Mineral water inhalations for bronchial asthma: a meta-analysis

Anatoliy D. Fesyun (1), Umberto Solimene (2), Andrey A. Lobanov (1), Irina A. Grishechkina (1), Sergei V. Andronov (1), Andrei I. Popov (1), Maxim Yu. Yakovlev (3), Elena P. Ivanova (1), Natalia P. Sanina (4), Igor V. Reverchuk (5), Maria Chiara Maccarone (6), Stefano Masiero (6,7)

(1) National medical research center for rehabilitation and balneology, Moscow, Russia; (2) Center Integrative Medicine, State University Milan, Italy; (3) Department of General Hygiene of I.M. Sechenov First Moscow State Medical University, Moscow, Russia; (4) Moscow regional research clinical institute named after M.F. Vladimirsky, Moscow, Russia; (5) Department of Psychiatry and Neurosciences of the IKBFU I. Kanta, Kaliningrad, Russian Federation;(6) Physical Medicine and Rehabilitation School, University of Padova, Padua, Italy; (7) Rehabilitation Unit, Department of Neuroscience, University of Padova, Padua, Italy.

Abstract

Bronchial asthma (BA) is a common disease that contributes significantly to the incidence rate and death rate worldwide. A widespread treatment method is the use of inhalations of mineral waters, with conflicting information about their effectiveness. Purpose of the study was to assess the generalized effect power of the course of inhalations of mineral waters on the disease progress in patients with BA. A search of randomized clinical studies in data bases Pubmed, EMBASE, ELibrary, MedPilot amd CyberLeninka, according to PRISMA strategy, published between 1986 and July 2021. Standardized difference of mean values and their 95% of CI were employed for calculation using the random effects model. The meta-analysis drawing on 1266 sources included 14 studies, with 2 of them being randomized controlled clinical studies, including the results of the treatment of 525 patients. All 14 articles contain a conclusion that the inhalation of mineral water has a positive effect on the course of the disease in patients with BA. The analysis demonstrated that the group of patients after mineral water inhalations, compared with the control group, showed improvement of forced expiratory volume (FEV_1), expressed both in % of the norm and in liters. The standardized difference of mean values FEV_1 (%) (Hedge's g) was 8.2 (95% CI: 5.87 – 10.59; 100%), FEV_1 values (liter.) (Hedge's g) was 0.69 (95% CI: -0.33-1.05). A significant heterogeneity of the results of individual studies was found (Q=124.96; tau2 = 14.55, I2 = 69.13%, p<0.0001 and Q=2.35; tau2 = 0, I2 = 0%, p<0.0001). Patients with mild, moderate, and hormone-dependent BA with a controlled and partially controlled disease course, after mineral water inhalations, compared with the control group, demonstrated a statistically significant decrease in the frequency and intensity of the cardinal symptoms of BA and improvement of FEV_1.

Key Words: mineral water; spa treatment; prevention; bronchial asthma; spirometry.

Eur J Transl Myol 33 (2) 11460, 2023 doi: 10.4081/ejtm.2023.11460

As defined by the Global Strategy for Asthma Management and Prevention (GINA) 2019, “bronchial asthma” (BA) is a heterogeneous disease characterized by chronic airway inflammation, the presence of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation”.[1] BA is one of the most common human diseases in all age groups. In Russia, according to epidemiological studies, the frequency of the current signs of BA (wheezing and rough breathing over the last 12 months) in the population of schoolchildren 13-14 years old averaged 9.7%, varying in different regions by more than 2 times.[2,3] The prevalence rates of asthma symptoms also vary in different countries: the highest rates between 11 and 14% prevail in the UK, Australia, and New Zealand, while the lowest ones – 2-3% are in Albania, Turkey, the Czech Republic and Romania.[2] The proportion of patients with bronchial asthma exacerbation in admission and emergency departments of hospitals in developed countries accounts for up to 12% of all admissions, while around 25% of them need hospitalization in specialized departments and about 5% in intensive therapy units.[4-7] Up to now, the death and morbidity rates with BA have remained high in some regions.[2,8] The concept of a "switch" therapy for the treatment of BA has been developed recently and it includes the prescription of various dosages of mono- and foxed combination medicinal products, used mainly in the form of metered-dose aerosols.[8] Inhalation therapy for BA is considered to be the best method of drug delivery due to the fact that it ensures the maximal penetration of active substances into the respiratory tract and has minimal systemic absorption.[2] Alongside studies of medical substances, scientific efforts were made to assess the treatment efficacy of inhalations of natural curative mineral-rich waters for patients with BA. Most of these studies made an assumption about a positive effect on the disease course of the direct action of the inhaled substance on the respiratory tract, due to the normalization of the structure and the purification of the mucous membrane,[9] as well as the anti-inflammatory and antiallergenic effects in the resorptive action of mineral water components.[9-30] However, a clear analysis of the results of these works is somewhat difficult due to a small number of patients participating in the studies or due to the publication of uncertain and, sometimes, conflicting results in some typescripts. Based on the aforesaid, after a preliminary analysis of the publications we decided to conduct a systematic analysis of the results of studies on the effectiveness of a program of inhalations (7-10 procedures) of mineral waters on BA evolution, evaluating the characteristics of the clinical course of the disease (the rate of exacerbations, the number of symptoms, the degree of the disease) and the changes of the main indicators of the respiratory function [FEV_1, forced vital capacity (FVC), peak expiratory flow PEV_1) before and after the treatment and in comparison with the control groups.

The purpose of this study was to assess the generalized effect power of the course of inhalations of mineral waters on the course of the disease in patients with BA.

Materials and Methods

PRISMA criteria were used for a complex search in MEDLINE databases (online analysis and search system of medical literature), CENTRAL (Cochrane Central Register of Controlled Trials), EMBASE (Excerpta Medica data base), Web of Science and MedPilot, CyberLeninka, eLIBRARY.RU.[31-35] Besides, the meta—analysis included also articles and theses papers kept in libraries only on paper-based media (libraries of research institutions: Federal State Budgetary Institution "National Medical Research Center of Rehabilitation and Balneology of the Ministry of Health of the Russian Federation, Federal State Budgetary Institution "Pyatigorsk State Research Institute of Balneology Federal Medical and Biological Agency of Russia").

The terms "mineral water", "thermal water", "balneotherapy", "balneology" were used in the systematic search, combined with the term "bronchial asthma", through the Boolean operator "AND" in all the fields. Besides, the terms, "asthma", "bronchoconstriction", " bronchial spasm", "bronchial hyper-reactivity", and "bronchial reactivity" were connected through "AND" with the terms "mineral water", "thermal water", "balneotherapy", "balneology". No limits were put regarding languages, dates of publications, length of the study or demographic data of the patients.

The following criteria were employed for inclusion of sources in the meta-analysis: access to complete texts; all the participants are adults (aged 18 or older, men and/or women), with a history of BA, who were diagnosed in accordance with the standard criteria that were effective at the beginning of the studies; the use of mineral salts or solutions of mineral salts by way of inhalations. The duration of the intervention was supposed to be at least 5 procedures. The treatment group included patients, who received inhalations of mineral water and solutions of mineral salts of various compositions. The study includes information about the use of mineral waters: sulfate, hydrocarbonate and bromine iodine, siliceous, and chloride. The control group included patients receiving inhalations of isotonic sodium chloride solution (ISCS) (placebo).

The analysis excluded, under Federal Law 61, Art. 43., Para 6, pregnant or oncological patients, hemodialysis patients, with human immunodeficiency virus or AIDS, as well as those, who have heart diseases.

The meta-analysis included clinical studies on the topic: "The use of inhalations of natural mineral water for the treatment of BA", having at least 3 or more points on the modified Jadad scale,[35] the presence of complete sets of statistical data, consisting of the mean, standard deviation and the sample size before and after the inhalation course of mineral water. Studies with the same parameter and different (subsequent) measurement times (5-14 days) were united with a single measurement (2 weeks). A search of the entire dataset for the statistical meta-analysis allowed us to calculate in this study only the following efficiency criteria: forced expiratory volume (FEV_1) in one second, and forced vital capacity (FVC).

