British Medical Bulletin, 2023, 1–30
https://doi.org/10.1093/bmb/ldad007

OXFORD

Invited Review

Whole-body cryotherapy as a treatment for chronic medical conditions?

Hanna Tabisz[1], Aleksandra Modlinska[1], Sławomir Kujawski[1], Joanna Słomko[1], and Pawel Zalewski[1,2,*]

[1]Department of Exercise Physiology and Functional Anatomy, Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń, Świętojańska 20, Bydgoszcz 85-077, Poland, and [2]Department of Experimental and Clinical Physiology, Laboratory of Centre for Preclinical Research, Warsaw Medical University, 1b Banacha Street, Warsaw 02-097, Poland

*Correspondence address. Department of Exercise Physiology and Functional Anatomy, Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń, Świętojańska 20, Bydgoszcz 85-077, Poland.
E-mail: p.zalewski@cm.umk.pl

Received 30 November 2022; Revised 12 April 2023; Accepted 19 April 2023

Abstract

Introduction: Whole-body cryotherapy (WBC) is a controlled exposure of the whole body to cold to gain health benefits. In recent years, data on potential applications of WBC in multiple clinical settings have emerged.

Sources of data: PubMed, EBSCO and Clinical Key search using keywords including terms 'whole body', 'cryotherapy' and 'cryostimulation'.

Areas of agreement: WBC could be applied as adjuvant therapy in multiple conditions involving chronic inflammation because of its potent anti-inflammatory effects. Those might include systemic inflammation as in rheumatoid arthritis. In addition, WBC could serve as adjuvant therapy for chronic inflammation in some patients with obesity.

Areas of controversy: WBC probably might be applied as an adjuvant treatment in patients with chronic brain disorders including mild cognitive impairment and general anxiety disorder and in patients with depressive episodes and neuroinflammation reduction as in multiple sclerosis. WBC effects in metabolic disorder treatment are yet to be determined. WBC presumably exerts pleiotropic effects and therefore might serve as adjuvant therapy in multi-systemic disorders, including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Growing points: The quality of studies on the effects of WBC in the clinical setting is in general low; hence, randomized controlled trials with adequate sample size and longer follow-up periods are needed.

Areas are timely for developing research: Further studies should examine the mechanism underlying the clinical efficacy of WBC. Multiple conditions might involve chronic inflammation, which in turn could be a potential target of WBC. Further research on the application of WBC in neurodegenerative disorders, neuropsychiatric disorders and ME/CFS should be conducted.

Key words: cognitive function, neuropsychiatric disorders, neurodegenerative disorders, chronic inflammation, obesity, metabolic disorders, cryotherapy

Introduction

Cryotherapy could be defined as cold exposure in a controlled manner for medical purposes; however, it is not a completely uniform term: various methods have been used to apply low temperatures. Local cold exposure could be provided by, inter alia, crushed ice,[1] ice bag,[2] cold gel pack,[3] and continuous or intermittent circulation of ice water from an insulated container to a pad placed onto the treatment area.[1] Whole-body cryotherapy (WBC) typically involves exposure to very cold and dry air (−110 to −195°C) for a period of 2 to 3 min in a temperature-controlled chamber.[4] Cold water immersion (CWI) applies exposure to the level from lower limbs to the sternum, without head exposure. The temperature of the water circa 4°C is most often provided. Moreover, methods aimed at cold exposure in a more localized way are also used in clinical practice. Table 1 provides information on methods applied in cryotherapy.

Whole-body cryotherapy (WBC) is a controlled exposure of the whole body to cold to gain health benefits.[4] There are multiple systems available that provide cryostimulation to the whole body. Cryochambers used in Poland typically include three chambers: the main chamber and two outer chambers. The patients first come into the outer chambers, where the temperature is set at −30 and −60°C, and are exposed here for 30 to 60 s to achieve the acute cold adaptation before entering the main chamber.[4] The temperature in the final inner chamber is typically set at between −100 and −130°C in a clinical setting, and patients are exposed here for up to 3 min.[5]

Lombardi et al. described in a systematic review the application of WBC in healthy athletes.[5] In our previous systematic review, we focused on the application of WBC in a group of older subjects.[6] We have concluded that WBC has the potential in improving performance and decrease symptom severity in some chronic conditions in older subjects as an element of a behavioural programme in combination with regular physical exercise.[6] From the time of publication of this review, multiple publications regarding the role of WBC in a clinical setting in various clinical groups have emerged. This is the first systematic review to examine WBC for various inflammatory diseases and is therefore of great clinical importance as a potential therapeutic option. Therefore, we have decided to perform a systematic review of the available literature on WBC effects in the general patient population.

Methods

Sources of data

The analysis was conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and Cochrane Review.[7,8] The current study was not

Table 1 Methods applied in cryotherapy

	Medium		
	Ice	Water	Gas
Global	Ice water immersion	Cold water immersion	Whole-body cryotherapy
Local	Crushed ice	Local cold water immersion (e.g. upper or/and lower limbs)	Cryosauna
	Ice bags	Circulation of ice water from an insulated container	Local exposure to liquid nitrogen
	Cold gel packs	Vests with water pipes	
		Wetted towel/paper	

registered. However, it was compared with other listings on the international prospective register of systematic reviews (PROSPERO). No systematic review with the aim of assessment of WBC as a treatment for chronic medical conditions in its broad sense was found. Therefore, we carried out a systematic review of published articles on the application of WBC in patients. Two investigators (H.T. and A.M.) independently searched the PubMed, EBSCO and Clinical Key databases for all full-text articles on application of WBC in patients. No publication screening software was used. Searching databases was done on September 22, 2022, using the terms 'whole body' AND 'cryotherapy' OR 'cryostimulation'. Filters applied in PubMed included full-text, clinical trial and randomized clinical trials. Duplicates were omitted during the analysis. Two co-authors (H.T. and A.M.) independently reviewed each publication. All titles of articles were analysed as well as the full text to determine whether they could be included in the review. Discordant opinions were resolved through discussions with the participation of a third investigator (S.K.). Articles were excluded if (i) not being available in English, (ii) examined group consisted of an animal model, (iii) studies in which cooling down was used not in a form of WBC, (iv) examined samples did not include patients with chronic disorders, (v) data described in the paper was produced in a pilot study that was extended in the subsequent paper from the same group, (vi) manuscripts were not available in full text (Fig. 1). Eventually, 51 studies were included in the current review (Fig. 1).

Data extraction

A standardized form was used to extract data from the included studies for the examination of study quality and synthesis of evidence. Extracted information included the following: year of publication; study sample, with inclusion and exclusion criteria; sample size; patient characteristics; WBC programme including its duration, characteristics of exposures including their frequency, duration and intensity (temperature inside the main chamber); outcomes and times of measurement; information for an assessment of the risk of bias. Data extraction forms were completed by one author and checked by a second author. Likewise, quality assessment was performed by one author and checked by a second.

Quality analysis of included studies

To analyse the quality of included studies, the Cochrane Collaboration's tool was used.[9] Quality of each study was assessed by three authors (H.T., A.M., S.K.) and then based on the mode (i.e. the most frequently assigned score) the score for each of dimension in each of the studies was chosen.

Graphical presentation of results

Sankey diagram was created using RAWGraphs 2.0 beta.[10] Edges in blue colour denote the conclusion obtained on patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), green colour

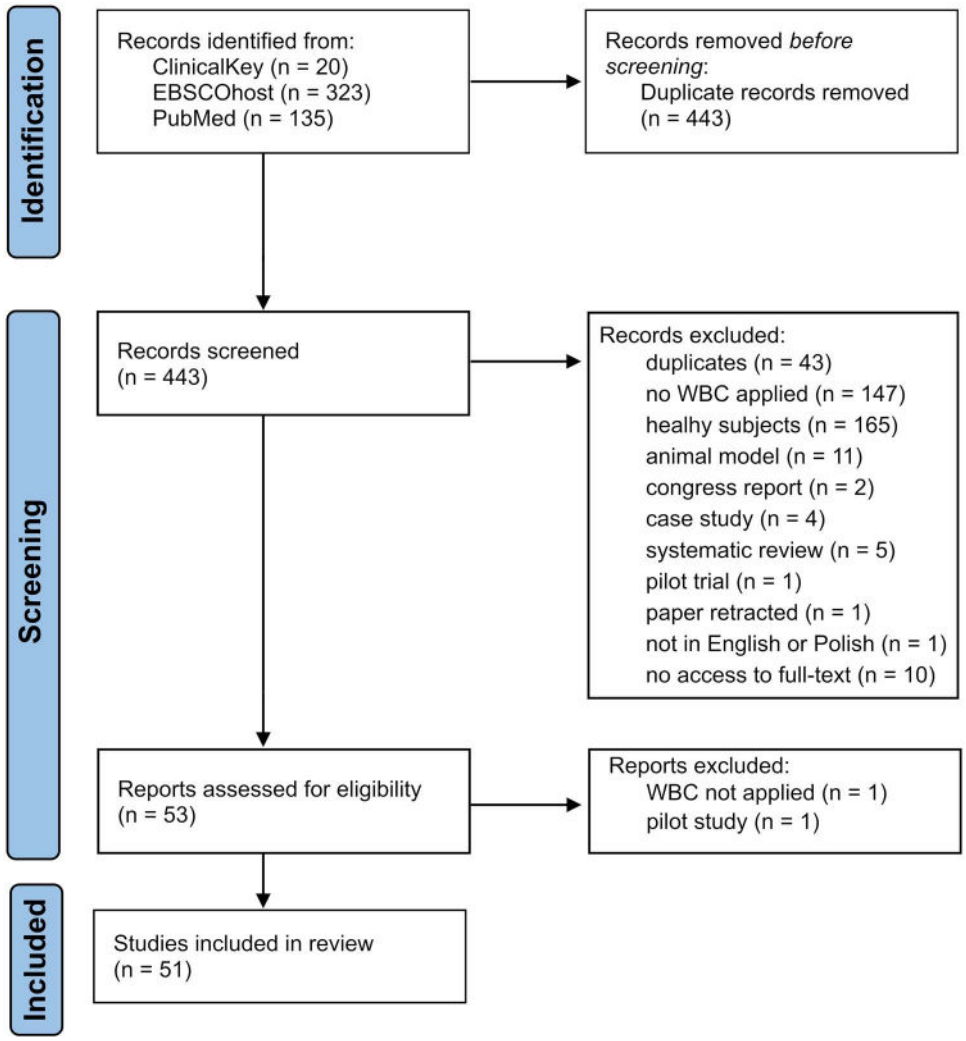

Fig. 1 Flow diagram of the process of selection of study materials.

denotes metabolic disorders, apricot colour denotes nervous system disorders and pink denotes systemic chronic inflammation. The width of the edges is proportional to the sum of the number of participants from particular studies or a study.

