.28 \cdot 10^{-4}$). Nitrogen dioxide, carbon oxide, benzene, formaldehyde, particulate matters and some other pollutants are the priority risk factors.

4. Prior to the implementation of the planned air protection activities, technological emissions from heat and power objectsannually cause approximately 87.5 thousand additional diseases with more than 44.8 % of them among children. Diseases of the respiratory system account for the major part in this additional incidence since their share is 80.03 %.

5. The implementation of the planned air protection activities at heat and power objects will lead to a local reduction in ambient air pollution. Levels of 10 chemicals are still expected to be higher than the existing hygienic standards; levels of 4 chemicals will decrease by 1.2–5.5 single MPL, by 1.1–5.8 average daily MPL, and by 2.1 average annual MPL; the situation will remain the same for 6 chemicals and their levels will be up to 22.3 single MPL and up to 3.03 average daily MPL higher than the hygienic standards. High and alerting levels of non-carcinogenic risks will persist for the respiratory organs, eyes, the hematopoietic, immune and cardiovascular system, development processes and systemic effects (up to 2.8–25.5 HI_{ac}, 3.5–22.6 HI_{ch}); carcinogenic risk levels will remain stable (CR up to $3.28 \cdot 10^{-4}$). The implementation of the planned air protection activities at heat and power objects will move approximately 50 thousand people from a zone with unacceptable acute health risks (above 3 HI) and more than 120 thousand people form a zone with unacceptable chronic risks.

6. Microscopy analysis of ash particles sized 0–100 μm has established their chemical structure that includes 10 various chemicals. Particles sized up to 10 μm prevail in the ana-

lyzed ash (63.8 %) and mostly contain calcium, magnesium, iron, and silicon (contributions range between 5.8 and 35.5 %). Due to them, ambient air in areas influenced by heat and power objects has a similar component structure.

7. We have assessed effectiveness of the air protection activities planned at FEC objects and AHS on the analyzed territory. As a result, we have established that the gross reduction in pollutant emissions corresponds to the target one stipulated in the Clean Air Federal project by 2024. At the same time, this planned reduction is not sufficient for achieving conformity with the existing hygienic standards, acceptable risk levels and reduction in risk-associated incidence in areas influenced by heat and power objects. Effectiveness of the planned air protection activities is ranked as 'unacceptable' (< 20 %) as per actual heath harm represented by additional incidence associated with influence of operating heat and power objects.

8. The results obtained by assessing effectiveness of the air protection activities planned at heat and power objects and expected ambient air quality, health risk levels and health harm after their implementation require some additional measures taken by economic entities and local authorities as well as orientation at using the best available technologies with respect to the most hazardous chemicals. Nitrogen dioxide, particulate matter, black carbon, carbon oxide, sulfur dioxide, dihydrosulfide, inorganic dust with silicon dioxide, in %: 20–70, dimethyl benzene, ethyl benzene, benzene, formaldehyde, and kerosene are the priority chemicals that should be covered by additional activities aimed at public health protection. Until proper ambient air quality is reached, according to the hygienic standards and health risk levels, it is advisable to perform systemic monitoring of public health in areas influenced by heat and power objects, to develop and implement complex medical and prevention activities.

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Research article

METHODICAL APPROACHES TO ASSESSING PUBLIC HEALTH RISKS UNDER COMBINED EXPOSURE TO CLIMATIC FACTORS AND CHEMICAL AIR POLLUTION CAUSED BY THEM

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The ongoing climate change makes its contribution to public health risks. These risks can be caused both due to direct impacts of the process and modifying influence exerted by climatic factors on chemical levels in ambient air. Given that, it is advisable to develop methodical approaches that give an opportunity to quantify public health risks under combined influence of climatic factors and chemical air pollution caused by them.

In this study, we suggest methodical approaches eligible for calculating, assigning a category and assessing acceptability of public health risks under climatic exposures considering their influence on chemical air pollution. We outline approaches to establishing priority climatic factors, calculating exposure levels and associated responses; making up a list of chemicals levels of which are influenced by climatic factors and probable health outcomes caused by exposure to them; identifying levels of chemicals associated with climatic influence; calculating and assigning a category for public health risks associated with combined exposure to climatic and chemical factors using a multiple logistic regression model.

We tested the approaches using data collected in Perm in 2020. As a result, we established an unacceptable health risk for working age population ($1.11 \cdot 10^{-4}$) due to cerebrovascular diseases (I60–I69). This risk was associated with combined exposure to climatic factors (heat waves) and associated chemical air pollution (high levels of carbon oxide). Risk levels for working age population and older age groups due to diseases of the circulatory system (ischaemic heart diseases (I20–I25) and other cardiac arrhythmias (I49)) were rated as permissible (acceptable), $7.68 \cdot 10^{-5}$ and $4.07 \cdot 10^{-5}$ accordingly. The contribution made by the analyzed climatic factor (heat waves) varied between 76.24 and 92.44 %; the analyzed chemical factor (carbon oxide), between 7.56 and 23.76 %.

Keywords: *climate, climatic factors, chemical air pollution, public health risk assessment, quantitative indicators, heat wave, carbon oxide, multifactorial models.*

Climate and climatic factors are among leading environmental influences that largely determine availability of comfortable living conditions for population and people's lifestyles. They produce direct effects on people's activities, their work capacity and social activity [1, 2]. Climate change is one of the most significant global issues in the 21st century [3]. A lot of changes observed at the moment have been going on for decades; over the recent years they have accelerated considerably and this raises a lot of concern on the global scale and undoubtedly influences people's lives worldwide [4, 5].

According to the Report on Climatic Peculiarities in the Russian Federation in 2021, air temperatures higher than the climate normals were observed practically all over the country. These average annual temperature conditions occurred due to extremely hot summer and cold winter [6, 7].

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Climate change is diverse and becomes apparent, in particular, through changing frequency and intensity of climatic anomalies and extreme weather events directly caused by the overall temperature growth[1]. Among them, we can mention heat waves and peatland combustion in the Central European Part of Russia in 2003; extreme heat and large-scale forest fires in 2010; draughts in the agricultural areas of the country in 2010 and 2012 and some others [8].

According to the RF President Order issued on December 17, 2009 No. 861-rp On the Climate Doctrine of the Russian Federation, an elevated public health risk (growing incidence and mortality rates) is a negative outcome of expected climate change[2]. This is due to climatic factors being able to influence changes in disease prevalence and character, including non-communicable diseases. Thus, for example, an extremely high air temperature (heat waves) can exacerbate cardiovascular diseases, respiratory diseases, kidney diseases, diseases of the nervous system; it can also induce an increase in mortality caused by diseases of the cardiovascular and respiratory systems, especially among elderly people [5, 9–11].

Outcomes of climate change can create a wide range of risks for human health. Together with direct effects produced by climatic factors, the latter can influence the composition and levels of chemicals in ambient air [12]. Probable mechanisms of such influences can include impacts exerted by air temperatures on rates of chemical reactions; air humidity, on formation and destruction of chemical compounds; cloudiness, on ambient air composition; near-ground temperatures and precipitations, on chemical emissions and deposition; changes in ground wind intensity over a continent, on mobility of dust particles in droughty areas and, consequently, aerosol burden in the troposphere, etc. [13–15]. For example, heat waves not only influence public health directly but also can cause short-term changes in ambient air pollution with nitrogen dioxide, carbon oxide, particulate matter, sulfur dioxide, etc. [5, 16–19].

Climatic parameters are considerably changeable both over time and space; this facilitates more intense transportation, transformation, accumulation, and dispersal of pollutants [20].

According to the WHO, events involving ambient air pollution might become more frequent and acute under future climate change [21].

Global climate change creates a peculiar situation for the Russian Federation considering its huge territory, geographical position, extreme diversity of climatic conditions etc. This situation necessitates advanced development of a comprehensive and well-thought approach to climate issues adopted by the state. This approach should rely on complex scientific analysis of certain factors and consider global climate change both on its national and international scale a top priority of the state policy pursued in the Russian Federation [22][3].

Therefore, ongoing climate change is able to influence public health due to both direct effects produced by climatic factors and modified chemical pollution in ambient air. To create conditions for proper public health protection, it is necessary to assess health risks in such a way so that these risks are quantified under combined exposure to climate change and associated chemical pollution in ambient air.

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[1] Dmitry Medvedev signed an order approving the Russian Federation Climate Doctrine. *President of Russia: official website*. Available at: http://en.kremlin.ru/events/president/news/6365 (March 03, 2023).

[2] O klimaticheskoi doktrine Rossiiskoi Federatsii: Rasporyazhenie Prezidenta Rossiiskoi Federatsii ot 17.12.2009 g. № 861-rp [On the Climate Doctrine of the Russian Federation: the RF President Order issued on December 17, 2009 No. 861-rp]. *The Russian Government*. Available at: http://government.ru/docs/all/70631/ (March 03, 2023) (in Russian).

[3] Ibid.

In this study, our aim was to develop methodical approaches to assessing public health risks under combined exposure to climatic factors considering their influence on chemical pollution in ambient air.

Materials and methods. We applied the fundamentals stipulated in the Methodical Guidelines MR 2.1.10.0057-12 Assessment of Risks and Damage due to Climate Change Influencing an Increase in Incidence and Mortality in Population Groups with Elevated Risks[4] and the Guide R 2.1.10.1920-04 Human Health Risk Assessment from Environmental Chemicals[5] as the methodical basis for developing approaches to assessing public health risks under combined exposure to climatic factors and chemical air pollution caused by them.

The suggested methodical approaches were tested within assessing public health risks created by exposure to climatic factors and chemical ambient air pollution caused by them in Perm in 2020.

Air temperature (heat waves) was chosen as a climatic factor to be analyzed. Data on average daily air temperatures (°C) collected in Perm over 2010–2020 were taken as initial information about the analyzed climatic parameter. These data were provided by the Unified State Fund of the Russian Federal Service for Hydrometeorology and Environmental Monitoring[6].

To achieve our aim, we calculated periods of heat waves in accordance with the procedure described in the Methodical Guidelines 2.1.10.0057-12[4]. Heat wave criteria were applied as a threshold of action for this factor.

Our initial data on population incidence were provided by a territorial fund for mandatory medical insurance after removing all the patients' personal data from them. We took data on daily numbers of applications for medical aid in Perm over 2010–2020 as per age groups (working age population, people older than working age) and as per the nosology category 'Diseases of the circulatory system' as well as specified diseases within this category.

We established what climatic factors would be able to induce a growth in chemical levels in ambient air and drew up a list of chemicals with their levels prone to change under climatic influence by analyzing relevant literature sources. Overall, we analyzed approximately 50 such sources including those found in WoS and Scopus.

Initial data on average daily levels of chemicals in ambient air in Perm over 2010–2020 were provided by the Perm Regional Office of the Federal Service for Surveillance over Consumer Right Protection and Human Wellbeing.

To calculate risk levels associated with effects of heat waves and carbon oxide, we cal-

[4] 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 (utv. i vved. v deistvie Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 17 yanvarya 2012 g.) [Assessment of Risks and Damage due to Climate Change Influencing an Increase in Incidence and Mortality in Population Groups with Elevated Risks (approved and put into effect by G.G. Onishchenko, the Head of the Federal Service for Surveillance over Consumer Right Protection and Human Wellbeing, the RF Chief Sanitary Inspector on January 17, 2012)]. Moscow, Rospotrebnadzor's Federal Center for Hygiene and Epidemiology, 2012, 48 p. (in Russian).

[5] R 2.1.10.1920-04. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu (utv. i vved. v deistvie Pervym zamestitelem Ministra zdravookhraneniya Rossiiskoi Federatsii, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 5 marta 2004 g.) [Human Health Risk Assessment from Environmental Chemicals (approved and put into effect by G.G. Onishchenko, the Head of the Federal Service for Surveillance over Consumer Right Protection and Human Wellbeing, the RF Chief Sanitary Inspector on March 05, 2004)]. Moscow, The Federal Center for State Sanitary and Epidemiological Surveillance of the RF Ministry of Health, 2004, 143 p. (in Russian).

[6] Spetsializirovannye massivy dlya klimaticheskikh issledovanii [Specialized data arrays for climatic research]. *Russian Scientific Research Institute for Hydrometeorological Information-World Data Center*. Available at: http://meteo.ru/it/178-aisori (October 15, 2022) (in Russian).

culated additional likelihood of incidence among working age population and population older than working age. The calculation relied on a multiple logistic regression model that described a relationship between daily incidence of circulatory diseases caused by combined exposure to heat waves and elevated carbon oxide levels associated with these waves (Formula). An additional daily carbon oxide level caused by heat waves is used as X_1 whereas X_2 is the difference in air temperatures on days with heat waves and days without them.

Risk levels were calculated as additional likelihood of incidence associated with exposure to heat waves (the number of days included into a wave over 2020) multiplied by average weighted severity of diseases used as health outcomes in this study. Severity of diseases was established in conformity with the WHO document entitled 'WHO methods and data sources for global burden of disease estimates 2000–2019' [23].

Results and discussion. We have developed approaches to assessing public health risks under combined influence of climatic factors and chemical air pollution caused by them. These approaches include the following stages:

1. Establishing priority climatic factors that can create a public health risk and associated health outcomes.

2. Calculating exposure to climatic factors.

3. Identifying a list of chemicals with their levels being influenced by climatic factors and probable health outcomes caused by exposure to them.

4. Establishing chemical levels associated with influence of climatic factors.

5. Calculating levels of public health risks and assigning their category under combined influence of climatic factors and chemical air pollution caused by them using a multiple logistic regression model.

1. Establishing priority climatic factors that can create a public health risk and associated health outcomes. A factor can be considered a priority for an analyzed territory in case values of indictors that describe it are authentically different from average values typical for this territory over an analyzed period or are beyond the established comfort ranges or threshold levels.

A threshold level / a boundary of a comfort range is a value that characterizes such an exposure to a climatic factor that is not likely to produce harmful effects on public health associated with influence of this factor. It is identified based on quantitative parameters of a relationship between exposures to climatic factors and prevalence of associated diseases. These parameters can be established either by analyzing relevant literature sources or by using mathematical modeling methods.

We analyzed research literature to identify health outcomes caused by influence of the selected climatic factors; namely, we searched for valid cause-effect relations that characterized a potential threat for human health posed by exposure to the analyzed climatic indicators. Various indicators can be eligible, for example, those describing influence of specific meteorological elements or indicators that describe complex effects produced by several climatic factors (for example, bioclimatic indicators such as equivalent–effective temperature (EET), physiological equivalent-effective temperature (PEET), radiation equivalent-effective temperature (REET), biologically active temperature (BAT), etc.)

2. Calculating exposure to climatic factors. Calculation of exposure to climatic factors has a peculiarity, that is, an exposure level does not cover the whole duration of exposure but only those periods when values of indictors describing climatic factors were beyond threshold levels or ranges within which negative health outcomes were unlikely. Besides, in some cases it is necessary to identify the excess level of an indicator over its threshold level or deviation from an established range (in °C, mm Hg, units used to measure an index, etc.).

3. Identifying a list of chemicals with their levels being influenced by climatic factors and probable health outcomes caused by exposure to them. Initially, it is

necessary to establish climatic factors typical for an analyzed territory, which would potentially be able to raise chemical levels in ambient air, and to make a list of such chemicals. In addition, ranges / thresholds of data effects are established for such factors. The latter do not produce any effects beyond these ranges / threshold, according to data available in literature.

If actual values of an analyzed climatic factor differ authentically from average values typical for a given territory over an analyzed period or are beyond established ranges / thresholds of effect, then they are able to have potential influence on levels of chemicals in ambient air on this territory. Given that, the ultimate list should include only those chemicals, levels of which change under influence exerted by climatic factors; we consider only factors with their values being beyond the ranges / thresholds established for indictors that describe them.

Health outcomes caused by exposure to the selected chemicals can be established both based on the Guide R 2.1.10.1920-04[7] and the results of literature analysis.

4. Establishing chemical levels associated with influence of climatic factors. First, it is necessary to establish an analyzed period, which will include those days / weeks / months when changes appeared in climatic factors and their indicators able to raise chemical levels in ambient air ('unfavorable periods'). Next, periods are established during which any influence on chemical levels in ambient air is unlikely ('favorable periods'). For each day in both 'unfavorable' and 'favorable' periods, actual levels of chemicals included in the list at the previous stage, are identified. The difference between chemical levels in days within 'unfavorable' and 'favorable' periods is considered a level caused by influence of climatic factors.

5. Calculating levels of public health risks and assigning their category under combined influence of climatic factors and chemical air pollution caused by them using a multiple logistic regression model. Risks of incidence are calculated as additional likelihood of incidence associated with influence exerted by climatic factors and chemical pollution in ambient air caused by them multiplied by average weighted severity of diseases as per disease classes used as health outcomes.

Additional likelihood of disease associated with combined exposure to unfavorable climatic factors and chemical pollution is calculated based on modeling cause-effect relations using multiple regression analysis.

In general, we can use the following multiple logistic regression model:

$$\Delta p = \frac{1}{1+e^{-(b_0+b_1x_1+b_2x_2)}},$$

where

Δp is additional likelihood of disease associated with combined exposure to the factors X_1 and X_2;

X_1, X_2 are the indicators describing levels of exposure to climatic and chemical factors;

b_0, b_1, b_2 are the parameters of the mathematical model.

All the models should be tested to identify the statistical significance of all the established relations ($p < 0.05$) and estimated by experts to check their conformity with biomedical concepts.

Exposure to climatic factors, chemical levels caused by influence of climatic factors and population incidence are taken as initial parameters. Applied data should have homogenous spatial and time level of detail.

[7] R 2.1.10.1920-04. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu (utv. i vved. v deistvie Pervym zamestitelem Ministra zdravookhraneniya Rossiiskoi Federatsii, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 5 marta 2004 g.) [Human Health Risk Assessment from Environmental Chemicals (approved and put into effect by G.G. Onishchenko, the Head of the Federal Service for Surveillance over Consumer Right Protection and Human Wellbeing, the RF Chief Sanitary Inspector on March 05, 2004)]. Moscow, The Federal Center for State Sanitary and Epidemiological Surveillance of the RF Ministry of Health, 2004, 143 p. (in Russian).

Mathematical models are created using data on incidence as per disease classes or specific nosologies influenced by both climatic factors and chemicals with their level prone to change under effects produced by these climatic factors.

We suggest the following classification to assign calculated risks into a specific category: $1.0 \cdot 10^{-6}$ or lower is a minimal risk; $1.1 \cdot 10^{-6}$–$1.0 \cdot 10^{-4}$, a permissible (acceptable) risk; $1.1 \cdot 10^{-4}$–$1.0 \cdot 10^{-3}$, an alerting risk; $> 10^{-3}$, a high risk. Alerting and high risks are considered unacceptable; in case such risk levels are established, it is advisable to develop certain measures aimed at preventing health disorders and creating favorable conditions for health protection. These measures should be aimed at protecting those organs and systems for which unacceptable risk levels were identified [24].

Also this stage might involve identifying specific contributions made by chemical and climatic factors to public health risks caused by them.

Therefore, the suggested methodical approaches make it possible to quantify public health risks and assign them into a specific risk category under combined exposure to climatic factors and chemical air pollution caused by them.

Air temperature is considered a leading climatic factor able to influence human health. According to the Report on Climatic Peculiarities in the Russian Federation in 2021, air temperatures higher than the climate normals were observed practically all over the country [7]. Growing frequency and intensity of climatic anomalies and extreme weather events, heat waves included, are a direct outcome of the overall growth in air temperature [16, 17, 21, 25][8].

An average temperature that could be considered a heat wave in Perm equals 27.5 °C. This value can be used as a level of exposure which is unlikely to produce any harmful effects on public health caused by heat waves. Nine heat waves were established to occur on the analyzed territory over the period between 2010 and 2020 indicating the relevance of the climatic factor for this territory.

Diseases of the circulatory system were used as health outcomes under exposure to heat waves according to data available in literature. To be more exact, we used hypertensive diseases (I10–I15), ischemic heart disease (I20–I25), other forms of heart diseases (I49–I50), and cerebrovascular diseases (I60–I64) [11, 26–30]. Working age population and population older than working age were established to be the most sensitive population groups under the analyzed combined exposure [11, 28].

Two heat waves were established to occur in Perm in 2020 at the stage involving calculation of exposure to climatic factors. The first one was between July 08 and 12 (5 days); the second, between July 14 and 16 (3 days). Daily air temperatures higher than their threshold level that identified a heat wave boundary on the analyzed territory (27.5 °C) ranged between 1.0 and 3.6 °C.

Heat waves in Perm can lead to a growth in levels of nitrogen dioxide, carbon oxide, particulate matter, and sulfur dioxide[9] [5, 18, 19].

In accordance with the Guide R 2.1.10.1920-04, the respiratory organs are used as target ones where health outcomes occur

[8] Dmitry Medvedev signed an order approving the Russian Federation Climate Doctrine. *President of Russia: official website*. Available at: http://en.kremlin.ru/events/president/news/6365 (March 03, 2023).

[9] 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 (utv. i vved. v deistvie Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 17 yanvarya 2012 g.) [Assessment of Risks and Damage due to Climate Change Influencing an Increase in Incidence and Mortality in Population Groups with Elevated Risks (approved and put into effect by G.G. Onishchenko, the Head of the Federal Service for Surveillance over Consumer Right Protection and Human Wellbeing, the RF Chief Sanitary Inspector on January 17, 2012)]. Moscow, Rospotrebnadzor's Federal Center for Hygiene and Epidemiology, 2012, 48 p. (in Russian).

under exposure to nitrogen dioxide, particulate matter, and sulfur dioxide; the cardiovascular system and development, carbon oxide.

We performed the relevant calculations using the actual levels of the analyzed chemicals. As a result, it was established that high air temperatures on the analyzed territory during heat waves created elevated average daily levels of nitrogen dioxide (the level was 0.03 mg/m^3 under normal conditions and 0.04 mg/m^3 under heat waves); carbon oxide (1.11 mg/m^3 and 1.83 mg/m^3 accordingly); and particulate matter (0.13 mg/m^3 and 0.16 mg/m^3 accordingly). Sulfur dioxide levels did not change. Chemical levels were higher than their average daily permissible ones (average daily MPL) only for particulate matter, being 0.1 average daily MPL higher. Additional growth in chemical levels caused by heat waves equaled 0.01 mg/m^3 (0.1 average daily MPL) for nitrogen dioxide; 0.72 mg/m^3 (0.2 average daily MPL) for carbon oxide; 0.03 mg/m^3 (0.2 average daily MPL) for particulate matter[10].

Diseases of the circulatory system associated with effects of heat waves and carbon oxide were used as health outcomes caused by combined exposure to climatic factors and chemical air pollution occurring due to their influence in Perm.

Table 1 provides the results of correlation-regression analysis (b_0, b_1 and b_2 are the model parameters, R^2 is the determination coefficient). We selected only statistically significant relations ($p < 0.05$).

We established authentic relationships between combined exposure to heat waves and carbon oxide and development of diseases from the following categories: 'ischemic heart disease' (I20–I25) and 'cerebrovascular diseases' (I60–I69) for working age population and additionally 'other cardiac arrhythmias' (I49) for population older than working age.

Biological plausibility of the created models is confirmed by specific mechanisms of influence exerted by heat waves and carbon oxide on the cardiovascular system. Due to effects of heat waves, hyperthermia usually stimulates hypotonia caused by vasodilation. Lower blood pressure makes for compensatory tachycardia; as a result, circulation becomes hyperdynamic and the cardiovascular system gets overstrained due to it [11]. Failure of hemoglobin oxygen-transportation function and associated developing hemic and tissue hypoxia are the leading components in pathogenesis of acute effects produced by carbon oxide. These hypoxias are further aggravated by hyperdynamic circulation caused by heat waves. Cerebral and cardiac tissues are the most susceptible to these effects and this is evidenced by the modeling results [31].

Additional likelihood of incidence caused by combined exposure to heat waves and carbon oxide was quantified for working age population in Perm as per several nosologies; it equaled $1.66 \cdot 10^{-5}$ for 'ischemic heart disease' (I20–I25) and $2.40 \cdot 10^{-5}$ for 'cerebrovascular diseases' (I60–I69). The calculated risk was $8.81 \cdot 10^{-6}$ for people older than working age as per 'other cardiac arrhythmias' (I49) (Table 2).

Table 1

The parameters of statistically significant multiple logistic regression models ($p < 0.05$)

Age group	Disease category as per ICD-10	b_0	b_1	b_2	R^2
Adult working age population	Ischemic heart disease (I20–I25)	-13.78	0.19	0.22	0.2
	Cerebrovascular diseases (I60–I69)	-11.84	0.01	0.11	0.1
Adults older than working age	Other cardiac arrhythmias (I49)	-15.66	0.48	0.3	0.2

[10] 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 g. № 2; vved. v deistvie 01.03.2021) [Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people (approved by the Order of RF Chief Sanitary Inspector dated January 28, 2021 No. 2; became valid on March 01, 2021)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (February 15, 2023) (in Russian).

Table 2

Public health risks in Perm associated with combined exposure to heat waves and chemical pollution with carbon oxide in ambient air

Age group	Health outcome	Additional incidence (per day under a heat wave)	Risk level (over 1 day under a heat wave)	Health risks for population in Perm caused by heat waves in 2020	Factor contribution, %	
					Heat waves	Carbon oxide
Working age adults	Ischemic heart disease (I20–I25)	$1.66 \cdot 10^{-5}$	$9.59 \cdot 10^{-6}$	$7.68 \cdot 10^{-5}$	88.35	11.65
	Cerebrovascular diseases (I60–I69)	$2.40 \cdot 10^{-5}$	$1.39 \cdot 10^{-5}$	**$1.11 \cdot 10^{-4}$**	76.24	23.76
Adults older than working age	Other cardiac arrhythmias (I49)	$8.81 \cdot 10^{-6}$	$5.09 \cdot 10^{-6}$	$4.07 \cdot 10^{-5}$	92.44	7.56

Risk levels were identified for the selected diseases of the circulatory system for working age population and people older than working age; they were $7.68 \cdot 10^{-5}$ (I20–I25) and $1.11 \cdot 10^{-4}$ (I60–I69) for the former age group and these risk levels are categorized as permissible (acceptable) and alerting (unacceptable) accordingly. The risk level identified for people older than working age was $4.07 \cdot 10^{-5}$ (I49); this level is considered permissible (acceptable).

Contributions made by heat waves to development of such diseases as 'ischemic heart disease' (I20–I25) and 'cerebrovascular diseases' (I60–I69) equaled 88.35 and 76.24 % accordingly; contributions made by carbon oxide were 11.65 and 23.76 % accordingly. Contributions made by the analyzed climatic factor (heat waves) and chemical factor (carbon oxide) to development of' 'other cardiac arrhythmias' (I49) equaled 92.44 % and 7.56 % accordingly for people older than working age. This indicates that the analyzed climatic factor had the greatest influence on development of these nosologies in Perm in 2020.

Therefore, when testing the suggested approaches, we established the unacceptable health risk ($1.11 \cdot 10^{-4}$) for working age adults in Perm in 2020 due to cerebrovascular diseases. This risk was associated with combined exposure to climatic factors (heat waves) and chemical air pollution caused by them (carbon oxide). Risk levels caused by diseases of the circulatory system within the selected nosologies (ischemic heart disease (I20–I25) and other cardiac arrhythmias (I49)) were considered permissible (acceptable) for working age population and people older than working age.

Conclusion. We have suggested methodical approaches eligible for calculating, assigning a category and assessing acceptability of public health risks under combined exposure to climatic factors and chemical air pollution caused by them.

This includes approaches to establishing priority climatic factors able to create elevated health risks and associated health outcomes; calculating exposure to climatic factors; identifying a relevant list of chemicals with their levels being prone to influence of climatic factors and probable health outcomes caused by their effects; establishing chemical levels associated with influence of climatic factors; calculating and identifying a category of health risks occurring under combined exposure to climatic factors and chemical air pollution caused by them using a multiple logistic regression model.

These approaches were tested using data collected in Perm. As a result, an unacceptable risk level ($1.11 \cdot 10^{-4}$) was established for working age population in 2020. This health risk was caused by cerebrovascular diseases (I60–I69) and was associated with combined exposure to climatic factors (heat waves) and chemical pollution with carbon oxide in ambient air caused by them. Risks levels caused

by diseases of the circulatory system (ischemic heart disease (I20–I25) and other cardiac arrhythmias (I49)) were categorized as permissible (acceptable) for working age population and people older than working age. They were $7.68 \cdot 10^{-5}$ and $4.07 \cdot 10^{-5}$ accordingly. The contribution by the analyzed climatic factor (heat waves) ranged between 76.24 and 92.44 %; the analyzed chemical factor (carbon oxide), between 7.56 and 23.76 %.

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Research article

CALCULATING THE NUMBER OF DISEASE CASES ASSOCIATED WITH ACUTE SHORT-TERM EXPOSURE TO HARMFUL CHEMICALS IN AMBIENT AIR

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The article addresses development of methodical approaches to calculating levels of health disorders caused by short-term exposure to ambient air pollution. We have established and parameterized relationships relevant for quantification of probable health outcomes as responses to elevated levels of chemicals in ambient air higher than their reference ones. These relationships were modeled using system analysis techniques and were based on dynamic data series on ambient air quality at the control points and the number of applications for medical aid in settlements with their overall population being more than 5 million people. We have formalized relationships that describe how intensively acute health disorders develop under short-term exposure to chemical levels in ambient air being higher than the reference ones that are identified at the control points. The resulting models rely on official data and can be used to predict and assess public health risks in any area where ambient air quality is monitored.

The formalized relationships were tested within identifying levels of incidence associated with acute short-term exposure to ambient air pollution in a large industrial center. It was established that, according to data collected in 2020, the highest associated incidence was caused by exposure to benzene (on average 0.364 mg/m^3 higher than the reference level) in ambient air and was detected as per such nosologies as 'Allergic rhinitis unspecified' and 'Predominantly allergic asthma'.

We are planning to use the results obtained at this stage in the research in further development of methodical approaches to assessing and predicting chemical health risks in areas influenced by hazardous chemical objects under short-term exposure to high levels of pollutants.

Keywords: *ambient air, public health risk, priority pollutants, mathematical modeling, applications for medical aid, chemical levels, associated incidence.*

Growth in life expectancy and life quality, health preservation and protection are priority trends in the state policy of the Russian Federation[1]. The set goals are being achieved by accomplishing a wide range of actions, including provision of sanitary-epidemiological wel-

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[1] O natsional'nykh tselyakh i strategicheskikh zadachakh razvitiya Rossiiskoi Federatsii na period do 2024 goda: Ukaz Prezidenta Rossiiskoi Federatsii ot 07.05.2018 № 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]. *President of Russia: the official web-site*. Available at: http://www.kremlin.ru/acts/bank/43027 (December 19, 2022) (in Russian); O natsional'nykh tselyakh razvitiya Rossiiskoi Federatsii na period do 2030 goda: Ukaz Prezidenta Rossiiskoi Federatsii ot 21.07.2020 № 474 [On national goals of the Russian Federation development for the period up to 2030: the RF President Order dated July 21, 2020 No. 474]. *President of Russia: the official web-site*. Available at: http://www.kremlin.ru/acts/bank/45726 (December 19, 2022) (in Russian); Kontseptsiya demograficheskoi politiki Rossiiskoi Federatsii na period do 2025 goda (utv. ukazom Prezidenta RF ot 9 oktyabrya 2007 g. № 1351) [The Concept of the demographic policy in the Russian Federation for the period up to 2025 (approved by the RF President Order dated October 9, 2007 No. 1351)]. *President of Russia: the official web-site*. Available at: http://www.kremlin.ru/acts/bank/26299/page/1 (December 19, 2022) (in Russian).

fare[2]. Thus, within the Ecology National project[3], the Clean Air Federal project[4] is being implemented by the RF Government in 2019–2024. It is aimed at reducing ambient air pollution in large industrial centers.

The project envisages using health risk indicators as eligible criteria to estimate performance and effectiveness of activities aimed at raising ambient air quality[5]. Special attention should be paid to assessing acute noncarcinogenic health risks that can occur already under short-term exposure to harmful chemicals (when duration of exposure does not exceed 24 hours).

The classical methodology for assessing public health risks under exposure to environmental pollutants is described in the Guide R 2.1.10.1920-04[6]. It relies on calculating hazard quotients and hazard indexes (HQ и HI) of chemicals penetrating the body through different ways. The methodology described in this Guide is relatively simple and is widely used to solve both theoretical and practical tasks involving assessment and management of public health risks [1–3].

At the same time, if we consider a risk a quantitative characteristic that reflects probable negative health outcomes, then use of hazard indexes as the sole estimation criteria imposes considerable limitations on performing hygienic analysis of an ecological situation in examined areas, calculating economic losses, substantiating relevant activities, identifying their expected effectiveness and performance.

Given that, a system approach seems able to provide a substantially greater analytical toolkit for health risk assessment. It involves formalizing cause-effect relations between environmental quality indicators and public health.

It is noteworthy that creating a system of cause-effect relations is a nontrivial task that requires the maximum objectivity at any stage in modeling, from creating a learning sample to substantiating a type of applied mathematical models and methods to identify model parameters.

At present, epidemiological research is widely used to formalize relationships [4]. Epidemiological studies give grounds for establishing relevant parameters of ‘concentration – outcome’ or ‘dose – response’ relationships. Several health outcomes caused by ambient air pollution are used most frequently including all-cause mortality [5, 6]; mortality caused by circulatory and respiratory diseases [7, 8]; hospital admissions due to circulatory and respiratory diseases [9, 10].

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[2] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2021 godu: Gosudarstvennyi doklad [On sanitary-epidemiological welfare of the population in the Russian Federation in 2021: the State Report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2022, 340 p. (in Russian).

[3] Pasport natsional'nogo proekta «Ekologiya» (utv. prezidiumom Soveta pri Prezidente RF po strategicheskomu razvitiyu i natsional'nym proektam 24.12.2018 (protokol № 16)) [The profile of the Ecology National project (approved by the Presidium of the RF President Council on strategic development and national projects on December 24, 2018 (the meeting report No. 16))]. *The Russian Government: the official web-site*. Available at: http://static.government.ru/media/files/pgU5Ccz2iVew3Aoel5vDGSBjbDn4t7FI.pdf (October 02, 2022) (in Russian).

[4] Pasport federal'nogo proekta «Chistyi vozdukh»: prilozhenie k protokolu zasedaniya proektnogo komiteta po natsional'nomu proektu «Ekologiya» ot 21 dekabrya 2018 g. № 3 [The profile of the Clean Air Federal project: the supplement to the meeting report of the meeting held by the project committee on the Ecology National project dated December 21, 2018 No. 3]. *The Kuzbas Ministry of Natural Resources and the Environment*. Available at: http://kuzbasseco.ru/wp-content/uploads/2019/09/%D0%A4%D0%9F%D0%A7%D0%B8%D1%81%D1%82%D1%8B%D0%B9-%D0%B2%D0%BE%D0%B7%D0%B4%D1%83%D1%85-%D0%9F%D0%B0%D1%81%D0%BF%D0%BE%D1%80%D1%82.pdf (October 02, 2022) (in Russian).

[5] MR 5.1.0158-19. Otsenka ekonomicheskoi effektivnosti realizatsii meropriyatii po snizheniyu urovnei zagryazneniya atmosfernogo vozdukha na osnovanii otsenki riska zdorov'yu naseleniya: Metodicheskie rekomendatsii (utv. Glavnym gosudarstvennym sanitarnym vrachom RF 02.12.2019) [The Methodical Guidelines MR 5.1.0158-19. Assessing cost effectiveness of activities aimed at reducing pollution levels in ambient air based on public health risk assessment (approved by the RF Chief sanitary Inspector on December 02, 2019)]. *MEGANORM: the system for regulatory documents*. Available at: https://meganorm.ru/Data2/1/4293720/4293720160.pdf (October 10, 2022) (in Russian).

[6] R 2.1.10.1920-04. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu [The Guide R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals]. Moscow, The Federal Center for State Sanitary and Epidemiological Surveillance of the RF Ministry of Health, 2004, 143 p. (in Russian).

Attention should be paid to the fact that practically all the findings of epidemiological studies that are reported in research literature represent particular cases of incidence and mortality typical for certain age groups, natural conditions, climate, socioeconomic conditions, workplace-related and occupational peculiarities and other limitations of sample populations. This narrows an area where identified relationships could be eligible. Moreover, most significant epidemiological studies were conducted in 90ties last century and there is no unified summarizing document that provides parameters of established relationships eligible for being widely used in assessing acute health risks.

The aim of this study was to substantiate and parameterize models describing cause-effect relations for quantification of acute public health risks caused by exposure to harmful chemicals in ambient air.

Materials and methods. Influence exerted by ambient air pollution on occurrence of acute health outcomes was modeled based on dynamic data series. These data covered the results of laboratory tests aimed at identifying chemical levels at stationary monitoring posts. These tests were conducted within profound screening investigations in 2021–2022. The data also covered daily applications for medical aid. Our analyzed territories were represented by large industrial centers with considerable levels of ambient air pollution.

The modeling procedure was divided into three stages. At the first stage, all the data were preliminarily prepared for the analysis; the second stage involved conducting dynamic analysis of selected indicators; relationship models were created at the third stage.

The preliminary data preparation included copying necessary data from the registers of applications for medical aid in residential areas close to the posts for ambient air quality monitoring; copying results of laboratory control over ambient air quality at the control posts on the analyzed territories; agreeing on relevant data arrays as regards territories, dates, and control points.

Our initial data at the first stage in the research were electronic tables with information about registered disease cases provided by the territorial offices of the Fund for Mandatory Medical Insurance and data on levels of chemical pollutants in ambient air at the control points identified as per the results of social-hygienic monitoring (SHM) and provided by Rospotrebnadzor's offices on the analyzed territories.

Within the preliminary data preparation, we agreed on relevant data covering territories for analysis, dates, and geographical positions of residential areas relative to the control points of ambient air monitoring. To do that, we performed geocoding of all the obtained data and specified residential areas close to the control points. These residential areas were represented by residential buildings located within a circle with 500 meters radius. Figure 1 provides an example of identifying specific zones on a given territory to show representativeness of posts for ambient air quality monitoring.

Daily applications for medical aid were identified for these specified zones; the values were measured in a number of cases per 100 thousand people for three different age groups (children aged 0–17 years, working age adults, adults older than working age) as per nosologies characterizing acute health outcomes under short-term exposure to harmful chemicals in ambient air (Table 1).

Such diseases as 'Other allergic rhinitis' (J30.3) and 'Predominantly allergic asthma' (J45.0) are given in two places in Table 1 since they can be signs of health disorders both in the respiratory organs and the immune system.

Single maximum concentrations of pollutants identified at the analyzed control points were used as affecting factors for modeling of relationships. Table 2 provides the list of chemicals identified at the control points as well as potential critical organs and systems affected by the enlisted chemicals (according to the Guide on Health Risk Assessment[7]).

[7] R 2.1.10.1920-04. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu [The Guide R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals]. Moscow, The Federal Center for State Sanitary and Epidemiological Surveillance of the RF Ministry of Health, 2004, 143 p. (in Russian).