Initially, the above-described search gave 1266 matches. The included studies were published between 1986 and July, 2021. First, abstracts of publications were analyzed to exclude duplicating, non-clinical publications (24) and those that don't deal with bronchial asthma (722).[36-38] After reading the complete texts of the publications out of the 540 remaining studies, 469 more studies were excluded due to the unavailability of the full text of the publication (Figure 1).[39,40] Further analysis included 51 articles, which were assessed by two independent

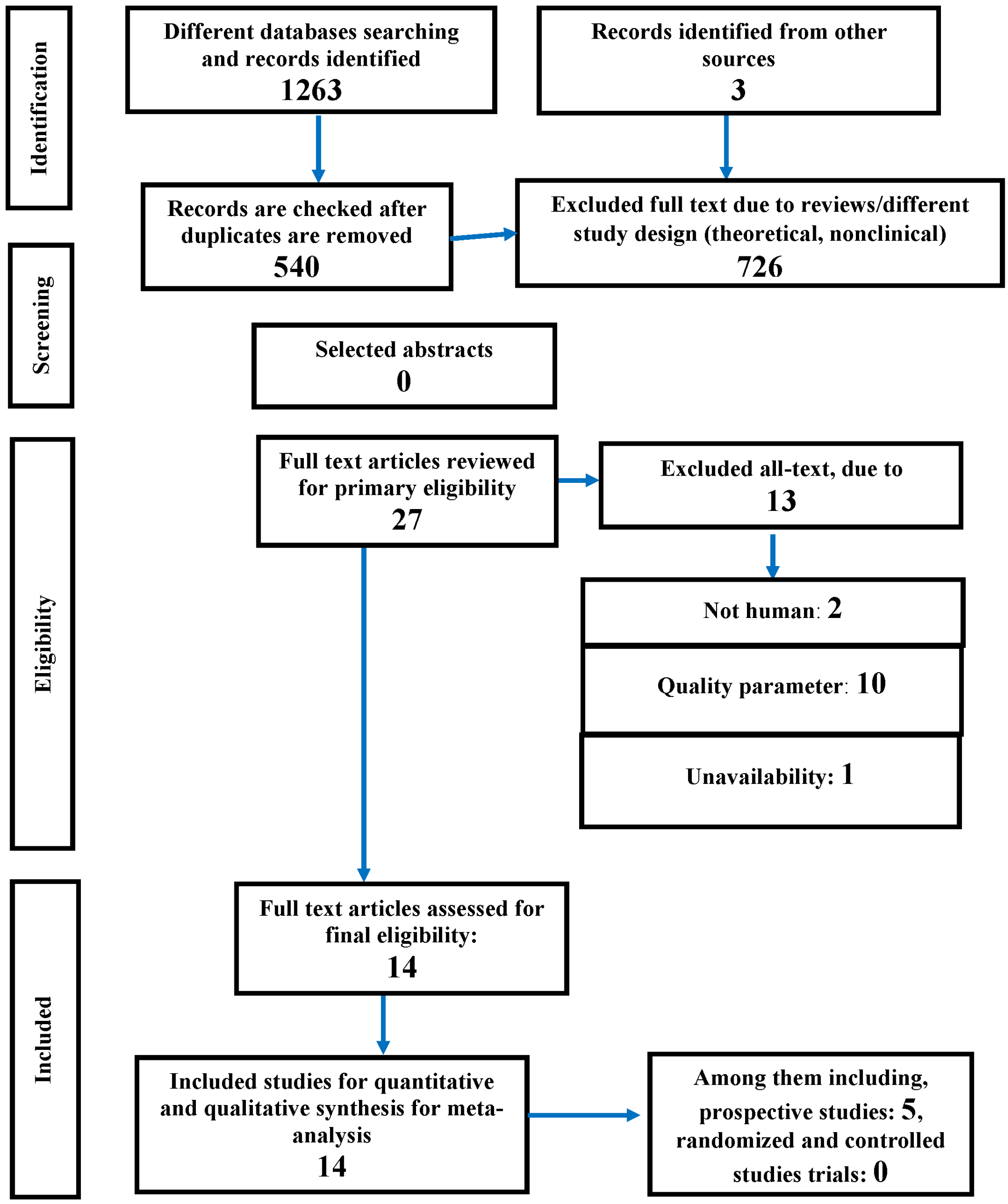

***Fig 1.** PRISMA Block diagram.*[32,46]

reviewers. The quality of publications (Tables 1 and 2) was assessed with the modified Jadad scale.[35] Based on this scale we analyzed randomization, blinding, and dropout of the participants, adding inclusion/exclusion criteria, side effects, and statistical techniques. If absent, these points were deducted. The minimal assessment level was 0 points; the maximal assessment level was 8 points. We set the minimal assessment level of at least three points to establish qualitative homogeneity, necessary for the meta-analysis. After the analysis we excluded 13 research papers because they did not report a complete description of the study design, statistical methods of results processing, mean or median values, standard deviations, and the number of patients in the control groups (placebo groups). Thus, the remaining 14 articles for our analysis were written in Russian, Japanese, and English and were conducted in Russia, Japan, and Italy (Tables 3 and 4; See: Supplementary materials).[11-29,41-45] More information about the included studies is given in Tables 3 and 4 (See: Supplementary materials): the set of data included the following indicators: researcher's name, year of publication, description of key points of the study design (randomization, placebo), number of participants in each

Table 1. *The modified Jadad scale.*[35]

Eight items	Answer	Score
1) Was the study described as Yes randomized?	Yes	+1
	No	0
2) Was the method of randomization appropriate?	Yes	+1
	No	-1
	Not described	0
3) Was the study described as blinding?	Yes	+1
	No	0
4) Was the method of blinding appropriate?	Yes	+1
	No	-1
	Not described	0
5) Was there a description of withdrawals and dropouts?	Yes	+1
	No	0
6) Was there a clear description of the inclusion/exclusion criteria?	Yes	+1
	No	0
7) Was the method used to assess adverse effects described?	Yes	+1
	No	0
8) Was the methods of statistical analysis described?	Yes	+1
	No	0

group; description of the mineral water, quantity, application method, period of application; the values of the indicators of the respiratory function before and after the use of mineral water.

As a measure of the effect, the standardized difference in mean values (Hedge's g) and 95% confidence intervals were calculated using a random effects model. Control Points: the studies were sorted by duration of observation (baseline level, 10-14 days). To assess heterogeneity, the results were assessed using the Q-test, while the degree of heterogeneity was assessed by I value,[2] and 95% of the confidence interval.[47] According to the Cochrane Collaboration tool, heterogeneity is classified as minor (0–40%), moderate (30–60%), essential (50–90%) and significant (75–100%).[47,48] Graphically, the main results were presented in the form of a forest plot. A small study effect and the effect of the publication bias (a particular selection of publications with a "positive" result for the meta-analysis) were assessed with the help of contour funnel plots.[47,48] Statistical estimations and construction of tree diagrams were made with the software Comprehensive Meta Analysis V3.3 (Biostat, NJ, USA). Significance level $p < 0.05$.

Results

We analyzed 14 studies, including 525 participants in total, who were adults aged between 30 and 79 (median age and mean value between 41 and 60 years). The sample sizes ranged from 4 people to 132. The mean value of FEV_1, in % of the expected value, ranged from 42.7±8-91 to 68.5±10.8 before the treatment and from 51.6 ±9.4 to 72.1±14.0 – after the treatment.[25,28] The mean value of FEV_1, in liters, ranged from 0.97±1.15 to 1.7±0.8 before the treatment and from 1.15±0.29 to 2.05±0.81 – after the treatment.[15,45] The mean value of FVC, in % of expected data or in liters was not taken into consideration (Tables 5 and 6; See: Supplementary materials). The search and analysis of research literature on the use of mineral water for BA treatment allowed the use of statistical analysis only for the data on the function of external respiration (FEV_1 in liters or in % of the expected value). Other indicators, such as data on the clinical picture and the nature of the course of the disease, could not be combined for the meta-analysis due to the heterogeneous description of the data, absence of numerical values in some publications to conduct the meta-analysis, or due to the absence of open access to the publication. Initially, the analysis was made using the data from studies where FEV_1 was extracted as a percentage of the expected value for patients with BA. In total, the analysis included 17 studies. The observed mean differences ranged from 1.3000 to 20.9000, meanwhile most of the assessments were positive (100%). The estimated mean difference, based on the random effects model, was 8.2322 on average, with a 95% confidence interval of 5.8748 to 10.5896 (Figure 2). Thus, the mean result was significantly different from zero ($z = 6.8444$, $p < 0.0001$). According to Q-test, the

Table 2. *Assessment of the quality of the pre-selected publications using the modified Jadad scale.*[35]