Results

Potential of WBC application to treat secondary symptoms in ME/CFS

Table 2 provides summary of reviewed clinical trials. The study provided by our laboratory was the first to provide initial data regarding the effects of WBC in ME/CFS.[11,12] Physical and emotional effort might induce post-exertional malaise in ME/CFS patients. It is well described that a session of physical exercise might induce multiple changes in the cardiovascular and pulmonary systems functioning in patients with ME/CFS suffering from PEM.[13] Therefore, in the study on the effects of WBC, the comparator groups consisted of healthy participants, to compare the effects of WBC on cardiovascular function, autonomic nervous system and cognitive function.[11,12] It has been shown that WBC

Table 2 Summary of reviewed clinical trials

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Bettoni, 2013	WBC group of patients with fibromyalgia (FM); $n = 50$ subjects, all subjects $n = 100$, age range 17–70 years	3 wks	15	5 d/wk	Single WBC session: in an atrium for 30 s at −60°C and the main chamber for 3 min at −140°C	Improvement in quality of life, pain and fatigue, scored by the GH, FSS and VAS
Bryczkowska, 2018	WBC group with multiple sclerosis (MS), $n = 30$ (women), mean age = 45.6, SD = 12.4	4 wks	30	5 d/wk	Single WBC session: in an atrium for 30 s at −60°C and in the main chamber for 3 min at −130°C. After the WBC session, there was a group kinesitherapy for 30 min	Modulation of systemic antioxidant potential in multiple sclerosis patients
Chruściak, 2016	WBC group with osteoarthritis (OA), $n = 50$, mean age = 50.1, SD = 10.9, range 29 to 73	NR	10	NR	Specifics of an applied intervention are not available	Pain perception and its frequency and the number of taken analgesic medications were reduced
Dulian, 2015	WBC group with obesity, $n = 12$, mean age = 38, SD = 9	NR	10	NR	10 days of WBC, single WBC session once a day, in the main chamber for 3 min, at −110°C	The anti-inflammatory effect is shown by reducing the high-sensitivity C-reactive protein (hsCRP) and Hpc concentration
Garcia, 2017	WBC group with trapezius myofascial pain syndrome, $n = 20$, mean age = 40.86 ± 11.04, age range of 23–56 years	5 wks	20	4 d/wk	Single WBC session: in the main chamber for 3 min, at −160°C	Pain perception was reduced
Giemza, 2013	WBC group, $n = 96$ males with chronic, lower back pain > 3 months, mean age = 69.2, range 65–75	3 wks	15	5 d/wk	Single WBC session: in an atrium for 30 s at −60°C, in the main chamber for 3 min at −120°C. After the WBC session, there was a group kinesitherapy for 45 min	Improvement in the range of motion of the lumbar spine and a decrease in the value of action potentials of the erector spinae muscles

(*Continued*)

Table 2 Continued

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Giemza, 2015	WBC group, $n = 80$ males with chronic, lower back pain > 3 months, mean age = 70.1, range 65–77	3 wks	15	Group A: 2 d/wk; group B: 5 d/wk	Single WBC session: in an atrium for 30 s at −60°C, in the main chamber for 3 min at −120°C. There was a group kinesitherapy for 45 min, 5 days a week	Pain perception was reduced
Gizińska, 2015	WBC group of patients with RA (rheumatoid arthritis), $n = 25$, mean age = 55.9, SD = 5.08, IQR = 51–60	2 wks	10	5 d/wk	Single WBC session: passing through an atrium at −10 and −60°C into the main chamber for 3 min at −110°C	Decrease in pain, fatigue, interleukin 6 and tumour necrosis factor, improvement in disease status and functional performance were observed in both groups. Significant improvement in the result of the questionnaire of health assessment was noted in group II
Happe, 2016	2 WBC groups were included, $n = 12$ patients with idiopathic restless legs syndrome (mean age = 56.9, SD = 16.1) in WBC group at −60°C. $n = 11$ patients at sham group at −10°C (mean age = 61.6, SD = 11)	4 wks	10	5 d/wk	Group 1: single WBC session in the main chamber for 3 min at −60°C ($n = 12$); group 2: in the main chamber for 3 min at −10°C ($n = 11$)	Improvements in disease symptoms and quality of life were observed in the −60°C group only. Local cryotherapy improved quality of life and sleep quality but not daytime sleepiness or disease symptoms. Reduction in the number of wake phases per night was observed in the −10°C group
Hirvonen, 2006	2 groups of WBC; a group with active seropositive RA (rheumatoid arthritis), WBC at −60°C, $n = 20$, mean age = 53, range 37 to 65; WBC at −110°C, $n = 20$, mean age = 50, range 21 to 61	1 wk	20	7 d, 3 times/d	Single WBC session at −60 or −110°C. There was an individual kinesitherapy not more than twice a day	WBC at −110°C decreased pain most markedly, but in general is equal to local cryotherapy, used in patients with RA to relieve pain and as an addition to conventional physiotherapy

(*Continued*)

Table 2 Continued

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Hirvonen, 2017	2 groups of WBC with RA (rheumatoid arthritis), WBC at −60°C, $n = 18$, mean age = 53, SD = 9; WBC at −110°C, $n = 17$, mean = 50, SD = 9	1 wk	20	7 d, 3 times/d	Single WBC session for 2 min at −60 or −110°C	WBC at −110°C caused an increase in TRAP (total peroxyl radical trapping antioxidant capacity of plasma) during the first treatment, but not through other modalities There were no significant changes with oxidative stress or adaptation
Klemm, 2021	WBC group with fibromyalgia (FM), $n = 23$, mean age 46 ± 9.8 years, 66% were female	3 wks	6	2 d/wk	Single WBC session: at −130°C, but the first session 90 s, the second 120 s and from the third session onwards a time of 180 s (3 min)	Pain reduction and decrease of IL-1, IL-6 and IL-10 levels
Klimenko, 2008	WBC group with atopic dermatitis (AD), $n = 18$, 10 men and 8 women, mean age not available	4 wks	12	3 d/wk	Single WBC session: first 2 chambers were meant for precooling (−30 and −60°C), for a very short time, then the main chamber for 1 to 3 min at −110°C	A steroid-sparing effect as it showed an improvement in pruritus and sleep disturbances
Kujawski, 2021	WBC group with CFS, $n = 32$ (26 females), mean age = 36.72 ± 8.4	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C, in the main chamber at −120°C. Exposure time was incremental: 1–3 days for 0.5 min, 4–5 days for 1 min, 6–7 days for 1.5 min, 8–9 days for 2 min and 10 days for 2.5 min. After the WBC session, there was a static stretching exercise session (SS)	Allostatic responses were observed in both groups
Kujawski, 2022	WBC group with CFS, $n = 32$, mean age = 36.7 ± 8.4	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C, in the main chamber at −120°C. Exposure time was incremental: 1–3 days for 0.5 min, 4–5 days for 1 min, 6–7 days for 1.5 min, 8–9 days for 2 min and 10 days for 2.5 min. After the WBC session, there was a static stretching exercise session (SS)	In the WBC group, a decrease in fatigue and an increase in cognitive functions (speed of processing visual information and set-shifting)

(*Continued*)

Table 2 Continued

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Kulis, 2017	WBC group, $n = 22$ women with spondyloarthrosis, mean age = 66.6 years, range: 65–70	2 wks	10	5 d/wk	Single WBC session: in an atrium for 30 s, at −60°C and in the main chamber for 3 min at −120°C. After the WBC session, there was a kinesitherapy that lasted for 40 min in total	A decrease in the indices of erythrocyte elasticity and aggregation was noted in women after combined therapy consisting of WBC and kinesitherapy
Lubkowska, 2015	WBC group with obesity, $n = 30$ (men), mean age = 39.06, SD = 9.36, range 23 to 54	4 wks	20	5 d/wk	Single WBC session: in an atrium for 30 s, at −60°C and in the main chamber for 2–3 min at −120°C. After the WBC session, the subjects exercised 3 times a week (45 min each), twice a week in the gym under the close supervision of an exercise physiologist and once a week a Nordic walking session in an open area	An increase in SOD (superoxide dismutase) activity, a decrease in the level of low-density lipoprotein and triglycerides were observed
Lukasik, 2010	2 WBC groups: $n = 20$ with RA (rheumatoid arthritis) and $n = 17$ with OA (osteoarthritis). The mean age is not available	4 wks	20	5d/wk	Single WBC session: in the main chamber at −140 to −160°C for 2 to 3 min	WBC reduced histamine levels in the blood of patients with rheumatoid arthritis
Ma, 2013	WBC group $n = 15$ patients with AC (adhesive capsulitis) of the shoulder, mean age = 56.1, SD = 6.3, all patients ($n = 30$), age range 47 to 66	4 wks	24	3 d/wk	Single WBC session: in an atrium for 1 min at −50°C and in the main chamber for 2.5 min, and after this back to the atrium at −50°C again for 0.5 min	Both treatments improved the range of motion, pain on the VAS scale and shoulder function. Addition of WBC to standard therapy was more effective in terms of improvement of pain, range and the results of a questionnaire on functional limitation and pain of the shoulder

(*Continued*)

Table 2 Continued

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Miller, 2010	WBC group with multiple sclerosis (MS) $n = 16$, 11 females and 5 males, mean age = 43.2, SD = 11.2	2 wks (3 cycles with a 3-month break after each cycle)	30	5 d/wk	Single WBC session: in an atrium at −60°C, and in the main chamber, with temperatures from −110 to −160°C for 2–3 min. The last cycle of WBC was connected with 14 days of supplementation of 10 mg of melatonin taken every evening at 6 p.m.	An increase of TAS (total antioxidative status), but not in antioxidative enzymes: SOD (superoxide dismutase) and CAT (catalase). Supplementation of melatonin with WBC led to an increase in the activity of SOD and CAT
Miller, 2011	WBC group with MS (multiple sclerosis), $n = 22$, 15 females and 7 males, mean age = 42.2 (SD = 15.2)	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C, and in the main chamber, with temperatures between −110 and −160°C for 2–3 min	An increase of TAS (total antioxidative status), but not in antioxidative enzymes: SOD (superoxide dismutase) and CAT (catalase)
Miller, 2013	WBC group with SPMS (multiple sclerosis patients with secondary progressive clinical form), $n = 22$, mean age = 48.6, SD = 12.5	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C, and in the main chamber, with temperatures between −110 and −160°C for 3 min. On the first visit, the participants were exposed to 10 sessions of extremely low temperature (−130°C) in a cryogenic chamber	An increase in UA (uric acid) blood level was observed, so it can improve the life of patients according to the Expanded Disability Status Scale
Miller, 2016	2 WBC groups: MS (multiple sclerosis) patients with chronic fatigue, divided into high-fatigue group, $n = 24$ (mean age = 55.6, SD = 4.2) and low-fatigue group, $n = 24$ (mean age = 55.7, SD = 3.2)	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C, and in the main chamber, with temperatures between −110 and −160°C for 2–3 min	Improvement in the functional status and the feeling of fatigue in both groups, greater changes were in the high-fatigue group