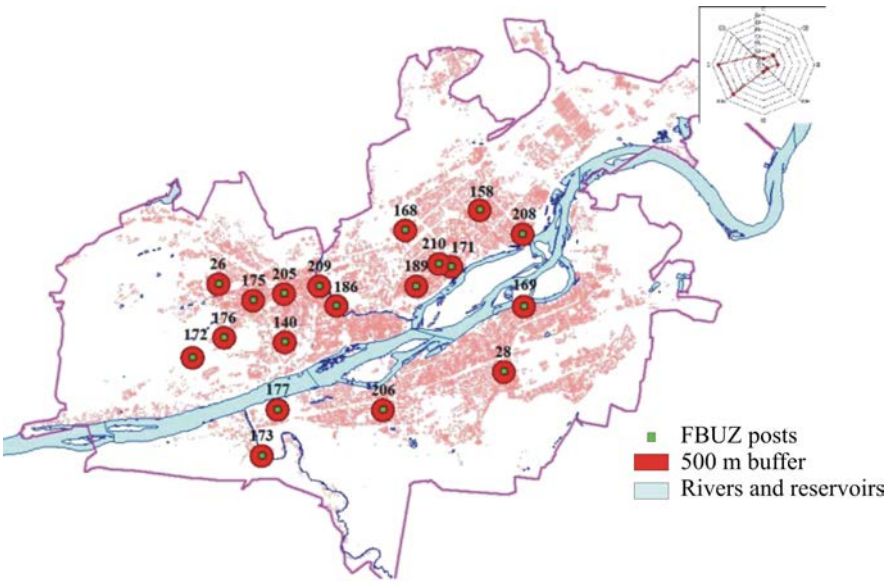

Figure 1. An example spatial location of residential areas close to the control posts of ambient air quality monitoring in a large industrial center

Table 1

The list of diseases that are considered typical health outcomes under acute short-term exposure to ambient air pollution

Critical organs and systems	Disease
Respiratory organs	J02.9 Acute pharyngitis, unspecified
	J04.0 Acute laryngitis
	J04.1 Acute tracheitis
	J04.2 Acute laryngotracheitis
	J20.9 Acute bronchitis, unspecified
	J30.3 Other allergic rhinitis
	J30.4 Allergic rhinitis, unspecified
	J31 Chronic rhinitis, nasopharyngitis and pharyngitis
	J37 Chronic laryngitis and laryngotracheitis
	J39.9 Disease of upper respiratory tract, unspecified
	J40 Bronchitis, not specified as acute or chronic
	J42 Unspecified chronic bronchitis
	J44 Other chronic obstructive pulmonary disease
	J45.0 Predominantly allergic asthma
	J45.8 Mixed asthma
	J45.9 Asthma, unspecified
	J46 Status asthmaticus
	J68 Respiratory conditions due to inhalation of chemicals, gases, fumes and vapors
	J96.0 Acute respiratory failure
Eyes and mucosa	H10 Conjunctivitis
	H16.1 Other superficial keratitis without conjunctivitis
	H16.2 Keratoconjunctivitis
	H16.8 Other keratitis
	H16.9 Keratitis, unspecified
Immune system	J30.3 Other allergic rhinitis
	J45.0 Predominantly allergic asthma
Central nervous system	R27 Other lack of coordination
	R51 Headache
	R53 Malaise and fatigue
	G47.9 Sleep disorder, unspecified

Table 2

The list of chemical identified at the control points for ambient air quality monitoring on the analyzed territories under short-term exposure

No.	Chemical	Critical organs and systems
1	1,2-dichloroethane	Immune system
2	Nitrogen (II) oxide	Respiratory organs
3	Nitrogen dioxide	Respiratory organs
4	Ammonia	Respiratory organs; eyes and mucosa
5	Acetaldehyde	Eyes and mucosa
6	Benzene	Immune system
7	Particulate matter	Respiratory organs
8	Particulate matter PM_{10}	Respiratory organs
9	Particulate matter $PM_{2.5}$	Respiratory organs
10	Phenol	Respiratory organs; eyes and mucosa
11	Hydrochloride	Respiratory organs
12	Dihydrosulfide	Respiratory organs
13	Dimethyl benzene (mixture of o-, m-, p- isomers)	Respiratory organs; eyes and mucosa; central nervous system
14	Dichloromethane (Methylene chloride)	Central nervous system
15	Copper oxide (recalculated as per copper)	Respiratory organs
16	Methylbenzene	Respiratory organs; central nervous system
17	Nickel (metallic nickel)	Respiratory organs; immune system
18	Nickel oxide	Respiratory organs; immune system
19	Ozone	Respiratory organs
20	Sulfur dioxide	Respiratory organs
21	Sulfuric acid	Respiratory organs
22	Tetrachloroethylene	Respiratory organs; eyes and mucosa
23	Formaldehyde	Respiratory organs; eyes and mucosa
24	Gaseous fluorides	Respiratory organs
25	Chlorine	Respiratory organs
26	Ethanethiol	Respiratory organs

Data on levels of pollutants in ambient air and public health were matched as per a component 'key parameter' that combined the analyzed territory, the number of a control point, and a date when examination (measurement) took place.

The data that were prepared at the first stage were analyzed in dynamics specifically for each chemical measured at control points. The analysis was aimed at identifying events characterized with levels of chemicals being higher than their reference values for acute exposure. In case no reference level was identified for a chemical, we applied single MPL instead. When such events occurred, their dates were fixed in a separate table together with values by which levels of chemicals exceeded the reference ones. A fact of a level being higher than its reference value was considered an exposure factor; a relative number of applications for medical aid during three days after the detected exposure was considered a probable response to it. Based on the results of this dynamic analysis, we drew up an electronic table that included the values by which chemical levels were higher than the reference ones and corresponding numbers of applications for medical aid during three days.

Relationships were modeled as per the results of dynamic analysis using regression analysis techniques and instruments provided by *R-studio* software package. Fixed values by which chemical levels were higher than reference ones were used as independent variables:

$$\Delta x_i(T) = x_i(T) - x_i^{ARfc}, \qquad (1)$$

where

Δx_i is the excess of the *i*-th chemical level over its reference level for acute exposure;

x_i is the maximum single level of the *i*-th chemical a day;

x_i^{ARfc} is the reference level for acute exposure to the *i*-th chemical;

T is a date when a level of a chemical was established to be higher than its reference level for acute exposure.

The summated numbers of applications for medical aid were used as dependent variables; they were summated over three days after a chemical level was established to be higher than its reference value for acute exposure for the first time:

$$z(T) = \sum_{t=0}^{2} z_{T+t} , \qquad (2)$$

where $z(T)$ is relative frequency of applications for medical aid during three days after a chemical level was established to be higher than its reference value for acute exposure, cases/100,000; z_{T+t} is relative frequency of applications for medical aid on the date $T+t$, cases/100,000.

The modeling itself involved creating models to describe cause-effect relations by using multiple linear regression analysis:

$$z = b_0 + \sum_i b_i \Delta x_i , \qquad (3)$$

where

z is relative frequency of health disorders, cases/100,000;

Δx_i is the value by which the level of the *i*-th chemical is higher than its reference level for acute exposure;

b_0, b_i are the model parameters.

We excluded certain chemicals from modeling in case their probable influence on incidence did not have any biological substantiation under acute exposure described in the biological plausibility matrix (Table 2).

Formalization of the relationships as regression models in the form (4) made it possible to quantify frequency of diseases associated with events involving acute exposure to levels of chemicals being higher than reference ones. Levels of associated incidence caused by single acute short-term exposure to chemical pollution in ambient air (Δz) were identified as per the following relationship:

$$\Delta z = \sum_i b_i \Delta x_i . \qquad (4)$$

Results and discussion. We analyzed levels of chemical pollution in ambient air at the selected control points on all the analyzed territories in dynamics over 2021–2022. As a result, we detected 4.7 thousand time intervals during which there were significant deviations in levels of chemicals from corresponding reference values identified for 26 pollutants.

Figures 2–5 provide typical examples of dynamics identified for levels of some chemicals measured at the selected control points with laboratory instruments. The green horizontal line in Figures 2–5 shows reference levels for acute inhalation exposures (Arfc); the red horizontal line shows maximum single permissible levels (single MPL).

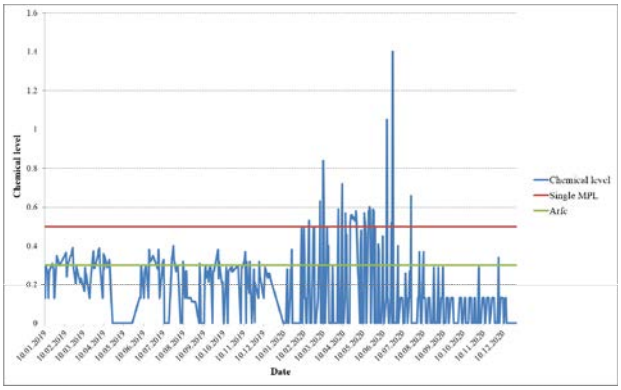

Figure 2. Levels of particulate matter measured at a control point for ambient air quality monitoring, in dynamics

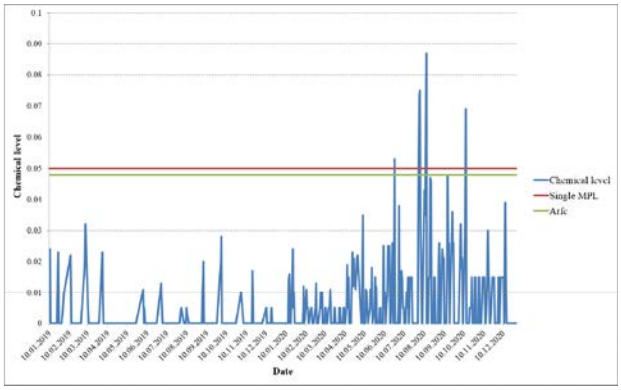

Figure 3. Levels of formaldehyde measured at a control point for ambient air quality monitoring, in dynamics

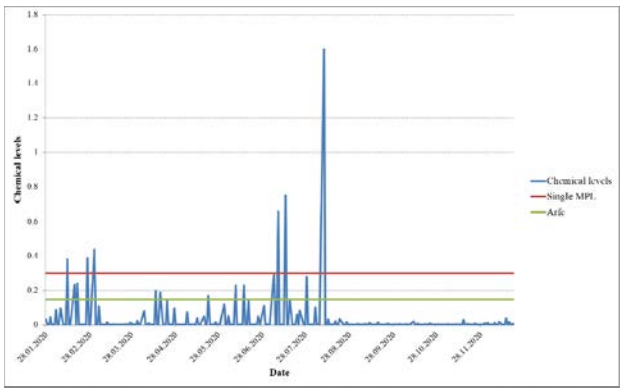

Figure 4. Levels of benzene measured at a control point for ambient air quality monitoring, in dynamics

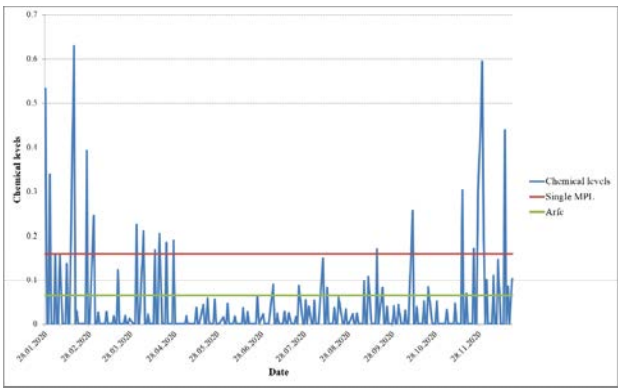

Figure 5. Levels of particulate matter $PM_{2.5}$, measured at a control point for ambient air quality monitoring, in dynamics

The detected events were compared with numbers of applications for medical aid by population living in close proximity to a control point for ambient air quality monitoring during three days after each detected event.

Having created aggregated data arrays on the events and frequency of diseases, we performed regression analysis of relationships between acute reactions represented by applications for medical aid and elevated chemical levels in ambient air. The analysis allowed establishing parameters for 13 multiple regression models presented in Table 3.

Within modeling, the formal relationships were tested to check their conformity with statistical significance; in addition, each model was examined to identify its biological plausibility together with explaining how diseases developed under acute short-term exposure to chemical pollutants.

Relationship modeling revealed that particulate matter produced most significant acute effects on public health. This pollutant is a major reason for growing number of applications for medical aid due to certain respiratory diseases. Multiple studies have reported the dust factor to be one of the most significant as regards both chronic and acute effects on health. Elevated levels of particulate matter in ambient air injure lung tissue and influence the development of non-communicable diseases [11]. PM of < 2.5 μm can cross the alveolar-capillary barrier, traveling to other organs within the body [12], and this can lead to a growing number of applications for medical aid. Thus, for example, growing numbers of applications for medical aid due to exacerbated respiratory diseases were registered in periods with elevated $PM_{2.5}$ levels in ambient air in Russia [13, 14], Taiwan [15], the USA [16, 17] etc.

Some international studies mention a correlation between growing levels of sulfur dioxide in ambient air and elevated risks of respiratory diseases. In particular, it was established that when a sulfur dioxide level grew by 10 μg/m^3, there was an associated growth in inpatient visits with respiratory diseases among working age people and people of retirement age, especially during a warm season (May – October) [18].

Moreover, profound investigations of comorbidity regularities established that ambient air pollution with benzene and particulate matter induced allergic rhinitis among children. Allergic rhinitis is diagnosed in 87.2 % [19] of preschool children under exposure to polycyclic aromatic hydrocarbons; each third child has bronchial asthma and recurrent bronchitis; respiratory diseases were accompanied with secondary immunodeficiency in 2/3 of the cases. Long-term exposure to $PM_{2.5}$ enhances allergic inflammatory cell expression in the nasal mucosa through increasing the expression of inflammatory cytokine and reducing the release of Treg cytokine [20].

Table 3

Parameters of the models describing relationships between acute reactions represented by applications for medical aid and elevated chemical levels

Age group	Nosology	Chemical factor	Model coefficients		Determination coefficient (R^2)	Model validity ($p < 0.05$)
			b_0	b_i		
Children	Other allergic rhinitis (J30.3)	Benzene	5.111	117.161	0.050	0.000
	Allergic rhinitis, unspecified (J30.4)	Particulate matter	4.045	33.598	0.012	0.031
	Conjunctivitis (H10)	Formaldehyde	9.005	3840.537	0.155	0.000
Working age adults	Chronic rhinitis, nasopharyngitis and pharyngitis (J31)	Particulate matter	6.167	16.425	0.010	0.045
	Bronchitis, not specified as acute or chronic (J40)	Particulate matter	7.428	24.106	0.018	0.009
	Other allergic rhinitis (J30.3)	Particulate matter $PM_{2.5}$	0.155	5.301	0.014	0.018
	Chronic laryngitis and laryngotracheitis (J37)	Sulfur dioxide	0.768	256.443	0.119	0.000
Adults of retirement age	Predominantly allergic asthma (J45.0)	Benzene	9.932	120.676	0.049	0.000
	Predominantly allergic asthma (J45.0)	Particulate matter	10.597	55.258	0.032	0.000
	Asthma, unspecified (J45.9)	Particulate matter PM_{10}	0.269	11.949	0.013	0.023
	Acute bronchitis, unspecified (J20.9)	Particulate matter $PM_{2.5}$	0.136	4.557	0.010	0.047
	Asthma, unspecified (J45.9)	Particulate matter $PM_{2.5}$	0.211	14.128	0.041	0.000
	Unspecified chronic bronchitis (J42)	Sulfur dioxide	9.638	644.733	0.025	0.002

Table 3 provides the modeling results given as the formal relationships. They correspond to the requirements of statistical significance and biological plausibility. The value of the parameter b_i is interpreted as a value describing the number of disease cases (cases/100 thousand people) occurring under exposure to a level of chemical 1 mg/m^3 higher than its reference value for acute exposure.

We took the model coefficients and the detected values by which identified chemical levels were higher than the reference level at the control points during one calendar year; relying on these data, and in accordance with the relationship (4), we identified the integral estimates of the number of disease cases caused by acute exposure to chemical pollution in ambient air.

We tested how the methodology could be implemented for assessing associated incidence caused by acute short-term exposure to ambient air pollution as per the established relationships provided in Table 3. The assessment relied on data concerning ambient air pollution in 2020.

Table 4 shows the number of cases when chemical levels were higher than their reference values in a large industrial center in 2020; in addition, it provides average values of the detected excesses in chemical levels.

We established parameterized relationships between acute health outcomes and elevated levels of certain chemicals (Table 3). Among them, elevated concentrations higher than reference levels were detected in a large industrial center in 2020 for such pollutants as benzene, particulate matter, particulate matter PM_{10}, $PM_{2.5}$. Thus, elevated benzene levels higher than the reference one were detected up to 37 times per year depending on a monitoring

post (the post No. 140) and 17.6 times per year on average in the city. An average value by which a benzene level exceeded its reference value equaled 0.364 mg/m^3 (Table 4).

We tentatively estimated incidence associated with the analyzed factors relying on the established relationships provided in Table 3, the number of cases when chemical levels were higher than their reference value (Table 4) and using the relationship (4). Associated incidence will be different depending on a place of living and exposure conditions; Table 5 provides the average estimates for the analyzed territory.

Thus, the highest associated incidence caused by exposure to benzene in ambient air was detected for such nosologies as 'Other allergic rhinitis' (J30.3) and 'Predominantly allergic asthma' (J45.0) and equaled 751.1 and 773.6 cases per 100, 000 people accordingly.

Table 4

The number of cases when chemical levels were higher than their reference values, average values of the detected excesses in chemical levels at the control points for ambient air monitoring on the analyzed territory

The control point No.	Benzene		Particulate matter		Particulate matter PM_{10}		Particulate matter $PM_{2.5}$	
	The number of peaks over a year	Average value Δx_i (T), mg/m^3	The number of peaks over a year	Average value Δx_i (T), mg/m^3	The number of peaks over a year	Average value Δx_i (T), mg/m^3	The number of peaks over a year	Average value Δx_i (T), mg/m^3
26	22	0.256	5	0.144	27	0.165	80	0.101
28	–	–	–	–	20	0.185	70	0.093
140	37	0.493	9	0.162	20	0.167	71	0.093
158	–	–	–	–	2	0.352	4	0.237
168	–	–	–	–	1	0.013	1	0.094
186	2	0.154	-	-	7	0.158	9	0.190
189	–	–	–	–	–	–	3	0.011
205	–	–	1	0.270	3	0.188	5	0.177
206	2	0.029	–	–	2	0.087	5	0.088
208	–	–	1	0.048	7	0.093	54	0.049
209	25	0.313	19	0.137	42	0.157	93	0.118
210	–	–	1	0.269	5	0.164	48	0.069
Average as per all posts	17.6	0.364	6	0.149	12.364	0.163	36.917	0.095

Table 5

Calculation of associated incidence: an example

Age group	Nosology	Chemical factor	Associated incidence, cases/100,000
Children	Other allergic rhinitis (J30.3)	Benzene	751.1
	Allergic rhinitis, unspecified (J30.4)	Particulate matter	30.1
Working age adults	Chronic rhinitis, nasopharyngitis and pharyngitis (J31)	Particulate matter	14.7
	Bronchitis, not specified as acute or chronic (J40)	Particulate matter	21.6
	Other allergic rhinitis (J30.3)	Particulate matter $PM_{2.5}$	18.7
People of retirement age	Predominantly allergic asthma (J45.0)	Benzene	773.6
	Predominantly allergic asthma (J45.0)	Particulate matter	49.5
	Asthma, unspecified (J45.9)	Particulate matter PM_{10}	24.0
	Acute bronchitis, unspecified (J20.9)	Particulate matter $PM_{2.5}$	16.0
	Asthma, unspecified (J45.9)	Particulate matter $PM_{2.5}$	49.7

To identify the absolute number of disease cases, it is necessary to perform additional calculations that consider a population number in a specific age group exposed to an analyzed factor. To achieve more qualitative estimates, it is necessary to assess spatial distribution of concentrations and a number of exposed people more profoundly. Ideally, we should use maps showing daily dispersal of pollutants over the whole analyzed territory with bound data on population numbers. These issues are possible areas for further research that addresses assessing acute health risks.

Conclusion. Therefore we have formalized the relationships based on system analysis and mathematic modeling; they describe how intensely acute health disorders develop under short-term exposure to elevated levels of chemicals in ambient air higher than their reference values observed at control points. The created models rely on official data and can be used to assess and predict health risks on any territory where ambient air quality is monitored.

The study results presented as methodical approaches and formalized relationships were tested in an actual urban environment; the resulting estimates are quite adequate and correspond to prior risks identified by using conventional methods.

We should point out that the model parameters described in this article can be applied in a wide area and provide an analytical base for identifying and ranking chemical health risks in areas influenced by hazardous chemical objects, estimating probable economic losses, analyzing possible demographic losses, etc.

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Competing interests. The authors declare no competing interests.

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Research article

PECULIARITIES AND RISKS OF MYOPIA IN CHILDREN ATTENDING COMPREHENSIVE SCHOOLS WITH DIFFERENT EDUCATIONAL PROGRAMS

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The contemporary educational process involves growing diversity and complexity of educational programs and intensity of educational loads. All this, in its turn, affects schoolchildren's health. Diseases of the eye and adnexa occupy the leading place among pathologies that are caused by unfavorable educational conditions. Prevalence of such diseases grows steadily over the whole period of getting secondary education.

The aim of this study was to examine peculiarities and assess risks of myopia in children attending comprehensive schools with different educational programs.

Overall, we examined 804 children from the 1st to 11th grade. The test group was made of 312 children who attended comprehensive schools with profound studies of some subjects. The reference group included 492 children who attended ordinary comprehensive schools. Both groups were identical as regards sex and age (p = 0.203–0.479). The study involved handing out questionnaires; estimating whether the organization of the educational processes conformed to the sanitary legislation of the Russian Federation. The research data were analyzed with conventional statistical methods, ROC-analysis, and logistic modeling.

We established several leading risk factors that caused myopia in students of comprehensive schools with profound studies of some subjects. They included 5.4–19.2 % higher educational loads; 1.4 times longer periods of PC use during classes; 1.5 times longer periods of work with digital technologies. The children from the test group tended to have myopia, including moderate and high one, 1.3–2.4 times more frequently; the disease occurred at a younger age; risks of the disease were typically higher in such schools (OR = 1.48–2.5). Causation of myopia by factors related to the educational process and digital initiation equaled R^2 = 0.52–0.77. Use of ROC-curves identified cut-off points that showed how long it took myopia to develop under the specific educational conditions in comprehensive schools with profound studies of some subjects (the 5th grade) and in ordinary comprehensive schools (the 7th grade).

ROC-analysis data indicate it is necessary to apply a differentiated approach to organizing preventive activities for children who attend comprehensive schools with different educational programs.

Keywords: *myopia, refractive disorders, accommodative dysfunctions, students, schools with different educational programs, educational process, relative risk, ROC-analysis, cut-off point.*

According to Rosstat data, diseases of the eye and adnexa account for approximately 5–6.0 % of the total incidence among both children aged 0–14 years and adolescents aged 15–17 years. Among them, the leading place belongs to refractive disorders and accommodative dysfunctions; no descending trends have been registered for the incidence of these diseases starting from 2005[1] [1]. According to the WHO data, approximately 370 million children and adolescents worldwide may have myopia [2]. Experts pay special attention to

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[1] Zdravookhranenie v Rossii. 2021: Statisticheskii sbornik [Healthcare in Russia. 2021: Statistical data collection]. *Rosstat.* Moscow, Federal State Statistics Service, 2021, 171 p. Available at: https://rosstat.gov.ru/folder/210/document/13218 (April 18, 2023) (in Russian).

the fact that the number of myopia cases identified during medical examinations at school is higher than the incidence of myopia identified after an actual application for medical aid. The former number reaches 30 % and some researchers predict a further growth in the incidence of myopia [1–3].

Results reported in accomplished longitudinal studies indicate a statistically significant growth in both functional and chronic diseases of the eyes over 11 years of studying at school; this growth reaches +106.8 and +1445.5 % accordingly [4, 5].

In the Russian Federation, the state is obliged to take on basic responsibilities for providing such learning conditions that do not pose any health hazard and exclude exposure to any harmful factors[2]. Some researchers have reported that negative effects produced by socioeconomic factors, the environment, and the organization of the educational process contribute to additional cases of diseases, including diseases of the eye and adnexa [1, 6, 7]. Irrational use of electronic devices by teachers in the learning process as well as children using smartphones or other electronic devices on their own and without any control is among leading risk factors making for the development of refractive disorders and accommodative dysfunctions [8–10].

At present, the procedure and terms of obligatory medical examinations of minors are stipulated in the Order by the RF Public Healthcare Ministry dated August 10, 2017 No. 514n "On the Procedure for conducting medical examinations of minors"[3]. The Order does not consider the contents and orientation of educational programs. According to some previous studies, prevalence of myopia tends to be higher among schoolchildren attending schools with profound studies of some subjects than among their counterparts who attend ordinary comprehensive schools [1].

The aim of this study was to examine peculiarities and assess risks of myopia in children attending comprehensive schools with different educational programs.

Materials and methods. Overall, we examined 804 children and adolescents from the 1^{st} – 11^{th} grades of comprehensive school. The test group was made of 312 students attending comprehensive schools with profound studies of some subjects (162 (51.9 %) boys and 150 (48.1 %) girls, their average age was 12.6 ± 2.9 years). The reference group included 492 students who attended ordinary comprehensive schools (235 (47.8 %) boys and 257 (52.2 %) girls, their average age was 12.3 ± 2.9 years). The groups were identical as regards sex and age (p = 0.203–0.479). The share of students from each grade was comparable in both groups and amounted to 8–11 %.

We relied on several criteria to include children and adolescents into the study: they attended either a comprehensive school with profound studies of some subjects or an ordinary comprehensive school; they did not have any acute communicable diseases; their parents or legal representatives provided a written consent to medical examinations.

The exclusion criteria were as follows: children attended a school with other types of educational programs; they had an acute communicable disease, including those affecting the eye; they suffered from a disease of the eye that did not involve refractive disorders or accommodative dysfunctions.

The study was accomplished within the scientific research task entitled 'Establishment of causes and conditions for the development of diseases in children associated with peculiarities of the contemporary educational process

[2] Ob osnovakh okhrany zdorov'ya grazhdan v Rossiiskoi Federatsii: Federal'nyi zakon ot 21 noyabrya 2011 g. № 323-FZ [On fundamentals of public health protection in the Russian Federation: the Federal Law issued on November 21, 2011 No. 323-FZ]. *GARANT: information and legal support*. Available at: https://base.garant.ru/12191967/#friends (April 21, 2023) (in Russian).

[3] O Poryadke provedeniya profilakticheskikh meditsinskikh osmotrov nesovershennoletnikh: Prikaz Ministerstva zdravookhraneniya RF ot 10 avgusta 2017 g. № 514n (s izmeneniyami i dopolneniyami) [On the Procedure for conducting medical examinations of minors: the Order by the RF Public Healthcare Ministry dated August 10, 2017 No. 514n (with alterations and supplements)]. *GARANT: information and legal support*. Available at: https://base.garant.ru/71748018/ (April 21, 2023) (in Russian).

and quality of the environment'. The study was accomplished during the period between April 01, 2020 and December 01, 2022.

We comparatively assessed whether the organization of the educational process conformed to the sanitary legislation of the Russian Federation[4].

The study involved handing out questionnaires to be filled in by the participants. The author's questionnaire was developed by experts from the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies and tested in 2015–2022. The questionnaires were filled in by parents of primary school children or by adolescents themselves who attended middle or senior school. Among other aspects, the questionnaire contained questions aimed at describing how schoolchildren interacted with different types of electronic devices and extra educational loads beyond educational programs provided at school.

Complex ophthalmological examination included visometry with Sivtseva tables, shadow-tests, autorefractometry, ophthalmoscopy with a direct ophthalmoscope, color sensitivity study with Rabkin's polychromatic tables, identification of the near and far point of vision, accommodation volume and reserves, strabismus quantification as per the Hirshberg's test, and binocular vision identification with the Worth Four Light Test.

We calculated prevalence of refractive disorders and accommodative dysfunctions; separately, prevalence of accommodative dysfunctions; prevalence of myopia including moderate and high one (the ratio between the number of diseases cases identified during a medical examination and the total number of examined schoolchildren multiplied by 100, (%)).

The present study was approved by the local Ethics Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (the meeting report No. 2 dated March 01, 2018). It was accomplished in conformity with the ethical principles stated in the WMA Declaration of Helsinki and the RF National Standard GOST-R 52379-2005 Good Clinical Practice (ICH E6 GCP). Parents or legal representatives of all the examined children gave their written informed consent to medical intervention.

Statistical analysis. Data were statistically analyzed with Jamovi statistical application, SPSS, and Excel-based software packages. When analyzing questioning data, we determined statistical significance of differrence between variables identified in subsamples and intensity of correlations between variables using correlation coefficients eligible for a specific quantity of samples (Spearman's, coefficient, Cramer' V, or phi coefficient) with a corresponding scale for estimating intensity of a correlation. Prevalence of diseases of the eye among schoolchildren attending analyzed schools was compared using Pearson's chi-square (χ^2) for fourfold tables; we also calculated a relative risk (*OR*) with 95 % confidence interval (*CI*). The results of logistic modeling are given as the determination coefficient (R^2) that indicates a per cent of variability for the dependent variable, Fisher's test (*F*), the constant (b_0), the regression coefficient (b_1), and statistical significance of a model (*p*). We built a ROC-curve (receiver operating characteristic) for the value indicating a 'grade'. The area under the curve or AUC, together with the

[4] SP 2.4.3648-20. Sanitarno-epidemiologicheskie trebovaniya k organizatsiyam vospitaniya i obucheniya, otdykha i ozdorovleniya detei i molodezhi (utv. Postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha RF ot 28 sentyabrya 2020 g. № 28; vved. v deistvie s 01.01.2021 g.) [SP 2.4.3648-20. Sanitary-epidemiological requirements to organizing education, leisure and health improvement of children and youth: Sanitary Rules (approved by the Order of the RF Chief Sanitary Inspector on September 28, 2020 No. 28; became valid on January 01, 2021)]. *GARANT: information and legal support*. Available at: https://www.garant.ru/products/ipo/prime/doc/74993644/ (April 11, 2023) (in Russian); 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 g. № 2; vved. v deistvie s 01.03.2021 g.) [SanPiN 1.2.3685-21. Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people: Sanitary Rules and Norms (approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 2; became valid on March 01, 2021)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (April 11, 2023) (in Russian).

model quality, was estimated as per conventional procedures. We relied on the Youden index values ((Se+Sp)-1) where Se is model sensitivity and Sp is model specificity) to identify a cut-off point of a grade for the development of myopia. In case the Youden index values were equal for different grades, we took a value for which sensitivity was close to specificity as a cut-off point. Differences were considered statistically significant at $p \leq 0.05$.

Results and discussion. Our comparative assessment of the education process established that some violations were common for both types of the analyzed schools such as duration of long breaks, switching between easy and difficult subjects during a day and a week, and even distribution of educational loads throughout a week. Apart from these violations, we established that small breaks between lessons on average equaled 9.66 ± 3.12 minutes in schools with profound studies of some subjects. This violated the requirements fixed in the item 3.4.16 of the Sanitary Rules SP 2.4.3648-20 (not shorter than 10 minutes) and was shorter than in ordinary comprehensive schools where the small breaks lasted 10.31 ± 3.09 minutes ($p = 0.045$).

We comparatively analyzed educational loads in hours and established that they were 19.2 and 5.5 % higher than their maximum permissible amount in primary and middle grades accordingly in comprehensive schools with profound studies of some subjects. In senior school, the educational loads were 5.4 % higher than the permissible amount in such schools. Our timing examinations of how long electronic teaching aids (ETAs) were used during classes revealed that an interactive whiteboard (IWB) was used 1.3–2.2 times longer than permitted during some classes in comprehensive schools with profound studies of some subjects. Average duration of IWB use was 1.2–2.6 times longer than in ordinary comprehensive schools ($p < 0.0001$). Average total IWB use was also up to 2.5 times longer in schools with profound studies of some subjects than in ordinary comprehensive schools ($p < 0.0001$–0.011). Duration of PC use during a class and the total PC use a day was 1.4–1.5 times longer than permitted in comprehensive schools with profound studies of some subjects; these indicators were 1.5–1.6 and 2 times higher accordingly in such schools than in ordinary comprehensive schools ($p < 0.0001$).

We analyzed how many electronic devices schoolchildren used and the age of their first contacts with such devices. As a result, we established that a half of students attending the analyzed comprehensive schools (52.5 %) usually contacted two different devices. However, the number of students who used 3 or even more devices was 1.5 times higher in schools with profound studies of some subjects than in ordinary comprehensive schools (33.1 against 22.1 %, $p = 0.001$; Cramer's V is 0.20; $p = 0.011$). In comprehensive schools with profound studies of some subjects, the number of schoolchildren who first used a tablet when they were younger than 6 years was 3.3 times higher (44.0 against 13.2 % in the reference group, $p = 0.004$; Cramer's V is 0.31; $p = 0.019$).

Our assessment of extra-school educational loads revealed that 1.4–1.5 times more respondents in the test group attended institutions of additional education (85.6 against 60.3 % in the reference group; $p < 0.0001$; the phi coefficient is 0.29; $p < 0.0001$) and were given homework in them (46.3 % in the test group and 31.4 % in the reference one; $p < 0.0001$; the phi coefficient is 0.15; $p < 0.0001$). Twenty-five point two percent of the children who attended schools with profound studies of some subjects and 20.3 % of those who attended ordinary comprehensive schools spent more than 20 hours a week on attending additional classes and doing homework, both given at schools and by institutions of additional education.

Table 1 provides the results of the complex eyesight diagnostics accomplished by an ophthalmologist. Refractive disorders and accommodative dysfunctions were 1.4 times more frequent in the test group than in the reference one; myopia was 1.3 times more frequent and moderate or high myopia was 2.4 times more frequent in the test group with its

Table 1

Ophthalmological examination of children attending two different types of schools

Examination results	The test group, $n = 312$		The reference group, $n = 492$		χ^2	p	*OR* (*CI*)
	n	%	n	%			
Refractive disorders and accommodative dysfunctions	181	58	202	41.1	21.3	< 0.001	1.41 (1.23–1.63)
Accommodative dysfunctions	56	17.9	69	14	2.24	0.163	1.28 (0.93–1.78)
Myopia	125	40.1	133	27	14.3	< 0.001	1.48 (1.22–1.81)
Moderate or high myopia	50	15.3	32	6.5	17.9	< 0.001	2.5 (1.62–3.75)

Table 2

Parameters of logistic regression models ‘Factor – probability of a response’

Factor	Response	b_0	b_1	F	p	R^2
Violation of maximum permissible weekly educational loads	Myopia	-6.73	0.21	30.0	< 0.001	0.52
Violation of permitted duration of PC use during classes	Myopia	-0.94	0.41	156.0	< 0.001	0.56
The number of used electronic devices	Refractive disorders and accommodative dysfunctions	-0.47	0.16	151.1	< 0.001	0.77

relative risk reaching 1.28–2.5 ($p < 0.001$). We did not establish any statistically significant differences between the groups with respect to separate accommodative dysfunctions and risks of their occurrence ($p = 0.163$).

We built one-factor logistic regression models to describe the relationship between refractive disorders and accommodative dysfunctions, myopia included, and factors of the educational process and lifestyle. As a result, we established statistically significant effects produced on the dependent variables by such factors as high weekly educational loads, irrational ETAs use at school, and the number of used electronic devices ($R^2 = 0.52–0.77$; $p < 0.001$) (Table 2).

We established a direct correlation between time spent on additional education and doing homework and higher frequency of myopia (the Spearman’s coefficient is 0.21; $p = 0.001$).

Our further analysis revealed that the median age at which myopia was diagnosed in schoolchildren attending schools with profound studies of some subjects tended to decline and amounted to 12 (11; 14) years against 13 (12; 14) years for schoolchildren who attended ordinary comprehensive schools ($p = 0.089$). We did not detect any statistically significant differences as regards the age at which accommodative dysfunctions occurred (12 (10; 13) against 11 (10; 14) years, $p = 0.532$).

Given the detected trend, we applied ROC-analysis in order to identify the critical threshold of studying at school (grade) for myopia development in schoolchildren attending the analyzed schools using the cut-off point. Good prognostic capabilities and reliability of the applied method were estimated as per the area of the ROC-curve above the line of the ‘worthless’ classifier for the value ‘grade’ with respect to myopia development both in the schoolchildren who attended comprehensive schools with profound studies of some subjects (AUC = 0.700; $p < 0.001$) and those attending ordinary comprehensive schools (AUC = 0.702; $p < 0.001$) with different values of the cut-off according to the ROC-analysis matrix.

For the schoolchildren who attended comprehensive schools with profound studies of some subjects, the cut-off point of the period of education for myopia development corresponded to the 5th grade (the maximum Yuoden index value is 0.31; the model sensitivity is

Table 3

Parameters of the ROC-analysis for identifying the cut-off point of a period of education for myopia development in the schoolchildren attending the analyzed comprehensive schools

Grade	Schools with profound studies of some subjects			Ordinary comprehensive schools		
	Sensitivity, %	Specificity, %	Yuoden index	Sensitivity, %	Specificity, %	Yuoden index
1	100	0	0.00	100	0	0.00
2	100	5.7	0.06	100	5.4	0.05
3	100	11.4	0.11	100	13.0	0.13
4	96.5	28.9	0.25	98.4	21.1	0.19
5	**88.2**	**42.5**	**0.31**	91.9	33.5	0.25
6	82.4	47.4	0.30	79.7	46.5	0.26
7	67.1	60.1	0.27	**69.9**	**57.8**	**0.28**
8	54.1	74.1	0.28	59.4	67.3	0.27
9	44.7	77.6	0.22	53.7	73.0	0.27
10	29.4	86.8	0.16	44.7	83.2	0.28
11	15.3	90.4	0.06	13.0	93.5	0.07

88.2 % and the model specificity is 42.5 %); the cut-off point corresponded to the 7th grade for the schoolchildren attending ordinary comprehensive schools (the maximum Yuoden index value is 0.28; the model sensitivity is 69.9 % and the model specificity is 57.8 %) (Table 3).

The aim of this study was to examine peculiarities and assess risks of myopia in children attending comprehensive schools with different educational programs.

We comparatively analyzed the organization of the education process and assessed whether it conformed to the valid sanitary legislation. As a result, we established that schools with profound studies of some subjects tended to have substantially elevated educational loads and violated the hygienic standards more frequently when drawing up timetables and organizing classes with ETAs use ($p < 0.0001$–0.045). All this increases 'ophthalmological costs' of learning. Our research data are consistent with the results reported by D.A. Eisfeld with colleagues [11] who investigated influence exerted by risk-inducing factors of the educational process and the environment on somatic health of students attending schools of different types; by A.G. Setko with colleagues [12] who examined peculiarities of the neuro-psychic state and life quality of students who attended innovative schools; by V.R. Kuchma and others [13] who estimated the organization of the educational process in profile classes in colleges. Statistically significant differences were identified when we compared the number of electronic devices used by schoolchildren and the age at which they had their first contacts with such devices, as well as volumes of additional educational loads beyond school ($p < 0.0001$–0.004). Direct influence exerted by the number of additional education institutions attended by schoolchildren on their health was confirmed in the study by O.P. Gritsina with colleagues [14, 15]. Uncontrollable use of gadgets by children and adolescents is another topical issue since it can contribute to eye disorders regardless of a school they attend [16].

Given the elevated weekly educational loads, too long periods of ETAs use during classes, and the growing number of electronic devices ($R^2 = 0.52$–0.77) used by schoolchildren who attend comprehensive schools with profound studies of some subjects, prevalence of refractive disorders and accommodative dysfunctions identified in this study is substantially higher than it is stated in the official statistical reports[5] [1]. Our research results do not

[5] Zdravookhranenie v Rossii. 2021: Statisticheskii sbornik [Healthcare in Russia. 2021: Statistical data collection]. *Rosstat.* Moscow, Federal State Statistics Service, 2021, 171 p. Available at: https://rosstat.gov.ru/folder/210/document/13218 (April 18, 2023) (in Russian).

contradict those reported in other studies with their focus on exposure to harmful factors of the educational process and its effects on schoolchildren's eyes [1, 7, 17, 18].

We identified that myopia tended to develop at a younger age in schoolchildren who attend comprehensive schools with profound studies of some subjects; frequency of myopia was 1.3–2.4 times higher among them and moderate or high myopia were also identified more frequently; we established relative risks of the disease for them to be equal to 1.48–2.5; the different cut-off points showing the grade during which myopia started to develop in schoolchildren were established as per the ROC-curves with good quality of the created models (AUC = 0.700; $p < 0.001$; AUC = 0.702; $p < 0.001$). All this indicates the necessity to pay greater attention to timely diagnostics of eye problems and diseases in schoolchildren considering the peculiarities of the contemporary educational process [19, 20].

Conclusions:

1. When educational programs involve profound studies of some subjects, the educational process and some lifestyle aspects associated with it are characterized with a growth in educational loads by 5.4–19.2 % against the hygienic standards; violated requirements to duration of short breaks and ETAs use during classes (the indicators are usually 1.3–2.2 times higher than the corresponding hygienic standards, $p < 0.0001$), early start of digital activity and highly intensive use of electronic devices (the Cramer's V is 0.20–0.31, $p = 0.011–0.019$) as well as active involvement into additional education (the phi coefficient is 0.29, $p < 0.0001$).

2. Under exposure to leading risk factors (weekly educational loads being higher than their maximum permissible level, irrational ETAs use during classes, and the growing number of used electronic devices), their contributions being confirmed by logistic modeling results ($R^2 = 0.52–0.77$, $p < 0.001$), myopia, including moderate or high myopia, develops 1.3–2.4 times more frequently and at an younger age, and the relative risk of the diseases also grows by 1.5–2.5 times ($OR = 1.48–2.50$; $CI = 1.22–3.75$; $p < 0.001$).

3. The ROC-analysis data indicate the significance of myopia development in schoolchildren attending comprehensive schools with profound studies of some subjects already in the 5th grade whereas it develops significantly in schoolchildren who attend ordinary comprehensive schools only in the 7th grade. This should be considered when developing and implementing health protection technologies at schools of different types.