Parameter	1	2	3	4	5	6	7	8	Total
Selected articles	Were the methods of statistical analysis described?	Was the method used to assess adverse effects described?	Was there a clear description of the inclusion/exclusion criteria?	Was there a description of withdrawals and dropouts?	Was the method of blinding appropriate?	Was the study described as blinding?	Was the method of randomization appropriate?	Was the study described as Yes randomized?	
Zaripova TN. et al.[39]	1	0	1	0	0	0	0	0	2
Ivashchenko NS. et al.[43]	1	0	1	0	0	0	0	0	2
Zaripova NN.[44]	1	1	1	0	0	0	1	0	4
Smirnova IN. et al. [42]	1	1	1	0	0	0	1	0	4
Mitsunobu F. et al.[18]	1	1	0	0	0	0	1	0	3
Osina TD.[50]	0	1	0	0	0	0	1	0	2
Samsonova IP.[49]	1	1	0	0	0	0	0	0	2
Corradi M. et al.[45]	1	1	1	0	0	0	1	1	5
Ashida K. et al.[29]	1	0	1	1	0	0	1	1	5
Okamoto M. et al.[24]	1	0	1	1	0	0	1	1	5
Tanizaki Y. et al.[28]	1	0	1	1	0	0	1	1	5

true results appeared to be heterogenous (Q (16) = 124.9577, p <0.0001, tau² = 14.5466, I² = 69.1313%). Forecast interval 95% for true results was between 0.3940 and 16.0704. Consequently, even when there was some heterogeneity, the true results of the studies, as a rule, coincided with the implied mean result. Examination of studentized residuals showed that two studieshad values more than ± 2.9738,[29,42] and had the most outlier results in the context of this model (Figure 3). Judging by Cook's distances, none of the studies could be considered significant enough. The regression test showed the asymmetry of the funnel graph (p = 0.0245), in contrast to the rank correlation test (p = 0.9032). In the analysis of FEV_1 data of the patients with BA in liters, 7 studies were included. The observed standardized mean differences ranged from 0.2490 to 1.3449, with most of the assessments being positive (100%). The calculated mean standardized difference of the mean values, based on the random effects model, was 0.6928 (95% of the confidence interval: from 0.3344 to 1.0511 (Figure 4). Thus, the mean result significantly differed from zero (z = 3.7889, p = 0.0002). According to Q-test, there was not a significant heterogeneity in the true results (Q (6) = 2.3476, p = 0.8851, tau² = 0.0000, I² = 0.0000%). Examination of studentized residuals showed that none of the studies had values more than ± 2.6901 and, consequently, there were no indications of outliers in the context of this model. Judging by Cook's distances, none of the studies could be considered highly influential. Neither the rank correlation nor the regression test revealed a funnel plot asymmetry (p = 1.0000 and p = 0.7793, correspondingly) (Figure 5). Thus, the estimated overall power of the effect of inhalations of mineral water on the index of external respiratory function, expressed both as a percentage of the expected value and in liters, was 100%, indicating a high degree of scientific evidence and the importance of the findings. The mean values and their standard deviations of the included studies are shown in Figures 2 and 4. Moreover, the studies assessing the impact of mineral water inhalation on FEV_1 in liters demonstrated a significant degree of heterogeneity in the mean values, while it was slightly lower in the studies assessing the impact of mineral water inhalation on the FEV_1 indicator as a percentage of the expected value, though it was still within the range of significant heterogeneity (Figures 3 and 5. See: Supplementary materials). The search and analysis of research literature on the use of mineral water for BA treatment allowed the use of statistical analysis only for the data on the function of external respiration (FEV_1 in liters or in % of the expected value). Other indicators, such as data on the clinical picture and the nature of the course of the disease, could not be combined for the meta-analysis due to the heterogeneous description of the data, absence of numerical values in some publications to conduct the meta-analysis, or due to the absence of open access to the publication. Initially, the analysis was made using the data from studies where FEV_1 was extracted as a percentage of the expected value for patients with BA. In total, the analysis included 17 studies. The observed mean differences ranged from 1.3000 to 20.9000, meanwhile most of the assessments

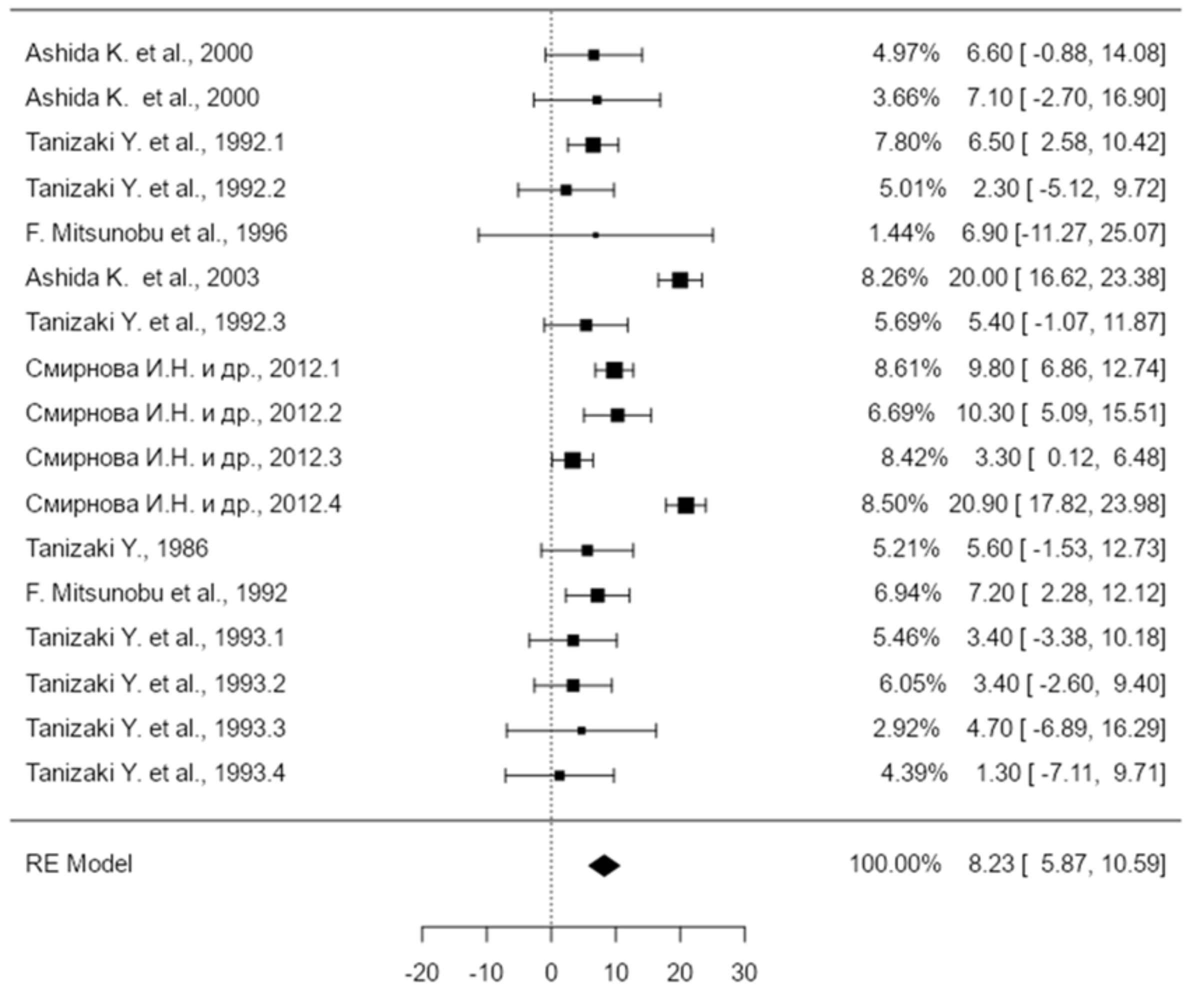

Fig 2. *Meta-analysis of studies of effect on FEV1 value, (%) after use of mineral water for BA (Forest plot)*[14,21,23,26,28,29,42,46]

were positive (100%). he estimated mean difference, based on the random effects model, was 8.2322 on average, with a 95% confidence interval of 5.8748 to 10.5896 (Figure 2). Thus, the mean result was significantly different from zero (z = 6.8444, p <0.0001). According to Q-test, the true results appeared to be heterogenous (Q (16) = 124.9577, p <0.0001, tau² = 14.5466, I² = 69.1313%). Forecast interval 95% for true results was between 0.3940 and 16.0704. Consequently, even when there was some heterogeneity, the true results of the studies, as a rule, coincided with the implied mean result. Examination of studentized residuals showed that two studies [29,42] had values more than ± 2.9738 and had the most outlier results in the context of this model (Figure 3). Judging by Cook's distances, none of the studies could be considered significant enough. The regression test showed the asymmetry of the funnel graph (p = 0.0245), in contrast to the rank correlation test (p = 0.9032). In the analysis of FEV_1 data of the patients with BA in liters, 7 studies were included. The observed standardized mean differences ranged from 0.2490 to 1.3449, with most of the assessments being positive (100%). The calculated mean standardized difference of the mean values, based on the random effects model, was 0.6928 (95% of the confidence interval: from 0.3344 to 1.0511 (Figure 4). Thus, the mean result significantly differed from zero (z = 3.7889, p = 0.0002). According to Q-test, there was not a significant heterogeneity in the true results (Q (6) = 2.3476, p = 0.8851, tau² = 0.0000, I² = 0.0000%). Examination of studentized residuals showed that none of the studies had values more than ± 2.6901 and, consequently, there were no indications of outliers in the context of this model. Judging by Cook's distances, none of the studies could be considered highly influential. Neither the rank correlation nor the regression test revealed a funnel plot asymmetry (p = 1.0000 and p = 0.7793, correspondingly) (Figure 5). Thus, the estimated overall power of the effect of inhalations of mineral water on the index of external respiratory function, expressed both as a percentage of the expected