(*Continued*)

Table 2 Continued

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Missmann, 2016	2 WBC groups with rheumatic disorders and elevated blood pressure: pharmacologically treated hypertension group, $n = 5$ (mean age = 61.2, SD = 7.6) and untreated hypertension group, $n = 5$ (mean age = 56.4, SD = 9.1), age range 35–69	3–4 wks	21	NR	Temperature of −15°C, followed by a room with −60°C, and the main chamber with −110°C for approximately 3 min	An increase in blood pressure after WBC was found in the whole sample and the normotensive group
Nugraha, 2014	WBC group with low back pain, $n = 28$, mean age = 54.7, SD = 9.47, range 18 to 65	2 wks	10	5 d/wk	Single WBC session: in the main chamber at −67°C for 3 min	In patients with low back pain, the feeling of pain decreased in both groups, the control group and the WBC group
Pawik, 2019	2 WBC groups: with MS (multiple sclerosis), $n = 20$, mean age = 45.8, SD = 10.1; with MS and gym $n = 20$, mean age = 48.8, SD = 12.2	2 wks	10	5 d/wk	Single WBC session: in an atrium for 30 s and the main chamber at −110°C during the first session and at −160°C on the last day of the study for 3 min. After the WBC group, 2 had physical exercise training with Thera Band, which lasted 60 min per session	Patients with gym showed an improvement in psychosocial well-being. In the group without gym, a reduction of depressive symptoms and improved functional status
Pilch, 2020	WBC group with obese/high body mass, $n = 12$, mean age = 29.08, SD = 4.19	4 wks	20	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s, and in the main chamber at −120°C for 2–3 min (except the first session, which lasted 1 min)	Heat shock protein gene expression changed. There was a significant difference in HSPA1A expression and HSPB1
Pilch, 2021	WBC group, male patients with obesity, $n = 10$, mean age = 22.10, SD = 2.33, range 20–35 years	4 wks	20	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s, in the main chamber at −120°C for 2–3 min	A decrease in TOS/TOC level (pro-oxidative status) was observed and an increase in CAT (catalase) activity

(*Continued*)

Table 2 Continued

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Pilch, 2022	2 WBC groups; WBC group with I class obesity $n = 9$, mean age = 31.1 ± 3.8; WBC group with II class obesity $n = 9$, mean age = 28.4 ± 3.6	4 wks	20	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s, in the main chamber at −120°C for 3 min	A decrease in the LEP (leptin) and TNF-alpha (tumour necrosis factor-alpha) levels was noted, but no other changes in the lipid profile
Ptaszek, 2021	WBC group with MS (multiple sclerosis), $n = 15$ women, mean age = 41.53 ± 6.98 years, range 34–55	4 wks	20	5 d/wk	Single WBC session: in an atrium at −60°C and in the main chamber at −120°C. The time of a single WBC session during the study period was respectively 1.5 min (1 treatment), 2 min (2 treatments), 3 min (3–20 treatments)	Changes in the levels of red blood cells (RBC), haemoglobin (HGB), haematocrit (HCT), elongation index, total extent of aggregation (AMP) and proteins (including fibrinogen)
Radecka, 2021	WBC group with multiple sclerosis (MS), $n = 60$, mean age = 44.95, SD = 11.83	4 wks	20	5 d/wk	Single WBC session: in the main chamber at −110°C. After WBC, the subjects participated in 15-min kinesiotherapy exercises conducted in groups of 5–6 people	Gait improvement and a decrease of fatigue. In the rest of the electromyograms, a decrease of flexor carpi radialis and an increase in extensor carpi radialis amplitude
Rivera, 2018	WBC group with FM (fibromyalgia), $n = 26$, age between 25 and 80 years; range not reported	3 wks	Alternate days (every second day) for 3 weeks	3 d/wk	Single WBC session in the main chamber at −196°C for 3 min	Pain perception was reduced
Romanowski, 2019	2 WBC groups with ankylosing spondylitis (AS), WBC with −110°C, $n = 32$, mean age = 47.1 SD = 10.17; WBC with −60°C, $n = 31$, mean age = 49.7 SD = 11.71	2 wks	8	4 d/wk	Single WBC session: in an atrium at −10°C for 30 s, in the second chamber at −60°C for 30 s, and the main chamber at −110 or −60°C for 3 min. After WBC, there were group exercises (general rehabilitation exercises, stretching) and free active exercises	A reduction of disease activity expressed in BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)

(*Continued*)

Table 2 Continued

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Rymaszewska, 2008	WBC group with depressive and anxiety disorders, $n = 26$, mean age = 47.04, SD = 13.05	3 wks	15	5 d/wk	Single WBC session: in an atrium at −60°C and in the main chamber at a temperature from −160 to −110°C for 2–3 min	A decrease in Hamilton's depression rating scale (HDRS) and Hamilton's anxiety rating scale (HARS)
Rymaszewska, 2020	WBC group with a depressive episode, $n = 30$, 21 females and 9 males, mean age 46.6, range 23–73	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s and in the main chamber at the temperature from −110°C on the first day to −135°C on further days for 2 min	Improvement in life quality, self-assessed mood and disease acceptance, so WBC can reduce mental health deterioration
Rymaszewska, 2021	WBC group with MCI (mild cognitive impairment), $n = 33$, mean age was 65.97 (±6.94)	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s and in the main chamber at the temperature from −110°C on the first day to −135°C on further days for 2 min	Improvement in mood, short-term memory, orientation and a reduction of BDNF (brain-derived neurotrophic factor) level
Senczyszyn, 2021	WBC group with SCD (subjective cognitive decline) and MCI (mild cognitive impairment), $n = 30$, mean age = 71.1, SD = 6.9	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s and in the main chamber at the temperature from −110°C on the first day to −130°C on further days for 2 min	Computerized cognitive training, in combination with WBC, leads to a reduction of depressive symptoms, improvement in general cognitive functioning, verbal fluency, learning ability and short-term memory, long-term memory and information processing
Sieklucka, 2019	WBC group with rheumatoid arthritis (RA), $n = 25$, mean age = 43.6, SD = 10.1	NR	20 treatment days	NR	Single WBC session: in an atrium at −60°C for 30 s and in the main chamber at a temperature from −120°C on the first day to −140°C on further days for 2 min	Reduction of C-reactive protein (CRP)
Stanek, 2005	WBC group with ankylosing spondylitis, $n = 16$, mean age: 47.4 ± 4.7	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C for 60 s and in the main chamber at −120°C	Increase in spine mobility

(*Continued*)

Table 2 Continued

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Stanek, 2018	WBC group with ankylosing spondylitis (AS), $n = 16$, mean age = 46.63, SD = 1.5	2 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s and in the main chamber at −120°C for 3 min	Decrease in the plasma hsCRP level, oxidative stress markers, Bath Ankylosing Spondylitis Diseases Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI)
Straburzyńska-Lupa, 2018	2 WBC groups with ankylosing spondylitis (AS), WBC with −60°C, $n = 21$, mean age = 50.8, SD = 12.24; WBC with −110°C, $n = 23$ mean = 47.7, SD = 9.97	2 wks	6	3 d/wk	Single WBC session: in an atrium at −10°C for 30 s, in the second chamber at −60°C for 30 s, and the main chamber at −110 or −60°C for 3 min. After WBC, there was a 30-min exercise therapy programme	Increase of the concentration of thiobarbituric acid reactive substances (TBARS), lower BASDAI, ASDAS-CRP and the IL-8 concentration
Straub, 2009	2 WBC groups with RA (rheumatoid arthritis) with or without glucocorticoids were exposed to WBC at −60°C, $n = 11$, mean age = 55.7, SD = 2.4 or −110°C, $n = 8$, mean age = 50.6, SD = 4.0	1 wk	20	7 d/wk	Single WBC session at −60°C for 2 min or at −110°C for 2 min	In patients with glucocorticoids, an inadequate cold stress response was noted
Szczepańska-Gieracha, 2013	2 WBC groups, WBC group 1 with spinal pain syndromes ($n = 34$), mean age 47.2 ± 12.4. WBC group 2 with peripheral joint disease ($n = 21$), mean age 50.2 ± 11.5	NR	10	NR	WBC sessions: from 1 to 2 min in the first two sessions to 3 min during the following eight sessions	Improvement of quality of life, mood and well-being
Varallo, 2022	WBC group with fibromyalgia and obesity, $n = 20$ female, mean age: 52.82 ± 7.78, range 18 to 65	2 wks	10	5 d/wk	Single WBC session: in the main chamber at −110°C for 2 min. After WBC, there was a rehabilitation programme, which lasted 3 h	Decrease in the severity of pain, depressive symptoms, disease impact and improvement of quality of sleep

(*Continued*)

Table 2 Continued

The first author, year	WBC group *N* (mean age ± SD)	Details of WBC protocols				The main outcome
		Time	No of exposures	Frequency	Methods of WBC	
Vitenet, 2018	WBC group with fibromyalgia syndrome (SFM), $n = 11$, mean age = 55, SD = 10	2 wks	10	5 d/wk	Single WBC session: in the main chamber at −110°C for 3 min	Improvement of health-reported quality of life was observed and what is important, the effect lasted for at least 1 month
Wiecek, 2019	WBC group with MetS (metabolic syndrome) and menopause, $n = 37$ women, mean age = 62.00	4 wks	20	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s and in the main chamber at −130°C for 3 min. After WBC, patients entered the room at 20–22°C and remained there for 20 min	Reduction in asprosin concentration
Wiecek, 2020	WBC group, $n = 19$ menopausal women with MetS (metabolic syndrome), mean age: 61.53 ± 3.99	4 wks	20	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s and in the main chamber at −130°C for 3 min	Decrease in the percentage of the total, trunk and android fat in the MetS group
Wyrostek, 2021	WBC group with high body fat percentage, $n = 14$, men, mean age = 29.64 ± 4.13	4 wks	20	5 d/wk	Single WBC session: in an atrium at −60°C for 30 s and in the main chamber at −120°C for 2–3 min	Differences in blood cells
Ziemann, 2013	2 WBC groups, WBC in obese patients with higher cardiorespiratory fitness: $n = 7$ mean age not reported; WBC with lower cardiorespiratory fitness, $n = 7$, mean age not reported	4 wks	10	5 d/wk	Single WBC session: in an atrium at −60°C for 20–30 s and in the main chamber at −110°C for 3 min	Decrease of concentrations of pro-inflammatory cytokines in the LCF and an increase of anti-inflammatory cytokine IL-10 in both groups

SD, standard deviation; IQR, interquartile range; NR, not reported.

might significantly affect dynamic control of homeostatic balance indicated by a change in network physiology after 10 sessions of WBC.[11] WBC led to a decrease in autonomic nervous system function symptom severity as well as improvement in processing speed of visual stimuli as well as in the set-shifting.[12] Further studies should assess the effects of WBC on patients with ME/CFS with higher severity as well as the sustainability of its long-term effects.