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Research article

HYGIENIC ASSESSMENT OF WORKING CONDITIONS AND OCCUPATIONAL INCIDENCE AMONG MINING WORKERS IN THE ARCTIC ZONE OF THE NORILSK INDUSTRIAL AREA

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The development of the Arctic zone as a strategic resource base and its rational use aimed at the economic growth acceleration is a key interest of the Russian Federation in this region. The occupational environment in mining industry is associated with unique working conditions. Underground mining makes workers' health protection the most significant task.

The aim of this study was to perform hygienic assessment of working conditions, occupational incidence and occupational health risks for workers employed in mining industry in the Arctic zone of the Norilsk industrial area. Occupational health risks were assessed using indicators outlined in the Guide R 2.2.2006-05 The Guide on Hygienic Assessment of Factors Related to Working Environment and Work Process. Exposure to occupational noise and considerable work hardness are priority factors in the analyzed industry that cause occupational diseases. Occupational diseases among workers employed in mining industry in the Norilsk industrial area belonged to six nosologies. Vibration disease, stages 1 and 2, makes the greatest contribution to the overall structure of occupational incidence since it accounts for 68.6 % in it. The second place belongs to two-sided sensorineural hearing loss, stages 1 and 2, 13.5 %. Radiculopathy occupies the third rank place accounting for 10.9 %.

Unacceptable occupational health risks were identified at 76.8 % of workplaces. A high share of workplaces with unacceptable occupational health risks leads to high occupational incidence among mining workers in the Norilsk industrial area, its levels being higher than the national average.

Keywords: *special assessment of working conditions, occupational factors, risk assessment, violation of hygienic standards, occupational diseases, mining industry, Arctic zone, Norilsk industrial area.*

The development of the Arctic zone as a strategic resource base and its rational use aimed at the economic growth acceleration is a key interest of the Russian Federation in this region[1] [1–5]. The occupational environment in mining industry is associated with unique working conditions, which, according to the International Labor Organiza-

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tion, pose a serious hazard for workers' health [6].

The Norilsk mining sector is the leading area in the Russian Federation as regards mining and production of nickel, copper, cobalt, silver, and platinum metals [7–11].

Protection of workers' health becomes the most significant task in Norilsk due to harsh climate in the Arctic zone and hard working conditions associated with underground mining [12–17].

In this study, our **aim** was to perform hygienic assessment of working conditions, occupational incidence and occupational health risks for workers employed in mining industry in the Arctic zone of the Norilsk industrial area.

Materials and methods. We analyzed the results of special assessment of working conditions at mining workers' workplaces in the Norilsk industrial area and occupational incidence over a 10-year period, from 2013 to 2022. All the relevant data for the analysis were taken from the State Report on Sanitary-Epidemiological Welfare of the Population in Krasnoyarsk Region and from the archives of the Rospotrebnadzor Regional Office in Krasnoyarsk. Occupational health risks were assessed using indicators outlined in the Guidelines R 2.2.2006-05 'The Guide on Hygienic Assessment of Factors Related to Working Environment and Work Process'[2].

Results and discussion. We analyzed working conditions at workplaces of 7872 workers employed in the mining industry in the Norilsk industrial area. As a result, we established that, according to the special assessment of working conditions (SAWC) performed in 2016, hygienic standards were violated as per one or several harmful occupational factors at 1838 workplaces (76.8 %).

The most common harmful occupational factors include occupational noise, work hardness, chemical factors, aerosols with predominantly fibrogenic effects, total and local vibration (Figure 1).

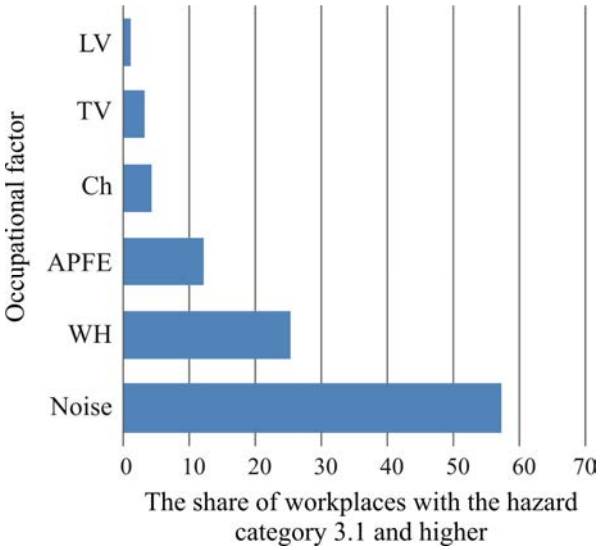

Figure 1. The share of workplaces (%) with the hazard category 3.1 and higher at mining enterprises in the Norilsk industrial area: LV is local vibration, TV is total vibration, Ch is chemicals in workplace air, APFE is aerosols with predominantly fibrogenic effects, WH is work hardness

According to the SAWC results, occupational noise was higher than the established hygienic standards at 1368 workplaces (57.2 %) and reached 105 dBA; this level is by 25 dBA higher than the maximum permissible one (MPL is 80 dBA) and therefore working conditions with this exposure are classified as having the hazard category 3.3 (harmful, the hazard degree is 3). The highest noise levels were established for such occupations as drilling unit operator, cargo handling machine operator, self-propelled mining machine operator, electric locomotive driver, working face miner, drift miner, blast-hole driller, breaker, hatch handler, and others.

[2] The Guidelines R 2.2.2006-05. Guide on Hygienic Assessment of Factors of Working Environment and Work Load. Criteria and Classification of Working Conditions (approved by the RF Chief Sanitary Inspector on July 29, 2005; became valid on November 01, 2005). *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200040973 (April 12, 2023) (in Russian).

The second place as per frequency belongs to work hardness according to the SAWC results. The hygienic standards were violated as per this harmful occupational factor at 606 workplaces (25.3 %). Most workplaces of basic mining occupations such as mining foreman, working face miner, underground miner, blaster, fueler, drift miner, drilling unit operator, cargo handling machine operator and some others have working conditions that belong to the hazard category 3.2 (harmful, the hazard degree is 2).

The hygienic standards established for levels of fibrogenic aerosols were violated at 291 workplaces (12.2 %) and working conditions there were classified as having the hazard category 3.1. Very high levels of aerosols with predominantly fibrogenic effects were identified only at two workplaces of timber-men and one workplace of an electric gas welder and therefore working conditions at these workplaces were classified as having the hazard category 3.2.

Chemical pollution in workplace air was established at 101 workplaces (4.2 %); working conditions were classified as having the hazard category 3.2 as per this factor only at four of them (electric gas welder, cargo handling machine operator, and drilling unit operator).

Total vibration was higher than the established hygienic standards at 74 workplaces (3.1 %) at mining enterprises located in the Norilsk industrial area. Levels that were 12 dB higher than permissible ones were identified at 26 of them (cargo handling machine operator, breaker, drilling unit operator) (the hazard category 3.2).

The hygienic standards established for local vibration were violated at 24 workplaces (1 %); local vibration levels were 6 dB higher than the permissible ones at eight of them (working face miner, drift miner, fueler), the working conditions had the hazard category 3.2.

Complex exposure to harmful occupational factors was established to produce negative effects on health of workers employed at mining enterprises in the Norilsk industrial area. Unsafe levels of such factors that exceeded MPL were identified at workplaces of cargo handling machine (CHM) operators, electric gas welders, drift miners, working face miners, self-propelled mining machine (SPMM) operators, mine testers, electric locomotive drivers, grinder operators, conveyer operators, hatch handlers, blast-hole drillers, workers responsible for timber delivery to a mine, breakers, and drilling unit operators (Table 1).

Having analyzed the SAWC results obtained at mining enterprises in the Norilsk industrial area, we established that the share of workplaces with negligible (tolerable) health risks was 23.16 %; low (moderate) risk, 34.28 %; average (considerable) risk, 27.3 %; high (intolerable) risk, 15.26 %. We did not identify any workplaces with extremely high (intolerable) health risks (Table 2).

Harmful working conditions and simultaneous exposure to several harmful occupational factors (the hazard category 3.1 and higher) caused 957 cases of occupational diseases that were diagnosed over 10 years from 2013 to 2022 at mining enterprises located in the Norilsk industrial area (Figure 2).

An occupational disease was diagnosed at an average worker's age being 50.4 years; working records for work under harmful and hazardous conditions, 23.1 years; working records for an occupation for which an occupational disease was diagnosed, 16.1 years. The greatest number of occupational diseases was identified among cargo handling machine operators, 226 (23.6 %); blast-hole drillers, 143 (14.9 %); working face miners, 126 (13.2 %); blasters (including blaster foremen), 89 (9.3 %); timber-men, 73 (7.5 %); drift miners, 69 (7.2 %); electric locomotive drivers, 53 (5.5 %); drilling unit operators, 44 (4.6 %). The remaining 14 % of occupational diseases were diagnosed in such occupations as hatch handlers, self-propelled mining machine operators, breakers, repairmen, welders, road workers, and some others.

Table 1

Hygienic assessment of occupational risks according to the SAWC for different workplaces at mining enterprises in the Norilsk industrial area

No.	Occupation	Harmful occupational factors (the hazard category 3.1 and higher)					
		Noise	Total vibration	Local vibration	Work hardness	APFE	Chemical factor
1	CHM operator	+	+	+	+	-	+
2	Drift miner	+	-	-	+	+	+
3	Working face miner	+	-	-	+	+	+
4	SPMM operator	+	+	+	+	+	+
5	Electric locomotive driver	+	+	-	-	+	-
6	Grinder operator	+	-	-	+	+	-
7	Drilling unit operator	+	+	+	+	-	-
8	Conveyor operator	+	+	-	+	+	-
9	Mine tester	+	-	-	+	+	+
10	Hatch handler	+	-	-	+	+	-
11	Blast-hole driller	+	-	-	+	+	-
12	Worker responsible for timber delivery to a mine	+	-	-	+	+	-
13	Breaker	+	+	-	+	+	-
14	Timber-man	+	-	-	+	+	-

Table 2

Hygienic assessment of occupational risks according to the SAWC for different workplaces at mining enterprises in the Norilsk industrial area

The number of work-places	Negligible (tolerable) risk		Low (moderate) risk		Average (considerable) risk		High (intolerable) risk		Very high (intolerable) risk	
	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
2392	554	23.16	820	34.28	653	27.30	365	15.26	-	-

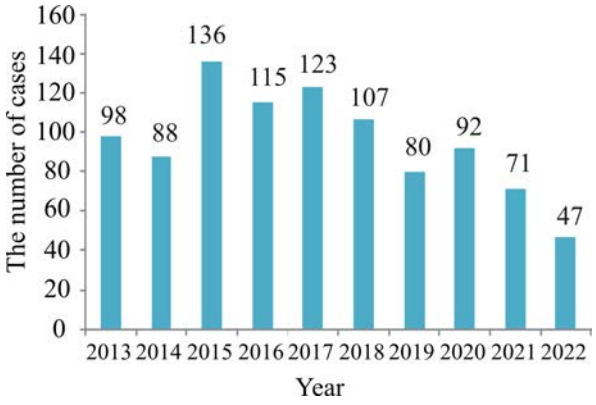

Figure 2. The number of confirmed occupational disease cases among workers employed at mining enterprises located in the Norilsk industrial area

Occupational diseases among workers employed in mining industry in the Norilsk industrial area belong to six nosologies. Vibration disease, stages 1 and 2, makes the greatest contribution to the overall structure of occupational incidence since it accounts for 68.6 % in it. The second place belongs to two-sided sensorineural hearing loss, stages 1 and 2, 13.5 %. Radiculopathy occupies the third rank place accounting for 10.9 %. Occupational respiratory diseases, malignant neoplasms of various localization, and diseases of the autonomous nervous system account for 7 %.

Our study has established that working conditions do not conform to the existing hygienic standards at more than 75 % of workplaces at mining enterprises located in the Norilsk industrial area. This level becomes obvious due to higher occupational incidence among mining workers; it is higher than both the average Krasnoyarsk level and the national average. An identified decline in levels of occupational diseases over the last three years requires further investigation and substantiation of reasons for the trend.

Harmful occupational factors have caused 93 % of all the established occupational diseases among workers employed in mining industry in the Norilsk industrial area. This can be due to automation of technological processes, active use of dust suppression inside a mine, and lower emissions from mining machinery equipped with internal combustion engines.

Seventy-five point seven percent of all the occupational diseases have been established for only six occupations, namely, cargo handling machine operators, blast-hole drillers, working face miners, blasters (including blaster foremen), timber-men, and drift miners. At these workplaces, a worker is simultaneously exposed to several harmful factors, between 2 and 5 usually, with their levels deviating from the maximum permissible ones.

Conclusion. Exposure to occupational noise and considerable work hardness are priority factors in the analyzed industry that cause occupational diseases; this is in line with findings by other authors [18–20]. Also the hygienic standards have been established to be violated at workplaces as per such factors as aerosols with predominantly fibrogenic actions and chemical pollution in workplace air. Combined exposure to several harmful occupational factors produces negative effects on workers' health and creates unacceptable occupational health risks at 76.8 % of the analyzed workplaces. A high share of workplaces with unacceptable occupational health risks leads to high occupational incidence among mining workers in the Norilsk industrial area, its levels being higher than the national average.

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Research article

WORK ENVIRONMENT OF THE AUTOMOTIVE INDUSTRY AS A RISK FACTOR OF DISEASES OF THE CIRCULATORY SYSTEM AMONG WORKERS

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This study has shown that working conditions of basic occupational groups in the automotive industry involve combined exposure to several harmful occupational factors. Major harmful occupational factors include intense noise, vibration, work hardness and chemical levels; their intensity varies between permissible levels (the hazard category is 2.0) and harmful ones (the hazard category 3.1–3.2, harmful working conditions with hazard levels 1 or 2). This may induce occurrence or exacerbation of basic non-communicable diseases such as diseases of the circulatory system (CSDs), occupational and work-related diseases.

CSDs were diagnosed in 37.7 % of workers employed at automotive productions. The most frequent diseases include hypertension (EH) that accounted for 28.2 %; cerebrovascular diseases (CVDs), 6.5 %; ischemic heart disease (IHD), 3.6 %. CSDs developed at an early age in workers exposed to harmful occupational factors belonging to the hazard category 3.1–3.2; these diseases became more frequent as work records got longer, and were more frequently exacerbated with acute cardiovascular conditions. We assessed the total cardiovascular risk using the SCORE scale and established that shares of people with high and very high cardiovascular risks were higher among painters, laboratory assistants responsible for chemical analysis, and repairmen. The attributive risk of new cardiovascular diseases ranged between 9.6 (turners) and 42.6 (repairmen) cases.

The highest occupational CSDs causation was identified for repairmen and mechanics at mechanical assembly production; average causation was established for stampers, painters, laboratory assistants dealing with chemical analysis, crane operators, and turners.

Keywords: *automotive industry, working conditions, occupational factors, workers, diseases of the circulatory system, risk, occupational causation.*

The automotive industry produces various makes of cars and accounts for 23 % of the total civil engineering output in Russia. Dozens of thousand workers are employed at car-making productions all over the country. Workers from the basic occupational groups have to work under such conditions that can be estimated as harmful, hazard category 1 or 2 (3.1 or 3.2). The priority harmful occupational factors include, first of all, some physical ones

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such as intense occupational noise and vibration; they are followed by chemical pollution in workplace air, predominantly with aerosols, and physical overloads [1–3]. Intensive noise and vibration at production, their quantitative and qualitative features, and duration of exposure to them throughout the entire work process frequently induce various health disorders caused by lower adaptive reserves of the body and weaker protection and compensatory reactions [4–6]. Most workplaces in this branch involve workers' exposure to a whole set of harmful production factors [1, 4]. Increasing production capacities in the automotive industry due to a higher demand on the market make their effects on the body even more significant, create elevated risks of acute and chronic diseases of various organs and systems including life-threatening states caused by cardiovascular pathology [7–10].

Out of more than 200 risk factors (RF) causing occurrence and progression of CSDs (diseases of the circulatory system), only about nine leading ones account for almost 95 % of the population health risk. They are essential hypertension, diabetes mellitus, dyslipidemia, tobacco smoking, strong alcohol abuse, abdominal obesity, depression / stress, low physical activity, and low consumption of vegetables / fruits [11–14]. Some studies reported that occupational risk factors could also make a substantial contribution to growing incidence of CSDs among workers. These factors include noise; toxic chemicals and aerosols in workplace air; harsh climate and microclimate; physical overloads and work intensity caused by the necessity to work in shifts and at night; stress and psychoemotional loads at a workplace due to high responsibility for the work process [9, 15–20].

This study is relevant since very few research works investigate prevalence of CSDs in workers employed in the automotive industry; we should remember that these diseases are a major cause of high mortality and disability among working age people. Given that, conformity to the safety requirements as regards exposure to occupational factors ensures health protections and provides the necessary levels of work capacity. This calls for developing scientifically grounded approaches to preventing diseases of the circulatory system and reducing risks of their development.

The aim of this study was to analyze incidence of CSDs among workers from various occupational groups exposed to a set of harmful occupational factors at workplaces in the automotive industry.

Materials and methods. We performed hygienic examination of working conditions at 250 workplaces at a leading car-making enterprise in Russia; the examination involved assessing quantitative and qualitative parameters of harmful occupational factors according to the Guide R 2.2.2006-05[1] and relied on data obtained by our own research and materials of the special assessment of working conditions (SAWC).

The modern production in the automotive industry involves a lot of processing operations including assembly, mechanical processing and subsequent assembly of components and large-size units as well as non-standard components.

The leading technical processes in car-making production are assembly of components and mechanical processing of pieces and non-standard units as well as large-size components. Mechanics at mechanical assembly production (MAP mechanics) is the leading and the largest occupational group at car-making enterprises; they are followed by stampers who are exposed to occupational noise with its levels higher than maximum permissible ones by 7–16 dBA as per the equivalent level (the hazard category 3.2), local vibration (the hazard category 3.1), physical overloads (lifting and moving heavy weights, local loads on the shoulder girdle) (the hazard category 3.1) (Table 1). Working

[1] Guide R 2.2.2006-05. Guide on Hygienic Assessment of Factors of Working Environment and Work Load. Criteria and Classification of Working Conditions (approved by G.G. Onishcheno, the RF Chief Sanitary Inspector on July 29, 2005; became valid on November 01, 2005). *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200040973 (January 06, 2023) (in Russian).

Table 1

The final assessment of working conditions at workplaces in the automotive industry

Occupation	Harmful occupational factors					The overall assessment of working conditions
	Chemical	Noise (L equiv.)	Micro-climate	Local vibration	Work hardness	
MAP mechanics	2	3.2	-	3.1	3.1	3.2
Stampers	-	3.2	-	3.1	3.1	3.2
Conveyor and crane operators	2	2	2	-	3.1	3.1
Turners; repairmen	2	3.1	-	-	3.1	3.1
Painters	3.1	3.1	-	-	3.1	3.2
Laboratory assistants responsible for chemical analysis	3.1	2.0	2.0	-	3.1	3.2

conditions for other occupational groups involve elevated exposures to the following occupational factors: conveyor operators and crane operators, work hardness; turners and repairmen, work hardness and noise; painters and laboratory assistants responsible for chemical analysis, exposure to such toxicants as phenol, toluene, formaldehyde, white spirit, lead and its compounds, xylene, ammonia, and chromium trioxide (the hazard category 3.2). In addition, painters are exposed to physical overloads (the hazard category 3.1) and noise (the hazard category 3.1).

Therefore, elevated noise and local vibration that are higher than their MPLs, high physical overloads, and elevated levels of highly toxic chemicals in workplace air able to create chemical health risks for workers are the leading adverse factors that make working conditions at the analyzed workplaces harmful for workers' health. Peculiar features of work processes at the analyzed productions create specific working conditions at workplaces of these basic occupational groups. These conditions involve combined exposure to several harmful occupational factors at most analyzed workplaces.

Workers' health was examined in 2018–2019 in conformity with the Order by the RF Ministry of Health and Social Development issued on April 12, 2011 No. 302n[2] by performing a periodical medical examination (PME). We examined 583 workers from the basic occupational groups: MAP mechanics (173 people), repairmen (99 people), turners (130 people), crane operators (67 people), conveyor operators (39 people), painters and laboratory assistants responsible for chemical analysis (75 people). The reference group included 150 production workers who were not exposed to harmful occupational factors at their workspaces. All the examined workers were comparable in terms of work records and age. The examination involved questioning based on a standard questionnaire to estimate a person's health relying on their complaints and to establish non-modifiable and modifiable factors of cardiovascular risks (as per the SCORE scale). In addition, all the workers were examined by a cardiologist.

We did not identify any significant differences as per work records or age between the analyzed occupational groups.

We determined a relative risk (RR) and its 95 % confidence interval (CI). Occupational causation of CSDs was estimated depending on relative risk (RR) levels and the etiological fraction (EF). All the calculations were performed using Microsoft Excel.

[2] Ob utverzhdenii perechnei vrednykh i (ili) opasnykh proizvodstvennykh faktorov i rabot, pri vypolnenii kotorykh provodyatsya obyazatel'nye predvaritel'nye i periodicheskie meditsinskie osmotry (obsledovaniya), i Poryadka provedeniya obyazatel'nykh predvaritel'nykh i periodicheskikh meditsinskikh osmotrov (obsledovanii) rabotnikov, zanyatykh na tyazhelykh rabotakh i na rabotakh s vrednymi i (ili) opasnymi usloviyami truda: prikaz Minzdravsotsrazvitiya RF ot 12.04.2011 № 302n [On Approval of the lists of harmful and (or) hazardous occupational factors or works that require mandatory preliminary and periodical medical examinations (check-ups), and the Order of accomplishing mandatory preliminary and periodical medical examinations (check-ups) of workers performing hard works or working under harmful and (or) hazardous working conditions: the Order by the RF Ministry of Health and Social Development dated April 12, 2011 No. 302n] (became invalid on April 01, 2021 based on the joint Order by the RF Ministry of Labor and RF Ministry of Health issued on December 31, 2020 No. 988n/1420n). *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/902275195 (December 24, 2022) (in Russian).

Table 2

CSDs prevalence in workers with basic occupations of the automotive industry (cases/100)

Occupation	EH	CVDs	IHD	Total
Stampers (*n* = 61)	24.6	6.5	6.5	37.7
MPA mechanics (*n* = 173)	33.1	6.4	2.5	41.6
Repairmen (*n* = 99)	43.4	7.0	10.1	60.6
Turners (*n* = 130)	21.5	4.6	1.5	27.6
Crane operators (*n* = 67)	16.4	11.9	0	28.8
Conveyor operators (*n* = 39)	10.3	5.1	0	15.3
Painters, laboratory assistants responsible for chemical analysis (*n* = 75)	31.5	5.3	4.0	41.7
Total (644)	28.2	6.5	3.6	37.7
The reference group (*n* = 150)	13.1	1.3	3.3	18.0

Results and discussion. We analyzed generalized qualitative and quantitative parameters of the examined occupational factors. As a result, we established that, according to the final assessment of working conditions, they corresponded to the hazard category 3.1 or 3.2 for the examined workers employed in the automotive industry. Exposure to occupational risk factors typical for car-making production can promote a growth in incidence of non-communicable, occupational and work-related diseases among workers.

Clinical and laboratory tests performed within the periodical medical examination revealed that diseases of the circulatory system were diagnosed in more than one third of the examined workers (37.7 %), primarily, essential hypertension (EH) (28.2 %), cerebrovascular diseases (CVDs) (6.5 %) and ischemic heart disease (IHD), (3.6 %) (Table 2). Such diseases of the circulatory system as lower limb varicose veins, atherosclerosis of the lower limb arteries or the aorta were diagnosed in singleton cases.

High risks of effects produced by occupational factors on the development of essential hypertension were identified for workers from basically all the analyzed occupational groups: stampers (RR = 1.84; CI: 1.01–3.36), MAP mechanics (RR = 2.47; CI: 1.56–3.90), repairmen (RR = 3.26; CI: 2.04–5.19), turners (RR = 1.23; CI: 0.63–2.43), and painters (RR = 2.40; CI: 1.42–4.06). The highest relative risk was identified for painters and laboratory assistants responsible the chemical analysis; repairmen and MAP mechanics followed. The examination established that, according to medical records, essential hypertension was diagnosed in the workers with the basic analyzed occupations at a considerably younger age (38–49 years) than in the workers from the reference group where the disease was more frequently diagnosed at an age of 50–62 years. We can assume that exposure to such harmful occupational factors as intense noise higher than the MPL and work hardness has its negative influence on EH occurrence and progression. We should mention that the SAWC performed for the analyzed workplaces did not estimate work intensity in any of the analyzed occupational groups and this fact raises certain concerns.

IHD was established in 3.6 % of the examined workers, basically, in the senior age group (50–59 years and older); the disease was diagnosed in singleton cases in the age group of 40–49 years. The analysis of IHD nosologic forms revealed that workers predominantly suffered from angina of effort (87.3 %); ischemic arrhythmia and post-infarction cardiosclerosis were quite rare (3.8 % and 8.9 % accordingly).

Developing IHD against long-term essential hypertension (not shorter than 7–10 years) was established in 17.8 % of all the workers with CSDs, mostly, in people older than 55 years. Complicated IHD was established in 0.7 % of the workers from the basic occupational groups and was represented by acute cardiovascular states (myocardial infarction and acute cerebrovascular accidents in medical case history). This was the reason for un-

scheduled capability assessment and the necessity to move some workers to another workplace without any exposure to harmful and hazardous occupational factors.

Cerebrovascular diseases were mostly diagnosed in workers older than 40 years and were represented by chronic vascular pathologies such as chronic cerebral ischemia at its initial stage. The pathology became more frequent in older workers with longer work records at car-making production.

Our assessment of the total cardiovascular risks using the SCORE system established higher shares of people with high and extremely high risks among painters, laboratory assistants responsible for chemical analysis and repairmen against the reference group ($p < 0.05$) (Table 3).

Work records longer than 8–10 years involve greater frequency of high and extremely high risks and lower frequency of moderate risks of unavoidable cardiovascular disasters. It is noteworthy that it was workers from the aforementioned occupational groups who worked under the most harmful working conditions (the hazard category 3.1–3.2) according to the hygienic criteria.

Assessment of posterior occupational risk should rely on such basic indicators as prevalence of cardiovascular diseases among workers with different occupations typical for the analyzed production as well as the level of their occupational causation identified by assessing relative risks (RR) and the etiological fraction of occupational risks in occurrence of cardiovascular pathology. It is also important to examine an attributive or additional risk (AR) of CSDs development (Table 4).

Table 3

Assessment of the total cardiovascular risk for workers employed in the automotive industry as per the SCORE scale ($p \pm m$)

Occupation	Total cardiovascular risk as per SCORE scale			
	low	moderate	high	extremely high
Stampers ($n = 61$)	11.7	45.7	28.7	13.9
MAP mechanics ($n = 173$)	8.9	50.2	30.2	10.7
Repairmen ($n = 99$)	9.7	44.4	31.8	14.1*
Turners ($n = 130$)	10.7	53.9	22.3	13.1
Crane operators ($n = 67$)	13.9	54.7	21.2	10.2
Conveyor operators ($n = 39$)	12.5	54.2	21.3	12.0
Painters, laboratory assistants responsible for chemical analysis ($n = 75$)	10.0	45.7	34.2*	10.1
The reference group ($n = 150$)	14.2	56.3	22.0	9.5

N o t e: *$p < 0.01$, the difference from the reference group is statistically authentic.

Table 4

Assessment of occupational causation and additional risks of CSDs in workers employed in the automotive industry

Occupation	RR	EF	AR, 100 people	Level of causation
Stamper ($n = 61$)	1.7	41.9	13.3	medium
MAP mechanics ($n = 173$)	2.3	56.5	23.3	high
Repairmen ($n = 99$)	3.4	70.5	42.6	high
Turners ($n = 130$)	1.5	33.3	9.6	medium
Crane operators ($n = 67$)	1.6	37.5	10.8	medium
Conveyor operators ($n = 39$)	0.7	-	-	absent
Painters, laboratory assistants responsible for chemical analysis ($n = 75$)	1.9	47.3	16.9	medium

N o t e: RR is relative risk, EF is etiological fraction, AR is attributive risk.

Additional (attributive) risks (AR) ranged between 9.6 (turners) and 42.6 (repairmen) new cases of cardiovascular diseases per 100 workers against the CSDs prevalence in the reference group.

The highest occupational causation of CSDs was identified for repairmen (the hazard category of working conditions is 3.1) (RR = 3.4; EF = 70.5 %) and MAP mechanics (the hazard category is 3.2) (RR = 2.3; EF = 56.5 %).

Medium occupational causation of CSDs was identified for stampers (the hazard category is 3.2) (RR = 1.7; EF = 41.9 %), painters and laboratory assistants responsible for chemical analysis (the hazard category is 3.2) (RR = 1.9; EF = 47.3 %), crane operators and turners (the hazard category is 3.1) (RR = 1.6; EF = 37.5 % and RR = 1.5; EF = 33.3 % accordingly).

We did not establish any occupational causation of CSDs for conveyor operators.

Diseases of the circulatory system occupy the leading place among reasons for extreme mortality and disability of working age people as per their prevalence and severity of their complications [20, 21]. Such lifestyle factors as consumption of fatty and refined foods, harmful alcohol use, tobacco smoking and use of electronic cigarettes, as well as low physical activity, hypertriglyceridemia and obesity are the major causes of the cardiovascular pandemic [20, 22]. At the same time, a risk of CSDs as an occupational pathology in workers who work under harmful and hazardous conditions occurs not only due to modifiable or non-modifiable lifestyle factors. It is caused by working under exposure to harmful occupational factors that are potentially able to induce the development of cardiovascular pathology and prolong its clinical course, just as we reported in our study [22–24].

Our research at a large car-making production has revealed that harmful working conditions are created by a set of occupational factors and factors related to work process such as noise, vibration, chemicals in workplace air, and physical overloads. Their intensity varies between permissible (the category 2.0) to harmful levels (the hazard category (3.1–3.2). Medical examination revealed CSDs in almost 40 % of the examined production workers; these diseases were detected among repairmen, MAP mechanics, stampers and painters authentically more frequently than in the reference group. Essential hypertension was diagnosed in practically each third worker (29.8 %); cerebrovascular diseases and ischemic heart disease were not so frequent, 5.6 % and 4.9 % accordingly. It is noteworthy that the risk of CSDs development was higher for workers with the analyzed occupations typical for the automotive industry at a younger age than for people who were not exposed to harmful occupational factors at their workplaces. In addition, CSDs often had complications such as acute cardiovascular events in workers with the basic occupations of the automotive industry. The risk assessment as per the SCORE scale identified high and extremely high risks of fatal cardiovascular complications for 32.7 % workers with the basic production occupations and 18.1 % had a medium risk.

Attributive risks of CSDs ranged between 9.6 (turners) and 42.6 (repairmen) new cases per 100 people. Our assessment of CSDs occupational causation established that the level of this causation was high for repairmen and MPA mechanics; it was medium for stampers, painters, laboratory assistants, crane operators and turners.

Therefore, the working environment at enterprises operating in the automotive industry is a significant risk factor able to cause CSDs occurrence and progression in workers. This is in line with findings reported by several authors who examined CSDs prevalence and clinical course in workers employed in various sub-branches of civil engineering. Production conditions create combined exposure to a set of harmful occupational factors, and not to just one isolated occupational factor, for a worker. As work records grow longer, chronic non-communicable pathology, CSDs included, occurs and progresses in workers under exposure to harmful occupational, social and communal factors. This leads to growing

numbers of applications for medical aid [4, 25, 26]. Some authors provide convincing evidence that exposure to intense noise and vibration together with non-occupational risk factors leads to growing incidence of cardiovascular diseases. This requires effective primary prevention aimed at reducing mortality among workers [27–29].

Conclusions. The analyzed set of harmful occupational factors is a risk factor able to promote CSDs development in workers employed in the automotive industry. These harmful occupational factors include intense occupational noise, vibration, and work hardness. The assessment of the total cardiovascular risk as per the SCORE scale revealed that a share of people with high and extremely high risks was higher than in the reference group among painters, laboratory assistants responsible for chemical analysis and repairmen. The attributive risk of new CSDs cases ranged between 9.6 and 42.6. Harmful working conditions in the automotive industry (the hazard category 3.1–3.2) are among reasons for the development of occupational CSDs in workers, the level of occupational causation varying from medium to high. Since the automotive industry is developing quite intensively, this requires solid substantiation provided for organizational and prevention activities aimed at protecting workers' health.

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Review

RISKS OF HAIs: PROBLEMS AND PITFALLS

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At present, a major challenge in research that addresses risks of hospital-acquired infections (HAIs) is the lack of methodological and theoretical studies generalizing the available knowledge in the sphere whereas applied works are plentiful. In recent years, methods of influence on the epidemic process of HAIs have been reassessed and some experts believe transition to the risk-based approach to be quite promising in this respect. This approach makes it possible to take timely measures aimed at reducing risks of such infections in advance. Since the risk-based approach within epidemiological safety is only starting to be integrated into the whole system of healthcare safety, development and specification of its individual components seems to be a promising trend in healthcare support. The key role in creating an effective system for control and surveillance over hospital-acquired infections belongs to activities related to development of scientific approaches to systematizing and unifying indicators that describe the subject area of HAIs risks in healthcare organizations of various profiles; improvement of the methodology for analyzing HAIs risks, the risk-based approach and risk management technologies within surveillance over such infections; optimization of science-based approaches to decision-making that relies on the risk-based approach and HAIs risk management technologies; development of methodical guidelines on monitoring, assessment, and prediction of HAIs risks in healthcare organizations of various profiles.

Keywords: *healthcare organizations, epidemic process, epidemiological safety, hospital-acquired infections, risks, risk parameters, risk management, risk-based approach.*

This review aims to discuss the current state of HAIs risk examination and the risk-based approach within epidemiological safety of healthcare; another aim is to identify activities necessary for the development of theoretical approaches to systematizing and unifying indicators that describe the subject area of risk.

The World Health Organization (WHO) considers patient safety a serious challenge of global healthcare that tends to get aggravated[1]. Provision of patient safety, just as healthcare quality, remains a priority target of any national healthcare system[2] [1–11]. According to WHO expert estimates, the occurrence of adverse events, resulting from unsafe care, is likely to be one of the 10 leading causes of death and disability worldwide. Annually, millions of patients suffer due to unsafe healthcare in hospitals and as a result 2.6 million

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[1] Patient safety. *WHO*. Available at: https://www.who.int/health-topics/patient-safety#tab=tab_1 (April 12, 2023).

[2] Bezopasnost' patsienta: rukovodstvo [Patient safety: the guide]. In: N.A. Levkina ed.; E.L. Nikonov transl. form English. Moscow, GEOTAR-Media, 2010, 184 p. (in Russian).

people die in low- and middle-income countries alone[3].

Globally as many as four out of 10 patients are harmed while receiving outpatient (ambulatory) care, with up to 80 % of the harm considered to have been preventable. Diagnostic errors contribute to approximately 10 % of patient deaths and account for 6–17 % of all unwanted harmful events in hospitals[3]. In high-income countries, each tenth patient is harmed when receiving inpatient care. Most harmful errors are related to diagnosis and prescription and the use of medicines [12]. According to the data reported in the meta-analysis by E.N. de Vries and others [13], which was based on examining more than 74,000 treatment cases, the median overall incidence of in-hospital adverse events was 9.2 %, with a median percentage of preventability of 43.5 %. Although more than half (56.3 %) of patients experienced no or minor disability, 7.4 % of events were lethal.

Hospital-acquired infections (HAIs; sometimes also called healthcare-acquired infections or HCAIs) are a major challenge for patient safety as they annually do harm to hundreds of millions worldwide [9, 10, 14]. Although the risk of HAIs is universal and occurs in every healthcare organization worldwide, its global burden remains unknown due to difficulties in acquiring reliable diagnostic data. This is due to absence of any systems for monitoring over HAIs in most countries or unified guidelines that could be used to diagnose such infections.

Up to now, HAIs remain a rather hidden and complex problem; therefore, no hospital or no country either can state that they have managed to solve it [15]. HAIs are diagnosed in 5–10 % of patients treated in hospitals; they can affect between 9 and 37 % patients in intensive care units with the overall mortality rate varying between 12 and 80 % [16–18]. In the Russian Federation, up to 30 thousand HAIs cases were registered annually (up to 2020) according to official statistical data (0.8 per 1000 patients); however, most experts believe the actual HAIs incidence is higher and equals not less than 2–2.5 million people [19]. The common criterion for considering an infection a HAI case is the direct association between its occurrence and healthcare. Most HAIs are associated with patients' risk factors due to concomitant illnesses, long stay in hospital, elevated susceptibility under high prevalence of invasive procedures and / or use of medical devices, and violation of aseptic and antiseptic rules, etc.

Recently, there has been a worldwide avalanche-like growth in interest in risk studies. The term 'risk' first appeared in European languages in the beginning of the 16th century; a theory says it is associated with the development of navigation and sea shipping. Probably, the original meaning of the verb 'to risk' occurred exactly in this sphere (from the Greek words 'rock' or 'cliff'); it meant tacking between rocks, going round a cliff (rock): the closer you get to rocks, the shorter and more dangerous your way is[4] [20]. General scientific interpretation of the risk as a philosophical category (in the ontological sense) is that 'the risk is likelihood of known and unwanted events in the future that are yet to come' [21]. Differences in interpreting and harmonizing various definitions and interpretations of 'risk' as a concept occur commonly. The 'risk' as a concept is interpreted by different authors as 'the combination of probability of an event occurrence and its outcomes'; 'the probability of an adverse event'; 'the combination of likelihood and outcomes of adverse events'; 'an event / a group of similar accidental events that damage an object having this risk' etc.[5] [22–25]. In the broad sense of the word, the term 'risk' most often means likelihood of an

[3] 10 facts on patient safety. *WHO*, 2019. Available at: https://www.who.int/news-room/photo-story/photo-story-detail/10-facts-on-patient-safety (April 12, 2023).

[4] Bol'shoi etimologicheskii slovar' russkogo yazyka [The big Russian etymological dictionary]; assembled by M.E. Klimova. Moscow, Dom slavyanskoi knigi, 2012, 960 p. (in Russian).

[5] Fletcher R., Fletcher S., Vagner E. Klinicheskaya epidemiologiya: Osnovy dokazatel'noi meditsiny [Clinical epidemiology: Fundamentals of evidence-based medicine]. Moscow, Media Sfera, 1998, 352 p. (in Russian).

unwanted event involving various losses or damage (loss of property, financial losses, health harm, social condemnation, etc.)[6] [21].

Methodological approaches to examining and assessing risks in healthcare first appeared in the Russian Federation in the second half of the last century when the first attempts were made to develop theoretical grounds for assessing prenosological states and premorbidity with respect to risks of probable human diseases [26]. Analysis of literature revealed that definitions used in studies focusing on risks, patient harm, or damage done to a healthcare organization, have different meanings [27, 28]. It is noteworthy that at present there are practically no articles or reviews that generalize knowledge concerning theoretical grounds of such a category as 'the risk'. Despite long-term and diversified investigations of 'the risk' we still cannot unambiguously interpret the essence of this multi-dimensional category due to the concept being truly universal and the terminology being diverse and inconsistent [20]. These differences create complications when different research data are compared and lead to potential errors in the interpretation of obtained results.

The existing risk classifications are based on different attributes but, as a rule, they tend to rely on risk classifications accepted in business and often fail to consider healthcare peculiarities [24, 28, 29]. Risks can be divided into natural and anthropogenic ones with respect to human activities. Healthcare defects are particular cases of anthropogenic risks [28]. Such risks may be associated with actual provision of healthcare and include diagnostic risks (incorrect diagnosis, failed informational interaction, etc.); treatment-related risks (surgical risks, risks of pharmacotherapy, risks related to interactions between experts and continuity in healthcare, risks of complications and unwanted reactions to medicines); rehabilitation risks (rehabilitation faults). In relation to healthcare, we can also consider risks of auxiliary processes possibly associated with finances (lack of funds); material support (absence of necessary medicines, cut-off of water or energy supply); risks related to patient diets (low quality foods, food poisonings); risks associated with cleaning in hospitals [28, 29]. Therefore, this antimony of terminological concepts and ambiguous interpretation of different risk signs indicate it is truly vital to unify concepts that describe the subject area of risks. According to Russian experts [23], this will promote objective assessment of epidemic process regularities, organization of epidemiological surveillance, and effective disease prevention.

At present, the 'risk' category is a key paradigm of the contemporary epidemiology [15, 20] and almost the most widespread concept [30, 31], medical literature included. The risk concept is applied in epidemiology to predict events, to identify a cause of a particular event, to identify diagnostic criteria and their reliability in assessing therapy and prevention[7]. The monograph Risk in Epidemiology published by B.L. Cherkasskii, RAS Academician, is among few efforts of such kind [32]. In this monograph, the academician provided scientific substantiation for the concept and methodology of risk management in epidemiology; he introduced the concepts of 'epidemiological risk' and 'epidemiological hazard', and explained differences between them that should be considered within risk-based epidemiological surveillance over communicable diseases. According to B.L. Cherkasskii, an epidemiological risk is a potential possibility that an epidemiological situation would get worse, this worsening either expected or having occurred due to harmful effects produced on the situation by certain risk factors [32].