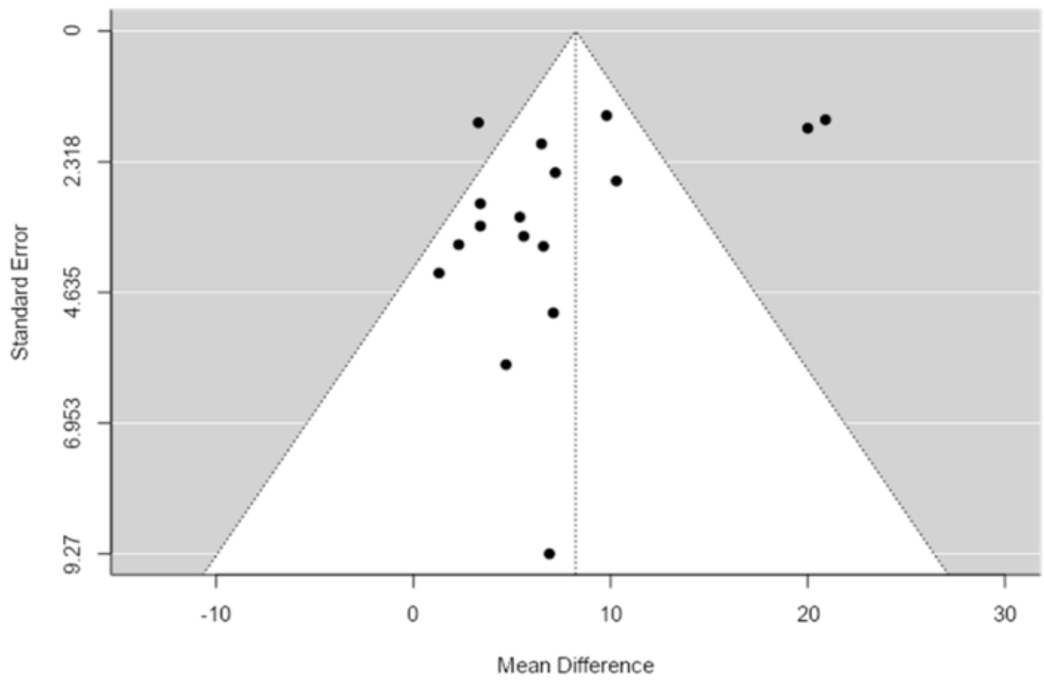

Fig 3. *Funnel plot (FEV$_1$ values, (%).*

value and in liters, was 100%, indicating a high degree of scientific evidence and the importance of the findings. The mean values and their standard deviations of the included studies are shown in Figures 2 and 4. Moreover, the studies assessing the impact of mineral water inhalation on FEV$_1$ in liters demonstrated a significant degree of heterogeneity in the mean values, while it was slightly lower in the studies assessing the impact of mineral water inhalation on the FEV$_1$ indicator as a percentage of the expected value, though it was still within the range of significant heterogeneity (Figures 3 and 5). The search and analysis of research literature on the use of mineral water for BA treatment allowed the use of statistical analysis only for the data on the function of external respiration (FEV$_1$ in liters or in % of the expected value). Other indicators, such as data on the clinical picture and the nature of the course of the disease, could not be combined for the meta-analysis due to the heterogeneous description of the dat absence of numerical values in some publications to conduct the meta-analysis, or due to the absence of open access to the publication. Initially, the analysis was made using the data from studies where FEV$_1$ was extracted as a percentage of the expected value for patients with BA. In total, the analysis included 17 studies. The observed mean differences ranged from 1.3000 to 20.9000, meanwhile most of the assessments were positive (100%). he estimated mean difference, based on the random effects model, was 8.2322 on average, with a 95% confidence interval of 5.8748 to 10.5896 (Figure 2). Thus, the mean result was significantly different from zero (z = 6.8444, p <0.0001). According to Q-test, the true results appeared to be heterogenous (Q (16) = 124.9577, p <0.0001, tau^2 = 14.5466, I^2 = 69.1313%). Forecast interval 95% for true results was between 0.3940 and 16.0704. Consequently, even when there was some heterogeneity, the true results of the studies, as a rule, coincided with the implied mean result. Examination of studentized residuals showed that two studies [29,42] had values more than ± 2.9738 and had the most outlier results in the context of this model (Figure 3). Judging by Cook's distances, none of the studies could be considered significant enough. The regression test showed the asymmetry of the funnel graph (p = 0.0245), in contrast to the rank correlation test (p = 0.9032). In the analysis of FEV$_1$ data of the patients with BA in liters, 7 studies were included. The observed standardized mean differences ranged from 0.2490 to 1.3449, with most of the assessments being positive (100%). The calculated mean standardized difference of the mean values, based on the random effects model, was 0.6928 (95% of the confidence interval: from 0.3344 to 1.0511 (Figure 4). Thus, the mean result significantly differed from zero (z = 3.7889, p = 0.0002). According to Q-test, there was not a significant heterogeneity in the true results (Q (6) = 2.3476, p = 0.8851, tau^2 = 0.0000, I^2 = 0.0000%). Examination of studentized residuals showed that none of the studies had values more than ±

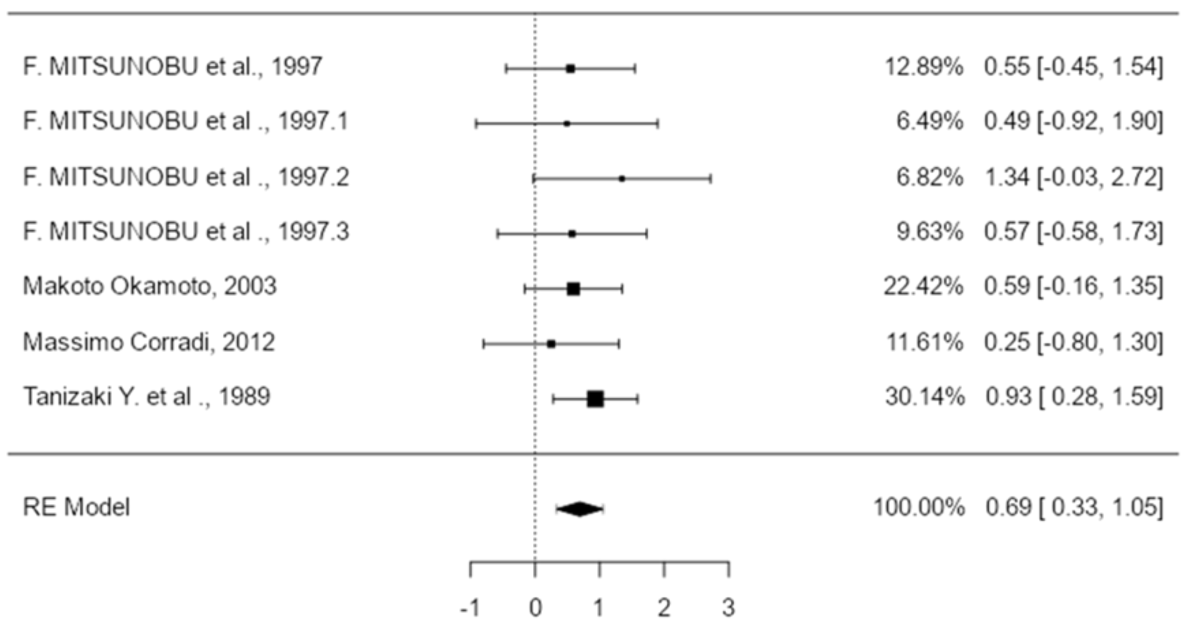

Fig 4. *Meta-analysis of studies of effect on FEV_1 value, (liter) after the use of mineral water for BA (Forest plot)* [18,21,24,45]

2.6901 and, consequently, there were no indications of outliers in the context of this model. Judging by Cook's distances, none of the studies could be considered highly influential. Neither the rank correlation nor the regression test revealed a funnel plot asymmetry (p = 1.0000 and p = 0.7793, correspondingly) (Figure 5). Thus, the estimated overall power of the effect of inhalations of mineral water on the index of external respiratory function, expressed both as a percentage of the expected value and in liters, was 100%, indicating a high degree of scientific evidence and the importance of the findings. The mean values and their standard deviations of the included studies are shown in Figures 2 and 4. Moreover, the studies assessing the impact of mineral water inhalation on FEV_1 in liters demonstrated a significant degree of heterogeneity in the mean values, while it was slightly lower in the studies assessing the impact of mineral water inhalation on the FEV_1 indicator as a percentage of the expected value, though it was still within the range of significant heterogeneity (Figures 3 and 5). The search and analysis of research literature on the use of mineral water for BA treatment allowed the use of statistical analysis only for the data on the function of external respiration (FEV_1 in liters or in % of the expected value). Other indicators, such as data on the clinical picture and the nature of the course of the disease, could not be combined for the meta-analysis due to the heterogeneous description of the data, absence of numerical values in some publications to conduct the meta-analysis, or due to the absence of open access to the publication. Initially, the analysis was made using the data from studies where FEV_1 was extracted as a percentage of the expected value for patients with BA. In total, the analysis included 17 studies. The observed mean differences ranged from 1.3000 to 20.9000, meanwhile most of the assessments were positive (100%). he estimated mean difference, based on the random effects model, was 8.2322 on average, with a 95% confidence interval of 5.8748 to 10.5896 (Figure 2). Thus, the mean result was significantly different from zero (z = 6.8444, p <0.0001). According to Q-test, the true results appeared to be heterogenous (Q (16) = 124.9577, p <0.0001, tau^2 = 14.5466, I^2 = 69.1313%). Forecast interval 95% for true results was between 0.3940 and 16.0704. Consequently, even when there was some heterogeneity, the true results of the studies, as a rule, coincided with the implied mean result. Examination of studentized residuals showed that two studies [29,42] had values more than ± 2.9738 and had the most outlier results in the context of this model (Figure 3). Judging by Cook's distances, none of the studies could be considered significant enough. The regression test showed the asymmetry of the funnel graph (p = 0.0245), in contrast to the rank correlation test (p = 0.9032). In the analysis of FEV_1 data of the patients with BA in liters, 7 studies were included. The observed standardized mean differences ranged from 0.2490 to 1.3449, with most of the assessments being positive (100%). The calculated mean standardized difference of the mean values, based on the random effects model, was 0.6928 (95% of the confidence interval: from 0.3344 to 1.0511 (Figure 4). Thus, the mean result significantly differed from zero (z = 3.7889, p = 0.0002). According to Q-test, there was not a significant heterogeneity in the