WBC effects on chronic disorders involving nervous system dysfunction

Rymaszewska et al. in their ground-breaking research assessed the effects of WBC on cognitive function in 21 patients suffering from mild cognitive impairment (MCI). Participants were assessed at three timepoints: at baseline, just after the WBC programme and after 2 weeks of follow-up. Multiple neuropsychological tests were used to evaluate cognitive function outcomes. In addition, levels of different interleukins (IL), such as IL-6, IL-8 and IL-10, but also brain-derived neurotrophic factor (BDNF) and NO were assessed.[14] Results of the initial report were confirmed in the subsequent randomized clinical trial.[15] WBC led to improvement in immediate recall and orientation in patients with MCI.[14] In the study of Senczyszyn et al., the effects of WBC combined with computerized cognitive training on cognitive function were assessed in adults with subjective cognitive decline and mild cognitive impairment.[16] WBC combined with computerized cognitive training led to an improvement in global cognitive function, verbal productivity, learning ability, immediate and delayed memory, attentional control and information processing. In addition, a decrease in the severity of depressive symptoms was noted.[16]

Tomaszewska et al. showed that WBC has the potential to treat patients as an adjuvant therapy in patients with depressive and anxiety disorders.[14] In another study by Rymaszewska et al., WBC reduced the severity of symptoms in patients with the diagnosis of depression.[17] Improvement was maintained after 2 weeks of the end of the WBC programme.[17]

WBC programme effects have been assessed in restless leg syndrome. WBC led to a decrease in periodic leg movements during sleep and wakefulness. Disruption of sleep diminished and increased total sleep time. In addition, WBC improved the quality of life as well as decreased daytime sleepiness.[18]

WBC effects on chronic disorders involving chronic inflammation of nervous system dysfunction

Among all the articles which were analysed, eight of the identified studies have assessed the role of WBC in patients with multiple sclerosis (MS).[19–26] Byczkowska et al. noted an improvement in systemic antioxidant potential.[19] Somewhat in line, Miller et al. observed that WBC improved total antioxidative status; however, no changes in superoxide dismutase and catalase were observed.[20] In the following study, Miller et al. noted that TAS improved more in depressive MS patients versus non-depressive.[21] In a study by Pawik et al., WBC was combined with a resistance exercise programme with the application of Thera Bands.[24] Combined intervention reduced anxiety and depressive symptoms in studied patients with MS.[24] In addition, WBC seems to increase the level of uric acid in MS patients, which is one of the potential biomarkers in MS.[22] In contrast, no significant effect of a series of 20 WBC sessions on changes in biochemical parameters related to blood examination in women with MS was noted.[25] WBC decreases the severity of symptoms in patients with multiple sclerosis with chronic fatigue, while greater effects were noted in the high-fatigue in comparison to the low-fatigue group.[23] In line with the results, Radecka et al. noted improvement in the function of skeletal muscle as well as reduction in fatigue in MS patients after WBC.[26]

The effects of WBC were assessed in five of the identified studies.[27–31] Bettoni et al. noted a positive influence of WBC on quality of life as well as pain and fatigue severity.[27] In addition, in the study of Vitenet et al., an improvement in quality of life related to health was noted in response to WBC in FM patients.[31] In line with that study, Rivera et al. also noted a symptomatic improvement in patients with FM after WBC.[29] Therefore, WBC was suggested by the authors as a potential adjuvant therapy in FM treatment.[29] In the study of Klemm et al., it was observed that FM patients showed a significantly different response in IL1, IL-6 and IL-10 levels in response to WBC compared to healthy controls.[28] The authors proposed that the change in the cytokine profile of patients with FM might potentially explain the clinical efficacy of WBC in FM patients.[28] Adding WBC to a multimodal treatment led to a greater decrease in disease impact and symptom severity reflected in the decrease of pain and depression symptoms and improvement of sleep quality.[30]

WBC effects in metabolic disorders

Dulian et al. showed that treating obese patients would reduce levels of high-sensitivity C-reactive protein (hsCRP) and hepcidin, which contributes to the anti-inflammatory nature of this treatment.[32]

In a study on obese patients by Lubkowska et al., the authors noted a significant reduction in triglyceride and low-density lipoprotein (LDL) levels in response to the intervention, with a slight increase in high-density lipoprotein (HDL) levels. It was noted that superoxide dismutase activity increased significantly after successive sessions of whole-body cryostimulation. In the case of catalase, a significant, gradual decrease in its activity was noted.[33]

Plich et al. in their first study on the effect of WBC on obese patients showed a significant reduction in fat mass and percentage of body fat and body weight of patients. C-Reactive protein concentrations were significantly higher at the start of the first session and after 10 treatments, but not after completing 20 sessions.[34] In a subsequent study, Plich et al. attempted to assess the effect of 20 WBC treatments on the blood prooxidant–antioxidant balance in obese individuals. Significantly higher levels of pro-oxidative potential (TOS/TOC) were observed and significantly decreased after a series of WBCs. Cryotherapy had no effect on the level of total antioxidative status (TAS/TAC), which was similar in each group.[35] In a recent study, Plich et al. analysed the relationship between body mass index (BMI) and the difference in whole-body stimulation effects, dependent on the number of treatments in obese men. The study found that 20 WBC treatments showed significant changes in the body composition of the subjects. Between 10 and 20 WBC sessions, a reduction in leptin and tumour necrosis factor α levels was shown. No changes in lipid profile were observed. In addition, however, a positive trend towards recovery of metabolic balance in adipose tissue was evident in subjects with stage I obesity during the study period. In this group of subjects, increased levels of HDL, reduced levels or ratios of HDL/LDL and triglycerides, and significantly reduced levels of visceral adiposity index were observed.[36]

Wyrostek et al. showed that 10 sessions of WBC disrupt the homeostatic state of the body's haematological parameters, whereas after 20 sessions of WBC in obese men they are restored to homeostasis.[37]

Ziemann et al. aimed to evaluate the anti-inflammatory effect of WBC in obese patients. The study showed that cold exposure affected the cytokine profile of the blood. However, the response depended on the physical capacity of the obese men. Concentrations of pro-inflammatory cytokines in the lower cardiorespiratory fitness group decreased by 19, 6.8 and 7.4% in IL-6, resistin and visfatin, respectively. The tumour necrosis factor α in the lower cardiorespiratory efficiency group decreased 4.3-fold from baseline. In the group with higher cardiorespiratory efficiency, the noticeable changes were smaller but significant. The anti-inflammatory cytokine IL-10 increased in both groups. No changes were observed in the leptin and adiponectin levels in either group.[38]

A study by Wiecek et al. investigated the effect of 20 WBC sessions in menopausal women with metabolic disorders. It was observed that after completion of all WBC treatments, the change in the asprosin concentration correlated negatively with risk factors for metabolic disorders such as fasting glucose, leptin/adiponectin ratio and atherogenic index of plasma.[39] In a subsequent study on menopausal women with metabolic syndrome, Wiecek et al. investigated the effect of WBC on body weight composition and blood concentrations of irisin, C-reactive protein and IL-6. After completing 20 WBC treatments, it was noted that the study women had significantly reduced abdominal obesity indirectly through IL-6 and irisin secretion. The authors indicated that WBC could be used as an adjunct in the treatment of the metabolic syndrome.[40]

The effects of WBC were assessed in a group of patients with rheumatic diseases and normal or moderately elevated blood pressure. A significant increase in blood pressure was observed after the application of WBC in the whole trial and patients in the normotensive group. WBC therapy in this group of patients appears to be safe compared to

the adverse blood pressure changes in adults under 70 years of age. The authors suggested that measuring blood pressure before and after any WBC therapy in this patient group is extremely important.[41]

WBC application in disorders involving chronic inflammation

Eight studies compared the impact of WBC on patients with rheumatoid arthritis. Hirvonen et al. showed that topical cryotherapy showed similar results to WBC as an adjunct to therapy and for pain relief. The authors also noted that WBC treatments can cause adverse effects and their availability is less and costs are much higher than topical cryotherapy.[42] In another study, an increase in the total peroxyl radical trapping antioxidant capacity of plasma was observed. This increase was short-lived and WBC treatment did not cause adaptation or significant oxidative stress within a week in rheumatoid arthritis (RA) patients.[43] In a study by Lukasik et al., beneficial effects of WBC were demonstrated, which may be due in part to effects on histamine release, degradation or production.[44] Sieklucka et al. showed that regardless of the type of therapy given, the condition of RA patients improved. A significant reduction in the C-reactive protein (CRP) marker was observed in the group of patients treated with WBC.[45] In a study by Straub et al., a lack of adequate sympathetic response to stress was observed in both RA patients with and without glucocorticoid treatment. In addition, plasma IL-6 levels were shown to increase under WBC in the group of patients without glucocorticosteroid treatment.[46] In a study by Gizinskaet al., it was shown that regardless of the type of therapy, similar improvements in disease activity, pain, fatigue, number of steps and walking time over a distance of 50 m were observed in both groups. There were also no differences in significant reductions in tumour necrosis factor α and IL-6. In addition, the traditional rehabilitation group showed better scores on the Health Assessment Questionnaire–Disability Index.[47]

Three studies, two conducted by Giemza et al. and one by Naughara et al., examined the effect of WBC on patients with chronic lower back pain. Naugraha et al. observed that the efficacy of WBC therapy was similar to a group of patients with a temperature of −5°C. WBC showed a positive effect by reducing pain in patients, while treatment at a higher temperature may be satisfactory for this study group.[48]

Giemza et al. observed that in the group of patients who were treated with WBC, there was an increase in the range of motion of the lumbar spine and significantly lower values of erector spinae muscle action potentials in the lumbar region compared to the group of patients who were not treated with WBC.[49] In a subsequent study by Giemza et al., it was shown that WBC applied daily had a greater effect on improving the condition of patients with chronic lower back pain compared to a group of patients who were treated with WBC only twice a week. It was concluded that WBC has a high efficacy in the treatment of this group of patients.[50]

Garcia et al. in their study observed a significant reduction in pain from the first WBC session. They concluded that WBC is a good analgesic for patients with trapezius myofascial pain syndrome.[51]

The effects of WBC were assessed in patients with spondyloarthrosis, where changes in the rheological parameters of blood were assessed. It was noted that only in the group that underwent both WBC and kinesitherapy did the study show a significant reduction in erythrocyte aggregation and elasticity indices.[52]