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[6] Matvienko D.A., Popova E.V., Savinskaya D.N. Riskologiya: uch. posobie [Riskology: manual]. Krasnodar, I.T. Trubillin's Kuban State Agrarian University Publ., 2014 (in Russian); Ryagin Yu.I. Riskologiya: uch. posobie v 2-kh ch. [Riskology: manual in 2 parts]. Moscow, Yurait, 2017 (in Russian).

[7] Kornysheva E.A., Platonov D.Yu., Rodionov A.A., Shabashov A.E. Epidemiologiya i statistika kak instrumenty dokazatel'noi meditsiny: izd. 2-e ispr. i dop. [Epidemiology and statistics as tools of evidence-based medicine: the 2nd ed., corrected and expanded]. Tver', 2009, 80 p. (in Russian).

When interpreting epidemiological safety, contemporary authors consider the risk a potential probability of infectious complications in patients or healthcare workers with different outcomes, right up to death [25]. Basing on up-to-date requirements to formulating scientific definitions, S.N. Shugaeva and others [23] suggested their variant of how to define the concept of epidemiological risk that would be eligible for the epidemiology of both communicable and non-communicable diseases. This risk is 'likelihood of negative influence on incidence (and / or its outcomes) among certain population groups exerted by external and / or internal factors occurring at a certain time and on a certain territory'. Many diverse terminological concepts and ambiguous interpretation of different risk signs determine the challenge of systematizing and unifying parameters (key concepts) that describe the subject area of risks in order to identify these risks and effectively manage them.

The risk is a key concept in etiological studies (risk factors), diagnostics (likelihood of identifying a disease provided there is one), treatment (likelihood of an adverse outcome or recovery), prevention, and prognosis[7]. At present, some deviations can be found in literature sources as regards understanding of definitions and interpretation of such superordinate concepts as 'risk factor', 'risk group', risk territory', and 'risk time' [23]. The term 'risk factor' was first introduced by William Kannen in 1961 in the epidemiological study that had started as far back as in 1947 in Framingham [33]. Those long-term observations made it possible to identify factors affecting occurrence and progression of cardiovascular diseases, atherosclerosis included. A theory of risk factors for diseases caused by atherosclerosis was developed[8] [34, 35]. The epidemiological dictionary by G.M. Last (2009) provides the following definition of a risk factor: 'a risk factor is an aspect of personal behavior or life-style, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent'[9]. The WHO experts define a risk factor as 'a property or a characteristic of a person, or a certain exposure that are associated with higher likelihood of a disease or injury' [36]. Definitions of a risk factor that are similar in their sense but still have some differences from those outlined above are provided in other literature sources, some manuals and reference books[10] [37].

HAIs risk factors are diverse and specific for each type of HAIs. In general, basic factors that determine most HAIs include patient characteristics (age, the number and severity of a primary and concomitant illness), epidemiological safety of employed medical technologies and in-hospital environment, as well as some other causes (duration of staying in hospital, availability of beds, a possibility to have an individual hospital room, etc.). HAIs risks are very different for different medical technologies and their levels can be identified. According to international data, HAIs risks are the highest in intensive care units, burn units, oncological and urological units, as well as units for treating injuries [38, 39]. Inadequate infection control also contributes to risks of these infections [14, 25].

By now, a considerable number of applied studies have been published with their focus on particular profiles of risk factors relevant to individual nosologies [40–45]. But at the same time, there are very few publications in the sphere that generalize knowledge about theoretical grounds of this epidemiological category [37]. Given that, it is still vital to fulfill a task outlined in the National Concept for Prevention of Healthcare-Associated Infections [19], a solution to which should help develop

[8] Vnutrennie bolezni. Kniga 5 [Internal diseases. Book 5]. In: E. Braunwald, K.G. Isselbakher, R.G. Petersdorf, D.D. Wilson, D.B. Martin, A.S. Fuchi eds; D.G. Katkovskii, S.Yu. Martsevich transl. from English. Moscow, Meditsina, 1995, pp. 361–417 (in Russian).

[9] Epidemiologicheskii slovar' [The epidemiological dictionary]. In: G.M. Last ed. Moscow, 2009, 316 p. (in Russian).

[10] Briko N.I., Zueva L.P., Pokrovskii V.I., Sergiev V.P., Shkarin V.V. Epidemiologiya: uchebnik: v 2-kh t. [Epidemiology: manual: in 2 volumes]. Moscow, Meditsinskoe informatsionnoe agentstvo, 2013, vol. 1, 832 p. (in Russian); Shkarin V.V., Blagonravova A.S. Terminy i opredeleniya v epidemiologii [Terms and definitions in epidemiology]. Nizhny Novgorod, NSMA Publ., 2010, 298 p. (in Russian).

scientific research aimed at identifying HAIs risk factors for specific patient groups treated in different healthcare organizations [15, 19].

Risk realization often leads to a situation when actual results obtained by application of medical technologies deviate from those planned for a particular patient; as a result, there are medical, moral, social, and financial consequences [25]. Despite all the successes achieved by modern healthcare, surgical interventions have not yet become completely safe and postoperative complications as well as mortality due to HAIs are still very frequent [46]. HAIs prevalence varies between 0.1 to 290 cases per 1000 patients depending on a type of a unit, initial severity of a patient state, aggressiveness of employed medical technologies, and effectiveness of implemented epidemiological safety measures. Prevalence of infections in the area where a surgical intervention took place equals 15–118 cases per 1000 operated patients; bloodstream infections, 3.5–12.2 cases per 1000 days of central venous catheterization; urinary tracts infections, 4.1–8.8 cases per 1000 days of catheterization; and post-ventilation pneumonia, 7.9–23.9 cases per 1000 days of artificial ventilation [21, 47]. Given that, it becomes especially vital to develop and implement conceptual approaches to the interpretation and assessment of HAIs risks, algorithms for assessing HAIs risks with respect to different medical technologies in hospitals of various profiles. Up-to-date approaches to HAIs prevention should rely on the concept of risk factors. But it is hardly sufficient to have a simple idea of what risk factors are relevant for a specific disease; instead, we should understand a level (rate) of risk created by each factor, their hierarchy and interaction [48].

Apart from identifying risk factors, some efforts should be taken to perform complex analysis of risk groups and spatial-temporal characteristics (risk time and territory) of incidence and / or its outcomes [32]. Identification of risk groups is a major task within epidemiological risk analysis. According to S.N. Shugaeva and others, a risk group (contingent) should be considered a part of population for which higher incidence and / or its consequences are identified or among which an epidemiological event is more prevalent [23].

Analysis of literature data has revealed that the existing systems for risk assessment have considerable drawbacks and only limited prognostic value. To identify cause-effect relations of HAIs occurrence and development, it is advisable to concentrate on stratification of risk groups. Stratification is the only way to examine and control values of other (apart from an exposure and a disease) variables in data analysis. In addition, stratification analysis basically aims to assess and, if necessary, to control 'interfering' factors. Over the last decade, some progress has been made as regards standardization of studies addressing risk stratification. Specifically, national registers are being created that provide an opportunity to obtain reliable predictors of unfavorable outcomes among patients, including those who have high perioperative risks [46]. Experts often use several approaches to stratify risk groups (risk – cohort) including demographic, social, occupational or clinical ones (premorbidity background, physiological or pathological state, comorbidity, and others). It is noteworthy that it is impossible to create a spatial-temporal risk profile (risk time and territory) without a detailed epidemiological description of what caused an unfavorable situation on a given territory, that is, without identifying risk factors and groups, but this subject deserves a separate discussion.

In recent years, methods of influence on the epidemic process of HAIs have been reassessed and some experts believe transition to the risk-based approach to be quite promising in this respect. This approach makes it possible to take timely measures aimed at reducing risks of such infections in advance[11] [20, 49, 50]. The authors proceed from the outstanding

[11] Noskova O.A. Epidemiologicheskie osobennosti i osnovnye napravleniya profilaktiki generalizovannykh gnoino-septicheskikh infektsii v pediatrii [Epidemiological peculiarities and basic trends in prevention of generalized purulent-septic infections in pediatrics]: the dissertation … for the Candidate of Medical Sciences degree. Irkutsk, 2020, 170 p. (in Russian).

necessity existing now within epidemiological surveillance and control of such infections. Namely, it is necessary to switch from a strategy that involves correction of an epidemic process based on incidence (following an adverse event that has already happened) to a risk assessment strategy together with developing and implementing a system for epidemiological safety based on this approach [20, 25, 51]. Since the risk-based approach within epidemiological safety is only starting to be integrated into the whole system of healthcare safety, development and specification of its individual components seems to be a promising trend in healthcare support [52].

Several parameters determine effectiveness of the risk-based approach. They include completeness and quality of information flows (epidemiological and microbiological monitoring, epidemiological monitoring of invasive procedures safety, monitoring of antimicrobial resistance and sensitivity of HAIs agents to disinfectants and bacteriophages, etc.), quality and effectiveness of epidemiological diagnostics, as well as risk management aimed at detecting, identifying, monitoring and assessing risks [25, 53], developing specific activities that should eliminate or minimize possible negative outcomes of risks.

Risk management is a discipline that aims to investigate adverse outcomes of healthcare by identifying and analyzing them, the ultimate goal being the development of effective prevention strategies [22]. At the same time, although quality management systems have been developed quite intensively in many spheres, healthcare has long remained a sphere where quality is associated only with personnel's education and experience[12]. In conformity with the National Standard GOST R ISO 31000-2019 Risk Management: Principles and Guide, the essence of risk management is to create a system of measures within an organization that prevents risks by identifying, analyzing, and assessing them[13]. It is noteworthy that risk managements systems have already been implemented in healthcare systems in foreign countries [24]. Different countries rely on different approaches to building up an organizational structure for a risk management system. Risk management in healthcare can be accomplished at four different levels: federal, regional, organizational (a healthcare organization), and a personal one (a healthcare worker) [28]. Few publications can be found in Russian literature that address risk management at the organizational level in healthcare organizations and rely on using qualitative HAIs indicators [48, 54]. We have not been able to find any studies that concentrate on managing HAIs risks at the regional level.

Risk management is based on a system or a set of activities aimed at analyzing all the incidents that concern patient safety. However, healthcare workers do not provide any information about unwanted events and errors in healthcare in 50–96 % of such cases [55]. International experts in patient safety have established several optimal methods to identify and assess errors and adverse events in health care. Such methods are anonymous data collection about incidents; retrospective analysis of patient case histories; questioning (interviewing) of healthcare workers and their patients; observing directly how healthcare is provided; reports about errors and adverse events made by healthcare workers; analysis of patients' complaints or legal actions taken by them; computer monitoring of electronic databases with medical data; autopsy studies; conducting clinical and anatomical conferences.

In their studies, foreign authors show effectiveness of such an approach since it al-

[12] Kornysheva E.A., Platonov D.Yu., Rodionov A.A., Shabashov A.E. Epidemiologiya i statistika kak instrumenty dokazatel'noi meditsiny: izd. 2-e ispr. i dop. [Epidemiology and statistics as tools of evidence-based medicine: the 2nd ed., corrected and expanded]. Tver', 2009, 80 p. (in Russian).

[13] GOST R ISO 31000-2019. Risk Management. Principles and guidelines: the RF National Standard; approved and implemented by the Order of the Federal Agency on Technical Regulation and Metrology on December 10, 2019 No. 1379-st. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200170125 (April 07, 2023) (in Russian).

lows identifying hidden risks that are never registered or investigated [56–58]. Various tools can be used to estimate effectiveness of a risk management system. A methodology based on specialized reference books has been developed; these books estimate key elements of a risk management system relying on quantitative expert evaluations [59]. At the same time it is noted that in Russian Federation any voluntary report about defects often leads to inspections, fines, and orders. As a result, healthcare workers are totally demotivated to perform risk monitoring and report any defects [28]. Risk management is a multidisciplinary task that considers contributions made by all the healthcare workers employed by a hospital: doctors, nurses, laboratory personnel, medical engineers, administrative staff, and others. Therefore, a basic goal in increasing healthcare safety is to create a risk management system within the Russian public healthcare together with the development of risk management technologies and a methodology for analyzing effectiveness of HAIs risk management.

To sum up, it is noteworthy that the key role in creating an effective system for control and surveillance over hospital-acquired infections belongs to the following activities:

- development of scientific approaches to systematizing and unifying indicators (key concepts) that describe the subject area of HAIs risks in healthcare organizations of various profiles;
- improvement of the methodology for analyzing HAIs risks, the risk-based approach and risk management technologies within surveillance over such infections;
- optimization of science-based approaches to decision-making that relies on the risk-based approach and HAIs risk management technologies, their implementation into healthcare practices;
- development of methodical guidelines on monitoring, assessment, and prediction of HAIs risks in healthcare organizations.

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Research article

INTER-COHORT ANALYSIS OF PARENTAL RISK FACTORS FOR DEVELOPMENT OF INFANTS

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Children develop rapidly in the first year of life and this period should create a solid ground for their health in future. Diseases of the nervous system, mental and behavioral disorders occupy leading places among causes of childhood disability. Given that, the aim of this study was to search for parental risk factors endangering physical and neuropsychic development of infants.

Infants living in Vologda region were selected as a research object. Our informational basis was represented by sample data of the prospective monitoring over children's health (894 children from five different cohorts born in 1998, 2001, 2004, 2014 and 2020); statistical and sociological data on prevalence of risk factors in Russia and in the region. The information was provided by healthcare workers (obstetrician-gynecologist, neonatologist, and pediatrician) and children's mothers. The applied methodology included inter- and intra-cohort sociological analysis; calculation of relative risk (RR) to assess a correlation between developmental delay and parental factors. Child development was assessed by a pediatrician using abnormal psychology and adaptation approaches. We analyzed Russian and foreign studies that focused on the same research subject.

We calculated relative risks of various social-demographic, socioeconomic, biomedical and environmental factors for the development of children who participated in the cohort monitoring. This allowed us to identify those with prognostic value including young age of parents (RR = 1.40); a single-parent family (RR = 1.46), bad relationships between spouses (RR = 1.36); low purchasing ability of a family (RR = 1.59), poor living conditions (RR = 1.66); a future mother being exposed to chemicals and toxic substances (RR = 1.31), gas pollution (RR = 2.02), hand high temperatures (RR = 1.56) at her workplace one year prior to childbirth; a smoking mother (RR = 1.56); a father having a sexually transmitted disease (RR = 3.23); abnormal pregnancy. The identified risk factors for child development occur prior to childbirth and are manageable. Awareness about them makes it possible to neutralize their negative influence when a pregnancy is being planned.

Our analysis of statistical and sociological data has revealed a descending trend for prevalence of practically all the analyzed risk factors. Still, some factors cause certain concern including high prevalence of smoking among women, future mothers included; prevalence of anemia in pregnant women; unresolved financial issues and poor living conditions of a considerable share of families who are expecting a child; effects produced on women by harmful working conditions. The results of this study can be used for developing programs aimed at protecting child's health at any level, from an individual to the national one.

***Keywords**: physical and neuropsychic development of a child, risk factors, age of a mother and father, harmful working conditions of a mother, parents' health, anemia, edemas, pregnancy, smoking, socioeconomic conditions, a single-parent family.*

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Early childhood is a critical period in the formation of all organs and systems. It is in the first years of life when the body develops resistance to adverse conditions of the surrounding world, the level of physical and neuropsychological development of children (P&NPD) is formed [1]. Therefore, health in this period is a kind of foundation and determines a person's development in the future throughout life.

Physical development of children includes anthropometric data (weight, body length, head and chest circumference, etc.), growth and body formation, including rates, stages, and critical periods of their change during growth. Any deviations from a norm in physical development indicate a relative disadvantage in the state of health, and a harmonious combination of indicators characterizes its normal formation. Assessment of physical development is based on comparing individual indicators with the average value of the accepted standards for this group in each region (which are recommended to be corrected every 5–10 years [2]). Any abnormalities in children physical development and biological maturation are an absolute indication for placing them on medical checkup.

Considering children's development, it is worth noting that deviations in the psychoemotional sphere are no less important than disorders of the somatic status.

Nervous system diseases occupy one of the leading places among pathologies in children and adolescents. According to the data of the Ministry of Health of the Russian Federation[1], the incidence of diseases of this nosological group among children from 0 to 14 years old in the country increased from 2000s (2,731 per 100 thousand children) to 2011 by 57 % (4,293 per 100 thousand children), with a subsequent decrease (by one third) to 2,876 cases per 100 thousand children by 2020.

We should also note that "nervous system diseases" as well as "mental and behavioral disorders" are the leading causes of disability among children (in 2020 – 27 % and 24 % of all children with disabilities). Moreover, this indicator has increased since 2010 by more than a third (by 40 and 35 %, respectively), as has the share in total disability (by 2 p.p.).

In the DSM-5 and ICD-11 classifications, neurodevelopmental disorders (NDD) are introduced as an overarching category of disorders characterized by impairments in cognitive functioning, communication skills, behavioral and/or motor skills. They include: general intellectual disability (intellectual developmental disorders), communication disorders (development language disorders), autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), specific learning disorders, and motor development disorders [3].

In the future, such children may have difficulties in mastering the curriculum, forming and observing moral and ethical norms and rules, and interacting with others[2]. Children with delayed neuropsychological development (NDP) at the age of 1 are at risk of mental development disorders at an early age [4]. Nevertheless, there is a problem: the untested system of dynamic observation of children with perinatal pathology and other risk groups in different childhood periods, untimely diagnosis and, accordingly, late start of therapeutic and corrective measures, which can lead to impaired formation of higher mental functions and delayed cognitive development. The complexity of prevention, diagnosis, and treatment of neurological pathologies, as well as the problem of adaptation and socialization of such children represent a very important challenge not only in pediatrics (in the future – therapy), but also in social medicine [5].

In this regard, timely diagnosis of developmental abnormalities in children in the first

[1] Sem'ya, materinstvo i detstvo. Zdravookhranenie, druzhestvennoe k detyam, i zdorovyi obraz zhizni. 3.17. Deti-invalidy po zabolevaniyam, obuslovivshim vozniknovenie invalidnosti [Family, Motherhood and Childhood. 3.17. Children with disabilities due to the diseases that caused the disability]. *Rosstat*. Available at: https://rosstat.gov.ru/folder/13807 (April 11, 2023) (in Russian).

[2] Razvarina I.N. Adaptatsionnyi podkhod k otsenke nervno-psikhicheskogo razvitiya detei mladshego shkol'nogo vozrasta: metodicheskie rekomendatsii dlya pedagogov-psikhologov, sotsial'nykh pedagogov i klassnykh rukovoditelei obshcheobrazovatel'nykh organizatsii [The adaptation approach to evaluating the neuropsychological development of children of elementary school age: Methodological recommendations for educational psychologists, social educators, and class teachers of general educational organizations]. Vologda, ISERT RAN, 2017, 23 p. (in Russian).

year of life is an extremely urgent task. Especially given the growth of the number of children with NDP lags, which was 150 % in the period from 2000 to 2018 (from 62.4 to 91.1 per 1,000 children aged 0–14). At the same time, the most significant NDP lags are noted in the lines of speech development and mental health [6]. The analysis has shown that children with mental retardation are the most numerous nosological group in Russia, accounting for about 40 % of the total population of children with disabilities [7]. In addition to the true increase in morbidity, this trend may be due to the application of new approaches to the education of children and the informatization of society, as well as certain flaws in the current system of professional examinations [6].

Assessment of the NDP is carried out at certain age periods (epicrisis time): in the first year – monthly, in the second year – once a quarter, in the third year – once a half-year, from the age of three years – once a year.

For instance, normally, by the end of the first year of life, a child should recognize themselves and their acquaintances in photographs; can transfer learned actions from one object to another, to toys; phonetically understands names of objects, actions, adults' names; does single word errands such as "bring", "find", "give" etc.; starts walking without support; recognizes relatives' voices; can speak 10–12 words consciously. When performing any tasks, a child's face should be focused. If they succeed, there is a joyful expression. Failure is accompanied by mimicry of displeasure. A child should be able to use a potty. A comprehensive medical assessment of child's health is given with mandatory consideration of all the above criteria (in accordance with the Order of the Ministry of Health of the Russian Federation 514, dated August 10, 2017 "On the procedure for conducting preventive medical examinations of minors"[3]).

Often, developmental delay is the first important symptom of both a functional condition and an existing disease. Timely diagnostics of the lagging P&NPD increases the level of children's health and will help to solve many problems, not only medical but also social ones[4]. Given the above, it is necessary to pay close attention to the dynamics of child development, including the intrauterine period, taking into account risk factors from both parents, using all stages of prevention of disorders.

The aim of the research is to identify mother and father risk factors for physical and neuropsychological development of a child at the age of 1.

The tasks of the research are:

1. To analyze the scientific literature on the topic of parental risk factors for child's development.

2. To calculate the relative risk of exposure to sociodemographic, socioeconomic, biomedical, and environmental factors by both parents for the development of a child in the first year of life.

3. To assess the prevalence and dynamics of the identified risk factors for the child's development over a 24-year cohort study.

4. To suggest directions for minimizing controllable parental risk factors promoting the development of children in the first year of life.

The object of the research is the Vologda region children of the first year of life. **The subject of the research** is the health of children in the first year of life.

Research methodology. Vologda Research Center of the Russian Academy of Sciences (VolRC RAS) has been conducting prospective monitoring ("Studying conditions of formation of health generation") of cohort observations of families with children since 1995. The informants who filled out the questionnaires are:

[3] O Poryadke provedeniya profilakticheskikh meditsinskikh osmotrov nesovershennoletnikh: Prikaz Ministerstva zdravookhraneniya RF ot 10 avgusta 2017 g. № 514n [On the procedure for conducting preventive medical examinations of minors: the Order of the Ministry of Health of the Russian Federation 514, dated August 10, 2017]. *GARANT*. Available at: https://base.garant.ru/71748018/ (April 10, 2023) (in Russian).

[4] Tkachuk E.A., Martynovich N.N. Otsenka nervno-psikhicheskogo razvitiya detei i osnovnye klinicheskie proyavleniya narushenii so storony nervnoi sistemy: uchebnoe posobie dlya studentov [Assessment of the neuro-psychological development of children and the main clinical manifestations of disorders of the nervous system: a training manual for students]. Irkutsk, Setevoi institut dopolnitel'nogo professional'nogo obrazovaniya Publ., 2020, 75 p. (in Russian).

1. Healthcare workers. At the time of inclusion in the cohort, they were: obstetrician-gynecologist (on the specifics of pregnancy and childbirth) and neonatologist (on the health status of an infant newborn). Thereafter, once a year it was pediatrician at child's place of residence (about features of child's P&NPD).

2. Child's parent (predominantly mother): at birth (retrospective answers about different aspects of mother's life and a child's father), in the first year of the child's life – at the age of 1, 6 and 12 months (about features of family's life, health and child development). Thereafter, it is annually.

3. Children participating in monitoring when they reach the age of 10.

The present study focuses on data collected during the first year of child's life from parents and healthcare workers. The sample consisted of 894 participants in five cohorts (166 children in 1998, 211 in 2001, 190 in 2004, 243 in 2014, and 227 in 2020) who were further monitored at the first year of age. We used an inter-cohort method to analyze the research data.

The control group included those children in whom, according to the answers of a local pediatrician (based on a child's medical records), to the question *"Do the child's physical and neuropsychological development indicators correspond to the norm?"*, the following answers are noted: *"There are minor deviations"* or *"Deviations from the norm are significant"*. On average, every third (n = 294) of the 894 participants was placed in this category. The comparison group was those children whose P&NPD at 1 year was normal (n = 600). A positive trend can be noted in the 2.8-fold decrease in the proportion of children with developmental disabilities from 47 % in 2001 to 17 % in 2020.

The most frequent diagnoses of children with developmental disorders in the first year of life were the following: perinatal encephalopathy (PEP), perinatal lesion of central nervous system (PLCNS), vertically transmitted infections (VTI) and congenital malformations, hyposomia and weight deficiency, rickets, anemia, vegeto-visceral disorder syndrome, exudative diathesis and dermatitis, hydrocephalus, epilepsy, joint dysplasia, cardiac anomalies (patent foramen oval (PFO), congenital heart defect (CHD)), hydrocephalic-hypertension syndrome, paratrophia, myotonical syndrome, developmental speech delay (DSD), neutropenia and other clarified CNS diseases, otitis media, ARVI. As we can see, the vast majority of them arose in the intrauterine period of child development.

Table 1

Characteristics of the research sample

Indicator	Cohort (year of birth)					Total
	1998	2001	2004	2014	2020	
Number of newborns recruited into the cohort, people	166	211	190	243	227	1037
Dropped out of the monitoring at the age of 1 year, people	19	34	44	39	7	143
P&NPD of a child at 1 year* corresponds to the norm, person	86	94	87	151	182	600
Lagging P&NPD at the age of 1 year**, people	61	83	59	53	38	294
in % of those remaining in the monitoring	41.5	46.9	40.4	26.0	17.3	-

Notes: *According to the answer of the pediatrician at the residence (on the basis of a child's medical records) to the question *"Do the child's physical and neuropsychological development indicators correspond to the norm?"*. The answer option is *"They correspond to the norm"*.

**We took into account only the following answers: "There are minor deviations" and "Deviations from the norm are significant".

Based on studying Russian and foreign literature, available medical-biological and sociological monitoring data, as well as our own earlier studies on health risk factors in infants, we have identified the following groups of factors, which came into existence even before the child is born:

1. Socio-demographic group: parental age and education level, marital status;

2. Socio-economic group: satisfaction with income level and housing conditions, family's purchasing power;

3. Biomedical group: (a) parents' anamnesis of chronic diseases, dangerous infections, (b) obstetric anamnesis of previous pregnancies and (c) features of the current pregnancy; (d) complications of childbirth; (e) bad habits of both parents (smoking);

4. Environmental effects: environmental conditions in family's residence and occupational hazards of both parents in the year before the child's birth (mental stress, increased noise, work in 2–3 shifts, high physical load, work on the assembly line, work at night, chemical and toxic effects, radiation and ultra-high frequency, dustiness, gas pollution, humidity, vibration, high and low temperature, and biological hazards).

In this paper, we analyze parent-related risks that had an impact on the development of a child before birth, without considering those factors that affect health and development in the first year of life. We will try to characterize the category of newborns who are at high risk of further P&NPD retardation in order to increase the attention of medical professionals to them starting from birth.

To assess the influence of the risk factors under consideration, we chose the relative risk index (RR)[5]. The RR is calculated on the basis of a four-field contingency table: risk factor (yes/no) × adverse outcome (yes/no):

$$RR = \frac{A \cdot (C + D)}{C \cdot (A + B)}$$

Table 2

Four-field contingency table

	Outcome (1)	No outcome (0)	Total
There is a risk factor (1)	A	B	A+B
There is no risk factor (0)	C	D	C+D
Total	A+C	B+D	A+B+C+D

If the RR is more than 1, the effect of the factor under consideration increases the risk of disease development (in our case, developmental delays), and the greater the RR value, the higher the probability. If the RR is less than 1, the factor is protective and reduces the probability of developmental delay. In each case, the statistical significance of the relative risk is necessarily assessed based on the values of the 95 % confidence interval (CI). We should note that the RR does not provide information about the magnitude of absolute risk but demonstrates the strength of the relationship between the influencing factor and developmental delay.

We performed statistical analysis of biomedical and sociological data using the SPSS statistical software package.

The scientific novelty of the study lies in the assessment of the influence of risk drivers for the development of children in the first year of life by both parents and family living conditions using an intergenerational analysis of several generations of children. The presented work allows deepening the knowledge about the degree of exposure to the most significant and controllable risk factors for child health even before birth.

Risk factors of a child's P&NPD: research analysis. Modern studies confirm that most of the neurological and psychiatric abnormalities and developmental disorders can be predicted long before their clinical manifestation at preschool age.

[5] Relative risk is defined as the ratio of event probabilities in one group to similar probabilities in another group. The RR was calculated as the ratio of the risk of a child's P&NPD lagging in the first year of life in the "exposed" group (exposed to the risk driver) to a similar risk in the "unexposed" group (not exposed).

We have identified a significant number of various risk factors that contribute to the formation of different variants of developmental deviations: medical and biological (associated with complications of pregnancy and childbirth, genetic disorders), medical and social (low income, one-parent families, socially disadvantaged), medical and organizational (inefficient system of prevention, flaws in the structure of care for certain groups of children, etc.), and also risk factors created by living conditions (exposure to adverse environmental factors, improper diets, hypodynamia, stress, impaired interpersonal contacts in a family, destructive education style etc.). It is worth considering that the multifactorial and combined nature of adverse influences heightens their effect and increases the likelihood of the development of deviations [4].

First, genetic diseases are an important predictor of developmental and/or intellectual disability in children. Among them, 25–30 % are chromosomal abnormalities, and 10 % are monogenic diseases (metabolic diseases, neuroectodermal syndromes, diseases with predominant lesions of the gray or white matter of the brain) [8].

The majority of previous studies consider the features of pregnancy and childbirth to be an important risk factor for the health and development of children in the first year of life, namely, diseases suffered by the mother, intrauterine growth restriction (IUGR), prematurity, use of cesarean section (CS) in childbirth, etc.

Classical infectious pathogens such as herpes simplex virus, rubella virus, toxoplasmosis and cytomegalovirus are known to have a direct teratogenic effect on a fetus, which can affect the development of the brain, leading to future neuropsychiatric effects. The link between schizophrenia in a child and a pregnant mother's flu was first described more than 30 years ago. Several current studies suggest that infections during pregnancy may increase the risk of developing autism spectrum disorders and depression in a child [9].

The IUGR is an integral indicator of intrauterine disadvantage, a predictor of increased morbidity, development of chronic disabling pathology, perinatal and infant mortality, as well as delayed physical and intellectual development and maladaptation in the postnatal period. In economically developed countries, the rate of babies born with the IUGR is 30–40 %, while in developing countries it is 70 % (against a background of a higher rate of low birth weight babies). It is known that perinatal morbidity in children with the IUGR ranges from 17–36 %, and perinatal mortality from 8–24 %[6].

The development and improvement of new reproductive technologies, advances in intensive care and nursing newborns of high-risk group with combined perinatal pathology, reducing mortality among premature and low birth weight babies, have the other side of the coin. All this becomes (along with abnormalities of pregnancy and childbirth) the cause of P&NPD disorders spreading among the child population. Morbidity among survivors, including abnormalities in the nervous system development, has increased, especially in extremely premature infants. Nearly half of their survivors have severe neurodevelopmental abnormalities. Long-term adverse outcomes of extremely premature infants include mental retardation (5–36 % of cases), cerebral palsy (9–18 %), blindness (1–9 %), and deafness (2–4 %) [10]. Late preterm infants (those born at 34 to 36 weeks gestation) are also considered to be at risk for adverse outcomes of the P&NPD, and, therefore, of learning ability [11].

Surgical delivery may be necessary to save a mother and a baby. But there is evidence that children born by cesarean section (CS) are exposed to various hormonal, physical, bacterial and medical influences that can adversely affect the health of a newborn. Separate works are devoted to the impact on cognitive and educational abilities of a child [12].

A number of modern studies reflect the contribution of the psychological component to child development in early childhood. For

[6] Zaderzhka vnutriutrobnogo razvitiya: uchebno-metodicheskoe posobie [Intrauterine growth restriction: Study guide]. In: prof. L.V. Kozlova ed. Smolensk, SMA Publ., 2011, 82 p. (in Russian).

example, it has been proven that mother's emotional well-being during pregnancy and after delivery is associated with normal motor and cognitive development of a newborn [13]. And exposure to deep maternal neglect in early childhood can interfere with child development. Mother's attachment, tenderness, and attention to an infant are the most important factors in infant's motor development [14]. For example, the development of children adopted before the age of six months is similar to that of their non-adopted siblings. If children were adopted later, they had a high risk of cognitive impairment, behavioral problems, autism, and hyperactivity [15], which is also confirmed by Russian studies [16]. Therefore, early medico-psychological intervention for children with adverse psychotraumatic experiences is the basis for their healthy development.

A number of scientific studies are aimed at finding risk factors for individual components of development (physical, speech, psychomotor, emotional, intellectual, etc.) in children of different ages.

For instance, the scientists of the Federal State Budget Institute Ivanovo Scientific-Research Institute named after V.N. Gorodkov, identified the following unfavorable prognostically significant biological risk factors for low body length in children: occupational hazards of a future mother (within five years prior to conception), pathology of the urinary tract system in a mother, threat of non-pregnancy, feto-placental insufficiency, oligohydramnios, cerebral ischemia of the III degree, bilateral intraventricular hemorrhage in a baby in the neonatal period, a baby on artificial ventilation for more than seven days, bronchopulmonary dysplasia, intrauterine infection, and intestinal dysbacteriosis in a baby. Social risk factors included unregistered marriage at the time of conception, vocational education, and father's occupation (as well as his lack of days off and irregular working hours). Maternal age over 35 years, unemployed status, third and subsequent pregnancies, presence of acute respiratory diseases in a mother during pregnancy, fetal malnutrition, and irregular working hours of a father may contribute to child underweight [17].

The Consortium of Health-Oriented Research in Transitional Societies (COHORTS) showed that low birth weight was associated with short stature, lower parental education, and lower family affluence [18].

A cohort study in Finland [19], aimed at identifying the determinants of speech development showed that the social status of both parents had an important predictive value for the language development of a child. And increased maternal anxiety correlated with poor language comprehension and a limited vocabulary of children by the age of 2.

Another study (on 1,314 children from the Children in Focus (CiF) sample of the Avon Longitudinal Study of Parents and Children (ALSPAC)) using multivariate regression models also confirmed a particular contribution to early language development of indicators of social disadvantage. For example, family income, housing, and material well-being are associated with the development of expressive and receptive language, and verbal comprehension in children at one year and three months [20].

Many studies have been devoted to finding the causes of attention deficit/hyperactivity disorder (ADHD) in children. Thus, the young age of a mother was identified as a risk factor. Children born to mothers aged 18–24 had an increased chance of ADHD (OR = 1.34) and learning disabilities (OR = 1.36). The mother's age of 35–39 years, on the contrary, acts as a protective factor for the development of ADHD in offspring (OR = 0.60) [21]. Another risk factor is intrauterine hypoxia, which was found in the anamnesis of children with ADHD much more often than in the general population [22, 23]. Maternal smoking during pregnancy also increases the risk of hyperactivity in offspring by 60 % (and in heavy smokers – by 75 %) [24]. In another study, it was proved that intrauterine exposure to high levels of non-ionizing radiation increases the likelihood of an unborn child developing hyperactivity with concomitant immune diseases [25].

A number of studies aimed at finding the causes of autism spectrum disorders (ASD) in children have revealed a history of specific complications in childbirth in such patients [26–28].

The mature age of a father can also lead to a decrease in the functioning of a child's brain [29].

A group of Russian scientists led by G.O. Momot conducted a study aimed at finding statistically significant risk factors for NPD disorders in children 4–6 years old. According to the data obtained, from the group of socio-biological factors, the lowest Apgar score at birth (RA = 2.700), burdened labor (RA = 2.489), pathologically occurring pregnancy (RA = 2.354) had the greatest negative impact. Among the socio-economic factors, the factor of incomplete family was significant (RA = 1.687) [6]. We have not found a similar comprehensive analysis of risk factors for the development of a child at an earlier age in the scientific literature.

Results and discussion. The table below shows all the prognostically significant risk factors identified by us at the time of a child's birth for its development in the first year of life.

The young age of parents, according to our calculations, is a risk factor for a mismatch of P&NPD indicators with the norm in the first year of life. If a mother is younger than 20, then RR = 1.42 (95 % CI: 1.09–1.85), if younger than 30, then the indicator is slightly lower – RR = 1.25 (95 % CI: 1.02–1.53). If a father is younger than 30 years old, the probability of developmental disorders of his child in the first year of life increased by 40 % (RR = 1.40; 95 % CI: 1.13–1.74).

Table 3

Significant risk factors of P&NPD of a child in the first year of life (*n* = 294)

Risk factors	Occurrence in the sample	RR	95 % CI
Family			
Financial situation of the family			
Low purchasing power of income[7]	*n* = 299	**1.59**	(1.30–1.94)
Low assessment of housing conditions[8]	*n* = 494	**1.66**	(1.37–2.03)
Marital status			
Incomplete family (single, widow, divorced)	*n* = 122	**1.46**	(1.15–1.84)
Lack of a good relationship with the spouse / child's father[9]	*n* = 183	**1.36**	(1.09–1.71)
On mother's side			
Age			
Age up to 20 years	*n* = 95	**1.42**	(1.09–1.85)
Age up to 30 years	*n* = 663	**1.25**	(1.02–1.53)
Harmful working conditions in the year before the child's birth			
Chemical and toxic substances	*n* = 94	**1.31**	(1.00–1.72)
Gas contamination	*n* = 24	**2.02**	(1.45–2.83)
High temperature	*n* = 49	**1.56**	(1.13–2.16)
Smoking			
Smoking before pregnancy	*n* = 272	**1.26**	(1.03–1.54)
Smoking during pregnancy	*n* = 117	**1.56**	(1.23–1.97)
Complications of the current pregnancy			
Anemia	*n* = 540	**1.23**	(1.02–1.49)
Edemas	*n* = 126	**1.53**	(1.22–1.91)
Protein detection in urine tests	*n* = 171	**1.53**	(1.24–1.88)
On father's side			
Age up to 30 years	*n* = 468	**1.40**	(1.13–1.74)
Vocational education and below	*n* = 587	**1.52**	(1.19–1.95)
Sexually transmitted diseases in the anamnesis	*n* = 2	**3.23**	(2.91–3.59)

N o t e : source of the data is own calculations based on cohort monitoring in the Vologda region (1,037 respondents born in 1998, 2001, 2004, 2014 and 2020).

[7] On the question "Please assess the possibility of meeting the needs of your family based on its total income", the answer variants were "There is enough money only to buy food"; "There is not enough money even to buy food, I have to go into debt".

[8] On the question "Your assessment of living conditions", the answer variants were "satisfactory"; "poor"; "very poor".

[9] On the question "What do you think is your relationship with your spouse?" (in 2020 – with a father of a child), the answer variants were "normal"; "could be better"; "I am not satisfied with it; bad"; "other".

We should note that the prevalence of this risk factor has been decreasing in recent years. The age pattern of fertility worldwide is shifting to older ages (for women, by 25–29 years; for men, by 30–34 years) [30]. According to demographers, the postponement of motherhood is due, among other things, to reproductive literacy and a woman's desire to finish higher education and achieve success in her career before the birth of children. The average age of a Russian mother at the birth of a child in the 2000s increased by three years (from 25.8 to 28.8 years), and in the Vologda region – by almost 4 (from 24.3 to 28.1 years) [10]. The average age of female participants in our cohort monitoring increased even more – by 6 years (from 24.8 in 1995 and 2001 to 31 years in 2020).

The education level of a mother did not demonstrate a connection with the P&NPD of her offspring, unlike a father. So, it was revealed that if he did not have a higher education at the time of the birth of his son or daughter, the risk of lagging the development of his child by the year increased by 50 % (RR = 1.52; 95 % CI: 1.19–1.95).

According to our calculations, the problem of family relations is an important predictor of impaired child development in the first year of life, which is consistent with other scientific studies. So, if a newborn's mother was single (unmarried, divorced or widowed), then the risk of lagging behind the norm of her one-year-old child's P&NPD indicators increased by 46 % (RR = 1.46; 95 % CI: 1.15–1.84). Moreover, we found that a one-parent family at the time of the child's birth remains a risk factor not only in the year, but also in the future, increasing the likelihood of violations of the NPD by 3–4 years by two-thirds (RR = 1.64; 95 % CI: 1.07–2.52), and by pre-school age (6–7 years) – almost by 4 times (RR = 3.89; 95 % CI: 2.09–7.23).

In turn, dissatisfaction with marital relations in an officially registered marriage also increases the likelihood of impaired development of a child at the age of 1 year by more than a third (RR = 1.36; 95 % CI: 1.09–1.71).

According to scientific research, single women who are expecting a child are exposed to the greatest stress, which is an important risk factor for the health of both mother and child [31, 32]. According to our earlier calculations, these women were more likely to develop anemia during pregnancy (RR = 1.20), IUGR of a fetus (RR = 2.22) and congenital malformations of a newborn (RR = 1.66); a child was significantly more likely to be ill in the first year of life (RR = 1.13), which may have a negative impact on child's P&NPD [33].

The institution of marriage in Russia has undergone significant negative changes in recent decades. There is a legitimization of cohabitation, procreation becoming a major motive to get married or postpone it, the emergence of new types of marriage (trial, guest or marriage at a distance) [34].