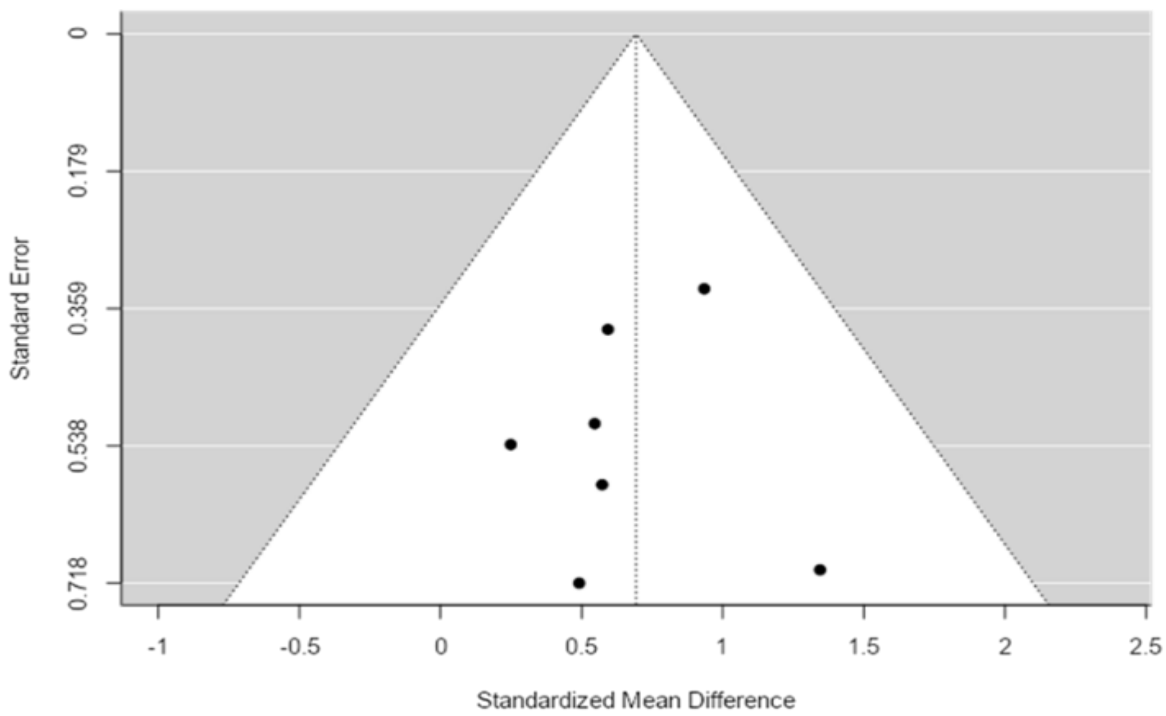

Fig 5. *Funnel plot (FEV1 values, (%).*

true results (Q (6) = 2.3476, p = 0.8851, tau² = 0.0000, I² = 0.0000%). Examination of studentized residuals showed that none of the studies had values more than ± 2.6901 and, consequently, there were no indications of outliers in the context of this model. Judging by Cook's distances, none of the studies could be considered highly influential. Neither the rank correlation nor the regression test revealed a funnel plot asymmetry (p = 1.0000 and p = 0.7793, correspondingly) (Figure 5). Thus, the estimated overall power of the effect of inhalations of mineral water on the index of external respiratory function, expressed both as a percentage of the expected value and in liters, was 100%, indicating a high degree of scientific evidence and the importance of the findings. The mean values and their standard deviations of the included studies are shown in Figures 2 and 4. Moreover, the studies assessing the impact of mineral water inhalation on FEV_1 in liters demonstrated a significant degree of heterogeneity in the mean values, while it was slightly lower in the studies assessing the impact of mineral water inhalation on the FEV_1 indicator as a percentage of the expected value, though it was still within the range of significant heterogeneity (Figures 3 and 5).

Discussion

This literature review and meta-analysis is the first systematic research approach to inhalation therapy with mineral waters in BA, used in accordance with a standardized worldwide research protocol and a generally accepted system of including and excluding research papers in the final analysis.

The review of the literature has shown that inhalations of mineral water affect the key mechanisms of BA pathogenesis: immunological response, production of inflammatory mediators, bronchial inflammation, and reversible limitation of respiratory flow. Mineral water inhalations reduce airway mucosal inflammation and cellular infiltration, affect IgE production, improve mucociliary clearance, sputum rheology, and bronchial drainage, and reduce lipid peroxidation activity. However, the methods used to investigate these mechanisms varied considerably between investigators, making it impossible to conduct a meta-analysis. In contrast, the study of respiratory function followed standardized protocols and was used by most authors who conducted clinical trials.

There are two main goals in the treatment of BA:

i) achieving and maintaining good control of symptoms of BA over a long period of time;

ii) minimising the risks of future exacerbations of BA, fixed airway obstruction and unwanted side-effects of therapy.

Analysis of the clinical picture of patients by pooled assessments was difficult due to the use of different data collection and processing methods. However, the key symptoms of BA, coughing, shortness of breath, wheezing (choking attacks) were reduced by 2.6-2.8

times as a result of the inhalation therapy. Meanwhile, not only the symptoms frequency decreased, but their intensity as well, and the need for asthma medication more than halved, which may indicate a good "control" of the disease in most cases. FEV_1, to some extent, is an integrated indicator of the reduced inflammatory activity in the bronchial wall. Considering that this indicator for BA is quite stable, even a slight improvement is a sign of a significant improvement in the disease course. In most studies, the FEV_1 indicator (except the group of patients with severe hormone-dependent BA) after therapy was more than 60% of the expected value, which means that there are no risks of frequent and severe future exacerbations of BA and no risk of reduced lung function later on. However, the increase was not as significant as with inhalation of glucocorticosteroids, long-acting beta-adrenoblockers, and montelukast.[54] Additionally, the authors of one of the studies evaluated the persistence of the treatment effect using long-term follow-up data, which was observed for 10.9±0.21 months after the therapy course. BA is often accompanied by chronic upper respiratory tract infections or frequent acute respiratory viral infections, which increase the risk of exacerbations of the disease. The use of mineral water inhalations is also effective in treating all the comorbid conditions listed above. In one study,[42] authors described good tolerability of mineral water inhalations in 91.4-99.0% of the patients, and no serious adverse events have been reported in any studies. This suggests a favorable safety profile for use of mineral water inhalations, comparable with that of inhalating glucocorticosteroids and long-acting β-adrenoblockers.[55-57] Although, most studies point to a decrease in the number of eosinophils in peripheral blood after a course of inhalation therapy and, in some studies, - a decrease in IgE content in case of sensitization to house dust mite, and the relationship between the serum content of cysteine leukotrienes B4, C4 and treatment efficacy of patients, still it is rather difficult to unambiguously identify and with sufficient certainty any phenotype/endotype or subtype of BA, for which inhalation of mineral waters would be pathogenetically justified and recommended.

Thus, inhalation therapy using mineral water is an effective treatment option for patients with mild, moderate, or severe hormone-dependent asthma, especially when the condition is controlled or partially controlled. It is also a cost-effective non-pharmacological treatment that can be used alongside baseline drug therapy. Additionally, it can be combined with other forms of pulmonary rehabilitation, climatotherapy and balneotherapy to further improve patient outcomes.[58]

We conducted a meta-analysis of published data to calculate an overall estimate of the power of the effect of mineral water inhalation in patients with BA. The main advantage of this study is the high strength of scientific evidence supporting the practical effectiveness of a course of inhalations, despite the significant degree of heterogeneity in the results of the included studies. However, a limitation of the study is that we did not analyze subgroups of patients with BA who may have different disease courses and are triggered by different exacerbating factors. Further limitations of the study are that: i) we did not analyze subgroups of patients with different types of BA or ii) the role of different triggers for exacerbations in patients; iii) the types and classes of mineral water used for inhalation varied across studies, with different chemical characteristics and content of microelements and ions; iv) in addition to inhalation therapy, patients received various balneological and physiotherapeutic treatments, selected based on current standards of therapy or traditional national treatment methods, such as "Onsen" in Japan.