The effects of WBC were also assessed in a group of patients with ankylosing spondylitis in four of the identified studies. Romanowski et al. showed that the group of subjects who participated in WBC at −110°C achieved reduced disease activity compared to the group of patients without WBC therapy.[53] In a study by Stanek et al., it was assessed that WBC achieved significantly greater improvements in spinal mobility indices compared to a group who received kinesiotherapy alone.[54] In a subsequent study by Stanek et al., the effect of WBC on cardiovascular risk factors in patients with AS was investigated. It was shown that parameter changes were significantly greater in the WBC group, which seems to be a good method of preventing atherosclerosis in this patient group.[55] Straburzyńska-Lupa et al. observed that there was a significant reduction in

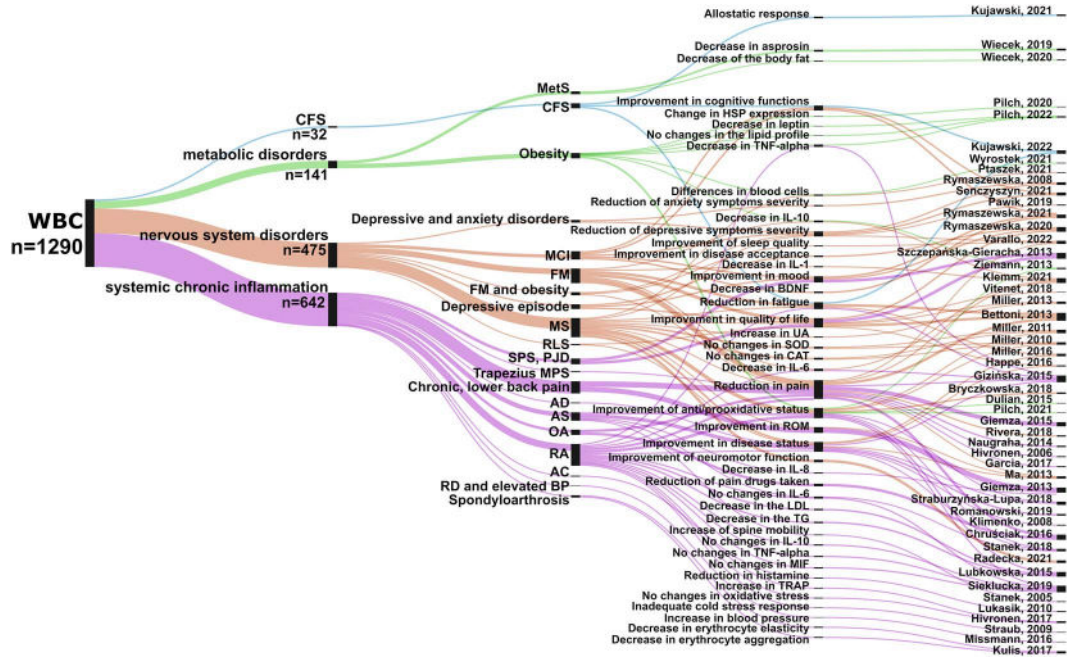

Fig. 2 Summary of the main studies explored. Edges in blue colour denote conclusion obtained on patients with ME/CFS, green colour denotes metabolic disorders, apricot colour denotes nervous system disorders and violet denotes systemic chronic inflammation. The width of the edges is proportional to the sum of the number of participants from particular studies or a study. CFS, chronic fatigue syndrome; MetS, metabolic syndrome; MCI, mild cognitive impairment; FM, fibromyalgia; MS, multiple sclerosis; RLS, idiopathic restless legs syndrome; SPS, PJD, spinal pain syndromes, peripheral joint disease; trapezius MPS, trapezius myofascial pain syndrome; AD, atopic dermatitis; AS, ankylosing spondylitis; OA, osteoarthritis; RA, rheumatoid arthritis; AC, adhesive capsulitis; RD, rheumatic disorder; HSP, heat shock protein; TNF-alpha, tumour necrosis factor-alpha; IL-10, interleukin 10; IL-1, interleukin 1; BDNF, brain-derived neurotrophic factor; UA, uric acid; SOD, superoxide dismutase; CAT, catalase; IL-6, interleukin 6; ROM, range of motion in anatomic part affected by the disease; IL-8, interleukin 8; LDL, low-density lipoprotein; TG, triglycerides; MIF, macrophage migration inhibitory factor; TRAP, total peroxyl radical trapping antioxidant capacity of plasma.

disease activity in all study groups, while only in the WBC patient group the concentration of thiobarbituric acid reactive substances was significantly higher. After WBC therapy, the Bath Ankylosing Spondylitis Disease Activity Index was significantly lower. The authors concluded that WBC therapy had a positive effect on reducing the clinical activity of patients with ankylosing spondylitis.[56]

Ma et al. in their study assessed that the addition of WBC along with other therapeutic interventions in a group of patients with symptoms of adhesive capsulitis resulted in a significant improvement in outcome.[57]

In a study by Chruściak et al., it was observed that the clinical status of patients with osteoarthritis improved significantly after WBC therapy. These patients reported a reduction in the severity and frequency of pain, as well as a reduction in the use of pain medication in this study group, which improved the extent of their physical activity and improved their well-being.[58]

Klimenko et al. noted that the use of WBC in patients with atopic dermatitis has the effect of reducing the need for steroids because this therapy has shown a significant reduction in sleep disturbance and improvement in pruritus.[59]

Figure 2 is a network graph (Sankey diagram) that represents a summary of the analysed studies. Total number of intervention-based studies applying WBC on patients was 1290. Majority of patients

Fig. 3 Risk of bias assessment of analysed studies.

suffered from a disorder related to a systemic chronic inflammation (642 patients) and nervous system disorders (475 patients). MS patients constituted the largest subgroup from the latter group. Improvement in cognitive function after WBC was noted in patients with CFS as well as MCI (Fig. 2). Improvement of prooxidant–antioxidant balance was noted in multiple studies, including interventions applied in patients with nervous system disorders, systemic chronic inflammation and metabolic disorder (obesity) (Fig. 2).

The risk of bias assessments for analysed studies is presented in Figure 3. None of the analysed studies seems to be free of the potential risk of bias. Overall, a high risk of bias and the lack of a control group, randomization and blinding procedure were noted in the majority of the analysed studies.

Discussion

Physiological reaction upon cold exposure such as a decrease in blood flow after local cryotherapy has been observed[60–64]; however, another study did not find any significant change.[65] Research on cold-induced vasodilation has a long history, reaching back to 1930[66]; however, its exact mechanism is as yet unknown.[67] In addition, current research proposes a hypothesis based on mechanisms of vasoconstriction to be underpinned by an increase in adrenergic α-receptor expression rather than sympathetic nerve activity per se, while sympathetic activity is reduced.[67] Therefore, the presence of episodic vasodilation in the response pattern on cold exposure of skin could be explained because of reduced sympathetic activity. In addition to this, disturbances in smooth muscle expression of α2C-receptors could also occur.[67] Some authors propose[68] that forearm postjunctional α-adrenergic vasoconstrictor norepinephrine responsiveness is decreased in older healthy men, and α1-subtype has been proposed to play the main role in this mechanism, compared to the α2. Other authors have noted that tonic decrease in sympathetic α-adrenergic vasoconstriction mediates basal whole-leg blood flow and vascular conductance.[69]

Ho et al. reported a reduction of 29.5% of blood flow in superficial regions (2-mm skin depths),[60] while Knobloch reported a 91% reduction.[64] In addition, blood flow decrease ranged between 45 and 74% reduced blood flow in deep regions (8-mm skin depth).[64] As a result of local vasoconstriction, decreased blood flow would lead to a reduction in the temperature of blood-supplied tissue. Mawhinney et al. showed that blood flow and tissue temperature decreased to a greater degree after CWI compared to WBC.[70] Other authors, using a Thermovision camera, noted differences between local versus WBC cryotherapy; the latter method stimulates more cold receptors.[71] Armstrong et al. showed that CWI decreased rectal temperature approximately twice as fast as air exposure.[72] The largest reductions in mean, minimum and maximum skin temperature occurred immediately after both CWI and WBC.[73] Skin temperature was significantly lower immediately after WBC compared to CWI. Both treatments significantly reduced skin temperature; however, WBC resulted in a greater decrease compared to CWI. This finding is interesting due to the differences in temperature of the medium (−110°C cold air in WBC for 3 min and 40 s vs 8°C water for 4 min) and localization (whole body vs immersion to the level of the sternum).[73] Thermal conductivity of water at 10°C is 0.5846 W/mK, which of air is circa 38.7 times greater than that of air (0.0151 W/mK at −110°C); therefore, CWI ought to be efficient in extracting heat because heat transfer occurs from high to low temperatures.[74]

Gregson et al.[75] examined the effects of two 5-min periods of immersion in 8 and 22°C water on subjects that spent 10 min total in each water temperature. Immersion at both temperatures resulted in similar whole-limb blood flow; more blood was distributed to the skin in the colder water. Butts et al. showed that rectal temperature, heart rate, thermal sensation and muscle pain were not significantly different during exercise for the cold shower and control trials.[76] Thermal sensation was reduced to a greater extent in cold shower conditions and the cooling rate was faster during cold showers compared to the control. Heart rate changes were greater during cold showers compared with control.[76] WBC disturbed muscle function compared to CWI and positively influenced perceptions of training stress compared to CWI. WBC appears to produce a similar influence as CWI resulting in an initial increase in sympathetic activity.[77] The delayed effects of WBC consisted of, inter alia, increased parasympathetic activation.[77–79] Zalewski et al. showed that WBC strongly stimulates the baroreceptor cardiac reflex in response to body fluid changes, which sequentially modulate heart rate and blood pressure control while supine.[80] CWI is presumably more effective in increasing parasympathetic reactivation after physical exercise exposure as there may also be a positive influence by hydrostatic pressure involved compared to WBC[74] and parasympathetic activation may be induced by not only cold-exposing methods that will induce vasoconstriction, such as water immersion at 34.6–35.0°C.[81] The thyroid is responsive

to cold exposure and, in turn, could influence the impact of hormones on cellular metabolism presumably by a decreased sensitivity of mitochondria to ADP and creatine and enzyme creatine kinase of, inter alia, mitochondrial and muscle isoenzyme LAD metabolism.[82]