According to statistics[11], the number of marriages in Russia was increasing from the year 2000 (6.2 per 1,000 people) only until 2011 (9.2). Then this indicator was decreasing (to 5.3 by 2020). The number of divorces fluctuates at the same level in the range of 4.7–4.0 per 1,000 people (exception: the pandemic year of 2020, with a minimum of 3.9 over the past 30 years).

According to surveys of Vologda region[12] population conducted regularly by VolRC RAS, over the past 22 years the proportion of married female residents of the region decreased by 10 %, and the proportion of single, on the contrary, increased by 65 % [35]. In contrast, the proportion of unmarried mothers participating in the cohort monitoring of children's health between 1998 and 2020 de-

[10] Shabunova A.A., Kalachikova O.N., Korolenko A.V. Demograficheskaya situatsiya i sotsial'no-demograficheskaya politika Vologodskoi oblasti v usloviyakh pandemii COVID-19: II regional'nyi demograficheskii doklad. [Demographic situation and socio-demographic policy of the Vologda region in conditions of the COVID-19 pandemic: II regional demographic report]. In: A.A. Shabunova ed. Vologda, VolRC RAS, 2021, 89 p. (in Russian).

[11] Demografiya. Braki i razvody [Demographics. Marriages and divorces]: official statistics. *Rosstat*. Available at: https://rosstat.gov.ru/folder/12781 (April 11, 2023) (in Russian).

[12] Source of data in the general female population of the region: Monitoring of socio-economic situation and social well-being, VolRC RAS.

creased 3.7-fold. This can indirectly confirm the fact that reproductive motives for marriage prevail among the population.

Self-evaluation of the relationships with a spouse over the 25 years of cohort monitoring is also improving. In 1995, only two-thirds of respondents characterized them as "good" and in 2020 – already 84 %. The same number is convinced that their marriage is based on love (in the early 2000s there were 3/4 of them), or on respect and similarity of views, system of values (a third of respondents).

Other significant risk factors for the development of a child in the first year of life, according to our calculations, are such socio-economic indicators as low purchasing power and poor living conditions of the family during the year preceding the birth of the child. Thus, if during pregnancy and childbirth, according to respondents' answers, "I only had enough money to buy food" or "I even ... had to go into debt", the risk of their child's P&NPD disorders increased by 60 % (RR = 1.59 %; 95 % CI: 1.30–1.94). If living conditions of a family were rated as "satisfactory", "poor" or "very poor", there was a two-third increase in the likelihood of child developmental delays at age 1 (RR = 1.66 %; 95 % CI: 1.37–2.03).

Parents' financial reserves provide living conditions and access to paid medical and educational services in order to maintain the health and development of a child, a possibility of full recreation. For example, pediatricians monitoring the health of young participants in our cohort study often noted antisocial family type and parental alcoholism in those children, who were diagnosed with P&NPD delay not only at one year old, but throughout their preschool years.

According to the monitoring data, there is a positive trend showing growth of well-being and purchasing power of families recruited into the cohorts (and at a higher rate than among the population of the region as a whole). The low level of purchasing power decreased almost 4-fold and amounted to 17 % in 2020[13]. The share of families whose income is "enough to buy everything necessary except for major purchases" increased 2.5-fold (76 %).

The self-assessment of housing conditions by the participants of the cohort monitoring also improved. In 2020 more than 70 % assessed them as "good" (in the late 1990s – 27 %). The level of communal facilities of the respondents is 80 %.

The growth of future parents' welfare has led to a 2.5-fold decrease (between 1998 and 2020) of those who expect deterioration of their living conditions after the birth of a child. The number of families able to provide a newborn child with a separate room grew by a quarter (24 %).

This indicates that not only the standard of living of the region's residents is growing but also the desire to strengthen their financial situation before the birth of a child.

Nevertheless, only half of the 2020 cohort has their own debt-free housing (one in nine is renting, and one in three is paying a mortgage).

Harmful working conditions of a woman a year before the birth of a child, according to our study, have a negative impact on their development in the first year of life. For example, if a mother was exposed to chemicals and toxic substances at a workplace three months before and during pregnancy, her child's risk of P&NPD delay increased by a third (RR = 1.31; 95 % CI: 1.00–1.72), with high temperature by 56 % (RR = 1.56; 95 % CI: 1.13–2.16), and with excessive gas contamination by twice as much (RR = 2.02; 95 % CI: 1.45–2.83).

We also found that the risk of CS increased by three-quarters among women who had to work with toxic and chemical substances in the year before birth (RR = 1.74) [36]. Nevertheless, we can note a favorable downward trend in the frequency of pregnant women's contacts (from 1998 to 2020) with chemical and toxic substances at a workplace (by a quarter from 7 to 5 % of respondents).

Scientists have already identified some aspects of the impacts exerted by parents' unhealthy lifestyles on the development of their offspring. For example, the British BCS70 co-

[13] Source: data from the monitoring "Study of the conditions for the healthy generation formation" and the monitoring of the socio-economic situation and social well-being, VolRC RAS.

hort study, found a strong correlation between maternal smoking during pregnancy and the appearance of behavioral disorders in a child in early childhood [37].

According to our calculations, maternal smoking before pregnancy increased the risk of developmental delays in her baby in the first year of life by one quarter (RR = 1.26; 95 % CI: 1.03–1.54) and by one half during pregnancy (RR = 1.56; 95 % CI: 1.23–1.97). We did not find a similar association with father's nicotine addiction. However, prior sexually transmitted diseases in a father tripled the likelihood of P&NPD disorders in his offspring by the age of 1 year (RR = 3.23; 95 % CI: 2.91–3.59).

As for the bad habits of pregnant women in our cohort study, they have undergone some changes over the past two decades. There was a slight decrease in the number of women who smoked before pregnancy (from 28 % of the 1998 cohort to 26 % of the 2020 cohort) and who did not quit their addiction even while expecting a baby (from 13 to 11 %, respectively). Thus, we note that in the last cohort recruited, one in four mothers smoked before pregnancy and one in ten smoked during pregnancy. And the volume of cigarettes consumed daily among them is increasing compared with the participants of the monitoring in the late 1990s. Perhaps this is caused by a change in the composition of cigarettes, the appearance of "lighter" versions of them.

Complications during pregnancy and the threat of pregnancy termination are well-known risk factors for adverse outcomes for the health and development of the child [32].

We confirmed that maternal anemia during gestation period increases by 23 % the chance of developmental abnormalities in her baby in the first year of life (RR = 1.23; 95 % CI: 1.02–1.49), and edema and presence of protein in urine tests by 50 % (RR = 1.53; 95 % CI: 1.22–1.91 and 1.24–1.88, respectively).

According to Rosstat calculations[14] from the Russian Ministry of Health data, the diagnosis of anemia in pregnant women both in 1995 and in 2020 remains almost at the same level (35 % of pregnant women whose births ended in childbirth; see Table 3). There was an increase in the rate in the first half of the 2000s. However, the number of anemias that complicated childbirth increased by a quarter during this period (from 209 per 1,000 births in 1995 to 261 in 2020). It is possible that the increase is associated with improved diagnostics.

The detection of edema in pregnant women has halved over the past quarter century (from 15 % of pregnant women in 1995 to 8 % in 2020), as well as their contribution to birth complications (from 157 to 84 cases per 1,000 births).

The prevalence of risk factors for pregnancy complications in the cohorts we recruited is as follows. In the cohorts recruited in 1998, 2001, and 2004, the prevalence of anemia in pregnant participants was 36–41 %, edema was 20–22 % and protein in urine tests was 29–31 % (Table 5)[15]. Anemia was diagnosed in 2014 in 24 % of pregnant women, and in 2020 – already 38 %. So, we can say that this risk factor of P&NPD of the child in the first year of life remains quite common (in the range of 35–40 %).

Findings and conclusion. As for today, Russia does not have a full-fledged system for monitoring the condition of newborns and early detection of developmental problems. Under the circumstances, early intervention practices, which involve an interdisciplinary approach with the participation of the spheres of medicine, education, psychology and the social sciences, are relevant. It is important to

[14] Zdravookhranenie. Pokazateli zdorov'ya materi i rebenka, deyatel'nosti sluzhby okhrany detstva i rodovspomozheniya. Sostoyanie zdorov'ya beremennykh, rozhenits, rodil'nits i novorozhdennykh [Healthcare. Indicators of maternal and child health, the activities of the child protection and obstetric services. Health status of pregnant women, women in labor, new mothers and newborns]. *Rosstat*. Available at: https://rosstat.gov.ru/folder/13721 (April 11, 2023) (in Russian).

[15] In 2014, the wording in the questionnaire designed for obstetricians and gynecologists changed, as a result of which there were open-ended questions about pregnancy complications, where no answer options were offered as before. Therefore, only 1–2 % of medical professionals noted the presence of edema and protein in the urine analysis.

Table 4

Prevalence of anemia and edema in pregnant women in Russia in 1995–2021

Disease	1995	2000	2001	2004	2005	2010	2014	2015	2020	2021
Of those, who completed their pregnancies suffered from, percent:										
Anemia	34.4	43.9	42.7	41.7	41.5	34.7	32.0	32.6	35.5	35.4
Edema*	14.9	21.4	21.2	21.5	21.6	18.1	14.6	9.2**	7.6	2.2
Number of diseases, which complicated childbirth (per 1,000 births):										
Anemia	209.5	267.9	274.7	257.9	259.5	230.8	235.0	235.3	261.7	258.1
Edema*	156.8	217.0	224.6	225.1	223.5	189.5	154.3	88.3**	84.2	85

Notes: * Edema, proteinuria and hypertensive disorders; ** The evaluation system has changed since 2015.

Table 5

Prevalence of anemia, edema and protein in urine among pregnant women participating in the cohort monitoring in Vologda region in 1998–2020 (in %)

Pregnancy complications	Cohort born in 1998	Cohort born in 2001	Cohort born in 2004	Cohort born in 2014	Cohort born in 2020
Anemia	36.1	41.2	36.8	23.5	37.9
Edema	21.7	22.3	19.5	0.8*	1.8*
Protein in urine	28.9	29.9	30.5	0.0*	0.9*

N o t e: *changes in 2014 in methodology and questions in the questionnaire for obstetricians and gynecologists.

improve forms of medico-social and educational impact, aimed not only at children and their health and developmental disorders, but also at a family. It is necessary to identify and minimize manageable risk factors, which is of great importance for building an adequate diagnosis, therapy and prevention of developmental disorders. Knowledge about the risk factors for the health and development of the child, which are already laid at the time of their birth, will help neutralize their negative impact even at the stage of pregnancy planning.

In this study, we calculated the relative risk for child development in the first year of life created by various socio-demographic, socio-economic, biomedical and environmental factors on the example of participants in a multi-year regional cohort monitoring of five waves. This allowed us to identify those with prognostic significance. Among these are young age of parents (under 20); one-parent families or broken relationships with partners; low purchasing power and poor family housing conditions; an expectant mother being exposed to chemicals, toxic substances, gas contamination and high temperatures at a workplace; smoking habits of a mother before and during pregnancy; pregnancy complications and a history of sexually transmitted diseases in a father's anamnesis.

A positive trend is the decrease in the prevalence of almost all risk factors. Nevertheless, given the negative consequences for the development of a child in the first year of life (and thus the aggravation of the situation in the future as a child grows older), we can conclude that a rather high level of smoking among women, including expectant mothers, the frequency of anemia in pregnant women, the unresolved housing and material problems of a significant proportion of families expecting a child, the impact of harmful working conditions on women are still the causes for concern.

In this connection, we believe that the experience of implementing early intervention programs aimed at the development of young children with developmental disorders or the risk of such disorders can be taken as the basis for interventions focused on comprehensive support of both mother and father, and a child before birth.

These include a system of measures to provide material support to a family, providing comfortable housing to a family before the

birth of a child, organizing accessible psychological and psychotherapeutic care, overseeing the health of expectant parents, especially those working in hazardous conditions, providing women with the necessary free medications during pregnancy.

In the process of assessing a child's perinatal risk of P&NPD, it is important for the diagnosis to be comprehensive and involve aspects of both child's condition and their immediate environment. Early intervention requires a team of specialists with different professional backgrounds: a pediatrician, neonatologist, pathologist, infectious disease doctor, venereologist, psychologist, psychotherapist, social worker, and a lawyer. In the evaluation process, each specialist uses his or her own professional tools and methods, but the results are analyzed collegially.

Thus, the following measures are necessary:

1. Development of normative acts to regulate the activities of early intervention programs and interdepartmental interaction.

2. Training of specialists, licensing of services.

3. Improving the professional skills of specialists and the development of appropriate training courses and trainings based on such principles as family-centeredness and interdisciplinarity.

4. Conducting multidisciplinary research studies to determine the effectiveness of existing or emerging programs.

Limitations of the study. (1) The study sample consisted of only those women who wished to participate in the monitoring, not all those who gave birth during the cohort recruitment period. We assume that women with serious complications of pregnancy and childbirth, and mothers of children with dangerous pathologies of intrauterine development were not included in our recruited cohorts. (2) One year later, 86 % of the five-wave cohort monitoring sample remains in the study. And the sample is shrinking every year. (3) We realize that there is an immeasurable mixture and combination of all internal and external factors which requires further study. (4) Changing the wording of the questions, excluding former questions and adding new ones to the questionnaires in some cases does not allow us to trace trends and specifics of the impact of risk factors.

Perspectives of the study. It is important to assess risk factors for child development in the first year of life, affecting a child after birth (such as breastfeeding, medical literacy and activity of parents, preventive measures, material situation and family relationships, and others). In this paper, we also intentionally did not consider the set of risk factors for child health and development related to the organization of medical aid in the healthcare and education system (level, quality and accessibility of medical and social care, etc.). In the future, we plan to conduct an in-depth study of institutional factors, including in terms of interagency cooperation.

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Research article

PREDICTING RISKS OF PROTHROMBOTIC READINESS UNDER COVID-19 USING GENETIC TESTING

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COVID-19 poses a significant hazard as regards decompensation of underlying chronic diseases, specific damage to the cardiovascular system, and a high risk of negative health outcomes such as thrombotic events. The coronavirus infection pathogenesis is rather complicated and has not been studied yet; this is largely due to peculiar features of the virus and the initial state of homeostasis in a patient.

In this study, our aim was to analyze molecular-genetic markers of homeostasis in patients with the new coronavirus infection COVID-19 as a prognostic trigger of developing pro-thrombotic readiness.

Hospitalized patients with COVID-19 were chosen as study objects. We performed molecular-genetic analysis of basic genes significant for homeostasis including several factors such as V (rs6025), II (rs1799963), I (rs1800790), VII (rs6046), XIII A1 (rs5985)), IGN A2 (rs1126643), IGN B3 (rs5918), and PAI-1 (rs1799889). The thrombinemia severity was identified by thrombin generation tests using the Ceveron®alpha automated coagulation analyzer with TGA-module.

Allelic variants of PAI-1, prothrombin (FII), and fibrinogen (FI) determined high thrombinemia as per the thrombin kinetics test (endogenous thrombin potential (AUC), peak thrombin concentration (peak-thrombin), time necessary to reach thrombin peak (tPeak), levels of fibrinogen and D-dimer) in COVID-19 patients during the entire hospitalization. We established that elevated thrombin generation becoming apparent through elevated levels of endogenous thrombin potential (AUC) might be a prognostic indicator of the pro-thrombotic state in patients with genetic polymorphisms of PAI-I and fibrinogen.

The study results indicate that pro-thrombotic readiness is determined genetically in case COVID-19 patients have allelic variants in PAI-I, prothrombin (factor II) and fibrinogen (factor I) genes.

Keywords: *COVID-19, genotype, risk, mutation, thrombinemia, polymorphism, thrombin, thrombosis.*

The COVID-19 pandemic created a wide-scale crisis in public healthcare causing millions of deaths all over the world. Clinical symptoms of the infection vary between mild and critical; pneumonia with acute respiratory distress syndrome and organ dysfunction is the most frequent severe case of the disease. A new outbreak of the coronavirus infection, in case the disease is severe, poses serious threats as regards decompensation of some initial chronic diseases, specific lesion of the cardiovascular system, a high risk of unfavorable outcomes such as thrombotic events [1]. Both foreign and Russian studies report high frequency of thrombotic events in hospitalized patients with non-critical COVID-19 despite conventional thrombotic prophylaxis. The coronavirus infection has rather complicated pathogenesis that has not yet been studied; it largely depends on peculiarities of the virus itself and the initial state of a patient's homeostasis [2]. Anti-inflammatory cytokines are known to be able to stimulate expression of tissue thromboplastin on immune cells and activate coagulation under COVID-19. Inflammation-induced endothelial dysfunction further accelerates prothrombotic readiness and elevated thrombin generation, inhibits fibrinolysis activity by reducing activity of urokinase-type plasminogen activator and in-

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creasing release of plasminogen activator inhibitor-1 (PAI-1) [3–7].

At present, special attention is being paid to genetic predisposition to the severe coronavirus infection. Thus, it was shown in some studies that changes in the gene of angiotensin-converting enzyme 2 (ACE2) altering the structure of this receptor could either facilitate or complicate penetration into a cell for the virus. Some data specifically indicate that functional deficiency of the ApoE protein under SARS-CoV-2 can promote progression of the disease and development of some complications; some studies discuss influence of HLA1 genes on the COVID-19 clinical course [8–11].

It is noteworthy that hereditary thrombophilia and its role in creating elevated risks of the infection caused by the SARS-CoV-2 virus have not been given relevant attention. Previously, some studies reported that hereditary high-risk thrombophilias such as factor II (prothrombin) mutation, factor V Leiden mutation, as well as allele variants in the PAI-1 gene can remain hidden during the whole life but such triggers as an injury, sepsis, or pregnancy can make them manifest themselves through organ disorders, progressing thrombinemia, thrombosis in various locations, and multiple organ dysfunction syndrome (MODS) in the most severe cases [7, 12, 13]. It is noteworthy that results of molecular-genetic analysis aimed at revealing prothrombotic polymorphisms in homeostasis genes can influence intensity and duration of anti-thrombotic therapy [7, 14–16].

At present, available and frequently applied laboratory tests do not give an opportunity to objectively and reliably predict a risk and severity of thrombinemia under COVID-19 in genetically predisposed patients and, consequently, to select an optimal anti-thrombotic prevention therapy.

In this study, our aim was to analyze molecular-genetic markers of homeostasis in patients with the new coronavirus infection COVID-19 as a prognostic trigger of developing prothrombotic readiness.

Materials and methods. A prospective clinical and laboratory study was accomplished during the COVID-19 pandemic (April 2020 – May 2021) in the Regional Center for Anti-Thrombotic Therapy of the E.E. Volosevich's First Municipal Clinical Hospital (Arkhangelsk). One hundred patients with average to severe and severe COVID-19 participated in it.

We applied several criteria to include patients into the study: they had PCR-confirmed COVID-19; they were hospitalized in a specialized COVID-19 unit; they gave their voluntary informed consent to participate in the study; their age was above 18 years. Exclusion criteria were as follows: refusal to take part in the study; a patient being younger than 18 years. The study design was approved by the Local Ethics Committee of the Northern State Medical University (the Meeting Report No. 2/20 dated April 23, 2020).

Laboratory tests were accomplished in the Regional Center for Anti-Thrombotic Therapy of the E.E. Volosevich's First Municipal Clinical Hospital (Arkhangelsk). Plasma samples were taken three times: first, when a patient was admitted to an in-patient hospital prior to application of any anti-thrombotic therapy; second, on the 3^{rd} – 5^{th} day of hospitalization when an anti-thrombotic therapy with low-molecular-weight heparin (LMWH) was being applied; third, on the 9^{th} – 10^{th} day of hospitalization under the ongoing anti-thrombotic therapy with LMWH.

Prothrombotic status was estimated by molecular-genetic analysis of venous blood taken from the ulnar vein by venipuncture into a vacutainer with ETDA (ethylendiaminetetraacetic acid), a sample volume being 4.5 ml. We analyzed samples of genome DNA extracted from peripheral blood leucocytes. Genotyping of polymorphisms and homeostasis mutations was performed by using the polymerase chain reaction (PCR) with subsequent restriction analysis of its product.

To analyze coagulation indicators (vacutainers with sodium citrate), the obtained blood samples were centrifuged under 3000 rpm for 15 minutes. According to the temporary methodical guidelines, version 11, that were valid at the moment this study was being accomplished, we identified prothrombin time (PT), D-dimer, activated partial thromboplastin time

(APTT) and fibrinogen with Sysmex CS-2000i blood hemostasis analyzer (Sysmex, Japan) during 30 minutes since the moment blood was taken into a vacutainers[1].

In addition, to estimate intensity of thrombinemia, we identified thrombin kinetics indicators using Ceveron® alpha fully automated coagulation analyzer with TGA-module and reagents produced by Ceveron TGA High (Technoclone GmbH, Austria). We measured and analyzed lag-time (tLag), time necessary to reach thrombin peak (tPeak), peak thrombin level (Peak), and endogenous thrombin potential (AUC).

Statistical analysis was performed using SPSS Statistics, version 20.0, and MedCalc software package. Quantitative variables are given as *Me* (median) and 25, 75 percentiles; qualitative data are given as relative frequency and 95 % confidence interval for a fraction. Quantitative data in dependent samples were compared with the unpaired two-samples Wilcoxon test. The critical level of statistical significance (p) was taken as equal to 0.05. We applied correlation analysis techniques (the Pearson's linear correlation coefficient and Spearman's rank correlation coefficient) and regression analysis techniques (multiple linear regression and multiple logistic regression).

Results and discussion. First, we analyzed severity of the new coronavirus infection. The analysis revealed that the median age of patients participating in the research was 63 [31; 85] years, women accounted for 60 % of them, and the 4th degree severity of the coronavirus pneumonia was identified in 56 % of the analyzed cases (Figure 1). Hospitalized patients with community-acquired pneumonia had the diseases with 4th degree of severity (SD) according to CT data; hospital-acquired pneumonia developed in one third of the patients and the 4th SD prevailed among them as well.

Actual clinical practice clearly indicates that laboratory diagnostics of prothrombotic readiness (thrombinemia) has a crucial role both in pathogenesis and intensive therapy of the new coronavirus infection COVID-19. At present, several laboratory markers are recommended by scientific societies as laboratory indicators of COVID-19-associated coagulopathy and inflammation [17, 18]. We should remember that recommended conventional or routine hemostasiological tests such as prothrombin time, activated partial thromboplastin time, levels of D-dimer and fibrinogen are not able to identify the actual prothrombin readiness under the new coronavirus infection or to predict severity of a prothrombotic state in a given patient. Table 1 provides the results of routine laboratory homeostasis indicators in COVID-19 patients analyzed in dynamics.

D-dimer levels were established to grow statistically significantly by the 4th hospitalization day despite the applied anti-thrombotic therapy with LMWH; fibrinogen and ferritin levels went down only by the 10th day of therapy (Figures 2 and 3). It should be noted that the aforementioned laboratory tests are laboratory markers for diagnosing both hypercoagulation and systemic inflammation [19, 20] and that routine clotting tests (APTT, INR) did not have any diagnostic significance to identify thrombinemia.

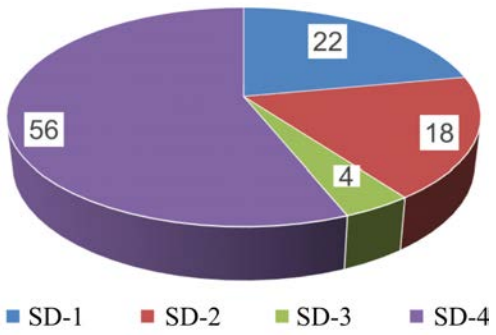


Figure 1. Degree of severity of the coronavirus infection according to lung computer tomography

[1] Profilaktika, diagnostika i lechenie novoi koronavirusnoi infektsii (COVID-19): Vremennye metodicheskie rekomendatsii. Versiya 11 (07.05.2021); utv. Zamestitelem Ministra zdravookhraneniya Rossiiskoi Federatsii E.G. Kamkinym [Prevention, diagnostics and treatment of the new coronavirus infection (COVID-19): Temporary methodical guidelines. Version 11 (May 07, 2021); approved by the Deputy to the RF Minister of Public Healthcare E.G. Kamkin]. *RF Public Healthcare Ministry*. Available at: http://nasci.ru/?id=40123&download=1 (March 30, 2022) (in Russian).

Table 1

Routine coagulogram indicators in COVID-19 taken in dynamics (Me [Q_1–Q_3])

Indicator	Hospitalization day		
	1st	4th	10th
Platelets, × 10^9/l	246 [85–407]	287 [70–615]	319 [179–500]*
APTT, sec	34.7 [30–47]	36.8 [30–49]	34.2 [23–79]
Fibrinogen, g/l	5.4 [2.3–6.8]	5.8 [3.2–6.5]	4.4 [2.8–7.2]**
D-dimer, mg/ml	1.16 [0.2–7.0]	1.6 [0.3–5.5]*	1.2 [0.1–4.2]**
INR, units	1.02 [0.8–1.0]	1.1 [0.9–1.1]	1.2 [1.0–1.2]

N o t e: *$p < 0.05$ means the difference from the 1st day is statistically significant; **$p < 0.05$ means the difference from the 4th day is statistically significant.

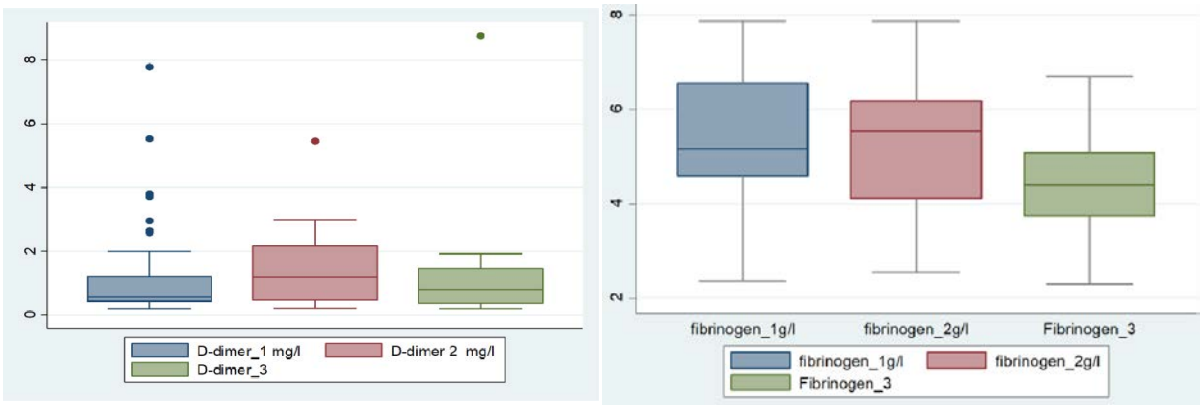


Figure 2. Levels of D-dimer (mg/l) and fibrinogen (g/l) taken in dynamics during hospitalization: the 1st, 4th, and the 10th day (n = 100)

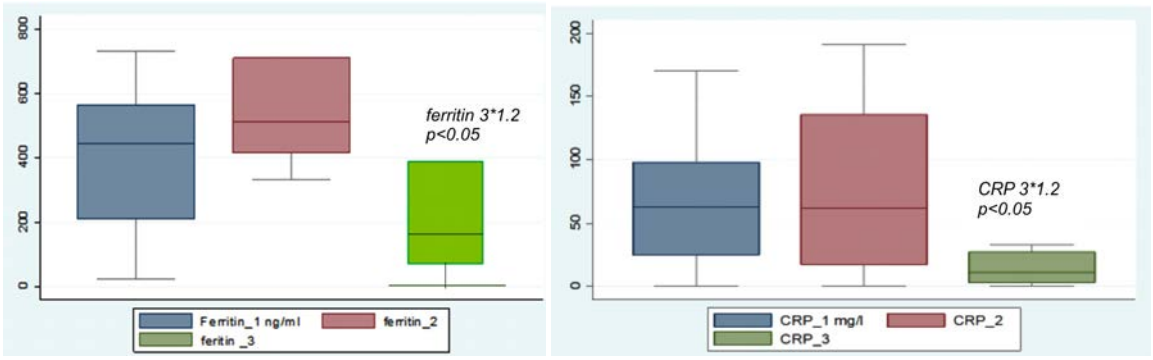


Figure 3. Levels of ferritin (ng/ml) and CRP (mg/l) taken in dynamics during hospitalization: the 1st, 4th, and the 10th day (n = 100)

We put forward a hypothesis that a hereditary genetically determined thrombophilic state could precede clinical signs of thrombinemia in some COVID-19 patients. This state involved an elevated risk of developing prothrombotic readiness against carriage of polymorphisms in fibrinogen, prothrombin and PAI-1 genes and its occurrence was associated with regulation of thrombin kinetics (generation). Given that, we believed it relevant to perform a molecular-genetic examination of COVID-19 patients to identify the occurrence of genetic polymorphisms in homeostasis indicating a genetically determined thrombophilic state.

According to the basic aim of our study, we performed molecular-genetic analysis of basic genes significant for homeostasis including several factors determining its coagu-

lation section (Factor V (rs6025), Factor II (rs1799963), Factor I (rs1800790), Factor VII (rs6046), Factor XIII A1 (rs5985)); platelet section (IGN A2 (rs1126643), IGN B3 (rs5918)), and fibrinolysis activity (PAI-1 (rs1799889)). They all were recommended for personified pharmacotherapy (Table 2) [21]. The accomplished molecular-genetic tests revealed the 'wild-type' being the most frequent genetic polymorphism as per all the examined genes significant for homeostasis in this patient group. The only differences were PAI-1 gene (rs1799889) where heterozygous and homozygous polymorphisms prevailed (49 % and 34 % of the cases accordingly) (Table 2).

The next stage in the research involved analyzing associations between genetic polymorphisms of homeostasis factors (FII 20210 G>A (rs1799963), FV 1691 G>A (rs6025), PAI-1 675 5G>4G (rs1799889)) and severity of COVID-19-associated coagulopathy by using recommended routine tests. The analysis revealed a statistically significant growth in fibrinogen levels by the 4th day (more than 6.0 g/l; $p < 0.001$) in carriers of the heterozygous allele variant in PAI-1, factor V and II genes. D-dimer levels changed as well but this change was not authentic; they tended to grow in most patients regardless of a genotype of analyzed homeostasis factors (Table 3).

According to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), mutations of factor II and V genes are among hereditary high-risk thrombophilias. Given that, we investigated possible associations between genetic polymorphisms of prothrombin FII 20210 G>A and V Leiden G>A genes and intensity of thrombinemia in COVID-19 patients. Our analysis revealed that thrombinemia was more intense in patients with genetic polymorphisms of the said genes (Figure 4).

Table 2

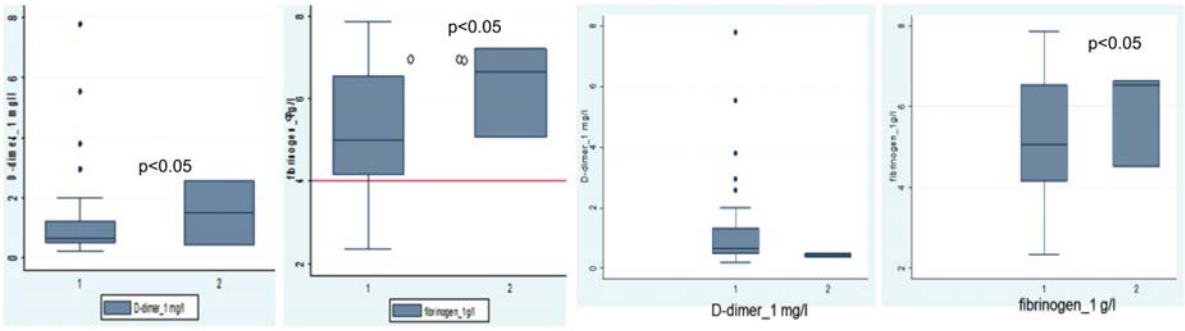
Genetic polymorphisms of homeostasis genes in COVID-19 patients ($n = 100$)

Analyzed genes	Genotype	Frequency, %	95 % CI
Factor XIII A1 (rs5985)	103 (G/G)	47.0	41.0; 53.8
	103 (G/T)	40.0	33.7; 46.0
	103 (T/T)	12.0	10.0; 15.4
IGN A2 (rs1126643)	807 (C/C)	43.0	45.0; 59.0
	807 (C/T)	38.0	31.5; 44.0
	807 (T/T)	19.0	17.0; 22.4
IGN B3 (rs5918)	1565(T/T)	66.0	60.0; 73.0
	1565(T/C)	26.0	19.0; 31.0
	1565(C/C)	12.0	10.0; 15.4
Factor V (rs6025)	1691 (G/G)	91.0	89.2; 92.8
	1691 (G/A)	6.0	4.2; 7.8
	1691 (A/A)	0	-
Factor II (rs1799963)	20210 (G/G)	93.0	90.6; 94.0
	20210 (G/A)	2.0	1.2; 4.4
	20210 (A/A)	0	-
PAI-1 (rs1799889)	–675 5G/5G	17.0	11.95; 22.51
	–675 4G/5G	49.0	42.2; 56.1
	675 4G/4G	34.0	30.8; 40.8
Factor I (rs1800790)	455 G/G	57.0	51.0; 63.8
	–455 G/A	37.0	30.7; 42.9
	–455 A/A	6.0	3.7; 9.4
Factor (VII rs6046)	10976 G/G	72.0	65.1; 78.2
	10976 G/A	23.0	17.0; 29.8
	10976 A/A	5.0	3.5; 7.9

Table 3

Thrombinemia intensity depending on allele variants in PAI-1, II and V factor genes

Genetic polymorphism	Hospitalization day					
	1st	4th	10th	1st	4th	10th
	D-dimer, mg/l (*Me*)			Fibrinogen, g/l (*Me*)		
PAI-I675 5G>4G (rs1799889)						
5G/5G (*n* = 17)	0.9	1.5	3.2	4.9	4.6	4.0
4G/5G (*n* = 49)	1.4	1.5	1.5	5.5	5.0	4.6
4G/4G (*n* = 34)	0.9	0.9	0.7	5.3	5.7	4.1
FV 1691 G>A (rs6025)						
GG (*n* = 91)	1.3	1.8	1.2	5.4	5.0	4.5
GA (*n* = 6)	0.7	0.5	1.1	5.9	6.7	3.7
FII 20210 G>A (rs1799963)						
GG (*n* = 93)	0.6	1.5	3.03	5.0	5.15	4.4
GA (*n* = 2)	2.6	0.2	0.4	6.0	6.7	4.1



1 – standard; *2* – heterozygous polymorphism

1 – standard; *2* – heterozygous polymorphism

Figure 4. Levels of D-dimer and fibrinogen upon admission to hospital in patients with polymorphisms of FII 20210 G>A and FV 1691 G>A genes

We performed regression analysis of independent thrombinemia predictors and a dependent variable (D-dimer level upon admission, the 1st day). The analysis revealed that a risk of a D-dimer level growing higher than 0.5 mg/l increased for patients with genetic polymorphisms of the PAI-1 gene (the heterozygous allele variant, β 95 % CI: 1.4 [0.6–2.13], p = 0.001; the homozygous allele variant, β 95 % CI: 2.0 [0.3–1.5], p = 0.008) and the heterozygous polymorphism of factor II (prothrombin) gene (Table 4).

According to multifactor analysis data, genetic polymorphism of the PAI-1 gene and ferritin levels higher than 200 pg/ml had authentic influence on an increase in D-dimer levels above their reference range (Table 5).

To achieve objectivity in assessing thrombinemia by laboratory tests, we applied a thrombin generation (kinetics) test (TGT). It shows how much thrombin is generated and kinetics of its generation thereby assessing the state of prothrombotic readiness [22, 23]. The results of the thrombin generation tests which we obtained in this study indicated an increase in pro-coagulation blood potential in COVID-19 patients already upon admission to in-patient hospital. Thus, we established that all the thrombin kinetics indicators changed statistically significantly in patients on the 1st day of hospitalization. This indicated significant activation of thrombin and occurring thrombinemia, or prothrombotic readiness (Table 6).

Table 4

Linear regression (D-dimer and genetic polymorphism)

Independent predictors	D-dimer		
	β	*p*	95 % CI
FV (rs6025) wild-type	1.2	0.1	-2.4; 2.27
-heterozygous polymorphism	0.7	0.2	0.1; 1.1
-homozygous polymorphism	1.0	0.3	0.31; 1.5
PAI-1 (rs1799889) wild-type	0.9	0.1	-0.43; 1.2
- heterozygous polymorphism	1.4	0.001	0.61; 2.13
- homozygous polymorphism	2.0	0.008	0.31; 1.5
FII (rs1799963) wild-type	1.0	0.6	
- heterozygous polymorphism	0.3	0.01	0.3; 1.9

Table 5

Regression analysis of independent thrombinemia predictors and D-dimer dependent variable upon admission (the 1st day)

Thrombinemia predictors	OR [95 % CI]	*p*
Genetic polymorphism in PAI-1 gene (rs1799889)	1.2 [0.1–2.5]	0.005
Ferritin level higher than 200 pg/ml	2.4 [1.1–5.4]	0.036
CRP level higher than 5.0 mg/l	0.1 [0.01−0.7]	0.999

Table 6

Thrombin generation test indicators in COVID-19 patients at the moment they were included into the study and prior to any anti-coagulant therapy

Analyzed indicator	*Me* [Q_1–Q_3]	Reference value
International normalized ratio (Tlag), min	2.46 [1.3–4.2]	7.8–13.6
Endogenous prothrombin potential (AUC, nM), nMol/min	4425.1 [3400–5070]	1379.4–1735.9
Peak thrombin level in a sample (Peak), nMol/min	862.43 [680.4–1040]	98.4–153.7
Time necessary to reach the peak (tPeak), min	5.87 [4.4–7.5]	16.7–23.2

The final stage in our study involved analyzing an association between polymorphisms of homeostasis genes and the thrombin generation test as a prognostic trigger indicating a risk of developing prothrombotic readiness in COVID-19 patients. The correlation analysis of the international normalized ratio (Tlag) and factor I (fibrinogen) genotypes revealed a moderate negative correlation; that is, a heterozygous polymorphism of the fibrinogen gene is associated with decreasing time of a lag in blood clotting. Both heterozygous and homozygous polymorphisms in the fibrinogen gene were associated with a growing peak thrombin level (Peak), which was authentically higher than in COVID-19 patients without such genetic polymorphisms (Figure 5).

Both heterozygous and homozygous polymorphisms of the PAI-1 gene were associated with shorter time necessary to reach the peak thrombin level (tPeak); that is, the peak thrombin level was reached faster in patients with alternative polymorphism of the PAI-I gene (Figure 6).

Correlation analysis of associations between levels of endogenous thrombin potential (AUC) and genotypes of the clotting factor genes I, II and PAI-1 indicated that alternative polymorphisms of the fibrinogen and PAI-1 genes were associated with elevated endogenous thrombin potential (Figure 7).