In conclusion, our meta-analysis demonstrates a statistically significant reduction in frequency and intensity of key clinical symptoms of BA with improvement in FEV_1, the main index of external respiratory function, in patients suffering with mild, moderate, and hormone-dependent BA with a controlled or partially controlled disease course after inhalation of mineral water when compared to the control group. Strength of recommendation is statistically significant at high degree.

List of acronyms

AIDS - acquired immune deficiency syndrome
BA - bronchial asthma
CENTRAL - cochrane central register of controlled trials
FEV_1 - forced expiratory volume
FVC - forced vital capacity
GINA - global Ssrategy for asthma management and prevention
IgE - immunoglobulin E
ISCS - isotonic sodium chloride solution
PEV_1 - peak expiratory flow
PRISMA - Preferred Reporting Items for Systematic reviews and Meta-Analyses
SIgA - specific immunoglobulin E

Contributions of Authors

ADF – development of the study design; US – development of the study design; AAL – development of the study design, data design; IAG – writing, review of publications on the topic of the article, data interpretation; SVA – review of publications on the topic of the article, statistical processing of data, data interpretation; AIP – review of publications on the topic of the article, data interpretation; MYuY – data interpretation; EPI - review of publications on the topic of the article, data interpretation; NPS, IVR - revision of the article; MCM - review of publications on the topic of the article, drafting the paper; SM - supervision of the article.

Acknowledgments None.

Funding None.

Conflict of Interest

The authors declare they have no conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Corresponding Author

Elena P. Ivanova, Ph.D, DMD, Head of International cooperation department, National Medical Research Center for Rehabilitation and Balneology of the Ministry of Health of the Russian Federation, Novy Arbat str., 32, Moscow, 121099, Russia; Phone: + 7-9853964266
Fax: +7 (499) 277-01-04.
ORCID iD: 0000-0002-2781-4325
E-mail: IvanovaEP@nmicrk.ru

E-mails and ORCID iD of co-authors

Anatoliy D. Fesyun: fad68@yandex.ru
ORCID ID: 0000-0003-3097-8889
Umberto Solimene: umberto.solimene@unimi.it
ORCID ID: 0000-0002-0172-0574
Irina A. Grishechkina: GrishechkinaIA@nmicrk.ru
ORCID ID: 0000-0002-4384-2860
Andrey A. Lobanov: alobanov89@gmail.com
ORCID ID: 0000-0002-6615-733X
Sergei V. Andronov: sergius198010@mail.ru
ORCID ID: 0000-0002-5616-5897
Maxim Yu. Yakovlev: masdat@mail.ru
ORCID ID: 0000-0002-5260-8304
Igor V. Reverchuk: bios@reverchuk.com
ORCID ID: 0000-0002-3498-9094
Andrei I. Popov: PopovAI@nmicrk.ru
ORCID ID: 0000-0002-0614-8116
Natalia P. Sanina: natalyasanina2@yandex.ru
ORCID ID: 0000-0002-0335-1899
Maria Chiara Maccarone: mariachiara.maccarone@phd.unipd.it
ORCID ID: 0000-0003-2793-1334
Stefano Masiero: stef.masiero@unipd.it
ORCID ID: 0000-0002-0361-4898

References

1. Global strategy for asthma: management and prevention. Revised 2017. Available online: www.ginasthma.com. (accessed on 29 May 2022)
2. Chuchalin AG. Pul'monologiya. Nacional'noe rukovodstvo. Kratkoe izdanie [Pulmonology. National leadership. Short edition]. GEOTAR-Media, 2020. Russian
3. Chuchalin AG, Khaltaev N, Antonov N. Chronic respiratory diseases and risk factors in 12 regions of the Russian Federation. International Journal of COPD. 2014; 9: 963–74. Russian.
4. Krahn MD, Berka C, Langlois P, Detsky AS. Direct and indirect costs of asthma in Canada, 1990. CMAJ. 1996 Mar 15; 154(6): 821-31. PMID: 8634960; PMCID: PMC1487808.
5. Weber EJ, Silverman RA, Callaham ML, Pollack CV, Woodruff PG, Clark S, Camargo CA Jr. A prospective multicenter study of factors associated with hospital admission among adults with acute asthma. Am J Med. 2002 Oct 1; 113(5): 371-8. doi: 10.1016/s0002-9343(02)01242-1. PMID: 12401531.
6. Braman SS, Kaemmerlen JT. Intensive care of status asthmaticus. A 10-year experience. JAMA. 1990 Jul 18; 264(3): 366-8. PMID: 2362333.
7. Salmeron S, Liard R, Elkharrat D, Muir J, Neukirch F, Ellrodt A. Asthma severity and adequacy of management in accident and emergency departments in France: a prospective study. Lancet. 2001 Aug 25;358(9282):629-35. doi: 10.1016/s0140-6736(01)05779-8. PMID: 11530150.
8. Nenasheva NM. Bronhial'naya astma. Sovremennyj vzglyad na problemu. [Bronchial asthma. A modern view of the problem]. GEOTAR-Media, 2018. Russian.
9. Khai Vu Do, Mitsunobu F. Spa Therapy for Bronchial Astma. Alternative and Complementary Therapies. 2004; June: 144-50.
10. Barabash EYu, Kalinina EP, Gvozdenko TA, Stepanova OP. Vliyanie kompleksnoj reabilitacionnoj terapii na sostoyanie interferonovogo statusa u pacientov s bronhial'noj astmoj [Influence of complex rehabilitation therapy on the state of interferon status in patients with bronchial asthma]. Byuleten' fiziologii i patologii dyhaniya. 2015; 57: 25-9. Russ.
11. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Okuda H, Takatori A, Ochi K, Harada H. Clinical effects of spa therapy on bronchial asthma. 1. Relationship to clinical asthma type and patient age. J Jpn Assoc Phys Med Baln Clim. 1993; 56: 143-50.
12. Tanizaki Y, Kitani H, Mifune T, et al. Ten-year study of spa therapy in 329 patients with bronchial asthma. J Jpn Assoc Phys Med Baln Clim. 1994; 57: 142-50.
13. Tanizaki Y, Kitani H, Okazaki M, et al. Clinical effects of spa therapy on bronchial asthma. 2. Relationship to ventilatory function. J Jpn Assoc Phys Med Baln Clim.1992; 55: 82-6.
14. Mitsunobu F, Mifune T, Hosaki Y, et al. Improvemant of forced vital capacity (FVC) by spa therapy in patients with bronchial ashma. J Jpn Assoc Phys Med Baln Clim. 1996; 59: 218-24.
15. Mitsunobu F, Mifune T, Hosaki Y, et al. Effects of spa therapy on asthmatics with low ventilatory function. Relationship to asthma type, patient age, and airway inflammation. J Jpn Assoc Phys Med Baln Clim. 1997; 60: 125-32.