Cold exposure of the head seems to result in an enriched physiological response compared to cold exposure of the rest of the body alone. Cholewka et al. showed that in response to WBC, the largest temperature decrease was observed on the lower extremities.[83] Moreover, there is a long history of examining the effects of face immersion on the response of many systems, inter alia, autonomic, cardiovascular,[84] respiratory[85] and diving response.[86] Differences in physiological response between cold exposure of the whole body compared to without head exposure could be explained by the dense expression of TRPM[8] receptor on the trigeminal nerve, which could be activated by cold and menthol[87] and by the fact that the head and hands have the highest density of adrenergic fibres, which potentially can influence differences in cardiovascular responses.[88] Moreover, if cold water submersion is taken into account combined with breath holding, then two antagonistic reflexes take place at the same time. The 'cold shock response' is related to activation of sympathetically driven tachycardia, while the 'diving response' involves parasympathetic activation leading to bradycardia.[89] Such 'autonomic conflict' was proposed by the authors as the one of the components of drowning risk.[89] Interestingly, there is a long history of research focused on brain cooling decrease in O_2 consumption, CO_2 production and other indicators of metabolism.[90] Small changes in the temperature of the brain tissue could influence reducing nitrosative and oxidative damage[91] and, in animal models of cardiopulmonary resuscitation, increase glutathione in blood and cerebrospinal fluid and improve the recovery of cerebral function.[92] Interestingly, mild hypothermia therapy with whole-body cooling had a greater effect on the suppression of free-radical production (measured on the base of urinary 8-OHdG level) than selective head cooling.[93]

On the other hand, the effects of local cryotherapy should be underlined. Loap et al.[94] used local cryotherapy on overweight patients. Layers of wetted paper were applied to the lower back and hips of the reclining subject, followed by symmetrical application of six probes placed pairwise, and temperature was set to −10°C, declining to −5°C over 30 min; the application duration was 40 min. The authors propose cold-induced thermogenesis induced by intensive cryotherapy as a way of obesity and overweight treatment. Local cryotherapy reduced leukocyte adhesion in the microvasculature in a rodent model of skeletal muscle injury.[95] Small differences in metabolome were shown between pre- and post-local cryotherapy. Moreover, no changes in the transcriptome or the activation of second messenger system parts were observed: p38 MAPK, ERK1/2, Akt or p70S6K in muscle.[96]

Similarities in mechanisms of action of cryotherapy and physical exercise

Cold-exposure therapy is widely used in sports to hasten recovery after strenuous physical exercise by, inter alia, improving muscle-repairing mechanisms. Presumably, acute response to cold is the reduction of muscle cell breakdown or increased cell permeability caused by oxidant agents produced during physical exercise[97]; therefore, it could be useful in improving recovery processes after physical exercise exposure. A recent review[6] proposed a physical exercise-mimicking role of WBC exposure in a view of a pulsatile expression of myokines, such as IL-6 and irisin. The authors described the following paradox in the consequences of fluctuation of immune system marker level. Chronic higher levels of IL-6, a common feature in obesity, via stimulating the hepatic synthesis of this IL-6, cause pro-inflammatory and potentially deleterious effects. On the contrary, contracting muscle, such as during physical exercise, stimulates the production of IL-6 in spike-like dynamics, which is a powerful anti-inflammatory mediator.[98] Therefore, the potential of WBC as supportive therapy for obesity and type 2 diabetes has been proposed.[6] Context-dependent

release of antioxidant IL-6 while contracting muscles during physical exercise is probably mimicked by cryotherapy.[98]

Some mechanisms of sarcopenia, such as the gradual loss of muscle mass and function in older people, overlap with mechanisms of muscle damage after strenuous physical exercise.[99] Cryotherapy programmes have resulted in the reduction of markers of oxidative stress, dichlorofluorescein and thiobarbituric acid reactive substances, in an animal model of muscle injury.[95] Whole body skin surface cooling before exercise increases lactate accumulation and decreases lactate threshold with sympathetic activation when exercise is performed in the coolest of the three used environments.[100]

Moreover, the activity of sympathetic and parasympathetic branches of the autonomic nervous system shows a similar pattern of dynamics in response to both physical exercise and cryotherapy. As was already mentioned, in the latter case an initial increase in sympathetic activity is noted[77] and increased parasympathetic activation was noted in terms of a delayed effect.[77–79] In line with that, undertaking a bout of aerobic exercise exposure leads to an acute increase in sympathetic heart muscle outflow, while after exposure is finished, a phenomenon called vagal reactivation occurs whose magnitude depends on the intensity of an exercise bout.[101] Sedentary adult males had increased rest-state heart rate variability, which is an indicator of greater vagal activation, after undertaking a 12-week moderate-to-vigorous-intensity exercise programme.[102] In addition, physical exercise and cold pressure test result in an acute and great increase in norepinephrine level and epinephrine to a much lower magnitude.[103] Catecholamine pattern response to stress shows an overlap between physical exercise and the cold pressor test, namely in an elevated norepinephrine level and epinephrine (although the increase of the latter is too much lower in magnitude).[103] Therefore, potentially, a cryotherapy programme, mimicking the action of physical exercise, could induce catecholamine level activity spikes, which could help in minimizing 'β-adrenergic desensitization' due to ageing.

Potential of WBC application to treat secondary symptoms in ME/CFS

WBC presumably exerts pleiotropic effects and therefore might serve as adjuvant therapy in multisystemic disorders, including ME/CFS. After decades of research, there is no biomarker(s) for ME/CFS, nor is there an effective treatment.[104] Post-exertional malaise (PEM) is one of the cardinal symptoms of ME/CFS. Therefore, in general, the most recent guidelines do not advise using therapies that might trigger PEM in susceptible patients. WBC might serve as adjuvant therapy in ME/CFS; however, results obtained by our group need to be replicated on a larger sample size including severe patients in a randomized clinical trial before implementing WBC into ME/CFS treatment guidelines.[12] Further studies should examine WBC effects on PEM triggering in a more variable sample in terms of baseline symptom presence and severity (including patients with severe PEM and cold intolerance).

WBC application in disorders involving chronic inflammation

WBC could be applied as adjuvant therapy in multiple conditions involving chronic inflammation because of its potent anti-inflammatory effects. Those might include systemic inflammation as in RA. What seems interesting is that currently in the field of sports medicine, there is a debate on the application of WBC just after a resistance training session.[105,106] Sessions including resistance training often aim to increase skeletal muscle size (i.e. hypertrophy) and improve strength. Acute inflammation seems to be one of many factors playing a role in the mechanism of skeletal muscle hypertrophy.[107] On the other hand, application of WBC just after sessions including resistance training sessions might have an inflammatory effect and eventually lead to a reduction of gain in skeletal muscle size in response to a physical exercise programme. However, the results of some studies are not fully in line with the above-described notion.[105,106] Therefore, specifics of the application of WBC in the resistance training programme are yet to be determined, i.e. the time

delay between the resistance training session and the application of WBC after.

WBC effects in metabolic disorders

WBC could serve as adjuvant therapy for chronic inflammation in some patients with obesity. Cold exposure could influence an increase in energy expenditure.[108] Both shivering and non-shivering thermogenesis could lead to an increase in resting energy expenditure in skeletal muscles, white adipose tissue and brown adipose tissue.[109] In adipose tissue, cold exposure could influence lipid catabolism and thermogenesis.[108,110] White adipose tissue, as well as brown adipose tissue, might induce metabolism pathways independent of Uncoupling Protein 1.1.[111] In brown adipose tissue, cold exposure might increase oxidative metabolism[110]; however, these mechanisms need to be confirmed in further studies. Even a single exposure to controlled cold temperature, which did not induce shivering, is sufficient to increase resting energy expenditure.[109]

Activity and content of brown adipose tissue are negatively related to BMI.[112,113] Caloric surplus activates the conversion of the brown to white adipose.[114] Therefore, it might be speculated that on the mean, obese patients would be characterized by the lower amount of brown and brown-like adipose cells, which might in turn limit an increase in resting energy expenditure induced by cold exposure.[110,115] On the other hand, cold exposure might lead to an increase in resting energy in white adipose tissue independently of brown adipose tissue.[113] Cold exposure activates mitochondria and resident immune cells that in turn might induce thermogenesis in white adipose tissue.[110,116] However, overall, the role of white adipose tissue in thermogenesis seems to be limited.

In summary, we conclude that the role of WBC in the treatment of obesity is rather limited. First of all, obesity is a phenotype; therefore, the population of those patients might be characterized by a heterogeneity both in pathogenesis and even possibly therapeutic options most effective in a specific subset.[117] Therefore, WBC might be applied as an adjuvant therapy for obesity composed of therapeutic options composed of selected diet modification to induce caloric deficit[118] and hypertrophy training programme, as fat-free mass seems to be a potent contributor to resting energy expenditure.[119] Therefore, by increasing free fat mass, it might be speculated that it would lead to body recomposition and maintenance of a state of a lower percentage of fat mass. Second, the increase in resting energy expenditure might be to a lesser extent in obese patients compared to healthy control. Third of all, there is an effect size of a single cold exposure in resting caloric expenditure (from mean of 1610 kcal/day before vs 1632 kcal/day after the cold exposure).[114] Therefore, even if cold exposure would be applied in the form of a programme and assessing synergistic effects of repeated sessions, still the effect size in increasing resting energy expenditure should be assessed as low.[112] Fourth, as a described effect relates to the exposure that would not induce shivering,[112] probably inducing shivering might increase resting energy expenditure in a significant physiologic manner. Nevertheless, induction of shivering would significantly reduce thermal comfort and therefore it might be speculated that it would lead to a dramatic decrease in adherence rate to the programme, which in turn would decrease its efficacy in increasing resting energy expenditure.

Nevertheless, as we have shown in the current review, WBC could be applied as adjuvant therapy in metabolic disorders to improve its comorbidities and co-existing symptoms, such as chronic inflammation.

WBC effects on chronic disorders involving nervous system dysfunction

WBC probably might be applied as an adjuvant treatment in patients with chronic brain disorders including mild cognitive impairment and general anxiety disorder and in patients with depressive episodes and neuroinflammation reduction as in multiple sclerosis. All of these disorders seem to be of a complex aetiology. In turn, knowledge gaps might have an influence on diminishing efficiency

of applied therapies. Presumably, an inflammatory response might be correlated with general anxiety disorder; however, its exact role in aetiology is still unknown.[120] Selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors present anti-neuroinflammatory effects, which can be part of its therapeutic mechanism noted in some patients with depression.[121] Effects of WBC on nervous system disorders might potentially go beyond its anti-inflammatory effects. However, the background of cognitive improvement after the short-term extreme cold application is largely unknown.[12] Acute cold stimulation effects on the brain might be related to an increase in the ventrolateral prefrontal cortex activity.[122] Acute effects of cold exposure might be related to an increase in parasympathetic cardiac outflow and greater cerebral O_2 extraction.[123]

Potential risks related to the WBC application

Noteworthy, the Food and Drug Administration (FDA) declared in its document published in 2016 describing WBC that 'FDA has not cleared or approved any of these devices for medical treatment of any specific medical conditions'.[124] One of the drawbacks from WBC application approval seemed to be related to insufficient available data regarding WBC effects.[124] As with the majority of pharmacological and non-pharmacological therapies, also WBC might be related to potential side effects. In the abovementioned document, FDA lists frostbites, burns and eye injuries as a consequence of extreme temperatures.[124] In addition, the risk of the therapy might be related to a technique used for cooling of the inside of the chambers. For instance, liquid nitrogen cooling might be related to a higher risk of asphyxiation, and the addition of nitrogen vapours to a chamber lowers the amount of oxygen in the room and can result in hypoxia, or oxygen deficiency.[124] As we have already mentioned in the current review, it seems that WBC exposure might lead to a transient increase in blood pressure. Therefore, the authors of the analysed study suggested monitoring blood pressure before and after any WBC therapy.[39] In general, cold exposure due to cold water swimming might lead to hypothermia, which in turn might be related to an increased risk of cardiac events.[125] In our previous study, we observed a transient decrease in core body temperature in response to WBC exposure.[126] In addition, swimming in cold open water might lead to acute respiratory symptoms, including swimming-induced pulmonary oedema.[127] However, there is rather a scarcity of information in available publications on the adverse effects of WBC. Therefore, further studies are needed to examine the risk factors related to cold exposure.[125] Such studies would help in establishing eventual exclusion criteria for WBC and overall cold-exposure-based therapies and might help in adjusting the therapy to a patient's baseline profile in a precision-medicine approach.