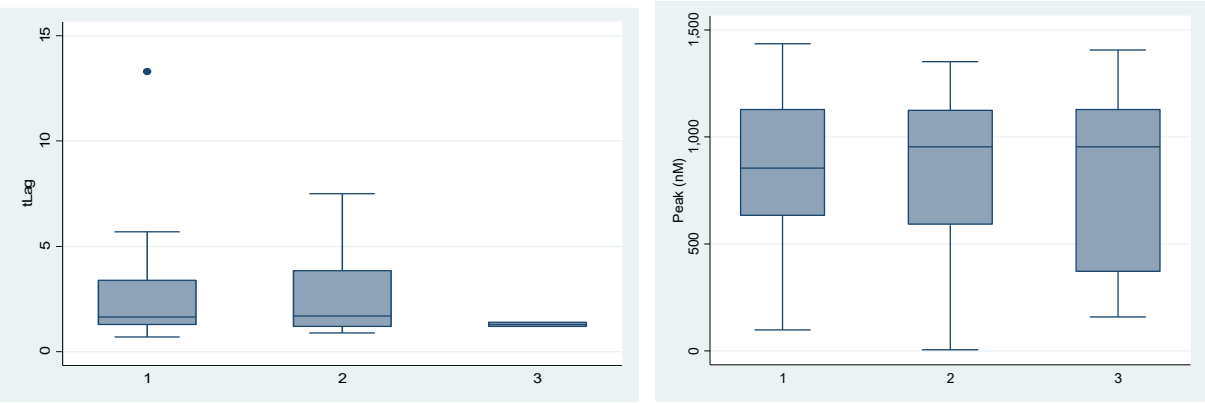


Figure 5. Correlation analysis between international normalized ratio (tLag), peak thrombin level (Peak thrombin, nmol/l) and factor I clotting genotypes (fibrinogen)

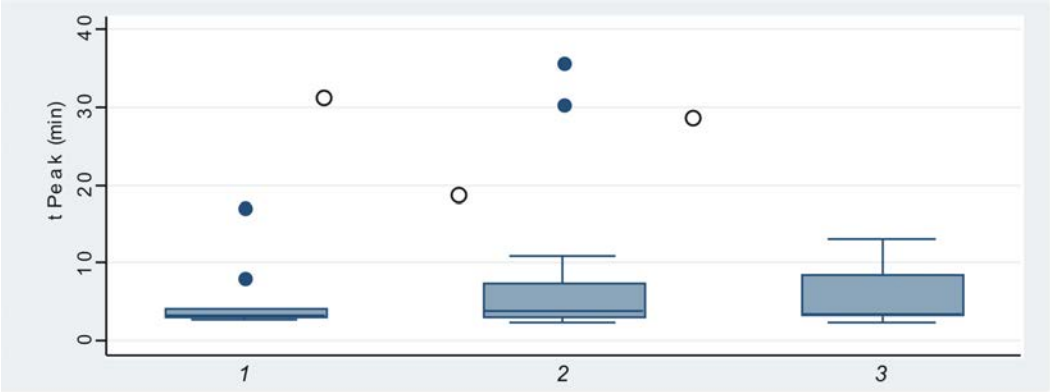


Figure 6. Analysis of correlations between time necessary to reach peak thrombin level (tPeak, min) and genetic polymorphisms of the PAI-1 gene: 1 is wild-type, 2 is heterozygous allele variant, 3 is homozygous allele variant

Figure 7. Analysis of correlations between levels of endogenous thrombin potential (AUC) and genotypes of the PAI-1, clotting factors II and I genes: 1 is wild-type, 2 is heterozygous allele variant, 3 is homozygous allele variant

Conclusion. Therefore, polymorphisms of PAI-1, prothrombin (FII), and fibrinogen (FI) genes determined high thrombinemia according to thrombin generation test indicators (endogenous thrombin potential (AUC), peak thrombin level (Peak thrombin), time necessary to reach the peak thrombin level (tPeak), fibrinogen and D-dimer levels) in COVID-19 patients over the whole hospitalization period. The study results indicate that prothrombotic

readiness is a genetically determined state in COVID-19 patients with allele variants in the PAI-1, prothrombin (factor II) and fibrinogen (factor I) genes. Elevated thrombin generation that became apparent through elevated endogenous thrombin potential (AUC) was shown to be a possible prognostic sign of prothrombotic readiness in patients with genetic polymorphisms of the PAI-1 and fibrinogen genes.

The accomplished pilot study showed that molecular-genetic testing aimed at identifying hereditary-determined thrombinemia could be considered a prognostic marker indicating an existing risk of developing prothrombotic readiness in patients with average to severe and severe COVID-19. The data obtained by this prospective clinical investigation prove the suggested molecular-genetic thrombinemia screening to be useful in treating COVID-19 patients. A clinician in a 'red zone' of a COVID-19 hospital is able to rely on an additional objective indicator that predicts thrombinemia in COVID-19 patients with acute inflammation.

Screening of genetic polymorphisms in medicine dealing with critical conditions is vital when a patient is given a pathogenetically justified antithrombotic therapy as well as within prevention activities. Our study results indicate that thrombinemia in COVID-19 patients is likely to have certain molecular mechanisms and that it is advisable to widely implement DNA-diagnostics into clinical practice for assessing severity of prothrombotic readiness and predicting its development.

Following the results of this study, a patent for invention No. 2789822 was issued on February 02, 2023.

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Research article

GLUTATHIONE AS A PROGNOSTIC FACTOR OF HEALTH RISK IN WORKING POPULATION

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Redox balance plays the key role in maintaining health. Optimizing glutathione levels has been proposed as a strategy for health promotion and disease prevention, although cause-effect relationships between glutathione status and disease risk or treatment have not been fully clarified. This study aims to estimate glutathione as a non-specific prognostic risk factor of health disorders in people exposed to industrial aerosols at their workplaces. Our observation covered the following occupational groups: workers employed at a metallurgic plant who contacted industrial aerosols (welding and silicon-containing aerosols with predominantly fibrogenic effects); patients with non-obstructive chronic industrial bronchitis (NCIB) without exacerbation; patients suffering from occupational chronic obstructive pulmonary disease (oCOPD) who were in a post-exposure period; workers who were not exposed to industrial aerosols at their workplaces. Total glutathione (TG), reduced glutathione (GSH) and oxidized glutathione (GSSG) were identified in whole blood by the Ellman method.

Elevated GSSG levels (higher than 100 μmol/l) and low values of the GSH/GSSG ratio (less than 10 units) were identified in more than 50 % of the workers exposed to industrial aerosols. These markers were established to have diagnostic sensitivity of more than 50 %, diagnostic specificity of more than 85 % and prognostic significance of more than 80 % for the examined groups. The GSSG level and GSH/GSSG ratio can be used as a prognostic indicator of health disorders in workers exposed to industrial aerosols and a possibility of chronic bronchopulmonary pathology developing in future.

Keywords: *reduced glutathione, oxidized glutathione, ratio of glutathione fractions, industrial aerosols, bronchopulmonary pathology, oxidative stress, risk factor, working population.*

Health protection is the most vital task within the state policy. It is closely connected with the quality of public healthcare in the country and development of effective programs aimed at protecting health of all population groups regardless of their social status, occupation or welfare[1]. Great

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attention is paid to health of working age population exposed to harmful occupational factors at their workplaces [1]. In this case, the key role belongs to preliminary and periodical medical examinations; among other things, their aim is to detect early signs of occupational and work-related diseases. Early diagnostics of diseases relies on biomarkers, or quantitative health indicators. A biomarker can be an indicator of a risk and progression of a disease; it can be used to diagnose a disease or estimate whether treatment is effective.

Glutathione as a biochemical marker is a good example. Although structural and functional relationships within the glutathione system have been investigated for decades, many issues regarding glutathione functions in health and in a pathological state still require profound examination.

Glutathione is a major intracellular antioxidant responsible for removing reactive oxygen species by an enzymatic or non-enzymatic way. Intracellular glutathione exists as a monomer in its reduced form (GSH) and as a disulfide dimer in its oxidized form (GSSG), which is formed due to GSH oxidation. Reduced and oxidized glutathione forms are the main cellular redox buffer. In physiologically normal conditions, GSH usually appears in higher concentrations than GSSG. Some authors consider the GHS / GSSG ratio to be a marker of oxidative stress (OS) [2]. GSH deficiency or lower GSH / GSSG ratios largely indicate OS is developing and cell antioxidant properties are weakened; elevated GSH levels are associated with enhanced antioxidant capabilities and resistance to OS [3]. Studies with their focus on glutathione fractions established that the GSH / GSSG ratio was approximately 10:1 in healthy people whereas any decrease in this ratio was a marker of oxidative stress [4].

Glutathione has many various functions. It protects cells against oxidative stress, supports the immune system functioning, participates in post-translation protein modification and also takes some part in DNA synthesis and recovery, cell proliferation and differentiation; it regulates cell death, apoptosis included. Glutathione plays a significant role in non-enzymatic protein glutathionylation thereby regulating a structure and functions of a protein, changing forms, charges and sizes of target proteins; it also protects proteins against further irreversible peroxidation [5].

Disorders in the glutathione system have been detected in many diseases. Lower levels of reduced glutathione and higher levels of oxidized one were identified in patients with type II diabetes, stroke, hypertension, after cardiac surgery, neurologic diseases, schizophrenia and Alzheimer disease [6–9]. Lower GSH and higher GSSG levels were observed in patients with many lung diseases including chronic obstructive pulmonary disease, bronchial asthma, idiopathic pulmonary fibrosis, cystic fibrosis, and acute respiratory distress syndrome [10, 11]. Redox balance was established to be crucial for maintaining health. Given that, optimizing glutathione levels has been proposed as a strategy for health promotion and disease prevention, although cause-effect relationships between glutathione status and disease risk or treatment have not been fully clarified [12]. Bearing multiple roles of glutathione in mind, we believe it is really difficult to establish a cause-effect relation between changes in GSH levels and progression of a disease [13].

The glutathione system includes several enzymes with vital antioxidant functions. Glutathione peroxidases neutralize hydrogen peroxide and reduce oxidized lipids [14]. Glutathione reductase reduces oxidized glutathione (GSSG) and maintains the permanent level of reduced glutathione (GSH) in cells [15]. Glutathione-S-transferases protect cells against environmental exposures due to detoxification acting as catalysts in GSH conjugation [16].

Under unfavorable conditions, the glutathione system aims to maintain homeostasis in the body by stimulating its enzyme systems responsible for keeping balance between specific fractions. That is, oxidized glutathione is rapidly transformed into reduced one; the glutathione system again recovers and performs its antioxidant functions. Exposure to harmful

environmental and occupational factors (ambient air pollution, tobacco smoke, radiation, chemical exposures at a workplace, industrial aerosols, noise exposure, chemical intake with food, etc.) stimulates excessive production of free radicals [17, 18]. According to results obtained by some researchers, harmful occupational factors disrupt well-balanced functioning of oxidant and antioxidant systems [6, 7]. In case free radicals are produced in excessive quantities and the system of free radical oxidation does not function properly, glutathione antioxidant functions might be impaired as well; ultimately, this leads to excessive formation of oxidized glutathione and a decline in levels of reduced one. Having generalized data of multiple research works on the subject, we can state that any failure in the glutathione system produces negative effects on the clinical course and forecast of various diseases already diagnosed in a patient and can also facilitate occurrence of new pathologies with varied genesis.

In this study, our aim was to estimate glutathione as a non-specific prognostic risk factor of health disorders in people exposed to industrial aerosols at their workplaces.

Materials and methods. Within this study, 245 people were observed; they were divided into five groups.

The 1st group (control) was made of practically healthy people employed in various branches who were free of any exposure to industrial aerosols at their workplaces (advertising agency staff, managers, office clerks and accountants); overall, there were 44 men in this group, their average age being 57 years (53–59), average work records, 13.9 ± 8.5 years.

The 2nd group included practically healthy people employed at a metallurgic plant in the Nizhniy Novgorod region (55 men aged 52 (47–54) years with work records being 13.8 ± 7.7 years) who were exposed to welding and silicon-containing aerosols with predominantly fibrogenic effects (electric gas welders, slingers, metal cutters, milling and rolling machine operators) and did not have any functional signs of impaired lung ventilation.

The 3rd group was made of practically healthy people employed at a metallurgic plant in the Nizhniy Novgorod region (39 men aged 51 (45–55) years, average work records being 13.3 ± 7.5 years) who were exposed to welding and silicon-containing aerosols with predominantly fibrogenic effects (electric gas welders, slingers, metal cutters, milling and rolling machine operators) and already had some functional signs of impaired lung ventilation.

The 4th group included workers with long-term work records employed at car production in Nizhniy Novgorod. They suffered from non-obstructive chronic industrial bronchitis (NCIB) caused by long-term exposure to welding and silicon-containing aerosols with predominantly fibrogenic effects. The workers in this group did not have exacerbation and were in a post-exposure period when this study was being accomplished. They were all being treated in the therapeutic clinic of the Nizhniy Novgorod Research Institute for Hygiene and Occupational Pathology of Rospotrebnadzor. Overall, the group included 29 people (14 men and 15 women) aged 59 (55–60) years with average work records under harmful exposure being equal to 27.8 ± 8.0 years.

The 5th group was made of workers with long-term work records employed at car production in Nizhniy Novgorod who suffered from occupational chronic obstructive pulmonary disease (oCOPD) with a stable clinical course. The disease had been caused by long-term exposure to welding and silicon-containing aerosols with predominantly fibrogenic effects. The workers in this group were also being treated in the therapeutic clinics of the Nizhny Novgorod Research Institute for Hygiene and Occupational Pathology of Rospotrebnadzor. Overall, there were 78 people in this group (12 women and 66 men) aged 59 (58–63) years with average work records under harmful exposure being equal to 26.0 ± 8.0 years.

People with acute communicable diseases, malignant neoplasms, diabetes mellitus or a chronic disease in exacerbation were excluded from the study.

All the observed patients gave their informed consent to participating in the study that was then approved by the Local Commit-

tee of Ethics of the Nizhniy Novgorod Research Institute for Hygiene and Occupational Pathology of Rospotrebnadzor.

Data on working conditions at workplaces of the workers from the 2nd and 3rd group were provided by their employer in accordance with the Federal Law No. 426 issued on December 28, 2013 On Special Assessment of Working Conditions[2]. According to this assessment, average shift levels of dusts with diiron trioxide varied between 0.65 to 7.2 mg/m^3 in different spots (MPC is 6.0 mg/m^3); silicon dioxide (its share in dusts varying between 10 and 70 %), between 0.44 and 2.4 mg/m^3 (MPC is 2.0 mg/m^3); electrocorundum, between 1.8 and 6.6 mg/m^3 (MPC is 6.0 mg/м^3). Average shift concentrations of silicon dioxide, electrocorundum and diiron trioxide levels in workplace air were by 1.1–1.2 times higher than MPC. The working conditions were assigned into the hazard category 3.1 (harmful conditions, hazard category 1).

COPD was diagnosed based on the criteria provided by the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease – GOLD, 2021 [19] and the Federal Clinical Recommendations of the Russian Respiratory Society [20]. NCIB was diagnosed based on the criteria fixed in the National Guide[3]. The disease was diagnosed as 'occupational' in accordance with the Provisions on Investigating and Accounting of Occupational Diseases (The RF Government Order issued on December 15, 2000 No. 967) [4] and the Order by the RF Ministry for Public Healthcare and Social Development issued on April 27, 2012 No. 417n On Approval of the List of Occupational Diseases[5].

All the participating workers had their breathing examined with a Spirolab III OXY spirometer (Italy), the following indicators being estimated in the process: forced vital capacity (FVC, %$_{standard}$), forced exhalation volume in 1 sec (FEV_1, %$_{standard}$), a calculated ratio of these two indicators (FEV_1 / FVC, %) or modified Tiffeneau-Pinelli index (MTPI) and maximum forced expiratory flow at FCV 75 % (FEF 75 %).

Levels of total (TG), reduced (GSH) and oxidized glutathione (GSSG) were identified in whole blood of all the examined workers by the Ellman method [21]. As sampling was completed, the blood samples were placed in ice and frozen under 70–80 °C below zero. At all stages in analyzing, the samples were centrifuged under 4 °C in a preliminary cooled centrifuged at 10,000 rpm for 10 minutes. The GSH / GSSG ratio was calculated and its value lower than 10 was estimated as critical; it indicated functional failure of the antioxidant system [4].

The results were statistically analyzed with variation statistics methods in Statistica 6.1 software package (StatSoft Inc, USA). We applied the Shapiro – Wilk test to examine how close the data were to normal distribution and to analyze equality of dispersions. In case data deviated from normality, non-parametric Mann – Whitney U-test was applied. The data

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[2] O spetsial'noi otsenke uslovii truda: Federal'nyi zakon ot 28.12.2013 № 426-FZ (prinyat Gosdumoi 23 dekabrya 2013 g., odobren Sovetom Federatsii 25 dekabrya 2013 g.) [On Special Assessment of Working Conditions: the Federal Law No. 426 issued on December 28, 2013 (approved by the State Duma on December 23, 2013, by the Council of Federation, on December 25, 2013)]. *KonsultantPlus*. Available at: https://www.consultant.ru/document/cons_doc_LAW_156555/ (November 01, 2022) (in Russian).

[3] Professional'nye zabolevaniya organov dykhaniya: natsional'noe rukovodstvo [Occupational respiratory diseases: the national guide]. In: N.F. Izmerov, RAS Academician, and A.G. Chuchalin, RAS Academician eds. Moscow, GEOTAR-Media, 2015, 792 p. (in Russian).

[4] Ob utverzhdenii Polozheniya o rassledovanii i uchete professional'nykh zabolevanii (s izmeneniyami i dopolneniyami): Postanovlenie Pravitel'stva RF ot 15 dekabrya 2000 g. № 967 [On Approval of the Provisions on Investigating and Accounting of Occupational Diseases (with alterations and addenda): The RF Government Order issued on December 15, 2000 No. 967]. *GARANT: information and legal portal*. Available at: https://base.garant.ru/182775/ (February 07, 2023) (in Russian).

[5] Ob utverzhdenii perechnya professional'nykh zabolevanii: Prikaz Ministerstva zdravookhraneniya i sotsial'nogo razvitiya RF ot 27 aprelya 2012 g. № 417n [On Approval of the List of Occupational Diseases: the Order by the RF Ministry for Public Healthcare and Social Development issued on April 27, 2012 No. 417n]. *GARANT: information and legal portal*. Available at: https://base.garant.ru/70177874/ (February 07, 2023) (in Russian).

were given as Med ± IQR (25–75 %). Chi-square test (χ^2) with Yates correction was applied to determine whether differences between qualitative indicators were statistically significant. In case a value of an expected fact was lower than 10, the exact Fisher's test was applied (Fisher's F-test). We calculated prognostic significance of glutathione fractions[6] as well as a risk of imbalance between its fractions in people exposed to industrial aerosols at their workplaces. To compare probabilities of outcomes depending on a risk factor, we created a fourfold contingency table, calculated a relative risk (*RR*) and its 95 % confidence interval (95 % CI). The indicator was considered positive if its value was > 1. The differences were considered valid if the confidence interval for this indicator did not include 1. We calculated odds ratio (*OR*) and 95 % confidence interval (95 % CI) to determine influence of a risk factor on a probability of an outcome. Critical significance of the study results was taken as $p < 0.05$. Values of p between 0.05 and 0.1 inclusively were estimated as a trend.

Results and discussion. Table 1 presents spirometry data of the examined workers.

The study revealed that the workers from the 2nd and 3rd group mostly did not have any health complaints although some functional disorders of lung ventilations were identified in the 3rd group (FEF 75 % varied between 37 and 68 %). Five workers in this group had initial NCIB signs including periodical coughing and minor shortness of breath; the workers did not make much of it. The average FEF 75 % was authentically lower in the 3rd group than in the 2nd one where it varied between 79 and 98 % ($p_{2,3} = 0.002$, the Mann – Whitney test) and was authentically by 20–29 % higher than FEF 75 % in the 4th and 5th group ($p_{3,4} = 0.02$; $p_{3,5} = 0.012$, the Mann – Whitney test).

Table 2 provides the results of identifying glutathione and its fractions in blood of the examined workers.

The analysis of the obtained data revealed valid differences in quantitative levels of glutathione and its fractions between the control group and the 3rd, 4th and 5th group. Authentic differences between the 1st and 2nd group were identified only as regards GSSG levels and GSH / GSSG ratios ($p^{GSSG}_{1,2} = 0.023$; $p^{GSH/GSSG}_{1,2} = 0.01$, the Mann – Whitney test). It is worth noting that authentic differences were also established between the workers with functional disorders of lung ventilation (the 3rd group) and the workers without such disorders (the 2nd group) as regards quantitative levels of glutathione and its fractions: ($p^{TG}_{2,3} = 0.015$; $p^{GSSG}_{2,3} = 0.01$; $p^{GSH/GSSG}_{2,3} = 0.019$; $p^{\%GSSG}_{2,3} = 0.021$, the Mann – Whitney test).

To calculate diagnostic sensitivity, diagnostic specificity and prognostic significance of glutathione fractions, we took the indicators with their values being authentically different in all the experiment groups of exposed workers and patients (groups 2–5) against the same values in the control group. GSSG and GSH / GSSG were selected relying on the data provided in Table 2. Diagnostic specificity identified for these two indicators equaled 93.2 % and 88.6 % accordingly. Table 3 provides data on diagnostic sensitivity and prognostic significance of GSSG fraction and the GSH / GSSG ratio in the examined workers exposed to industrial aerosols and patients with bronchopulmonary pathologies.

The analysis of the obtained data revealed that elevated GSSG levels (higher than 100 μmol/l) were identified in the groups 2–4 with frequency higher than 50 % (diagnostic sensitivity). Diagnostic sensitivity was the same in both groups of the workers exposed to industrial aerosols at their workplaces ($\chi^2 = 2.045$, $p_{2,3} = 0.153$) and was authentically by 7–8 times higher in them against the control ($F = 0.00007$, $p_{1,2} < 0.05$; $F = 0.00000$, $p_{1,3} < 0.05$). Similar results were obtained for the groups of patients with NCIB and oCOPD: diagnostic sensitivity was the same in both groups ($\chi^2 = 0.534$, $p_{4,5} = 0.466$) and was authentically higher than in the control ($F = 0.00001$, $p_{1,4} < 0.05$; $F = 0.00001$, $p_{1,5} < 0.05$).

[6] Pavlovskaya N.A. Rannyaya diagnostika professional'nykh zabolevanii: rukovodstvo [Early diagnostics of occupational diseases: guide]. Moscow, GEOTAR-Media, 2020, 128 p. (in Russian).

Table 1

Spirometry indicators in the examined workers, Med ± IQR (25–75 %)

Groups	FVC, %	FEV_1, %	MTPI	FEF 75 %
Group 1 (control) (n = 44)	100.6 (95–113)	98.5 (94–106)	0.86 (0.80–0.98)	82 (80.1–85.2)
Group 2 (FEF 75 % equal to 70 % and above) (n = 55)	105.8 (96–117)	95.4 (91–101.2)	0.92 (0.83–0.98)	89 (81.0–96.0)
Group 3 (FEF 75 % below 70 %) (n = 39)	98.4 (88.7–102.5)	100 (96–109)	0.89 (0.81–0.95)	58 (46.5–64.0)
Group 4 Patients with NCIB (n = 29)	65.5 (58–74)	59 (54–71.5)	0.78 (0.73–0.85)	46 (41.8–49)
Group 5 Patients with oCOPD (n = 78)	62 (61–75)	50 (52–63)	0.65 (0.65–0.69)	41 (38.7–43)

Note: FVC is forced vital capacity, % of the standard value; FEV_1 is forced expiration volume in 1 sec, % of the standard value; MTPI is modified Tiffeneau – Pinelli index; FEF 75 % is the maximum forced expiratory flow with an expiration being 75 % of FVC.

Table 2

Quantitative indicators of glutathione and its fractions in workers exposed to industrial aerosols, patients with NCIB and oCOPD, (Med ± IQR (25–75 %))

Indicator	The experiment groups				
	Group 1 (control) (n = 44)	Group 2 (FEF 75 % equal to 70 % and above) (n = 55)	Group 3 (FEF 75 % Lower than 70 %) (n = 39)	Group 4 Patients with NCIB (n = 29)	Group 5 Patients with oCOPD (n = 78)
Glutathione fractions (reference levels)	Levels of glutathione and its fractions (Med ± IQR (25–75 %)				
TG (900–1500 μmol/l)	1270.8 (1145.8–1370.5)	1269.5 (1128.5–1401.3)	993.9 (856.1–1121.5)	1000.1 (891.3–1101.1)	968.2 (820.1–1060.2)
GSH (750–1300 μmol/l)	1072.5 (1002.5–1272.8)	1035.6 (910.0–1144.5)	990.5 (933.3–1077.6)	806.7 (632.5–869.9)	783.4 (584.2–929.4)
GSSG (45–100 μmol/l)	62.6 (28.8–109.6)	96.0* (71.5–123.4)	110.8* (87.5–164.5)	109.4* (71.7–127.4)	99.7* (49.1–129.8)
GSH / GSSG (equal to 10 and above)	19.6 (9.9–40.9)	11.1* (6.8–13.3)	8.7* (5.9–11.9)	6.7* (4.7–11.5)	8.7* (5.8–14.6)
% GSSG of TG (less than 10 %)	4.0 (2.6–7.2)	4.1 (2.9–8.8)	9.0 (7.9–13.7)	11.4 (7.1–14.4)	9.3 (6.0–12.9)

Note: * means p (the Mann – Whitney test) indicating a statistically significant difference in GSSG levels and GSH / GSSG ratios against the control ($p < 0.05$).

Table 3

Diagnostic sensitivity and prognostic significance of GSSG and GSH / GSSG in workers exposed to industrial aerosols and patients with bronchopulmonary pathology, %

Indicator (reference values)	The experiment groups				
	Group 1 (control) (n = 44)	Group 2 (FEF 75 % equal to 70 % and above) (n = 55)	Group 3 (FEF 75 % Lower than 70 %) (n = 39)	Group 4 Patients with NCIB (n = 29)	Group 5 Patients with oCOPD (n = 78)
	Diagnostic sensitivity (frequency of identified elevated (↑) and low (↓) levels, %)				
GSSG (45–100 μmol/l)	6.8 (↑)	50.9 (↑)	58.9 (↑)	55.2 (↑)	44.9 (↑)
GSH / GSSG (equal to 10 and above)	11.4 (↓)	52.7 (↓)	53.8 (↓)	62.1 (↓)	61.5 (↓)
	Prognostic significance (%)				
GSSG (45–100 μmol/l)	-	88.2	89.6	89	86.8
GSH / GSSG (equal to10 and above)	-	82.2	82.5	84.5	84.4

Lower GSH / GSSG ratios (less than 10 units) were identified with 50–60 % frequency in all the examined groups. In the groups of the exposed workers, diagnostic sensitivity of the GSH / GSSG ratio was the same (χ^2 = 0.588, p = 0.444) and was authentically by 4–5 times higher against the control (χ^2 = 10.783, $p_{1,2}$ = 0.002; χ^2 = 15.426, $p_{1,3}$ < 0.001). In the groups of the patients with NCIB and oCOPD, diagnostic sensitivity of the GSH / GSSG ratio was also the same (χ^2 = 0.30, p = 0.863) and was authentically higher than in the control group (χ^2 = 18.542, $p_{1,4}$ < 0.001; χ^2 = 26.818, $p_{1,5}$ < 0.001).

We identified high prognostic significance (80 % and above) for the GSH / GSSG ratio and GSSG levels for the workers exposed to industrial aerosols. We established a significant risk of improper GSH / GSSG ratios for the workers exposed to industrial aerosols at their workplaces (*RR* = 3.208, 95 % CI (1.143–9.002), p < 0.05). This relative risk level indicates that industrial aerosols with fibrogenic effects have certain influence on impairments of the glutathione system functioning. We established that a risk of impairments in the glutathione system functioning was by 12 times higher under exposure to industrial aerosols (*OR* = 11.632, 95 % CI (2.369–57.099)); by 11 times higher for the patients with NCIB (*OR* = 10.632, 95 % CI (2.008–56.334)); by 10 times higher for the patients with oCOPD (*OR* = 10.400, 95 % CI (2.192–49.346)) against the control group.

Therefore, our study results indicate that more than a half of the examined workers exposed to industrial aerosols had negative changes in the glutathione system. This indicated that the redox balance was impaired, oxidative stress was developing and antioxidant protection with glutathione participation was weakened. Similar changes were identified in the patients with bronchopulmonary pathologies, NCIB and oCOPD, who were in a post-exposure period. Although any contacts with industrial aerosols had long ceased, the glutathione system remained impaired in the patients with bronchopulmonary pathology regardless of a therapy; the mechanism of this impairment requires further investigation. It is noteworthy that glutathione is a non-specific marker that describes antioxidant protection of the body and its prognostic role in development of a particular disease will obviously depend on exogenous risk factors influencing workers. In occupational pathology, it is extremely difficult to find highly specific informative tests for a particular occupational disease since its development is highly influenced by harmful occupational factors. These factors, apart from their direct influence on organs and systems, can affect a biomarker and its metabolism. Given that, a possibility to use tests with their sensitivity exceeding 50 % and prognostic significance being not less than 80 % is quite justified in occupational pathology.

In this study, we made an attempt to analyze informative value of glutathione fractions. The analysis established that reduced glutathione had low sensitivity (7.5 % in the workers exposed to industrial aerosols and 42 % in the patients with chronic bronchopulmonary pathology) despite high specificity (its lower values were not detected in any workers form the control group). It can be applied only as an indicator of a progressing disease and developing complications. Oxidized glutathione levels and reduced to oxidized glutathione ratio are much more informative. Both indicators have sufficient diagnostic specificity (more than 80 %) and sensitivity (more than 50 %) in all the examined groups. They can be applied both to create risk groups among people exposed to industrial aerosols at workplaces for more profound monitoring of their health and as indicators pointing at a risk that development of a bronchopulmonary pathology is quite probable. In patients with NCIB and oCOPD caused by exposure to industrial aerosols, these indicators can be a signal that a disease might progress unfavorably and a current treatment can hardly be considered effective.

Undoubtedly, it is hard to identify cause-effect relations between development of a particular pathology and impairments of the glutathione system. To achieve this, more profound investigations are required. Our study results do not provide clear evidence of a role

glutathione might play in development of bronchopulmonary pathology, in particular NCIB and oCOPD, since its functions are too diverse. Still, we can't fail to note that weaker antioxidant protection in which glutathione plays the key role leads to elevated oxidative stress, an important component in COPD progression. However, too little attention is paid by clinicians, occupational pathologists included, to accomplishing treatment and prevention activities aimed at reducing excessive quantities of free radicals and strengthening antioxidant protection of the body including the glutathione system. It is necessary to perform more profound examination of effects produced by environmental and occupational factors on free radical oxidation and antioxidant protection.

Many studies show that 'anti-oxidant approaches', including proper diets, vitamin therapy, neuroprotectors and anti-inflammatory drugs that neutralize reactive oxygen species, can have certain therapeutic effectiveness when they are used to treat various diseases. Issues of applying glutathione and its metabolites in therapy are being discussed actively [22–24].

Based on the accomplished study, oxidized glutathione and reduced to oxidized glutathione ratio were selected as the most informative prognostic indicators of health risks for workers exposed to industrial aerosols at their workplaces and a probability that a bronchopulmonary pathology would develop in them in future.

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Research article

IMMUNOCHEMICAL MARKERS OF EFFECT UNDER EXPOSURE TO RISK FACTORS CAUSING VIBRATION DISEASE OF DIFFERENT ETIOGENESIS: COMPARATIVE ASSESSMENT

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In recent years, it has become especially vital to identify prognostic risks of health disorders in workers exposed to harmful occupational factors. This is necessary for substantiating an occupational origin of a disease and biomarkers of exposure and for optimizing the occupational risk assessment methodology.

The aim of this study was to compare and analyze immunochemical markers of effect (cytokines, heat shock proteins, and neuronal antibodies (AB)) in blood serum of patients with vibration disease (VD) induced by exposure to different types of vibration in order to substantiate the most informative diagnostic risk indicators concerning the disease development and clinical course.

Cytokines, heat shock proteins, and antibodies to regulatory proteins of nervous tissue were identified in blood by ELISA tests. We established unidirectional statistically significantly more apparent changes in patients who had VD caused by combined exposure to both whole body vibration and local vibration against those who had VD caused by exposure to local vibration only. These changes included hyperactivated pro-inflammatory reactions of the immune response (IL-1β, TNF-α, INFγ), growing concentrations of antibodies to proteins: S-100, MBP, NF-200, GFAP, and voltage-gated Ca-channel. The differences were that patients with VD under combined exposure to both types of vibration had greater production of pro-inflammatory IL-8 and HSP27 whereas people with VD caused by exposure to local vibration only had a decrease in HSP70 levels.

The study results confirmed more apparent neuro-immune inflammation in patients with VD caused by combined exposure to both whole body vibration and local vibration. This may indicate more significant risk factors of the disease and gives an opportunity to identify the most sensitive biomarkers eligible for diagnosing VD of different etiogenesis.

Keywords: *vibration disease, cytokines, heat shock proteins, neuronal antibodies, inflammation, local and whole body vibration.*

In recent years, it has become especially vital to identify prognostic risks of health disorders in workers exposed to harmful occupational factors. This is necessary for substantiating an occupational origin of a disease, biomarkers of exposure, and peculiarities of a biological response to exposures [1, 2]. Vibration disease (VD) is a well-known polysyndrome disease affecting both the peripheral and central nervous system[1] [3]. Cerebrospinal, thalamic, and cortical centers of vibrational sensitivity as well as the hypothalamus are involved in the pathological process [4, 5]. The leading VD syndromes include distal vegetative-sensory polyneuropathy and angiodystonia. Multiple studies have reported that dysfunctions in the nervous system are accompanied with changes in the immune system at any stage of VD occurrence and clinical course [6–9]. At present, workplaces in production typically involve combined exposure to both whole body and local vibration. Local vibration affects the body through the hands whereas whole body vibration affects the whole body in most cases and this has certain influence on the clinical course of the disease. At the same time, researchers predominantly give attention to pathogenesis, clinical course and diagnostics of VD caused by local vibration. Very few works provide some evidence

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of additive effects produced by whole body and local vibration together [10]. However, there are no data in literature as regards comparative assessment of the neuro-immune response in patients with VD of different etiogenesis. Obviously, such data are necessary for developing the occupational risk assessment methodology and personified approaches to diagnostics and treatment of the disease.

In this study, our aim was to compare and analyze immunochemical markers of effect (cytokines, heat shock proteins, and neuronal antibodies (AB)) in blood serum of patients with vibration disease (VD) induced by exposure to different types of vibration in order to substantiate the most informative diagnostic risk indicators concerning the disease development and clinical course.

Materials and methods. We performed laboratory and immunological examinations of 137 men who had VD. The first group included 50 patients with VD caused by chronic exposure to local vibration (their age was 48.34 ± 0.88 years). Their occupations were drifts miners, working face miners, and welders-riveters. The second group was made of 53 patients with VD caused by combined exposure to whole-body and local vibration (their age was 52.21 ± 0.49 years). Their occupations were drilling unit operators, heavy truck drivers, and tracked vehicle drivers. The examined patients from these two groups had harmful working conditions at their workplaces; these conditions belonged to the hazard category 3.2 as per work intensity and the hazard category 3.3 as per work hardness. All the examined patients in the first and second group had an occupational disease diagnosed under occupational contacts with vibration. They did not have any comorbidity (obesity, diabetes mellitus, essential hypertension, etc.) or any chronic diseases in exacerbation. The third group included 34 healthy men who did not have any chronic diseases when they were examined (their age was 50.35 ± 1.69 years) and were not exposed to vibration at their workplaces. Biomaterials were sampled prior to the beginning of the COVID-19 pandemic. We estimated levels of pro-inflammatory cytokines (IL-1β, TNF-α, IL-2, IL-8, IL-10, IL-4, INFγ) in blood serum by ELISA tests using reagent kits manufactured by Vector-Best LLC (Novosibirsk). Heat shock proteins HSP27, HSP70 were quantified by ELISA tests using ELISA kits HSP70, HSP27 Assay Design (Enzo Life Sciences, USA). We identified antibodies (ABs) using standard test systems ELI-Neuro-Test produced by Immunkulus Moscow Scientific-Production Association and estimated levels of the most informative ABs of IgG class to the following proteins: S-100, NF-200 (neurofilament protein), GFAP (glial fibrillary acidic protein), MBP (myelin basic protein), and VGCC (voltage-gated Ca-channel).

The results were statistically analyzed using STATISTICA 6.0 applied software (StatSoft, USA). The distribution normality was checked using the Shapiro – Wilk test. The results are given as median (*Me*), lower (Q_{25}) and upper (Q_{75}) quartiles. The statistical significance was taken at $p < 0.05$.

The patients were examined in conformity with the ethical standards stipulated by the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, as of 2000, and the Rules of Clinical Practice in the Russian Federation (the Order by the RF Public Healthcare Ministry issued on June 19, 2003).

Results and discussion. We compared levels of some pro- and anti-inflammatory cytokines in blood serum of the patients with VD depending on occupational exposures. This allowed us to reveal general regularities and differences between the compared groups. The patients from both the first and the second group had statistically significantly higher levels of pro-inflammatory IL-1β ($p < 0.00001$ and $p < 0.00001$ accordingly) and TNF-α ($p = 0.0006$ and $p = 0.001$ accordingly) than the healthy people in the third (control) group (Table).

In addition, we detected an increase in levels of another pro-inflammatory mediator IL-8 in the second group in comparison with the control one ($p = 0.003$) and the patients with VD caused by local vibration ($p = 0.0003$). The latter did not have any differences as per IL-8 levels from the control group. We analyzed

Table

Comparative assessment of some immunochemical indicators in patients with VD, *Me* (Q_{25}–Q_{75})

Indicator	Units of measurement	The first group (n = 50)	The second group (n = 53)	The third group (n = 34)
IL-1	pg/ml	12.57 (6.14–36.6) *p = 0.0000	10.52 (6.17–39.17) *p = 0.0000	3.4 (1.21–6.19)
IL-2	pg/ml	3.39 (2.37–5.39)	4.79 (2.44–7.71)	4.22 (2.67–6.33)
IL-4	pg/ml	0.01 (0.01–0.01)	0.01 (0.01–0.57)	0.01 (0.01–0.69)
IL-8	pg/ml	6.63 (1.47–8.52)	13.09 (6.65–29.77) *p = 0.003; •p^{1-2} = 0.0003	5.08 (1.41–13.40)
IL-10	pg/ml	0.58 (0.01–1.4)	0.01 (0.01–1.33)	0.01 (0.01–1.54)
TNFα	pg/ml	1.87 (1.50–2.86) *p = 0.0006	1.87 (0.84–3.3) *p = 0.001	0.73 (0.01–1.47)
INFγ	pg/ml	0.87 (0.01–2.24)	1.75 (0.72–21.7) *p = 0.0000; •p^{1-2} = 0.002	0.01 (0.01–1.16)
HSP27	pg/ml	2.93 (0.41–6.83)	7.53 (6.76–9.63) *p = 0.0003	1.7 (0.57–3.61)
HSP70	pg/ml	0.1 (0.04–0.36) *p = 0.019	0.39 (0.33–0.42)	0.37 (0.13–0.41)
S-100	arbitrary unit	0.585 (0.54 –0.686) *p = 0.00001	1.14 (0.942–1.19) *p = 0.000007; •p^{1-2} = 0.00004	0.285 (0.240–0.410)
GFAP	arbitrary unit	0.556 (0.483–0.618) *p = 0.00002	0.828 (0.525–0.903) *p = 0.000009; •p^{1-2} = 0.009	0.368 (0.310–0.430)
NF-200	arbitrary unit	0.565 (0.449–0.661) *p = 0.000001	0.813 (0.662–0.854) *p = 0.000001; •p^{1-2} = 0.0005	0.306 (0.250–0.320)
VGCC	arbitrary unit	0.582 (0.516–0.686) *p = 0.000005	0.833 (0.751–1.12) *p = 0.0000005; •p^{1-2} = 0.00001	0.215 (0.170–0.326)
MBP	arbitrary unit	0.453 (0.370–0.558) *p = 0.000004	0.679 (0.522–0.758) *p = 0.000005; •p^{1-2} = 0.0009	0.300 (0.270–0.360)

N o t e: * means difference from the third group; • means difference between the 1st and 2nd group.

levels of INFγ responsible for interaction between multiple cellular systems in three groups and revealed that the median of this indicator was statistically significantly ($p <$ 0.002) higher in the second group than in the first and third one ($p <$ 0.00001). At the same time, the indicator tended to grow in the patients from the first group.

Heat shock proteins (HSPs) or stress proteins are important indicators able to provide the most adequate description of a non-specific cell reaction to external stimuli. Several studies reported that circulating extracellular proteins could have some immune-regulatory properties and immune cells, in their turn, could be a source of HSP extracellular pools [9, 11, 12]. Given that, it seemed advisable to include comparative analysis of changes in certain markers into our study (HSP27 and HSP70) since they describe the functional state of cells (Table). Our investigation of extracellular HSP27 indicated that its levels were statistically significantly higher in the patients from the second group as opposed to the third group (p = 0.00003); local vibration only induced its ascending trend. This fact might be

evidence of direct damage to cells that facilitated release of the aforementioned proteins and their exit to the extracellular space [13]. HSP70 levels in blood serum identified in the patients from the second group did not have any difference from the control group; still, the patients from the first group with VD caused by local vibration had statistically significantly lower levels of this protein against the control ($p < 0.019$). This decrease in HSP70 levels in blood serum identified in the patients in the first group obviously indicates the protein accumulates inside cells [14]. Some authors believe that heat shock proteins can obtain some autoantigen properties and this may induce vessel injury [15] and endothelium membrane injury, the most susceptible targets under VD. This fact was evidenced by some experimental research [16]. Therefore, to get a comprehensive and complex insight into peculiarities of immune biochemical processes in patients with VD of different etiogenesis, we investigated neurospecific antibodies (ABs), which were the most informative under occupational diseases of the nervous system. The data provided in the Table indicate that the patients with VD, both from the first and second group, had statistically significantly ($p < 0.05$) higher levels of AB to the following proteins: S-100; MBP; NF-200; GFAP; voltage-gated Ca-channel (VGCC). The analysis also revealed that the median values of all the identified auto-ABs were statistically significantly higher in the patients with VD caused by combined exposure to whole body and local vibration than in the patients with VD induced by local vibration only. The most apparent differences were established for ABs to S-100 protein as their levels were almost twice as high in the patients with VD caused by combined exposure to whole-body and local vibration ($p < 0.00004$) than in the patients with VD caused by exposure to local vibration. Excessive ABs concentrations persisting for a long time are known to be able to promote immune-metabolic dysfunctions in involved nervous tissues with their intensity varying from mild to complete destruction of the said tissues[2] [17]. We should remember that S-100 multifunctional proteins could produce both protective and destructive effects on nervous tissues depending on their concentration. S-100 proteins regulate interaction between glia and neurons in general thereby providing functional homeostasis of brain cells [18]. Taking into account literature data and our study results, we can conclude that changes in the nervous system are more apparent in patients with VD caused by combined exposure to whole body and local vibration. This may indicate that risk factors of the disease occurring under such exposure are more significant.