16. Tanizaki Y, Kitani H, Okazaki M, et al. Clinical effects of spa therapy on bronchial asthma. 9. Suppression of bronchial hyperresponsiveness. J Jpn Assoc Phys Med Baln Clim. 1993; 56: 135-42.
17. Mifune T, Mitsunobu F, Hosaki Y, et al. Spa therapy and function of adrenocortical glands in patients with steroid-dependent intractabla asthma (SDIA). Relationship to clinical asthma type, and clinical efficacy. J Jpn Assoc Phys Med Baln Clim. 1996; 59: 133-40.
18. Tanizaki Y, Mifune T, Mitsunobu F et al. Rehabilitation for patients with respiratory disease Spa efficacy in relation to pathophysiological characteristics of bronchial asthma Acta Medica Okayama. 1998: 80-93.
19. Tanizaki Y, Kitani H, Okazaki M, et al. Clinical effects of spa therapy on bronchial asthma. 5. Efficacy of inhalation with iodine salt solution. J Jpn Assoc Phys Med Baln Clim. 1992; 55: 179-84.
20. Kitani H, Mitsunobu F, Mifune T, et al. Clinical effects of spa therapy on bronchial asthma. 3. Efficacy of fango therapy. J Jpn Assoc Phys Med Baln Clim. 1992; 55: 127-33.
21. Mitsunobu F, Kitani H, Okazaki M, et al. Clinical effects of spa therapy on bronchial asthma. 6. Comparison among three kinds of spa therapies. J Jpn Assoc Phys Med Baln Clim. 1992; 55: 185-90.
22. Mitsunobu F, Kitani H, Mifune T, et al. Clinical effects of spa therapy on bronchial asthma. 12. Effects on asthma with hypersecretion. J Jpn Assoc Phys Med Baln Clim. 1993; 56: 203-10.
23. Tanizaki Y. Improvement of ventilatory function by spa therapy in patients with intractable asthma. Acta Med Okayama 1986; 40 (1): 55-9.
24. Okamoto M, Ashida K, Mitsunobu F, et al. Effects of spa therapy combined with dietary supplementation with n-3 fatty acids on bronchial asthma. J Jpn Assoc Phys Med Balneol Climatol 2003; 66: 171-9.
25. Ashida K, Mitsunobu F, Hosaki Y, et al. Decrease in low attenuation area (LAA) of the lungs on high resolution computed tomography (HRCT) by long-term spa therapy in patients with asthma. J Jpn Assoc Phys Med Balneol Climatol 2003; 66: 115-22.
26. Tanizaki Y, Kitani H, Okazaki M et al. Spa therapy improves ventilatory function in the small airways of patients with steroid-dependent intractable asthma (SDIA). Acta Med Okayama. 1992; 46(3): 175-8.
27. Tanizaki Y, Sudo M, Kitani H, Araki H. Spa therapy for bronchial asthma. Clinical effects of inhalation of iodine salt solutions. Paper of the Institute for Environmental Medicine, Okayama University Medical School. 1989; 60: 19-24.
28. Tanizaki Y, Kitani H, Okazaki M et al. Clinical effects of complex spa therapy on patients with steroid-dependent intractable asthma (SDIA). Arerugi. 1993; 42 (3 Pt 1): 219-27.
29. Ashida K, Mitsunobu F, Mifune T et al. Clinical effects of spa therapy on patients with asthma accompanied by emphysematous changes. J Jpn Assoc Phys Med Balneol Climatol. 2000; 63: 113-9.
30. Khaltaev N, Solimene U, Vitale F, Zanasi A. Balneotherapy and hydrotherapy in chronic respiratory disease. J Thorac Dis. 2020 Aug;12(8):4459-4468. doi: 10.21037/jtd-gard-2019-009. PMID: 32944359; PMCID: PMC7475532.
31. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009 Oct;62(10):e1-34. doi: 10.1016/j.jclinepi.2009.06.006. Epub 2009 Jul 23. PMID: 19631507.
32. Moher A, Liberati J, Tetzlaff J, Altman DG Preferred reporting elements for systematic reviews and meta-analysis: a PRISMA statement. Annals of Internal Medicine. 2009; 151 (4): 264–9.
33. Rebrova OYu, Fedyaeva VK. Meta-analyzes and assessment of their methodological quality. Russian version of the AMSTAR questionnaire. Meditsinskie tekhnologii. Otsenka i vybor. 2016; 1: 10−6. Russian
34. Ressing M, Blettner M, Klug SJ. Systematic literature reviews and meta-analyses: part 6 of a series on evaluation of scientific publications. Dtsch Arztebl Int. 2009 Jul;106(27):456-63. doi: 10.3238/arztebl.2009.0456. Epub 2009 Jul 3. PMID: 19652768; PMCID: PMC2719096.
35. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1-12. doi: 10.1016/0197-2456(95)00134-4. PMID: 8721797.
36. Zajak D. Inhalations with thermal waters in respiratory diseases. J. of Ethnopharmacology. 2021; 281: 114505.
37. Zając D, Russjan E, Kostrzon M, Kaczyńska K. Inhalations with Brine Solution from the 'Wieliczka' Salt Mine Diminish Airway Hyperreactivity and Inflammation in a Murine Model of Non-Atopic Asthma. Int J Mol Sci. 2020 Jul 7;21(13):4798. doi: 10.3390/ijms21134798. PMID: 32645931; PMCID: PMC7370210.
38. Romeyke T, Nöhammer E, Scheuer HC, Stummer H. Integration of naturopathic medicine into acute inpatient care: An approach for patient-centred medicine under diagnosis-related groups. Complement Ther Clin Pract. 2017 Aug;28:9-17.

doi: 10.1016/j.ctcp.2017.04.004. Epub 2017 Apr 13. PMID: 28779943.
39. Zaripova TN, Smirnova IN, Antipova II. Nemedikamentoznaya aerozol'terapiya v pul'monologii. [Non-drug aerosol therapy in pulmonology]. STT, 2014. Russian
40. Gete NA. Ingalyacionnaya nebulajzernaya terapiya zabolevanij respiratornoj sistemy u detej: Prakticheskoe rukovodstvo dlya vrachej [Inhalation Nebulizer Treatment of Respiratory System Disorders in Children: A Practical Guide for Physicians]. Color – Studio, 2008. Russian
41. Zaripova TN, Smirnova IN, Moskvin VS, Antipova II. Nemedikamentoznaya aerozol'terapiya kombinirovannym gryazevym preparatom «Tonus plyus» v pul'monologii [Non-drug aerosol therapy with the combined mud preparation "Tonus plus" in pulmonology]. Byulleten' sibirskoj mediciny. 2003; 3: 80-9. Russian
42. Smirnova IN, Zaripova TN, Antipova II et al. Vliyanie aerozol'terapii mineral'nymi vodami na sostoyanie funkcii vneshnego dyhaniya u bol'nyh bronhial'noj astmoj i hronicheskoj obstruktivnoj bolezn'yu lyogkih.[Influence of aerosol therapy with mineral waters on the state of the function of external respiration in patients with bronchial asthma and chronic obstructive pulmonary disease] Sibirskij medicinskij zhurnal. 2012; 7: 42-5. Russian
43. Ivashchenko NS, Patutin VN. Preimushchestva metodiki kombinirovannogo primeneniya mineral'noj vody 1-L BiS v sostave kompleksnogo sanatornogo lecheniya bol'nyh bronhial'noj astmoj [Advantages of the methodology for the combined use of mineral water 1-L BiS as part of the complex sanatorium treatment of patients with bronchial asthma] Novye tekhnologii. 2010; 4: 147-52. Russian
44. Zaripova TN, Smirnova IN, Antipova II, Cherno VA. Obosnovanie ispol'zovaniya mineral'nyh vod Kuzbassa v pul'monologicheskoj praktike [Justification of the use of Kuzbass mineral waters in pulmonary practice]. Medicina v Kuzbasse. 2014; 13(1): 16-21. Russian.
45. Corradi M, Folesani G, Gergelova P et al. Effect of salt-bromide-iodine thermal water inhalation on functional and biochemical lung parameters. ISRN Pulmonology. 2012: 1–8.
46. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41. doi: 10.1016/j.ijsu.2010.02.007. Epub 2010 Feb 18. Erratum in: Int J Surg. 2010;8(8):658. PMID: 20171303.
47. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.
48. Higgins JP, Thomas J. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, 2019.
49. Samsonova IP. Korrekciya giperreaktivnosti dyhatel'nyh putej u chaste boleyushchih detej I podrostkov s boleznyami organov dyhaniya ingalyaciyami Konstantinovskoj mineral'noj vodoj [Correction of airway hyperresponsiveness in frequently ill children and adolescents with respiratory diseases by inhalation of Konstantinovskaya mineral water] Byulleten' fiziologii I patologii dyhaniya. 2007; 24: 69-70. Russian.
50. Osina TD. Vliyanie peloidoterapii na mestnye factory zashchity dyhatel'nyh putej u detej [Influence of peloid therapy on local factors of airway protection in children]. Byulleten' fiziologiiipatologiidyhaniya. 2001; 9, 45-48. Russian.
51. Ivashchenko NS, Patutin VN. Sravnitel'naya harakteristika effektivnosti lecheniya pul'monologicheskih bol'nyh v sanatorii «Laba». [Comparative characteristics of the effectiveness of treatment of pulmonary patients in the sanatorium "Laba"]. Novye tekhnologii. 2010: 2; 145-50. Russian.
52. Wark P, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. Cochrane Database Syst Rev. 2018 Sep 27;9(9):CD001506. doi: 10.1002/14651858.CD001506.pub4. PMID: 30260472; PMCID: PMC6513595.
53. Di Marco M, De Novellis AMP, Carluccio V, Bozzelli R, Orlando M, Lanuti P. Short- and long-term beneficial effects of medicinal mineral water administration. Environ Geochem Health. 2020 Feb;42(2):353-364. doi: 10.1007/s10653-019-00290-x. Epub 2019 Oct 19. PMID: 31630285.
54. Avdeev SN, Arhipov VV. Ingalyacionnaya terapiya [Inhalation therapy]. GEOTAR-Media, 2020. Russian.
55. Stempel DA, Raphiou J, Kral K, Yeakey A, Buaron K, Emmett A, Prazma ChM, Pascoe S., et al. AUSTRI, a large Randomized Study in Adolescents and Adults with Asthma, Assessing the Safety and Efficacy of Salmeterol in Combination with Fluticasone Propionate Compared to Fluticasone Propionate Alone. The Journal of Allergy and Clinical Immunology. 2016; 137 (2): 389.
56. 6-month Safety and Benefit Study of ADVAIR in Children 4-11 Years Old (VESTRI). Available

online: https://clinicaltrials.gov/ct2/show/NCT01462344 (accessed on 12 May 2022).

57. Rachelefsky GS, Liao Y, Faruqi R. Impact of inhaled corticosteroid-induced oropharyngeal adverse events: results from a meta-analysis. Ann Allergy Asthma Immunol. 2007 Mar;98(3):225-38. doi: 10.1016/S1081-1206(10)60711-9. PMID: 17378253.
58. Maccarone MC, Masiero S. Spa therapy interventions for post respiratory rehabilitation in COVID-19 subjects: does the review of recent evidence suggest a role? Environ Sci Pollut Res Int. 2021 Sep;28(33):46063-46066. doi: 10.1007/s11356-021-15443-8. Epub 2021 Jul 17. PMID: 34273080; PMCID: PMC8286038.