Observed increase of systolic blood pressure is temporary and usually does not reach above 20 mmHg. What is more important is that these changes do not provoke any harm to essentially hypertensive or hypertensive subjects either. Recommended duration of a single WBC session should be about 150–180 s, which is long enough to ease a positive compensation to acute cold exposure.[88]

Limitations of analysed studies

Multiple studies on the effects of WBC in the clinical setting are of low quality; hence, randomized controlled trials with adequate sample size, blinding and longer follow-up periods are needed.

Conclusion

WBC could be applied as adjuvant therapy in multiple conditions involving chronic inflammation because of its potent anti-inflammatory effects. Those might include systemic inflammation as in RA. In addition, WBC could serve as adjuvant therapy for chronic inflammation in some patients with obesity.

WBC probably might be applied as an adjuvant treatment in patients with chronic brain disorders including mild cognitive impairment and

general anxiety disorder and in patients with depressive episodes and neuroinflammation reduction as in multiple sclerosis. WBC effects in metabolic disorder treatment are yet to be determined. WBC presumably exerts pleiotropic effects and therefore might serve as adjuvant therapy in multi-systemic disorders, including ME/CFS.

Multiple research on the effects of WBC in the clinical setting are of low quality; hence, randomized controlled trials with adequate sample size and longer follow-up periods are needed.

Further studies should examine the mechanism underlying the clinical efficacy of WBC. Multiple conditions might involve chronic inflammation, which in turn could be a potential target of WBC.

Authors' contributions

Hanna Tabisz (Conceptualization, Resources, Writing—original draft), Aleksandra Modlinska (Conceptualization, Resources, Writing—original draft), Sławomir Kujawski (Methodology, Resources, Validation, Visualization), Joanna Slomko (Methodology, Visualization), and Pawel Zalewski (Conceptualization, Methodology, Project administration, Writing—review & editing)

Acknowledgements

None.

Conflict of interest statement

The authors have no potential conflicts of interest.

Financial disclosure

None declared.

Data availability

No new data were generated or analysed in support of this review.

References

1. Barber FA. A comparison of crushed ice and continuous flow cold therapy. *Am J Knee Surg* 2000;13:97–101; discussion 102.
2. Bleakley CM, McDonough S, MacAuley D, et al. Cryotherapy for acute ankle sprains: a randomised controlled study of two different icing protocols. *Br J Sports Med* 2006;40:700–5.
3. Airaksinen OV, Kyrklund N, Latvala K, et al. Efficacy of cold gel for soft tissue injuries a prospective randomized double-blinded trial. *Am J Sports Med* 2003;31:680–4.
4. Dębiec-Bąk A, Skrzek A. Porównanie rozkładu temperatury powierzchniowej ciała kobiet i mężczyzn za pomocą termowizji. *Acta Bio-Optica et Informatica Medica Inżynieria Biomedyczna* 2012;1:25–30.
5. Lombardi G, Ziemann E, Banfi G. Whole-body cryotherapy in athletes: from therapy to stimulation. An updated review of the literature. *Front Physiol* 2017;8:258.
6. Kujawski S, Newton JL, Morten KJ, et al. Whole-body cryostimulation application with age: a review. *J Therm Biol* 2021;96:102861.
7. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
8. In: Julian PT Higgins, Sally Green (eds.). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester. John Wiley & Sons Ltd, 2008. https://doi.org/10.1002/9780470712184.
9. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
10. Mauri M, Elli T, Caviglia G, Uboldi G, Azzi M. RAWGraphs: a visualisation platform to create open outputs. In *Proceedings of the 12th biannual conference on Italian SIGCHI chapter*. CH Italy'17, 2017:1–5.
11. Kujawski S, Bach AM, Słomko J, et al. Changes in the allostatic response to whole-body cryotherapy and static-stretching exercises in chronic fatigue syndrome patients vs. healthy individuals. *J Clin Med* 2021;10:2795.
12. Kujawski S, Słomko J, Godlewska B, et al. Combination of whole body cryotherapy with static stretching exercises reduces fatigue and improves functioning of the autonomic nervous system in chronic fatigue syndrome. *J Transl Med* 2022;20:273.
13. Lim EJ, Kang EB, Jang ES, et al. The prospects of the two-day cardiopulmonary exercise test (CPET) in ME/CFS patients: a meta-analysis. *J Clin Med* 2020;9:4040.
14. Rymaszewska J, Ramsey D, Chładzińska-Klejna S. Whole-body cryotherapy as adjunct treatment of

depressive and anxiety disorders. *Arch Immunol Ther Exp (Warsz)* 2008;56:63–8.
15. Rymaszewska J, Lion KM, Stańczykiewicz B, et al. The improvement of cognitive deficits after whole-body cryotherapy – a randomised controlled trial. *Exp Gerontol* 2021;146:111237.
16. Senczyszyn A, Wallner R, Szczesniak DM, et al. The effectiveness of computerized cognitive training combined with whole body cryotherapy in improving cognitive functions in older adults. A case control study. *Front Psych* 2021;12:649066.
17. Rymaszewska J, Lion KM, Pawlik-Sobecka L, et al. Efficacy of the whole-body cryotherapy as add-on therapy to pharmacological treatment of depression—a randomized controlled trial. *Front Psych* 2020;11:522.
18. Happe S, Evers S, Thiedemann C, et al. Whole body and local cryotherapy in restless legs syndrome: a randomized, single-blind, controlled parallel group pilot study. *J Neurol Sci* 2016;370:7–12.
19. Bryczkowska I, Radecka A, Knyszyńska A, et al. Effect of whole body cryotherapy treatments on antioxidant enzyme activity and biochemical parameters in patients with multiple sclerosis. *Fam Med Prim Care Rev* 2018;20:214–7.
20. Miller E, Mrowicka M, Malinowska K, et al. The effects of whole-body cryotherapy on oxidative stress in multiple sclerosis patients. *J Therm Biol* 2010; 35:406–10.
21. Miller E, Mrowicka M, Malinowska K, et al. Effects of whole-body cryotherapy on a total antioxidative status and activities of antioxidative enzymes in blood of depressive multiple sclerosis patients. *World J Biol Psychiatry* 2011;12:223–7.
22. Miller E, Saluk J, Morel A, et al. Long-term effects of whole body cryostimulation on uric acid concentration in plasma of secondary progressive multiple sclerosis patients. *Scand J Clin Lab Invest* 2013;73:635–40.
23. Miller E, Kostka J, Włodarczyk T, et al. Whole-body cryostimulation (cryotherapy) provides benefits for fatigue and functional status in multiple sclerosis patients. A case–control study. *Acta Neurol Scand* 2016;134:420–6.
24. Pawik M, Kowalska J, Rymaszewska J. The effectiveness of whole-body cryotherapy and physical exercises on the psychological well-being of patients with multiple sclerosis: a comparative analysis. *Adv Clin Exp Med* 2019;28:1477–83.
25. Ptaszek B, Teległów A, Adamiak J, et al. Effect of whole-body cryotherapy on morphological, rheological and biochemical indices of blood in people with multiple sclerosis. *J Clin Med* 2021;10:2833.
26. Radecka A, Knyszyńska A, Łuczak J, et al. Adaptive changes in muscle activity after cryotherapy treatment: potential mechanism for improvement the functional state in patients with multiple sclerosis. *NeuroRehabilitation* 2021;48:119–31.
27. Bettoni L, Bonomi FG, Zani V, et al. Effects of 15 consecutive cryotherapy sessions on the clinical output of fibromyalgic patients. *Clin Rheumatol* 2013; 32:1337–45.
28. Klemm P, Becker J, Aykara I, et al. Serial whole-body cryotherapy in fibromyalgia is effective and alters cytokine profiles. *Advances in Rheumatology* 2021;61:3.
29. Rivera J, Tercero MJ, Salas JS, et al. The effect of cryotherapy on fibromyalgia: a randomised clinical trial carried out in a cryosauna cabin. *Rheumatol Int* 2018;12:2243–50.
30. Varallo G, Piterà P, Fontana JM, et al. Is whole-body cryostimulation an effective add-on treatment in individuals with fibromyalgia and obesity? A randomized controlled clinical trial. *J Clin Med* 2022;11: 4324.
31. Vitenet M, Tubez F, Marreiro A, et al. Effect of whole body cryotherapy interventions on health-related quality of life in fibromyalgia patients: a randomized controlled trial. *Complement Ther Med* 2018;36:6–8.
32. Dulian K, Laskowski R, Grzywacz T, et al. The whole body cryostimulation modifies irisin concentration and reduces inflammation in middle aged, obese men. *Cryobiology* 2015;71:398–404.
33. Lubkowska A, Dudzińska W, Bryczkowska I, et al. Body composition, lipid profile, adipokine concentration, and antioxidant capacity changes during interventions to treat overweight with exercise programme and whole-body cryostimulation. *Oxid Med Cell Longev* 2015;2015:1–13.
34. Plich W, Wyrostek J, Major P, et al. The effect of whole-body cryostimulation on body composition and leukocyte expression of HSPA1A, HSPB1, and CRP in obese men. *Cryobiology* 2020;94:100–6.
35. Pilch W, Wyrostek J, Piotrowska A, et al. Blood prooxidant/antioxidant balance in young men with class II obesity after 20 sessions of whole body cryostimulation: a preliminary study. *Redox Rep* 2021;26:10–7.
36. Pilch W, Piotrowska A, Wyrostek J, et al. Different changes in adipokines, lipid profile, and TNF-alpha levels between 10 and 20 whole body cryostimulation sessions in individuals with I and II degrees of obesity. *Biomedicine* 2022;10:269.
37. Wyrostek J, Piotrowska A, Czerwińska-Ledwig O, et al. Complex effects of whole body cryostimulation