The identified peculiarities of immunochemical indicators in patients with VD of different etiogenesis were consistent with and confirmed by the results of neurophysiological examinations performed on the same people. Registration of somatosensory evoked potentials revealed greater changes in neurons of the central afferent pathways in the somatosensory zone of the cortex and cervical section of the spinal cord in the patients with VD caused by combined exposure to whole body and local vibration [19]. Neuroenergy mapping identified some distinguishing features in the same patients, namely, an increase in constant potential levels in patients with VD caused by combined exposure was determined in the central region and in the right temporal region under exposure to local vibration [20]. This allows identifying the most informative biomarkers for risk factors causing VD of different etiogenesis.

Conclusion. Therefore, we established unidirectional statistically significantly more apparent changes in patients who had VD caused by combined exposure to both whole body vibration and local vibration against those who had VD caused by exposure to local

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vibration only. These changes included hyper-activated pro-inflammatory reactions of the immune response (IL-1β, TNF-α, INFγ), growing concentrations of antibodies to proteins of nervous tissue: S-100, MBP, NF-200, GFAP, and voltage-gated Ca-channel; they were quite different from effects caused by exposure to local vibration. The patients with VD under combined exposure to both types of vibration had greater production of pro-inflammatory IL-8 and HSP27 whereas people with VD caused by exposure to local vibration had a decrease in HSP70 levels. The study results confirmed greater risks that neuro-immune inflammation would develop in patients under combined exposure to whole body and local vibration and made it possible to identify the most sensitive biomarkers (IL-1β, TNF-α, INFγ, ABs to S-100) eligible for VD diagnostics and prediction of its clinical course.

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Research article

POLYMORPHISM OF THE APOE GENE AS A RISK FACTOR OF OBESITY IN WORKERS EXPOSED TO OCCUPATIONAL HAZARDS AT FERROUS METALLURGY ENTERPRISES

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Obesity contributes to the development of severe concomitant diseases and substantially degrades the quality of life. This pathological condition is caused by multiple risk factors including hazardous workplace exposures and genetic predisposition. The ApoE gene participates in regulation of lipid metabolism. Its most significant polymorphisms are rs429358 and rs7412 with the resulting e2, e3 and e4 alleles.

This study did not consider effects of electromagnetic fields generated by office electrical equipment or the lifestyle of the subjects. The sample included people with a large age difference due to the rarity of the apolipoprotein e2 and e4 alleles. The sample was not standardized by age and years of work experience.

The aim of this study was to investigate associations between the ApoE gene polymorphisms and body mass index in workers employed at a metallurgic plant.

We examined 328 male office workers and workers of a converter workshop. The body mass index (BMI) was calculated based on the results of instrumental measurements of weight and height using the conventional formula. DNA was isolated from peripheral blood using the LumiPure DNA gel extraction kit, and polymorphisms were determined using amplification by Calero et al with modifications and horizontal agarose gel electrophoresis. The data were analyzed using the Kruskal – Wallis test.

Statistically significant differences were established in the blue-collar workers. The highest mean BMI value was established in the e2 allele carriers.

We found that people with the e2 allele in their genotype were more prone to obesity. We also assume a potential association between the unsafe work environment and a more pronounced manifestation of the phenotype. These findings can be used for identifying individuals at risk and taking timely preventive measures.

Keywords: *ApoE, obesity, risk factors, BMI, lipid metabolism, ferrous metallurgy, harmful working conditions, cholesterol.*

Obesity is one of the main risk factors for the development of serious cardiovascular diseases, such as stroke, coronary heart disease, pulmonary embolism, etc., and musculoskeletal disorders, with osteoarthritis being the principal concomitant pathology leading to disability [1–3]. According to the Federal State Statistics Service (Rosstat), in the year 2019, 17.8 % of men and 24.5 % of women in the Russian Federation were obese (obesity

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classes I to III) while 46.9 % of men and 34.7 % of women were overweight [4].

It has been previously shown that people aged over 40 and those having low physical activity are more likely to be overweight and obese. Little is known, however, about the prevalence of obesity in people employed in industries with unsafe working conditions. It is generally accepted that excess adipose tissue accumulates when energy intake exceeds energy expenditure; yet, both occupational risk factors and genetic predisposition can also contribute to higher prevalence of obesity among the working population [5–8].

Apolipoprotein E (APOE) is one of the regulators of fat metabolism in the body of mammals. It is involved in the transport of triglycerides and cholesterol to various tissues by interacting with lipoprotein receptors of target cells. It is a key regulator of cholesterol redistribution [9–11]. The most important polymorphisms for the APOE gene are rs429358, which is characterized by the substitution of the amino acid cysteine for arginine at position 112, and rs7412 with the substitution of arginine for cysteine at position 158 [12, 13].

The study of the relationship between genetic predisposition, occupational risk factors, and morbid obesity makes it possible to identify criteria for assessing health risks and contributes to elaboration of effective preventive measures for the population at risk.

Our **objective** was to investigate associations between the APOE gene polymorphisms and the body mass index in workers employed at a metallurgic plant.

Materials and methods. We examined 328 male employees of a ferrous metallurgy enterprise aged 23 to 66 years (mean age: 43.61 ± 9.04 years). The sample was divided into 142 cases, all working in a basic oxygen furnace shop and exposed to occupational hazards, and 186 controls selected from administrative/management personnel.

The body mass index (BMI) was calculated based on the results of instrumental body height and weight measurements using the conventional formula. DNA was isolated from peripheral blood using the LumiPure DNA gel extraction kit and polymorphisms were then determined using amplification by Calero et al with modifications and horizontal agarose gel electrophoresis [14].

PCR mixtures. We prepared two PCR mixtures: mixture A based on Arg primers (Arg112 and Arg158) and mixture B based on Cys primers (Cys112 and Cys158). Each mixture contained 10 µl of BioMaster HS-Taq PCR-Color (2x), 0.4 µL of each primer, 0.8 µL of a common primer, DMSO, water, and 2.5 µl of the DNA sample. Amplification was carried out using a T100 Thermal Cycler (BIO RAD, USA) under the following conditions: preliminary denaturation for 5 min at 95 °C followed by 35 three-step cycles: denaturation for 30 s at 95 °C, primer annealing for 30 s at 61 °C, elongation for 60 s at 72 °C, followed by the final elongation during 15 min at 72 °C. The results were visualized using horizontal agarose gel electrophoresis.

For statistical analysis, the data on each patient were recorded twice in order to compensate for the data loss when selecting only one allele, so each study participant with a heterozygous genotype was taken into account in both groups at once. The use of genotypes for the analysis was considered inappropriate due to resulting small sample sizes impeding application of appropriate statistical methods. The data were analyzed using the Kruskal – Wallis test in Statistica 12 (StatSoft Inc).

Results and discussion. In this study, we examined the relationship between APOE gene alleles and the body mass index in employees of a ferrous metallurgy enterprise presented in the table.

Each cohort was divided into three subcohorts depending on the allele present. When analyzing the whole sample, no statistical differences were found, but we observed a tendency towards manifestation of the phenotype in people carrying the e2 allele ($p = 0.074$).

The mean body mass index in workers with different APOE gene alleles

Cohort	e2	e3	e4	*p*
Administrative / management personnel	27.48 ± 4.45 (*n* = 7)	28.05 ± 4.54 (*n* = 316)	28.11 ± 4.32 (*n* = 49)	0.683
Workers of the basic oxygen furnace shop	29.24 ± 4.53 (*n* = 21)	28.21 ± 4.52 (*n* = 225)	28.36 ± 4.55 (*n* = 38)	**0.038**

N o t e s : e3 – normal genotype; e2 and e4 – mutant genotypes. The table shows mean values and the error of the mean; the number of alleles considered is in brackets; statistically significant differences ($p \leq 0.05$) are in bold. The comparison was made within cohorts between alleles.

No statistically significant differences were found within the control cohort ($p = 0.683$), which probably indicates the absence of an external factor affecting the manifestation of phenotypic traits in office workers.

In contrast to the controls, BMI values in workers of the basic oxygen furnace shop were allele dependent ($p = 0.038$), with the highest mean value established in the APOE e2 carriers. It is worth noting that the sample included people with a large age difference, so the data might be distorted by the absence of phenotype manifestations in younger subjects and the presence of concomitant diseases leading to weight gain in the older ones. We decided to include these groups of workers due to the rarity of the e2 and e4 alleles.

Hence, we can assume the relationship between the presence of the e2 allele of the APOE gene and weight gain. A statistically significant effect of this APOE variant on obesity has not yet been established, so it is impossible to ascertain that the correlation found in this study will be true for other populations, since anthropometric data are strongly influenced by such factors as ethnicity, sex, lifestyle, and concomitant diseases [15–17].

It is worth mentioning, however, that there exists a relationship between conformation of the APOE protein and its binding activity. Weisgraber states that APOE3 and APOE4 were equally effective at binding to low density lipoprotein receptors on cultured human fibroblasts, while APOE2 showed only 1 % binding capacity. This fact is associated with the development of type 3 hyperlipoproteinemia, which can lead to obesity if not managed. According to the author, the presence of the e2 allele is not an absolute prerequisite of hyperlipoproteinemia and, as mentioned earlier, external factors play the main role in the development of this metabolic syndrome [18–20].

Conclusion. We established that people with the e2 allele in the genotype are more likely to develop obesity; besides, the relationship between the exposure to occupational hazards and a more pronounced manifestation of the phenotype is possible. These findings can facilitate identification of individuals at risk and promote timely preventive measures.

Research limitations. The study did not take into account health effects of electromagnetic fields generated by office electrical equipment and lifestyle of the subjects. The sample consisted of people with a large age difference owing to the rarity of the apolipoprotein e2 and e4 alleles. The sample was not standardized by age and years of work experience.

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Conflict of interest. The authors have no conflicts of interest to declare.

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Research article

EXPOSURE TO AIRBORNE NICKEL AND PHENOL AND FEATURES OF THE IMMUNE RESPONSE MEDIATED BY E AND G IMMUNOGLOBULINS

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Ambient air pollution with potentially allergenic technogenic haptens facilitates occurrence of atopic reactions and creates favorable conditions for future development of allergic pathologies in exposed population.

The aim of this study was to estimate formation of an IgE-mediated and IgG-mediated specific immune response to low-molecular chemical compounds introduced into the body by inhalation (nickel and phenol used as examples).

The test groups were made of children (n = 99) and adults (n = 57) who lived under exposure to airborne nickel and phenol in levels not exceeding maximum permissible ones (up to 0.7 MPL). The reference groups included children (n = 95) and adults (n = 53) who lived on a conventionally clean territory.

In the test groups, average daily exposure doses of airborne nickel and phenol varied between $0.7 \cdot 10^{-6}$ and $9.3 \cdot 10^{-6}$ mg/(kg·day) for children and between $3.5 \cdot 10^{-6}$ and $5.0 \cdot 10^{-5}$ mg/(kg·day) for adults (the doses were created by emissions from a non-ferrous metallurgy plant); this was 1.5–3.0 times higher than the same indicators in the reference groups. Levels of IgG specific to nickel were more than two times higher in the exposed groups; the exposed children had elevated levels of IgG specific to phenol in their blood, practically three times higher than in the reference group ($p < 0.05$). By using logistic regression models, we established a significant probabilistic cause-effect relation between elevated nickel levels in children's blood and elevated levels of IgE-specific to nickel ($R^2 = 0.87$; $F = 468.58$; $p < 0.05$). The assessment of the odds ratio made it possible to verify the relationship between nickel levels in blood and the increase in the level of IgE specific to nickel in children (OR = 8.96; 95 % CI = 2.00–40.15) and in adults from the test group (OR = 3.12; 95 % CI = 1.10–9.40).

The study results indicate that exposure to low levels of airborne nickel and phenol induces hypersensitivity to technogenic haptens in the exposed children and adults. Its distinctive features are an IgE-mediated reaction to nickel and IgG-mediated reaction to phenol. Hyperproduction of immunoglobulin E specific to nickel as well as IgG-antibodies specific to phenol in the exposed children and adults reflects levels of exposure to airborne nickel and phenol and is a peculiarity of a hyperactive immune response developing in the analyzed children on the test territory.

Keywords: *nickel, phenol, airborne exposure, specific IgG, specific IgE, reagins, sensitivity to haptens, atopic reaction.*

Over the last 20 years, we have witnessed intensive urbanization, rapid industrialization and population growth; all these processes play a significant role in increasing anthropogenic environmental pollution and create elevated risks of allergic diseases [1]. According to The World Allergy Organization (WAO), allergic diseases are diagnosed in 30–40 % of the world population. Statistical data indicate that allergy is more widely spread among children and young people [2].

Hypersensitivity to technogenic haptens that penetrate the body by inhalation is a quite common immunological dysfunction. Thus, in our previous studies, we reported hapten-associated elevated levels of G class antibodies to phenol adducts in preschool children and schoolchildren of different age; these levels were related to excessive phenol in blood [3, 4]. Only IgG specific to formaldehyde are usually identified under exposure to airborne phenol and formaldehyde [5]. However, a di-

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rect relationship has been established between an increase in a bisphenol S (BPS) concentration in the body and IgG specific to BPS in women with bronchial asthma [6]. Women and children are more susceptible to phenol and its derivatives than men [7]. Phenol has been established to be able to stimulate deviation of the immune response towards Th2; the chemical has also been reported to be prone to affect aryl hydrocarbon and estrogen receptors [3]. Some authors have diagnosed respiratory dysfunctions (shortness of breath and wheeze) in preschool children caused by exposure to phenol; however, they have not identified and association between this exposure and the course of bronchial asthma [8]. At the same time, other researchers have established a relationship between development of bronchial asthma and phenol introduced by inhalation in adult patients [9]. Systemic effects produced by phenol have been reported to determine reproductive dysfunctions [10] and development of metabolic syndrome [11]. Phenol is highly likely to be able to deposit in fat tissues that induce inflammation by hyperproduction of cytokines; as a result, all these effects combined create elevated risks of allergy. A highly positive IgG-response to allergens has been shown to be three times more frequent in patients with obesity [6]. Regardless of introduction, the highest levels of many phenol compounds are identified in urine and lower levels are usually identified in blood serum or breast milk, which is due to the fact that phenols are mostly excreted by the kidneys [6]. Phenol has a relatively short half-life. However, persistent exposure creates relatively stable long-term levels of phenol compounds in biological media and this means it is fair to perform single estimation of phenol levels in the body [6]. Transition metals such as iron (Fe), zinc (Zn), copper (Cu), cobalt (Co), manganese (Mn), and nickel (Ni) are essential microelements and can be found in many enzymes participating in fundamental biological processes. Effects of nickel on the inborn and adaptive immunity when it is forming a response to a food or airborne allergen have been reported in some studies [12]. Nickel has been proven to be able to change metabolism of other metals [13]. Nickel is also an adjuvant for other metals [13]. When nickel penetrates the body by inhalation, it induces lung fibrosis; trachea, larynx and lung cancer; inflammatory non-communicable bronchopulmonary diseases; cardiovascular diseases; damage of the kidneys, and immunological dysfunctions. Inhalation exposure to nickel also facilitates its deposition in the brain and marrow, lung tissues, and the cardiac muscle [12–14]. Some researchers report that inhalation introduction of nickel causes asthma and rhinoconjunctivitis; at the same time, other authors have not established similar relationships. However, it has been noted that prevalence of bronchial asthma correlated with age and grew during pubescence [14]. Among young adults (aged 20–40 years), prevalence of nickel-associated sensitization is the highest and then the indicator starts to decline at an older age. The established trend is caused by declining hyperreactivity of the immune system with age. Allergy to nickel is more frequent among women than among men (15.7–22.9 and 4.3–6.65 % accordingly) [13]. Nickel has high allergenic potential and in some cases can act as an immunotoxic and carcinogenic agent [13]. Allergic contact dermatitis caused by exposure to nickel develops in 10–20 % of population [15]. Elevated levels of IL-6, IFN-γ и TNF-α, IL-2 in biological media (blood serum and bronchial secretion) were identified under nickel contamination [16]. When nickel penetrates the body through skin or the respiratory system, it induces the development of type I and IV allergic reactions mediated by reaginic antibodies and allergen-specific T-lymphocytes [17]. However, it is very difficult to describe how an allergic reaction develops and exact mechanisms of allergy to nickel have not yet been clarified [14]. Several authors insist that only such transition metals as nickel and chromium are allergenic [18–20]. Nickel and manganese can be found in particular matter; the latter have porous surfaces and electrostatic properties and are therefore able to interact with al-

lergens and induce a specific immune reaction [16, 21–23]. It has been established in experimental models *in vitro* and *in vivo* that manganese and nickel increase expression of the class II HLA-molecules, CD86-antigen, CD23-antigen and production of Th2-cytokines resulting in more intensive sensitization and allergic inflammation [24, 25].

Therefore, prevalence of allergic diseases and their dynamics being dependent on intensity of anthropogenic influence on the environment have been observed over the last decades. This confirms the necessity to search for updated diagnostic methodological approaches and to use them to timely identify how sensitive various population groups are to environmental pollutants. In future, these approaches will provide effectiveness of medical and preventive activities and reduce risks of developing allergic reactions to anthropogenic factors, including technogenic chemical ones.

In this study, our aim was to estimate the formation of an IgE-mediated and IgG-mediated specific immune response to low molecular weight compounds introduced into the body by inhalation (nickel and phenol used as examples).

Materials and methods. Biomedical tests were accomplished in conformity with the requirements fixed in the WMA Declaration of Helsinki (1964, 2013). An individual written informed consent to examinations and personal data processing was obtained from all the participants or their legal representatives. Overall, we examined 304 adults (aged 30–45 years) and children (aged 3–7 years) in both test and reference groups. The participants lived in areas with different anthropogenic loads in the Eastern Siberia. We applied the following criteria to include participants into the study: they had been living on the examined territories for at least five years prior to the examinations; they had not had any acute communicable diseases for at least two weeks prior to the examinations. Participation in another study was an exclusion criterion. The test groups included children (n = 99) and adults (n = 57) who lived under inhalation exposure to emissions from a non-ferrous metallurgy plant: airborne phenol and nickel (the test territories). The reference groups were made of children (n = 95) and adults (n = 53) who were not exposed to these chemicals in ambient air (the reference territories). We compared chemical levels in the collected air samples with the standards for ambient air quality. As a result, nickel levels were established to reach 0.03 average daily MPC (maximum permissible concentration) on the test territories; phenol levels, 0.68 average daily MPC. On the reference territories, nickel levels reached 0.02 average daily MPC; phenol levels, 0.22 average daily MPC. Chemical analysis of children's blood included phenol quantification by gas chromatography in accordance with the Methodical guidelines MUK 4.1.2102-4.1.2116-06[1] using the Kristall 2000 capillary gas chromatographer (JSC CDO CHROMATEC, Russia). Nickel levels were identified in biological media by mass-spectrometry with inductively coupled plasma (ISP-MS) using the Agilent 7500cx mass spectrometer in accordance with the Methodical guidelines MUK 4.1.3230-14[2]. Phenol and nickel levels in biological media of the children and adults from the test groups were estimated comparatively against the same indicators in the reference groups.

[1] Opredelenie vrednykh veshchestv v biologicheskikh sredakh: Sbornik metodicheskikh ukazanii MUK 4.1.2102–4.1.2116-06 [Determination of harmful chemicals in biological media: the collection of methodical guidelines MUK 4.1.2102–4.1.2116-06]. Moscow, the Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2008, 183 p. (in Russian).

[2] MUK 4.1.3230-14. Metody kontrolya. Khimicheskie faktory. Izmerenie massovykh kontsentratsii khimicheskikh elementov v biosredakh (krov', mocha) metodom mass-spektrometrii s induktivno svyazannoi plazmoi; utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii A.Yu. Popovoi 19 dekabrya 2014 g. [Methodical guidelines MUK 4.1.3230-14. Control techniques. Chemical factors. Measurement of mass concentrations of chemical elements in biological media (blood, urine) with mass spectrometry with inductively coupled plasma; approved by A.Yu. Popova, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on December 19, 2014]. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/495856222 (January 19, 2023) (in Russian).

Levels of IgG specific to phenol, IgE specific to nickel were identified with the allergosorbent method; the total IgE level was identified with ELISA tests performed with the ELx808IU microplate reader (Bio-Tek, USA).

We checked the normality of distributions in the analyzed groups using the Kolmogorov – Smirnov test. To describe data that were distributed normally, we used the simple mean (*M*) and the standard error of the mean (*m*). We tested the null hypotheses that the simple means were equal in two independent groups with normal distribution using the two-sample Student's t-test. Sample data were compared with the reference values using the one-sample Wilcoxon signed rank test. We applied simple logistic regression analysis to predict probability of immune response dysfunctions. The odds ratio (OR) and its 95 % confidence interval were calculated to assess the relationship between the studied responses and the impact of factors. The null hypotheses were tested at the level of significance taken as equal to 0.05. Data were statistically analyzed using Statistica 6.0 software package (StatSoft, USA).

Results and discussion. We established that an average daily exposure to airborne nickel amounted to $0.7 \cdot 10^{-6}$ mg/(kg·day) and to airborne phenol $9.3 \cdot 10^{-6}$ mg(kg·day) for children in the test group; for the reference group, average daily exposure to airborne nickel equaled $0.4 \cdot 10^{-6}$ mg/(kg·day); phenol, $3.0 \cdot 10^{-6}$ mg/(kg·day). Average daily exposure doses were also established for the adults in the test group and equaled $3.5 \cdot 10^{-6}$ mg/(kg·day) for airborne nickel; $5.0 \cdot 10^{-5}$ mg/(kg·day) for airborne phenol. For the reference group, these exposure doses were equal to $2.3 \cdot 10^{-6}$ mg/(kg·day) for nickel and $1.62 \cdot 10^{-5}$ mg/(kg·day)[3] for phenol. Obviously, average daily intake of nickel and phenol was on average 1.5 and 3.1 times higher accordingly for the test groups against the reference ones.

Chemical and analytical tests established no statistically significant differences between nickel in blood of the children from the test group (0.1125 ± 0.0098 mg/dm^3) and the same indicator in the reference group (0.1143 ± 0.0069 mg/dm^3; p = 0.751 and 0.1088 ± 0.0065 mg/dm^3; p = 0.753). The share of blood samples with elevated nickel levels, higher than those identified in the reference groups, equaled 50 % in the test groups. Phenol levels were established to be statistically significantly (p = 0.026–0.048) 2 times higher in biological media of the children (0.0732 ± 0.0158 mg/dm^3) and adults (0.0490 ± 0.008 mg/dm^3) from the test groups against the same indicators in the reference ones (0.0379 ± 0.0083 mg/dm^3; p = 0.026 and 0.0249 ± 0.0099 mg/dm^3; p = 0.048). The share of samples with excess phenol in blood equaled 75.0 % in each test group against the same indicator in the corresponding reference group.

Comparative characteristics of the specific sensitization profile established that levels of IgE specific to nickel were statistically significantly (p = 0.002–0.021) 2.6 times higher on average in blood serum of the children and adults from the test groups against the same indicator in the corresponding reference ones. Estimation of the IgG-mediated reaction revealed that the children exposed to phenol had statistically significantly (p = 0.046) 2.8 times higher levels of IgG-antibodies specific to phenol against levels established in the unexposed children (Table). The adults from the test group had statistically significantly ($p < 0.05$) 2.3 times higher average group levels of IgG specific to phenol against the upper limit of the reference range.

[3] O sostoyanii i ob okhrane okruzhayushchei sredy Rossiiskoi Federatsii v 2018 godu: Gosudarstvennyi doklad [On the condition and protection of the environment in the Russian Federation in 2018: the State report]. Moscow, The Ministry of Natural Resources and Environment of the Russian Federation; SPO Kadastr, 2019 (in Russian); Sostoyanie zagryazneniya atmosfery v gorodakh na territorii Rossii za 2017 g.: Ezhegodnik [The ambient air pollution in cities in Russia over 2017: the annual data collection]. Saint Petersburg, Rosgidromet's Voeikov Main Geophysical Observatory, 2018, 234 p. (in Russian).

Table

Specific sensitization profile in the test and reference groups

Subjects	Test group	Reference group	*p*
IgE total, IU/cm^3 (% of samples above the reference range) *RR* 0–9.99, IU/cm^3			
Children	75.375 ± 17.567 (38.3 %)	87.767 ± 25.64 (43.3 %)	0.445
Adults	88.125 ± 27.137 (18.9 %)	88.943 ± 55.982 (11.8 %)	0.977
IgE spec. to nickel, IU/cm^3, (% of samples above the reference range) *RR* 0–1.55, IU/cm^3			
Children	0.387 ± 0.146 (2.1 %)	1.014 ± 0.349 (16.5 %)	0.002
Adults	0.465 ± 0.215 (8.6 %)	1.340 ± 0.703 (22.0 %)	0.021
IgG spec. to phenol, c.u. (% of samples above the reference range) *RR* 0–0.13, c.u.			
Children	0.049 ± 0.054 (8.7 %)	0.139 ± 0.069 (36.2 %)	0.046
Adults	0.126 ± 0.086 (32.0 %)	0.300 ± 0.188 (62.5 %)	0.091

The share of samples with elevated levels of G class antibodies to phenol adducts and class E antibodies to nickel adducts, higher than the reference levels, equaled 36.2 and 16.5 % accordingly in blood serum of the children from the test group against 8.7 and 2.1 % in the reference one (4.2 and 7.9 times higher accordingly). In the adults from the test group, the shares of samples with elevated levels of IgG specific to phenol and IgE specific to nickel that were higher than the reference levels equaled 62.5 and 22.0 % accordingly against 32.0 and 8.6 % in the reference group (2.0 and 2.6 times higher accordingly). The odds ratio assessment demonstrated an association of hapten load (nickel) with an increase in the level of nickel-specific IgE in children in the test group (OR = 8.96; 95 % CI = 2.00–40.15) and in adults in the test group (OR = 3.12, 95 % CI = 1.10–9.40).

We created mathematical logistic regression models that allowed establishing a statistically significant probabilistic cause-effect relation between growing levels of nickel and IgE-antibodies specific to nickel in children's blood ($b_0 = -5.53$; $b_1 = 28.44$; $R^2 = 0.87$; $F = 468.58$; $p < 0.001$).

Chronic exposure to phenol, and nickel in doses not higher than MPC (0.03–0.68 average daily MPC) clearly facilitates an immunologically mediated growth in sensitivity of the body to chemical factors (haptens) in children and adults. We established that IgE-mediated sensitization to nickel was more apparent in children living under possible exposure to priority airborne chemical factors than in adults living under the same conditions; production of immunoglobulin G specific to phenol was also much more intensive in children than in adults.

Persistent penetration of airborne low molecular weight compounds (LMWC) through the airways determines their accumulation in various biological media in the body and this is often associated with developing hypersensitivity. Under normal physiological conditions, cells of the adaptive immune system adequately recognize and remove antigens (haptens). However, an excessive immune reaction to usually harmless chemicals can be accompanied with allergy and inflammation. Permanent inflammation occurs in places that are repeatedly affected by allergens. Chronic allergic inflammation is associated with tissue remodeling and substantial changes in the barrier function of damaged epithelium, which increases a risk of infection. Mast cells, T-cells, eosinophils, basophils, neutrophils, monocytes / macrophages, thrombocytes, NK-cells, and Th-2 cytokines are basic participants responsible for development of chronic allergic inflammation. The immune system in children functions with a certain peculiarity which is Th-2-deviation of the immune response characterized with intensified production of allergen-specific IgE and eosinophilic inflammation as well as activation of the inborn immunity factors making inflammatory reactions

last longer [2]. A peculiarity of the adult immune system is an ability of the adaptive immune system to pose certain limitations on functioning of the inborn immune system in order to minimize immune-associated pathological damage to tissues.

The body response to LMWC, which are not recognized by TCR or antibodies, is associated with creation of a hapten-protein conjugate. Haptenization is obligatory for interactions between low molecular weight compounds and the adaptive immune system. Obviously, sensitization to LMWC can be considered an excessive adaptive immune response to a hapten [13]. Hyperreactivity to organic compounds and metals develops in a very different way. In case of sensitization to organic compounds (those having a phenyl ring), creation of a hapten-protein conjugate is determined by a covalent association. Metal ions (in particular, nickel) form spatially highly defined coordination bonds as per the donor-acceptor mechanism. It is these very specific coordination complexes that facilitate immune recognition and the triggering of an immune response culminating in the acquisition of sensitization to nickel [23]. Cross-reactivity between transition metals is quite possible since ion of one metal can be replaced with ion of another metal with the same charge and similar properties [13]. Inclusion of several metals (nickel, manganese, chromium, cobalt) of a carrier protein into the antigen determinant underlies creation of a new hapten determinants and this also explains occurrence of cross-reactions to these metals.

The linkage between an allergen and IgG and Fc-epsilon-receptor 1 (FcεRI) is necessary for induction of mast cell degranulation. $CD23^{+}$-receptor (FcεRII) is expressed on B- and T-lymphocytes and antigen-presenting cells. It controls the immune response, regulates IgE homeostasis and is responsible for transporting reaginic antibodies through the airway and intestinal epithelium [24, 25]. $CD23^{+}$-receptor binding on B-cell, on the one hand, prevents activation of effector cells; on the other hand, it facilitates presentation by delivering an antigen to dendritic cells. FcεRI was established to be able to bind free IgE thereby inducing allergic inflammation, and FcεRII, which has the low affinity with IgE, mostly binds the immune complex IgE-allergen (IgE-IC) [24]. Soluble CD23 (sCD23) show a range of sizes but all bind IgE. They are thought to promote or inhibit IgE synthesis, depending on their oligomerization state [26]. It is noteworthy that the airway and intestinal epithelium is a major participant in the development of allergic inflammation [27]. Epithelial cells directly activate antigen-presenting cells and indirectly activate type 2 innate lymphoid cells (ILC2). An allergen induces Th-2-polarization of the immune response together with hyperproduction of allergen-specific IgE and ILC2. The role played by ILC2 in developing allergic reactions and tissue reparation has been reported. Lesions of epithelium under the Th-2 shift in the cytokine profile make for IgM synthesis being switched to IgE [27]. A level of specific IgE in blood serum can persist for a long time after an exposure to an allergen ceases. Reagin reactions mediate promotion of inflammation and bronchial hyperreactivity. IgE has been assumed to possibly play a regulatory role. Excess non-specific IgE has been shown to be able to inhibit allergen-induced mast cell degranulation and basophils in skin [26]. Specific IgG antibodies enter cross-reactions with allergens and inhibit their binding to IgE due to competition between epitopes. Some experts believe that induction of such antibodies prevents allergic inflammation [27]. The role that the aryl hydrocarbon receptor plays in production of all types of antibodies and switching between their different classes (IgG – IgE) as well as IgG isotypes in a plasmatic cell has been evidenced [4]. The study results are clearly in line with previous reports by other authors stating that an excess immune response could possibly develop under exposure to LMWC in low doses; the results also confirm higher risks of allergic diseases for people exposed to technogenic chemical factors.

Conclusion. In the test groups, average daily exposure doses of airborne nickel and phenol varied between $0.7 \cdot 10^{-6}$ and $9.3 \cdot 10^{-6}$ mg/(kg·day)

for children and between $3.5 \cdot 10^{-6}$ and $5.0 \cdot 10^{-5}$ mg/(kg·day) for adults. This is 1.5–3.0 times higher than the same indicators in the reference groups. Comparative characteristics of the sensitization profile created for the children and adults living under exposure to airborne nickel and phenol in low doses revealed some peculiarities in the development of elevated sensitivity to haptens, namely, an IgE-mediated reaction to nickel and IgG-mediated reaction to phenol. The results reported in this study make it possible to recommend using IgE and IgG as indicators of susceptibility to allergic diseases in adults and children living under chronic exposure to low doses of nickel and phenol, chemicals with obvious allergenic potential.

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Review

THE SIGNIFICANCE OF GREEN SPACES FOR PROTECTING HEALTH OF URBAN POPULATION

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Green spaces (green infrastructure, green areas) are important components of urban environment. They are able to mitigate health outcomes of climatic risks, exposure to urbanization and adverse environmental factors. Bigger areas covered with plants should increase their accessibility for people living in cities. Analysis of the results reported in foreign studies that addressed influence of green spaces on public health proves that they promote physical activity by urban citizens, sports included, development of interpersonal communication and social interactions, improve mental health, and reduce prevalence of diabetes mellitus and other diseases.

In some cases massive construction of residential housing and public buildings in Russian megacities and large cities led to reduction in green areas. The existing construction standards in Russia do not consider the recommendation of the WHO/Europe that requires accessibility of green spaces within a 15–20 minute walking distance and provision of 9 m^2 of green spaces per person. Utility of green spaces for public health depends on evenness of their distribution. In case their distribution is mosaic, their benefits for public health and protection capacities are reduced.

The present review shows the importance, needs and advantages of developing green infrastructure with continuous canopy that create potent green shading.

Keywords: *public health, mental health, obesity, health risks, diabetes, physical activity, green spaces, green infrastructure, city planning, urban studies, megacities.*

Creation of large green spaces in cities is one of few ways to protect health of people who are exposed to the aggressive urban environment. The issue has come into the limelight recently due to dynamic urbanization; this process causes a lot of concern that people in large cities are going to have reduced contact with natural greenness. Also, effective methods of remote sensing are available now; they allow better quantification of green spaces relying on values of the Normalized Difference Vegetation Index (NDVI) and this provides another incentive to investigate this issue. Green spaces protect health since they can function as places for recovery; places for social interaction and physical activity; they are also able to mitigate risks of harmful exposure to ambient air pollution, noise, and abnormally high temperatures.

The UN Sustainable Development Goals declare that by 2030 it is necessary to '*provide universal access to safe, inclusive and accessible, green and public spaces, in particular for women and children, older persons and persons with disabilities*'[1]. Although there is common understanding that green spaces are

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[1] News UN in Russia. *United Nations in the Russian Federation*. Available at: http://www.unrussia.ru/en/un-in-russia/news (January 15, 2023).

necessary for protecting and improving public health, only one review has been published in Russian [1], which provides a general idea of basic trends in foreign research on the issue as well as some information about the significance of green spaces for public health published in 2022 [2]. However, this work does not provide any quantitative health risk indicators in a situation when necessary open green spaces or green infrastructure are either absent or barely accessible or when green spaces are located too far from residential areas. Therefore, we have set a task to provide healthcare workers, ecologists, constructors, urbanists, and experts in urban planning with necessary knowledge about the actual utility of green infrastructure, both existing and under development, and about reduction in public health risks evidenced by findings reported in outstanding epidemiological studies.

The concept of green infrastructure as an integral component of the ecological frame in any city has been described in detail in publications by Klimanova and others [3]. Instead of the traditional Russian term 'greenness, green plants', the authors of these works suggest using the term 'green infrastructure', which means 'integrity, connection, and hierarchy of green elements that provide stability of the environment thereby accomplishing the major function of green spaces'. This concept is in line with foreign publications where the term 'green infrastructure' as something more than just a green space is being used more and more often. The definition of green infrastructure which is widely cited now is as follows: '*green infrastructure is an interconnected network of green space that conserves natural ecosystem values and functions and provides associated benefits to human populations*' [4]. Parks, boulevards, forests, city gardens and many other forms of public and private components of the natural landscape (greenness) taken together in one complex can also be considered green infrastructure.

However, architects point out that work with green infrastructure requires, first of all, knowledge of biology and ecology as its integral part and not of urban planning or considering the concept of 'green corridors' developed within this subject [5]. For example, L. Lunts[2], an architect, mentioned the necessity to consider a type of vegetation depending on climatic conditions in his manual on urban green development issued as far back as 50 years ago. This is especially vital at present due to climate change and occurrence of so called 'heat islands' in cities where public health risks are elevated.

Benign effects of greenness are associated, among other things, with overall improvement of urban residents' health including declining incidence of chronic diseases (for example, diabetes mellitus and cardiovascular diseases), development of cognitive functions in adults, mental health protection, and more favorable pregnancy outcomes (for example, normal birth weight) and a decline in premature deaths [6–13].

Most epidemiological studies with their aim to assess influence of green spaces on public health have relied on using cross-sectional or descriptive methods. Cohort studies, including prospective ones, are used significantly rarer; they can provide the best evidence but they are also the most complicated[3].

1. Basic characteristics of green spaces in cities. The system of indicators to assess green spaces in cities was first developed by the state authorities within the Development of Comfortable Urban Environment Federal project of the Housing and Urban Environment National project. Within the project, the basic target is to raise the index of urban environment quality by 30 points. Such indexes are based on 38 indicators that are distributed into

[2] Lunts L.B. Gorodskoe zelenoe stroitel'stvo [Urban green development]: the manual for higher education institutions. Moscow, Stroiizdat, 1974, 275 p. (in Russian).

[3] Revich B.A., Avaliani S.L., Tikhonova G.I. Ekologicheskaya epidemiologiya [Environmental epidemiology]: the manual for higher educational institutions. In: B.A. Revich ed. Moscow, Akademiya, 2004, 384 p. (in Russian); Vlasov V.V. Epidemiologiya [Epidemiology]: the manual, 3rd ed., revised and supplemented. Moscow, GEOTAR-Media, 2021, 496 p. (in Russian); Briko N.I., Pokrovskii V.I. Epidemiologiya [Epidemiology]: the manual for higher educational institutions. Moscow, GEOTAR-Media, 2017, 368 p. (in Russian).

six groups describing six types of urban spaces. ‘Green spaces” is one of them; it, in its turn, consists of six indicators. The most significant indicators describe reduction in health risks caused by exposure to ambient air pollution and noise and growth in urban residents’ mobility and levels of their physical activity. Such indicators include ‘the share of public green spaces in the whole area of green spaces’; ‘level of greenness’, that is, the share of the city area covered with greenness in the whole city area; ‘effectiveness of management’, that is, the share of urban residents who have access to public green spaces.

In 2020, the indexes of urban environment quality were estimated for 1116 cities in Russia, including 15 cities with population exceeding one million people. Among these megacities, the lowest values as per the ‘green spaces’ indicator were established in Omsk, Yekaterinburg and Volgograd; the highest ones, in Moscow, Saint Petersburg, Ufa, Perm, Kazan, and Nizhniy Novgorod [14]. In our opinion, the values established in Moscow and Saint Petersburg require some clarification since green spaces are very heterogeneous in these two cities.

Unfortunately, the ‘green spaces’ characteristic within the aforementioned Federal project does not include the most informative indicator of greenness levels in cities, the Normalized Difference Vegetation Index (NDVI)[4]. Still, the index was applied in the fundamental study conducted by experts from the Geographical Department of M.V. Lomonosov Moscow State University [3, 15]. The term ‘open green spaces’ is used in urban planning documents and multiple medical articles and it seems much more suitable when considering designs for new urban areas.

Green infrastructure is becoming more and more significant these days when microclimate in cities gets warmer and more and more soils and grounds are ‘closed’ in centers of Russian cities, that is, it is very hard to find land spots with open soils not covered with asphalt. Most studies describe green spaces and their areas relying on remote sensing and the Normalized Difference Vegetation Index (NDVI)[4]. Some publications provided much more detailed descriptions of green spaces with such data as exact numbers of trees, squares of greenness, and squares of canopy cover. The descriptions were provided specifically for forests, trees, shrubs, grass, arborous marsh plants, agricultural lands and gardens [16]. Green spaces are described with different values such as the ratio of the area covered by tree vegetation to the whole city area; provision with greenness in square meters per one resident; peculiar configuration of an ecological frame with greenness (mosaic, along a river, peripheral, and some others) [3].

These teams of geographical experts assessed green infrastructure in 15 largest cities in Russia using the share of territories covered by tree vegetation and provision with canopy cover. As a result, they divided these 15 cities into several groups. Two of them, Volgograd and Omsk, have small shares of areas covered with trees, 16 and 18 % accordingly; Yekaterinburg and Perm have the biggest areas covered with forests, 59 and 61 % accordingly. The medium values were established in Voronezh, Kazan, Krasnoyarsk, Rostov-on-Don, and other cities. The other indicator was the square of the whole tree vegetation per one resident; its minimal values were established in four cities (Chelyabinsk, Perm, Rostov-on-Don, and Volgograd); the maximum ones, in Yekaterinburg and Novosibirsk [3]. It is obvious from the analysis of this work and the study by Dyachkova [14], that green spaces and their quantity can be assessed quite differently depending on indicators used in this assessment.