Disclaimer

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Submission: May 11, 2023
Accepted for publication: May 24, 2023

Eur J Transl Myol 33 (2) 11460, 2023 doi: 10.4081/ejtm.2023.11460

Supplementary Materials: Table 3. Design of the included studies.[32,46]

Author	**Year**	**Design**	**Mineral substance under study**	**Control**	**Method of inhalation**	**Adverse events**	**FEV_1**	**FVC**	**VC**
Zaripova TN. et al.[44]	2014	Randomized clinical trials in parallel groups, in patients with bronchial asthma, chronic obstructive pulmonary disease and chronic bronchitis	I Carbon dioxide siliceous-iron mineral water II Hydrocarbonated sodium mineral water	0,9% sodium chloride	1 time per day 10-15 minutes 10-12 procedures	-	-	-	-
Smirnova IN. et al.[42]	2012	Comparative randomized clinical trials in parallel groups	I Chloride mineral waters II Hydrocarbonated mineral waters III Bromide mineral waters IV Siliceous mineral waters	0.9% sodium chloride	In each group (4) 1 time per day, 10-12 minutes 12-15 days	-	Quantitative test	Quantitative test	Quantitative test
Mitsunobu F. et al.[18]	1998	Study in parallel groups	1 ml potassium iodide salt solution inhalations	-	30 minutes 1 time per day, 5 times per week	-	-	-	-
Mitsunobu F. et al.[15]	1997	Study in parallel groups	Inhalations of radon waters in complex therapy Onsen	-	30 minutes 1 time per day 5 times per week	–	Quantitative test	Quantitative test	Quantitative test
Corradi M. et al.[45]	2012	Study in parallel groups	Sodium chloride bromine-iodine thermal mineral water	Healthy people, not been exposed to inhalation	30 minutes, daily, 1 time per day, for 12 consecutive days				

Ashida K. et al.[29]	2003	Study in parallel groups	Inhalations of mineral waters in complex therapy	–	30 minutes, 1 per day, 5 per week	–	Quantitative test	Quantitative test	Quantitative test
Ashida K. et al.[25]	2000	Study in parallel groups	Inhalations of mineral waters in complex therapy	–	30 minutes, 1 per day, 5 per week	–	Quantitative test	Quantitative test	Quantitative test
Okamoto M. et al.[24]	2003	Cohort study	Inhalations of mineral waters in complex therapy	–	30 minutes, 1 per day, 5 per week, for 8 weeks	-	Quantitative test	Quantitative test	Quantitative test
Okamoto M. et al.[14]	1996	Cohort study	Inhalations of mineral waters in complex therapy	–	30 minutes, 1 per day, 5 per week	–	Quantitative test	Quantitative test	Quantitative test
Tanizaki Y. et al.[19]	1992	Cohort study	1 ml potassium iodide solution inhalations	-	30 minutes, 1 per day, 5 per week	-	Quantitative test	Quantitative test	Quantitative test
Tanizaki Y. et al.[23]	1986	Cohort study	Complex sanatorium-and-spa treatment including inhalation of 1 ml of potassium iodide solution	–	30 minutes, 1 time per day, 5 times per week	–	Quantitative test	Quantitative test	Quantitative test
Tanizaki Y. et al.[28]	1993	Cohort study	Complex sanatorium-and-spa treatment including inhalation of 1 ml of potassium iodide solution	–	30 minutes, 1 time per day, 5 times per week	–	Quantitative test	Quantitative test	Quantitative test

Supplementary Materials: Table 4. Included studies.[32,46]

Author	Year	Jadad, total score	Number of patients total/exposure/control group	Average age: Age range	Duration of treatment	Control points	Inclusion criteria	Exclusion criteria
Zaripova TN.[44]	2014	4	118 30/54/34	between 30 and 60 years	10-12	2 (before, after 10-12 days of the treatment course)	Consent; stable BA of mild and moderate severity	Chronic obstructive pulmonary disease, chronic bronchitis, uncontrolled and severe BA; refusal
Smirnova IN. et al.[42]	2012	3	112 19/17/16/22/10	46.5±0,6	12-15	2 before and after 12-15 days of exposure	Consent; stable BA	Chronic obstructive pulmonary disease, exacerbation of BA; refusal
Mitsunobu F.et al. [18]	1998	3	12 6/6	Median age 56.8	5	3 (before, after 6 months, 1 year after the treatment course)	Consent; stable BA	Exacerbation of bronchial asthma and other diseases, Chronic obstructive pulmonary disease; refusal
Corradi M. et al.[45]	2012	5	20/22.17	Median age 41	12	Before and after treatment	Bronchial disease	Acute respiratory infections within three weeks, and recent use of medication (antihistamines, bronchodilators)
Ashida K. et al.[25]	2000	5	132/-	Median age 60	1 год до 2 лет	Before and after	Bronchial asthma	–

Okamoto M. et al.[14]	1996	5	14/-	-	8 weeks	Before and after	Bronchial asthma	–
Tanizaki Y. et al.[23]	1986	5	20/50/32/21/12/10/9/- In the study groups that are exposed to various mineral waters	–	1 year	Before and after treatment	Bronchial asthma	–

Supplementary Materials: Table 5. Before and after treatment (FEV1 %) (n-461).

Authors	Mineral water	Control group	Exposure group			Control group			Total participants
			M	SD	N	M	SD	n	N
Tanizaki Y. et al., 1992	Inhalations of radon waters in complex therapy Onsen	Before treatment	63.50	10	50				82
			62.00	15.40	32				
		After treatment	70.00	10	50				82
			64.30	14.90	32				
Ashida K. et al., 2000, Ashida K. et al., 2003	Inhalations of mineral waters in complex therapy (Thermal water of hot springs)	Before treatment	42.7	8.91	11				149
			54.7	9	6				
			52.10	14.00	13 2				
		After treatment	49.30	9	11				149
			61.8	8.3	6				
			72.10	14.00	13 2				
Tanizaki Y. et al., 1992	Inhalations of 1 ml potassium iodide solution	Before treatment	60.70	15.70	37				37
		After treatment	66.10	12.5	37				37
F. Mitsunobu et al., 1998 Tanizaki Y., 1986	Complex sanatorium-and-spa treatment including inhalations of 1 ml of potassium iodide salt solution	Before treatment	59.40	15.60	6				31
		Before treatment	65	10.3	25				
		After treatment	70.6	15	25				31
		After treatment	66.30	16.50	6				
F. Mitsunobu et al., 1992	Inhalations of radon waters in complex therapy Onsen	Before treatment	64	10.5	36				36
		After treatment	71.2	10.8	36				
Tanizaki Y. et al., 1993	Complex sanatorium-and-spa treatment including inhalation of 1 ml of potassium iodide solution	Before treatment	68.5	10.8	25				52
		Before treatment	67.4	7.6	36				
		Before treatment	56.1	15.2	21				

		Before treatment	50.3	8.8	12				
		After treatment	71.9	11.6	21				52
		After treatment	70.8	7.4	12				
		After treatment	60.8	10.9	10				
		After treatment	51.6	9.4	9				
Smirnova I. N., 2012	4 types of mineral water 1 time per day in every group, 12 minutes. 12-15 days I Chloride mineral waters II Hydrocarbonated mineral waters III Bromide mineral waters IV Siliceous mineral waters before/after treatment	0.9%NaCl Before/After treatment	57.2 /67.0	5.41/ 3.68	19	62. 0/7 0.5	5.40 /4.5 2	10	84
			58.0/ 68.3	8.63/ 6.76	17				
			58.2/ 61.5	3.72/ 5.33	16				
			45.7/ 66.6	3.31/ 6.06	22				

Supplementary Materials: Table 6. Before and after treatment (FEV in liters) (n-61).

Authors	Mineral water	Control group	Exposure group			Control group			Total participants
			M	SD	N	M	SD	n	n
Mitsunobu F. et al., 1997	Inhalations of radon waters in complex therapy Onsen	Before treatment	1.2	0.31	8				23
		Before treatment	1.11	0.27	4				
		Before treatment	1.14	0.3	5				
		Before treatment	0.97	0.29	6				
		After treatment	1.42	0.44	8				–
		After treatment	1.29	0.36	4				
		After treatment	2.05	0.81	5				
		After treatment	1.15	0.29	6				
Okamoto M. et al., 2003	Inhalations of mineral waters in complex therapy	Before treatment	1.54	0.61	14				14
		After treatment	1.86	0.42	14				–
Corradi M., 2012	Sodium chloride bromide-iodine mineral water	Before treatment	1.7	0.8	7				7
		After treatment	1.9	0.7	7				–
Tanizaki Y., 1989	Complex sanatorium-and-spa treatment including inhalation of 1 ml of potassium iodide salt solution	Before treatment	1. 63	0.21	20				20
		After treatment	1.84	0.23	20				–