At present, there is no standard in urban planning that specifies the mandatory greenness on a territory; but some construction standards and rules that had been valid until 2016 stipulated that the share of greenness should be equal to 40 %. When it comes down

[4] This index is calculated as per a specialized formula and shows the ratio of sunlight reflection coefficients in infrared and red spectral zones.

to how useful green spaces are for urban residents' health, we should remember that greenness should have an even structure and not a mosaic one since the latter weakens its protective properties. Another important indicator that describes utility of green spaces is their location within walking distance, which, according to the recommendation of the WHO/Europe, should not exceed 15–20 minutes and provision should equal 9 m^2 of green spaces per person [17]. This large-scale review by the WHO/Europe covers different systems of indicators that support urban planning in order to provide sustainable health and provides some of them that describe the environment in cities. These indicators are used in such UN programs as UN-Habitat, ISO (the International Organization for Standardization) and some others. They are applied within risk-based urban planning, which should consider levels of ambient air pollution based on average annual concentrations of fine-dispersed particles ($PM_{2.5}$ and PM_{10}) as well as excessive mortality caused by ambient air pollution, insufficient provision with green spaces per one person etc.

The role of different greenness including vertical one ('green parking lots', gardens on roofs, and other objects) has been described in many Russian publications, for example, in the review by Weber, Kucherov and Lylov [18]; but these studies did not consider influence exerted by greenness on public health using methods of evidence-based medicine. There has been a drastic growth in the number of foreign publications in the sphere starting from 2000. Our search in the Library of the US National Institute of Health (PubMed) has revealed more than 405 articles following the search request 'green place and health' published by January 01, 2023 including more than 10 reviews published between 2017 and 2022 [6–13].

Most studies rely on various indicators to estimate influence of green spaces on health; predominantly, they use the Normalized Difference Vegetation Index (NDVI) but it cannot be applied to estimate heterogeneity of greenness. For example, green spaces differ as per their objectively measured benign properties (such as tree canopy, pedestrian walkways, and sitting places) and other, more subjective ones (emotional or spiritual bond between an object and a person). At the same time, proximity to motorways with intensive traffic or absence of easy access can make visit to green spaces more difficult.

2. Green spaces and mental health. Availability of many evidence-based epidemiological studies prompted the WHO to initiate a review [19] to sum up their findings including those addressing effects produced by green spaces on children's mental health. Some reviews have also focused on studies that investigated influence of green spaces on children's physical health [20, 21]. This new knowledge on children's mental state (as regards any issues with peers, hyperactivity or inattention symptoms, behavioral or other issues) has been obtained by using computerized neuropsychological tests aimed at estimating children's cognitive development. All the studies mentioned at least one indicator that described a socioeconomic status, that is, a family income, parents' education and / or employment, access to green spaces for walks, and housing costs. The evidence provided in 21 studies consistently suggested a beneficial association between green space exposure and children's and adolescents' emotional and behavioral difficulties [22].

Low levels of physical activity raise a lot of concern regarding children's mental health; this is also typical for Russia. For example, according to the study conducted in Kaunas (Lithuania), every additional hour of time spent in parks was associated with decreased sedentary behavior and a lower risk of poor health; shorter park usage was associated with the risk of poor health and the general risk of mental difficulties in 4–6-year-old children [23]. The medical expert society in Russia acknowledges the problem; in 2020, the National Medical Center for Children's Health together with the Russian Society for the School Healthcare Development published the article with evidence that '*informatization of the social processes with use of electronic teaching*

aids that has been growing steadily over the last years has already deteriorated children's health'[5] [24].

A major issue in assessing influence of green spaces on a child's mental health is the necessity to isolate effects produced by this very factor after adjusting (considering) those produced by many other ones. Great attention has always been paid to the role played by socioeconomic factors since a place where a child' family lives depends exactly on them. Patients who lived in the greenest areas had many physical or mental disorders much less frequently (after the adjustment for most probable socioeconomic and demographic factors) than their peers who lived in areas where greenness was minimal. It is remarkable that the most significant deviations in mental development were identified in children with mental disorders who lived in areas with scarce greenness.

In 2009, the findings of a remarkable study were published; it established associations between green spaces near housing and medical diagnoses put by healthcare organizations for primary medical and sanitary aid for approximately 345 thousand Dutch patients from various age groups. Patients, who lived in the greenest areas, after considering socioeconomic and demographic factors, were much less frequently diagnosed with certain physical or mental disorders in comparison with patients who lived in areas with the poorest greenness [25]. Since then, more and more studies have been estimating associations between greenness and children's and adolescents' mental health. The authors of the study that involved meta-analysis of 21 publications highlight these associations between green spaces and adolescents' mental health [22]. According to them, children who live near green spaces have fewer problems with their peers and are rarer diagnosed with 'hyperactivity' [26].

Positive effects produced by green spaces on mental health have also been evidenced for other age groups; for example, urban citizens were more likely to have depression [27] or suicidal indicators in case they lived in areas with the smallest number of parks and green zones [28]. There is evidence of an association between frequent visits to parks and a person's emotional state and their satisfaction with life [29]. Peculiarities of the design and upkeep of parks are also significant [30].

There is increasing attention and evidence for a positive relation between the amount of green space in the living environment and people's health and well-being, especially for low-income and poor urban residents [25]. Proximity to parks was associated with more frequent physical activity and weight loss (for example, [31]), lower incidence of ischemic heart disease (for example, [25]). Some studies also report the association between influence of green spaces and benefits for mental health occurring regardless of physical activity due to such effects as perceived availability of green spaces for rest and recovery (for example, [32]). These benefits include better spirits and higher self-esteem, lower levels of stress and cognitive fatigue, greater attention focusing and promotion of emotional recovery [33]. Greenness provides a safe space for social interactions and this can lead to lower social isolation, creation of social capital, a rise in social solidarity, sense of belonging and more solid trust between residents living in the same area. Therefore, urban green spaces are directly associated with life quality of urban residents.

When discussing better mental health of urban residents who live near parks, we should mention the role that belongs to sports; parks with sport grounds create favorable conditions for such activities [27] (the minimal time that should be spent on physical exercises is 20 minutes; the optimal time, 90 minutes). On the other hand, criminal risks, crime rates, and

[5] Kuchma V.R., Selova A.S., Stepanova M.I., Barsukova N.K., Aleksandrova I.E., Aizyatova M.V., Grigor'ev O.A., Komarov D.B. [et al.]. Gigienicheskie normativy i spetsial'nye trebovaniya k ustroistvu, soderzhaniyu i rezhimam raboty v usloviyakh tsifrovoi obrazovatel'noi sredy v sfere obshchego obrazovaniya [Hygienic standards and specific requirements to the organization, maintenance and modes of work in the digital educational environment in general education]: guide. Moscow, National Medical Research Center for Children's Health of the RF Ministry of Health, 2020, 20 p. (in Russian).

anti-social behavior are likely to grow on blighted green areas [34].

The systemic review of publications aimed at identifying and generalizing findings about how effective green spaces were for improvement of adults' mental and physical health revealed that mental health indicators were much more likely to improve than physical health ones. The analysis of findings reported in 16 studies confirmed the hypothesis that greenspace exposure promoted lower incidence of depression in urban citizens [21].

A study on the analyzed subject with a highly unusual design was conducted in Denmark. In this small country, experts investigated associations between mental health and living near greenness in childhood for more than 940 thousand people. The control group was made of people born between 1985 and 2003. Green space presence was assessed at the individual level using high-resolution satellite data to calculate the Normalized Difference Vegetation Index within a 210 × 210 m square around each person's place of residence from birth to the age of 10. Risk for subsequent mental illness, such as depression, anxiety, and use of psychoactive substances, was up to 55 % higher for those who lived with the lowest level of green space during childhood compared with those who lived with the highest level of green space. The association between mental disorders and greenspace exposure remained authentic even after adjusting for socioeconomic factors, parental history of mental illness, and parental age [35, 36]. In addition, proximity of public parks to places of residence (400–8000 meters) contributed to better mental health of women and reduced prevalence of depression among them (especially in young women and homemakers) [37].

The issue of green spaces and health of megacity residents, which we are considering in this review, is also extremely vital in the South-East Asia. Several studies have been conducted in China to assess influence of green spaces on mental health of megacity residents, one of them in Shenzhen (17 million people). It is noteworthy that this study relied not only on the aforementioned Normalized Difference Vegetation Index (NDVI), but also Quick Bird – 2 high-resolution remote sensing image data; mental health was assessed using specifically designed questionnaires. The study findings are authentic and indicate the significance of creating larger green spaces in megacities [38].

Having compared the results of studies that address effects produced by greenness on people's mental health in such countries as South Korea and Iran (with drastic differences in their socioeconomic conditions), we observed quite a similar situation. In Korea (169 thousand examined participants), depression and suicidal ideation was 16–27 % higher in areas with minimal greenness after adjustment for all the potential variables. People without moderate physical activity had higher odds for self-reported depression and suicidal ideation than those with moderate physical activity [28]. In Iran, frequent visits to parks also made for better emotional state of a person [29].

Studies with their focus on estimating influence of green spaces on mental health are gradually switching from using questionnaires or psychological tests to instrumental examinations, MRI included [39]. Nevertheless, a few studies do not give evidence of positive effects produced by greenness on health; on the contrary, they concentrate on probable deterioration of a criminal situation in green spaces [34, 40]. It is also reported in some studies that additional green spaces in some city areas can result in higher housing costs and property values; this, in its turn, leads to displacement of people with a lower socioeconomic status into other areas with less greenness in them [41].

Loneliness can be another reason for mental ill-being. Psychological problems associated with loneliness in a city, a megacity in particular, are an extremely important challenge for contemporary healthcare, sociology, urban studies, and other disciplines that investigate the issue of 'a person in a city'. Loneliness is widespread in the contemporary society and this raises a lot of concern in healthcare workers, sociologists, psychologists and experts in other areas. Persistent loneliness trou-

bles people across the life span, with its prevalence being as high as 61 % in some groups of elderly people [42].

Loneliness as a social phenomenon has been examined in detail within the famous study entitled the Russian Monitoring of Economic Status and Public Health performed by the Higher School of Economics National Research University and Demoskop LLC with the participation of the Carolina Population Center at the North Carolina University [43]. The study findings indicate that 3 % of Russians feel lonely all the time and 40 % feel lonely periodically. According to sociologists, women more often feel lonely and they suffer more from this state than men. This is also related to the fact that women remain single more frequently than men and loneliness can be observed in various age groups, including young people. In elderly people, loneliness can lead to poor health and exacerbation of chronic diseases.

Green spaces in residential areas or in proximity to them promote better physical and mental health of lonely people; 22 studies have provided evidence of it over the last years and 11 out of them have been cross-sectional. According to the review of these studies, of 132 associations, 88 (66.6 %) indicated potential protection from green space against loneliness, with 44 (33.3 %) reaching statistical significance ($p < 0.05$). Most of the studies in this review were conducted in high-income countries [42]. Over the last five years, a new state policy has been developed in the USA, Spain, Singapore, Australia and some other countries; its specific aim is to create more green spaces in cities as a part of the strategy to reduce loneliness.

3. Green spaces and obesity, diabetes. Over the last forty years, the number of obese people worldwide has almost tripled. The issue has become so serious for public healthcare that experts in prevention medicine consider it a world epidemic [44]. Obesity is a recognized factor of early deaths and declining life expectancy at birth. The number of obese people older than 18 years has reached almost 2 billion all over the world and prevalence of the disease is expected to grow; according to the WHO estimates, by 2025 the shares of obese people can reach 18 % among men and 21 % among women [45]. Up to 3.5 million deaths worldwide are associated with obesity, which often involves poorer life quality and shorter life expectancy. Obesity is a serious health issue not only in developed countries: prevalence of overweight and obesity grew from 5 to 13 % in developing countries as well over the period between 1980 and 2013 [46]. In the USA, total public healthcare spending associated with overweight and obesity is expected to double each decade and reach 16–18 % of the total public healthcare expenses.

Overweight is becoming a more and more vital issue in Russia as well; our country is among those where prevalence of obesity is the highest. The literature review that addresses prevalence of obesity and elevated body mass index (BMI) among adults in Russia provides the results of several projects (WHO MONICA Project, 1985–1995; HAPIEE 2003–2005 and some others) [47]. Thus, obesity was diagnosed in 10.7 million men and 18.7 million women in 2014 [48] or, according to the WHO data, in 18.1 % men and 26.9 % women[6]. A growth in the number of people with elevated BMI is also evidenced by findings of the epidemiological study conducted in Moscow (random samples in several districts in 1975–2014); this growth is close the world trends but is still not so significant [49]. According to the WHO study, obesity is growing not only among adults but among adolescents as well [50].

Obesity is a basic risk factor able to cause many non-communicable diseases including cardiovascular and oncological ones, strokes, diabetes, cancer and asthma as well as mental disorders. Obesity turned out to be a risk factor

[6] Prevalence of obesity among adults, BMI >= 30 (age-standardized estimate) (%), 1975–2016, Both sexes. *WHO*. Available at: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-obesity-among-adults-bmi-=-30-(age-standardized-estimate)-(-) (February 13, 2023).

of COVID-19 mortality. Prevalence of obesity is a huge financial burden for a government, public healthcare system, and people. To prevent obesity is a serious challenge for practitioners and researchers dealing with healthcare issues.

More and more studies accept the fact that prevalence of obesity is caused by social and environmental factors. Urban design peculiarities can promote obesity by limiting opportunities for people to have any physical activity [51]. Green spaces in cities are considered a crucial factor for health improvement including maintenance of healthy weight.

Many studies report a negative relation between access to green spaces and obesity, time spent on watching TV, BMI and children's weight. A distance to the closest green space measured by using a GIS in 10 studies was often used to estimate access to the closest green space. In addition, indicators of greenness levels included the average NDVI value at different distances from a place of residence, the number of green spaces, tree density at a 0.5-km distance from a residential area, a distance to the closest park or any other green space and some others [52].

The large-scale study (700 thousand people) was conducted in two American cities with different climate, Phoenix with low greenness levels and Portland with sea climate and vast green spaces. In this study, cause-effect relations between access to green spaces and urban residents' weight were estimated. Greenness along city streets was proven to be a predictor of healthy weight. Each 10 % of growth in such greenness within 2 km was associated with 18 % lower risks of overweight or obesity (odds ratio (*OR*) = 0.82, 95 % CI: 0.81–0.84 in Phoenix; 0.82, 95 % CI: 0.81–0.83 in Portland). Prevalence of overweight or obesity was 18 % lower in greener areas (*OR* = 0.87 for Portland, 95 % CI: 0.81–0.92) [16]. Similar relations were established in New York. A higher density of street trees (at the 75th vs 25th percentile) was associated with 12 % lower prevalence of obesity [53]. Similarly in Spain, residential proximity to forests was associated with 39 % and 25 % lower relative prevalence of excessive screen time and overweight/obesity accordingly [54]. Many studies reported a positive correlation between healthy weight and green spaces within 500 m radius from home [55, 56].

Evidence of a relationship between children's BMI and green spaces is not so apparent. The review that addressed the issue considered research articles published prior to January 01, 2019. Sample sizes ranged between 108 and 44,278 cases. The authors of the review believe that it still remains difficult to draw a clear conclusion on the association between access to green space and BMI and it is necessary to conduct further prospective studies on the matter [57]. The necessity of such studies has also been mentioned by some other authors [25, 58, 59].

Obesity as a health issue is to a certain extent related to physical activity and this indicator is mentioned in the documents issued by the Rosstat[7] and The Ministry of Sports of the Russian Federation. According to these sources and questionnaires, the share of people who systematically do sports and/or physical exercises does not exceed 30 % in Russia. Therefore, it has become extremely vital to install more equipment for doing sports or everyday exercises in green spaces. The role of green spaces as an important factor able to motivate people to have physical activity and to prevent type 2 diabetes has been investigated in a large-scale study of urban population conducted in the USA. This prospective cohort study included 5574 people. Its aim was to investigate a relation between green spaces and type 2 diabetes. Green spaces were estimated as per the normalized difference vegetation index identified from satellite imagery within 1 km radius from participants' homes; type 2 diabetes was diagnosed by a doctor relying on

[7] Dolya grazhdan, sistematicheski zanimayushchikhsya fizicheskoi kul'turoi i sportom [The share of citizens who systematically do sports and physical exercises]. *EMISS: gosudarstvennaya statistika [state statistics]*, 2020. Available at: https://fedstat.ru/indicator/59266 (January 18, 2023) (in Russian).

fasting glucose levels, use of insulin, and use of hypoglycemic medicine. Of the 5574 study participants with no prevalent diabetes at baseline, 886 (15.9 %) developed incident diabetes over the study period. For each IQR increase in NDVI, the risk of developing diabetes was 21 % less among those with higher neighborhood NDVI compared to lower, controlling for individual characteristics, neighborhood-level covariates, and diabetes risk factors (*OR* = 0.79; 95 % CI: 0.63–0.99) [60].

4. Green spaces, mortality and incidence among urban residents. Ambitious projects are being implemented in many cities worldwide with their aim to create vaster green spaces with a closed tree canopy cover. These expensive measures have been substantiated, among other things, by findings of some longitudinal studies evidencing relationships between access to green spaces and mortality. Thus, some quantitative indicators were calculated to identify a relationship between green spaces and mortality risks for 1645 people who had a stroke between 1999 and 2008. It turned out that the hazard was lower for patients living in locations in the highest quartile of green space compared to the lowest quartile. This association remained statistically significant after adjustment for residential proximity to a high traffic road [61]. Lower cardiovascular mortality was identified for hospitalized patients with type 2 diabetes and myocardial infarction [62].

Longitudinal studies with more than 8 million people participated in them involved using the Normalized Difference Vegetation Index NDVI calculated from a space image with spatial resolution 30 × 30 meters. The findings were estimated using meta-analysis and as a result it was established that the NDVI was associated with air temperatures. The retaliate risk value *OR* = 0.96 (95 % CI: 0.94–0.97) indicates that it is trees, and not grass-plots or lawns, that ensure a decrease in high air and soil temperatures thereby creating more comfortable conditions. Trees also promote a decline in public health risks caused by exposure to extremely high temperatures; that is, they help reduce mortality among urban residents [63], including that caused by circulatory diseases [64]. The same has been proven in other studies [33, 65]. Their authors applied such an indicator as ‘the square of tree cover or a share of ground covered by tree canopy’ based on aerospace images made by LIDAR [66].

For example, municipal authorities in Philadelphia (1.6 million) have set a strategic goal to be achieved by 2025. The goal is to increase the total forest area in the city and to achieve the 30–40 % tree canopy cover, a level recommended for all the American cities. The necessity to implement such a program is caused by Philadelphia being drastically different from 10 other largest US cities as per such indicators as population incomes (the lowest level) and higher mortality (the applied all-cause mortality rate for the city’s adult residents in 2015 was 887 deaths per 100,000 people compared with 733 deaths per 100,000 people in the USA overall) [67]. Therefore, together with some other healthcare programs aimed at reducing mortality, the greenness program is also about to begin. It is largely based on a hypothesis that such high mortality rates would be prevented in case tree canopy cover increased by 30 %. The plan was to reduce excessive mortality among the city residents by 2025, first of all, in areas with low socioeconomic status. In 2015, the overall number of premature deaths associated with scarce greenness reached 403 cases in Philadelphia (95 % CI: 298–618), of which 244 (95 % CI: 180–373) occurred in districts with lower socioeconomic indicators. Squares of green spaces in the city were estimated using the LIDAR.

The authors used quite an interesting technique for dividing the city territory into zones. It was divided into 384 tracts and socioeconomic status of each tract was identified as well as the existing and necessary squares of closed tree canopy covers. Of 384 census tracts in Philadelphia, 80 already meet or exceed the 30 % tree canopy cover goal, and 103 census tracts could meet the goal by planting trees in areas currently covered with grass or shrubs. Average household incomes in the

city coincided with the total greenness in the city districts; as a rule, there were fewer trees or greenness in districts with lower socioeconomic status than in richer ones. Increases in tree canopy cover were estimated to provide a decrease in population mortality and, consequently, considerable health and economic benefits [11].

In Moscow, a similar method for dividing the city territory into zones was applied by N.B. Barbash, Candidate of Geographical Sciences from the Moscow Institute for the General Town Planning Scheme. This was done to identify micro-districts with elevated population density, elevated levels of ambient air pollution, and proximity to green spaces[8]. Later, the cross-sectional epidemiological study with its focus on prevalence of bronchial asthma in children identified locuses of areas with the highest values of this indicator [68]. The findings of this study (of course, together with economic, ecological, and some other reasons) were used by the Moscow Institute for the General Town Planning Scheme to substantiate the necessity to relocate some enterprises and to reinforce the pulmonologic service for children.

The largest European project aimed at assessing influence of greenness on mortality was implemented in 2015 in 49 large cities located in 31 European countries. Square areas of greenness were estimated as per the Normalized Difference Vegetation Index (NDVI) and the percentage of green area was estimated at a fine grid-cell level 250 × 250 meters. The project established that annual mortality was by 43 thousand cases lower in cities where green areas were located within 15–20 minute access for population. This accounted for 2–3 % (95 % CI: 1.7–3.4) of the total natural-cause mortality; 245 cases (95 % CI: 184–366) of lost years of life per 100 people. Among European capitals, Athens, Brussels, Budapest, Copenhagen, and Riga showed some of the highest mortality burdens due to the lack of green space [69].

Relationships between access to green spaces and incidence have not been studied as profoundly as it was with mortality rates. Still, the issue has been investigated in more than 60 publications in English where green spaces are described with the Normalized Difference Vegetation Index (NDVI) and indicators reflecting qualitative parameters of tree cover [70]. For example, higher land-cover diversity promoted a decline in prevalence of chronic diseases [71] and bronchial asthma in children [72]. Higher density of trees in parks was associated with lower prevalence of cardiovascular diseases [73, 74] and better life quality [75, 76]. Health is also influenced by a scale of 'green spot', that is, closed tree canopy cover in a city. Most studies found certain evidence of a relationship between various health indicators and large green areas, including body mass index [77, 78], mortality caused by circulatory diseases [64], depressions [79], all-cause mortality including cardiovascular one [12], obesity, prevalence of type 2 diabetes, osteoporosis, and other health disorders [33]. Access to green spaces can promote lower cortisol levels, pulse rate and blood pressure [52].

Recently, some studies have provided evidence of multisensory influence exerted by park vegetation including visual, hearing and tactile feelings that ensured a recovery effects produced by a visit to a park [80]. Higher density of trees among park vegetation had an association with lower prevalence of cardiovascular diseases [73].

Discussion. The issue of green spaces in cities has been given more and more attention not only by architects, constructors, or experts on creation of urban green spaces but healthcare researchers as well. The necessity to create green infrastructure with tree ranges is confirmed by epidemiological studies conducted in many countries. The COVID-19 pandemic and post-pandemic issues have also attracted additional interest to the subject since people started to spend more time in green spaces willing to overcome the consequences of strict

[8] Barbash N.B. Metodika izucheniya territorial'noi differentsiatsii gorodskoi sredy [The methodology for investigating territorial differentiation of the urban environment]. Moscow, Institut geografii AN SSSR Publ., 1986, 180 p. (in Russian).

quarantine and resulting psychological problems [81–83].

Mechanisms that underlie effects of green spaces on health have not been studied completely; still, there is solid evidence that visits to green spaces contribute to eliminating negative outcomes of stress and exposure to ambient air pollution, noise, high temperatures; they improve cognitive functions; they promote social interactions and higher levels of physical activity. The analysis of research results reported in many countries worldwide proves that it is necessary to develop urban green spaces. We have found solid confirmation of hypotheses that when green spaces are within a walking distance, this leads to greater mobility of urban residents, lower prevalence of diabetes and cardiovascular diseases among them. Green spaces are a vital component of the urban environment; they play a key role in mental well-being of urban residents, produce positive effects on people suffering from depression. Health risks tend to go down in areas with green spaces with closed tree canopy cover.

In Russia, some singleton articles have been published with their focus on influence of green spaces on health; one of these studies has been conducted in Ufa where green infrastructure has 30 scores and the Normalized Difference Vegetation Index (NDVI) is high as well; that is, green infrastructure is quite developed in the city [3]. Individual carcinogenic risks were assessed in this city based on data about benz(a)pyrene levels in ambient air provided by the Bashkortostan Office for Hydrometeorology and Environmental Monitoring. The risks turned out to be within their permissible levels. For comparison, similar study was conducted in Arkhangelsk where industries and energy production were not so well developed and greenness levels were lower than in Ufa where the Normalized Difference Vegetation Index (NDVI) identified well-developed vegetation. The authors of this study believe that high greenness in a city reduces risks created by benz(a)pyrene in ambient air [84]; health risks are predominantly caused by levels of fine-dispersed particles. People living in another Russian megacity, Chelyabinsk, were questioned in order to identify any psychological problems; the questioning revealed more apparent effects produced by stress-factors in a district in the city where green areas were scarce [85].

Urban green infrastructure is considered by economists a most significant element of ecosystem services. Intensive urban development has already made urban areas unstable in some cities [86, 87] and, consequently, created green space deficiency. It is especially true for rapidly developing Krasnodar where the water-green city frame is absent, trees are not preserved systematically, and the number of existing parks and public gardens is not sufficient. The newly developed general town planning scheme stipulates about 400 green areas different in their sizes but they are not combined into unified green infrastructure [88]. On the other hand, we can mention some very successful town planning solutions aimed at creating a large green infrastructure in a district in Kazan (20 thousand people). A three-time growth in the conventional greenness level, that is, up to 60 % of the total area, will make the district much more comfortable. According to the nature capital model developed by the Dutch National Institute for Public Health and the Environment, in summer, air temperatures will go down by 2 $^{\circ}$C and the average wind speed will decrease by 8 m/sec in this district; the number of people satisfied with air temperature will grow by 6 % in winter and by 8 % in summer against the traditional scenario [86].

The state policy as regards comfort provided by the urban environment has started to change in our country as well. For example, the issue is given a lot of attention in the Program for Development of Recovery Potential of Public Green Spaces included in the Green Spaces section of the Comfortable Urban Environment Federal project. Within this Program, green spaces were estimated in Yekaterinburg using several indicators including shares of public green spaces in the total square area of green spaces (%), level of greenness (%), quality of greenness, attraction

of green spaces. Recommendations have been developed on how to achieve proper quality of the urban environment in Ekaterinburg; they include various recovery activities and measures aimed at making sport grounds more accessible for people with limited mobility [89]. However, healthcare workers also need to know what percentages of people from different age group have green areas within 15–20 minute walking distance from the total population as per separate districts.

The scales of researches aimed at assessing quality of green spaces and their influence on health are growing steadily. The results indicating their utility have been more apparent for people living in areas with large tree canopy. There is a demand for additional prospective studies that include estimating quality of green spaces and consider factors able to distort analysis. Investigations that concentrate on assessing quality of green spaces have practical significance for urban planning.

Cities with high population density tend to face some challenges in renovation; in particular, it is often difficult to preserve green areas and easy access to them for population groups with different socioeconomic status. Therefore, it is necessary to search for compromises between town developers, constructors, municipal authorities, on the one hand, and healthcare experts, ecologists, and experts in green infrastructure, on the other hand. In addition, it would be advisable to give responsibility over planning and managing green spaces as well as control of their quality to town planning authorities, offices for architecture and planning or any other managerial structures responsible for creating a comfortable urban environment. This issue should be supervised by them and not by housing and communal services or offices responsible for improvement of city areas. Since space is limited in any city, changes in quality of existing green areas can help maintain and even improve quality of life in urban societies, especially given the ongoing climate change.

Protection of urban residents' health requires development of green spaces as well as planning of city landscapes considering health risks and developing new recommendations on optimal population density. Economists believe that 'the complex approach to creating the urban environment with emphasis on residents' health and well-being not only satisfies the demands of a modern urban resident but is also beneficial for urban economies and the country economy as a whole' [88]. Further development of green spaces requires closer coordination between town planning organizations and relevant municipal services responsible for territorial improvement. Parks, public gardens, boulevards and other green spaces are too important for creating a more comfortable urban environment and protecting urban citizens from harmful environmental exposures. Therefore, it is advisable to take responsibility over them from municipal authorities on territorial improvement and assign it to structures responsible for rational use of natural resources and environmental protection.

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Review

ELECTROMAGNETIC FIELDS OF CELLULAR COMMUNICATION AS A HEALTH RISK FACTOR FOR CHILDREN AND ADOLESCENTS (REVIEW)

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Modern telecommunication technologies rely on using radio-frequency electromagnetic field (RF EMF). They have brought many useful services into our life able to solve multiple issues. However, we should bear in mind that this exposure is open, uncontrollable and permanent. Given that, it seems relevant to investigate possible negative influence exerted by RF EMF on health of children and adolescents since this population group is the most vulnerable and sensitive to any external exposure.

This review analyzes Russian and foreign studies with their focus on chronic influence of RF EMF created by cellular communication means on health of children (aged 6–10 years) and adolescents (aged 11–16 years).

We have established several manifestations of health disorders in children and adolescents including asthenic syndrome (headache, irritability, increased fatigue, sleeping disorders, periodical pains in the heart and joints); mental deadaptation (anxiety, stress, depression, etc.); as well as their combinations.

Along with all the aforementioned syndromes, effects produced by exposure to RF EMF become apparent through some indirect signs of memory and attention failure such as forgetfulness (inability to recall the necessary information in time) and inattention (inability to concentrate on an event or activity) and even through growing frequency of respiratory diseases.

Basing on the analyzed studies by Russian and foreign researchers, we can conclude that they provide solid evidence of negative influence of electromagnetic fields created by cell phones on health of children and adolescents.

Therefore, implementation of modern gadgets and their active use by children and adolescents should be accompanied with assessment of actual threats posed by them, health risk assessment, and development of scientifically substantiated standards for their safe use.

Keywords: *electromagnetic radiation, health, risk factor, asthenic syndrome, mental deadaptation, mobile phones, children, adolescents.*

Radiofrequency electromagnetic fields (RF EMF) are a well-known anthropogenic environmental factor able to produce various negative health effects, as reported by M.H. Repacholi in his work as far back as in 1998 [1]. Undoubtedly, telecommunication technologies that rely on using RF EMF have brought many useful services into our life able to solve multiple tasks with just one ‘mouse click’. However, we should bear in mind that this exposure is open, uncontrollable and permanent: given that, a range of negative outcomes caused by exposure to RF EMF is constantly growing.

Children and adolescents are the primary targets of this exposure; at present, these population groups are among the most active users of mobile devices and simultaneously the most vulnerable to their effects.

In 2009, V. Khurana and others reported in their work that children tended to start using a mobile phone (MP) at age 3 and this fact seemed sensational [2]; but later, H.K. Kabali with colleagues established in

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their study performed in the USA that more than one third of babies started to use a smartphone or a tablet already during infancy and at age 2 most children used mobile devices daily [3]. Similar findings were reported by A.O. Kılıç with colleagues in Turkey [4].

It is noteworthy that most publications on negative health effects of RF EMF on children and adolescents were issued in 2006–2013 and were mostly foreign. At present, the overwhelming majority of research that addresses RF RMF influence concentrates on youths and young adults; however, this review considers findings reported in studies concentrating exclusively on such age groups as children and adolescents.

Negative influence exerted by RF EMF on health of children and adolescents as the population group that is the most vulnerable to any environmental exposures has been repeatedly highlighted by Yu.G. Grigoryev in his publications [5–10].

Available data indicate that several target organs and systems are primarily affected by exposure to RF EMF created by modern technologies, in particular, mobile phones (MP) (2G–4G). First, negative effects are produced on the brain, genital system, and the entire intrauterine development; the thyroid gland is affected by using mobile devices with construction peculiarities of a new mobile generation (the antenna is usually located at the bottom of a smartphone) [11]. In addition, implementation of 5G technology produces negative effects on sclera and skin [12, 13].

Therefore, the aim of this review was to analyze studies that addressed effects of RF EMF on growing generations, specifically, on two separate age groups: children (between 3 and 10) and adolescents (between 11 and 16). However, some analyzed studies consider a rather wide age range that can cover several different age groups. This often creates certain difficulty in systematizing data when the results are analyzed.

Our analysis revealed that authors, as a rule, questioned either respondents themselves (children and adolescents) or their parents (when respondents were aged 3–10 years) in their studies. They also relied on a wide range of statistical analysis methods when analyzing their research results.

To describe basic effects produced by exposure to RF EMF on children and adolescents, we used a classification provided in the article [14], which specifies asthenic (headache, irritability, increased fatigue, sleep disturbances, periodical heart or joint pains), asthenovegetative (hypertension and bradycardia), and hypothalamic (neurocirculatory dystonia and hypertension) syndromes as well as mental deadaptation (failure to adapt to living conditions).

We can conclude, basing on literature data, that most health effects were related to asthenic syndrome and to a lesser extent to mental deadaptation.

Asthenic syndrome signs. Asthenic syndrome is known to be one of the most frequent health disorders; however, at present no conventional definitions, classifications, or concepts are available in literature that can fully explain its pathogenesis. Asthenia is a polymorph syndrome and can manifest both with specific symptoms such as headache, irritability, increased fatigue, sleep disturbances, and periodical pains in the heart and joins as well as with their combinations.

The prospect cohort study by S.Y. Kim with colleagues revealed that excessive use of smartphones (more than 1 hour a day) by children aged 5–8 years led to shorter sleep duration and its poorer quality (more frequent nocturnal waking) [15]. Unlike the study by S.Y. Kim with colleagues, O.A. Vyatleva and A.M. Kurganskiy did not identify any statistically significant correlations between MP use and frequency of sleep disturbances in primary schoolchildren (aged 6–10 years). However, the total duration of MP talks was considerably shorter in the analyzed cohort than in the study by S.Y. Kim with colleagues. [16]. Difficulty in falling asleep was statistically significantly associated with use of the mobile Internet [17].

The greatest number of asthenic syndrome manifestations has been identified for adolescents.

Thus, no significant correlation between MP use and sleep disturbances was identified for young adolescents (aged 10–12 years) [16]. Nevertheless, it was established that use of mobile phones at night was associated with some adverse health outcomes for sleep such as later waking, shorter duration of sleep, restless sleep and some others. These disorders were shown to be more intensive in case a gadget was used in darkness [18–20].

An association between MP usage and sleep disturbances was much more apparent in older adolescents [16, 21, 22], including MP usage late at night [23, 24] and when a MP was used for more than 5 hours a day [25].

In addition, it was established that the total duration of talks was statistically significantly longer among girls than among boys in all the age groups (between 6 and 18) and the greatest negative health outcomes occurred at the age of 14–15 years. In particular, intensity of MP use correlated with frequency of headaches for boys and with difficulty in falling asleep for girls [26].

However, the longitudinal study by J.E. Lee with colleagues established that long MP use increased the risk of poor sleep quality but not short sleep duration [27].

Such symptoms as headache and vertigo are also more frequent in adolescents and depend on MP usage. Thus, O.A. Vyatleva and A.M. Kurganskiy established a correlation between headache and MP usage. However, it was less apparent in adolescents aged 11–13 years than among those aged 14–16 years [16]. Nevertheless, a significant increase in the share of children who suffered from headaches was established when the total duration of MP talks ranged between 12 and 32 minutes a day [28].

Dose-response frequency of headache and warming of the ear depending on duration of MP-use was identified in the study by R. Durusoy and others [21]; tinnitus was identified in adolescents who used wire headsets; wireless headsets involved headache and more frequent nocturnal waking [29]. It was also established that mobile phone use by adolescents could lead not only to headache but migraine and skin itch as well [30].

A statistically significant correlation between fatigue and MP usage was established for schoolchildren aged 9–12 years in the study by F. Zheng and others [31]. Similar findings were reported both for primary schoolchildren [32], including a correlation between feeling tired (the subjective feeling of fatigue, *comment by the authors*) and the number of mobile phone talks [28], and for senior adolescents [21, 22, 24], as well as rapid exhaustibility, headache, and physical ill-being [24].

Mental deadaptation and other symptoms. Anxiety is an individual psychological peculiarity and the most widespread mental disorder in adolescents associated with growing up. In addition, contemporary children and adolescents tend to more frequently have such mental disorders as stress (psychophysiological tension) and depression (an affective mental disorder). As noted by many researchers, such short-term changes tend to often develop into various actual mental disorders. These events are caused by multiple reasons and intense use of various gadgets, mobile phones being certainly the leading ones, is one of them.

It is due to all the aforementioned that investigation of mobile phone use and severity of various mental dysfunctions is a quite relevant issue at present.

Anxiety in primary schoolchildren was shown to depend on MP use [28, 32]. It is interesting to note that the prospect cohort study with participating primary schoolchildren reported an association between growing anxiety levels and switching to smartphones as well as longer use of the mobile Internet [17].

Depression in adolescents intensifies in case they use a mobile phone for more than two hours a day spending this time in social

networks and online chats; the effect is much more apparent than that produced by Internet use, gaming or watching videos [25]. J. Liu with colleagues, having compared MP usage on weekdays and weekends, established that duration of mobile phone use longer than 2 h/day on weekdays and longer than 5 h/day on the weekend was associated with increased risk of depressive symptoms [33]. In addition, girls were established to be more susceptible to elevated risks of smartphone addiction and depression than boys [34].

It was also established that uncontrolled MP use by adolescents before sleep and at night could lead to some serious outcomes for their mental health such as suicidal feelings and greater proneness to self-injury [20].

However, it is noteworthy that anxiety, depression and mental disorders were estimated through questioning in all the studies, that is, they were subjectively estimated by participating respondents.

Active use of mobile phones has resulted in occurrence of new mental disorders (nomophobia, smartphone addiction, etc.); however, these issues have not been addressed in the present review.

In our opinion, studies where various health disorders in children and adolescents are identified in cohorts covering a wide age should be considered separately.

For example, children and adolescents aged between six and 16 years took part in the study by S.M.J. Mortazavi. In this study, statistically significant associations were found between the time mobile phones were used in talk mode and the number of headaches, vertigo, and sleeping problems per month [35]. Similar symptoms were identified for the cohort that included children from primary, middle and senior school who were active smartphone users (their age was between 6 and 18 years). In particular, among those overusing mobile devices (more than 4 hours a day), the most commonly experienced symptoms included headaches, sleep disturbances and neck/shoulder pain as well as poorer ability to concentrate [36]. However, data specific for each age group (primary, middle, or senior school) were analyzed in this study only for mobile phone use. All the remaining parameters were analyzed for the whole data array.

Sleep disturbances associated with using a mobile phone before sleep were identified by the online survey among adolescents of both sexes aged 12–19 years [37]. Similar findings were reported for adolescents aged 14–18 years [38].

Users of mobile phone and computer more often complained of headache, joint and bone pain, hearing loss, vertigo/dizziness, and tension-anxiety symptoms as it was established by the questioning of respondents older than 9 years. Female respondents complained more often of headache, vertigo/dizziness, fatigue, and tension-anxiety than male ones [39].

The study by A.J. Buabbas with colleagues provided direct evidence of a relationship between anxiety, stress and depression and smartphone use; it included middle and senior schoolchildren (aged between 11 and 21 years). In addition, anxiety, stress and depression caused by gadget overuse (more than 4 hours a day) were shown to be higher for females [40].

However, we believe all these studies to have a certain drawback, that is, they investigate health disorders in children and adolescents as per the whole age group without any division into specific age periods. This can substantially distort the results since health outcomes have their age-specific peculiarities, as it was previously shown in this review.

In conclusion, we should note that, apart from asthenic syndrome and mental deadaptation, a correlation was established between MP use and some indirect signs of memory and attention failure such as forgetfulness (inability to recall the necessary information in time) and inattention (inability to concentrate on an event or activity) [17]. However, forgetfulness and inattention were established by questioning and, therefore,

were estimated subjectively rather than objectively.

In addition, it was shown that certain health risks (for example, risks of respiratory diseases) depended on a model of a mobile phone, its radiation level and mode of its use, as it was shown in the studies by O.A. Vyatleva and A.M. Kurganskiy for primary shcoolchildren [16, 28, 32]; health risks related to a growing number of diseases that involved a fever were identified for senior adolescents [26].

Conclusion. Therefore, the research results give evidence of negative effects produced by RF EMF on health of children and adolescents. In this case, this does not concern some specific signs of somatic or mental dysfunctions in children or adolescents; this is about the whole set of disorders that are able to deteriorate health of the growing generation. This should be realized quickly in this rapidly changing modern world of new telecommunication technologies that are changing our entire way of life. Implementation of new technologies should be accompanied with assessment of actual threats posed by using them and development of scientifically substantiated standards for their safe use, especially for children and adolescents.

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