on hematological markers in patients with obesity. *PloS One* 2021;4:e0249812.
38. Ziemann E, Olek RA, Grzywacz T, et al. Whole-body cryostimulation as an effective method of reducing low-grade inflammation in obese men. *J Physiol Sci* 2013;63:333–43.
39. Wiecek M, Szymura J, Sproull J, et al. Decreased blood asprosin in hyperglycemic menopausal women as a result of whole-body cryotherapy regardless of metabolic syndrome. *J Clin Med* 2019;8:1428.
40. Wiecek M, Szymura J, Sproull J, et al. Whole-body cryotherapy is an effective method of reducing abdominal obesity in menopausal women with metabolic syndrome. *J Clin Med* 2020;9:2797.
41. Missmann M, Himsl M, Mur E, et al. Impact of whole body cryotherapy at 2110 C on subjects with arterial hypertension. *Arch Immunol Ther Exp (Warsz)* 2016;64:75–82.
42. Hirvonen HE, Mikkelsson MK, Kautiainen H, et al. Effectiveness of different cryotherapies on pain and disease activity in active rheumatoid arthritis. A randomised single blinded controlled trial. *Clin Exp Rheumatol* 2006;24:295–301.
43. Hirvonen HE, Kautiainen H, Moilanen E, et al. The efect of cryotherapy on total antioxidative capacity in patients with active seropositive rheumatoid arthritis. *Rheumatol Int* 2017;37:1481–7.
44. Wojtecka-Lukasik E, Ksiezopolska-Orlowska K, Gaszewska E. Cryotherapy decreases histamine levels in the blood of patients with rheumatoid arthritis. *Inflamm Res* 2010;2:253–5.
45. Sadura-Sieklucka T, Sołtysiuk B, Karlicka A, et al. Effects of whole body cryotherapy in patients with rheumatoid arthritis considering immune parameters. *Reumatologia* 2019;6:320–5.
46. Straub RH, Pongratz G, Hirvonen H, et al. Acute cold stress in rheumatoid arthritis inadequately activates stress responses and induces an increase of interleukin 6. *Ann Rheum Dis* 2009;68:572–8.
47. Gizińska M, Rutkowski R, Romanowski W, et al. Effects of whole-body cryotherapy in comparison with other physical modalities used with kinesitherapy in rheumatoid arthritis. *Biomed Res Int* 2015;2015:1–7.
48. Nugraha B, Günther JT, Rawert H, et al. Effects of whole body cryo-chamber therapy on pain in patients with chronic low back pain: a prospective double blind randomised controlled trial. *Eur J Phys Rehabil Med* 2015;51:143–8.
49. Giemza C, Matczak-Giemza M, Ostrowska B, et al. Effect of cryotherapy on the lumbar spine in elderly men with back pain. *Aging Male* 2013;3:183–8.
50. Giemza C, Matczak-Giemza M, De Nardi M, et al. Effect of frequent WBC treatments on the back pain therapy in elderly men. *Aging Male* 2015;3:135–42.
51. García-Espinoza ÓA, Salas-Fraire Ó, Flores-Garza PP, et al. Analgesic effect of whole body cryotherapy in patients with trapezius myofascial pain syndrome: a longitudinal, non-blinded, experimental study. *Medicina Universitaria* 2017;76:115–22.
52. Kulis A, Misiorek A, Marchewka J, et al. Effect of whole-body cryotherapy on the rheological parameters of blood in older women with spondyloarthrosis. *Clin Hemorheol Microcirc* 2017;66:187–95.
53. Romanowski MW, Straburzyńska-Lupa A. Is the whole-body cryotherapy a beneficial supplement to exercise therapy for patients with ankylosing spondylitis? *J Back Musculoskelet Rehabil* 2019;1:1–8.
54. Stanek A, Sieroń A, Cieślar G, et al. The impact of whole-body cryotherapy on parameters of spinal mobility in patients with ankylosing spondylitis. *Ortop Traumatol Rehabil* 2005;5:549–54.
55. Stanek A, Cholewka A, Wielkoszyński T, et al. Whole-body cryotherapy decreases the levels of inflammatory, oxidative stress, and atherosclerosis plaque markers in male patients with active-phase ankylosing spondylitis in the absence of classical cardiovascular risk factors. *Mediators Inflamm* 2018;2018:1–11.
56. Straburzyńska-Lupa A, Kasprzak MP, Romanowski MW, et al. The effect of whole-body cryotherapy at different temperatures on proinflammatory cytokines, oxidative stress parameters, and disease activity in patients with ankylosing spondylitis. *Oxid Med Cell Longev* 2018;2018:1–8.
57. Ma S-Y, Je HD, Jeong JH, et al. Effects of whole-body cryotherapy in the management of adhesive capsulitis of the shoulder. *Arch Phys Med Rehabil* 2013;94:9–16.
58. Chruściak T. Subjective evaluation of the effectiveness of whole-body cryotherapy in patients with osteoarthritis. *Reumatologia* 2016;6:291–5.
59. Klimenko T, Ahvenainen S, Karvonen S-L. Whole-body cryotherapy in atopic dermatitis. *Arch Dermatol* 2008;6:806–8.
60. Ho SS, Illgen RL, Meyer RW, et al. Comparison of various icing times in decreasing bone metabolism and blood flow in the knee. *Am J Sports Med* 1995;1:74–6.
61. Knobloch K, Kraemer R, Lichtenberg A, et al. Microcirculation of the ankle after Cryo/cuff application in healthy volunteers. *Int J Sports Med* 2006;27:250–5.
62. Knobloch K, Grasemann R, Jagodzinski M, et al. Changes of Achilles mid portion tendon microcirculation after repetitive simultaneous cryotherapy and

compression using a Cryo/cuff. *Am J Sports Med* 2006;12:1953–9.
63. Knobloch K, Grasemann R, Spies M, et al. Intermittent KoldBlue® cryotherapy of 3x10min changes midportion Achilles tendon microcirculation. *Br J Sports Med* 2007;6:e1–7.
64. Knobloch K, Grasemann R, Spies M, et al. Midportion Achilles tendon microcirculation after intermittent combined cryotherapy and compression compared with cryotherapy alone: a randomized trial. *Am J Sports Med* 2008;11:2128–38.
65. Selkow NM, Day C, Liu Z, et al. Microvascular perfusion and intramuscular temperature of the calf during cooling. *Med Sci Sports Exerc* 2012;5:850.
66. Lewis T. Observations upon the reactions of the vessels of the human skin to cold. *Heart* 1930;15:177–208.
67. Hodges GJ, Mallette MM, Cheung SS. Cutaneous neural activity and endothelial involvement in cold-induced vasodilatation. *Eur J Appl Physiol* 2018; 5:971–8.
68. Dinenno FA, Dietz NM, Joyner MJ. Aging and forearm postjunctional α-adrenergic vasoconstriction in healthy men. *Circulation* 2002;11:1349–54.
69. Dinenno FA, Tanaka H, Stauffer BL, et al. Reductions in basal limb blood flow and vascular conductance with human ageing: role for augmented α-adrenergic vasoconstriction. *J Physiol* 2001;3:977–83.
70. Mawhinney C, Low DA, Jones H, et al. Cold water mediates greater reductions in limb blood flow than whole body cryotherapy. *Med Sci Sports Exerc* 2017;49:1252–60.
71. Cholewka A, Stanek A, Wójcik M, et al. Does local cryotherapy improve thermal diagnosis similar to whole-body cryotherapy in spinal diseases? *J Therm Anal Calorim* 2017;2:1155–62.
72. Armstrong LE, Crago AE, Adams R, et al. Whole-body cooling of hyperthermic runners: comparison of two field therapies. *Am J Emerg Med* 1996;4:355–8.
73. Costello JT, Culligan K, Selfe J, et al. Muscle, skin and core temperature after −110°C cold air and 8°C water treatment. *PloS One* 2012;11:e48190.
74. Holmes M, Willoughby DS. The effectiveness of whole body cryotherapy compared to cold water immersion: implications for sport and exercise recovery. *International Journal of Kinesiology and Sports Science* 2016;4:32–9.
75. Gregson W, Black MA, Jones H, et al. Influence of cold water immersion on limb and cutaneous blood flow at rest. *Am J Sports Med* 2011;6:1316–23.
76. Butts CL, McDermott BP, Buening BJ, et al. Physiologic and perceptual responses to cold-shower cooling after exercise-induced hyperthermia. *J Athl Train* 2016;3:252–7.
77. Hausswirth C, Schaal K, Meur YL, et al. Parasympathetic activity and blood catecholamine repsonses following a single partial-body cryostimulation and a whole-body cryostimulation. *PloS One* 2013;8: e72658.
78. Westerlund T, Uusitalo A, Smolander J, et al. Heart rate variability in women exposed to very cold air (−110°C) during whole-body cryotherapy. *J Therm Biol* 2006;31:342–6.
79. Schaal K, Le Meur Y, Bieuzen F, et al. Effect of recovery mode on post-exercise parasympathetic reactivation in elite synchronized swimmers. *Appl Physiol Nutr Metab* 2013;38:126–33.
80. Zalewski P, Klawe JJ, Pawlak J, et al. Thermal and hemodynamic response to whole-body cryostimulation in healthy subjects. *Cryobiology* 2013;3:295–302.
81. Pump B, Shiraishi M, Gabrielsen A, et al. Cardiovascular effects of static carotid baroreceptor stimulation during water immersion in humans. *Am J Physiol Heart Circ Physiol* 2001;6:2607–15.
82. Athéa Y, Garnier A, Fortin D, et al. Mitochondrial and energetic cardiac phenotype in hypothyroid rat. Relevance to heart failure. *Pflugers Arch* 2007; 455:431–42.
83. Cholewka A, Stanek A, Sieroń A, et al. Thermography study of skin response due to whole-body cryotherapy. *Skin Res Technol* 2012;2:180–7.
84. Hayashi N, Ishihara M, Tanaka A, et al. Face immersion increases vagal activity as assessed by heart rate variability. *Eur J Appl Physiol Occup Physiol* 1997; 5:394–9.
85. Andersson JP, Linér MH, Fredsted A, et al. Cardiovascular and respiratory responses to apneas with and without face immersion in exercising humans. *J Appl Physiol* 2004;3:1005–10.
86. Sterba JA, Lundgren CE. Breath-hold duration in man and the diving response induced by face immersion. *Undersea Biomed Res* 1988;5:361–75.
87. Bautista DM, Siemens J, Glazer JM, et al. The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature* 2007;448:204–8.
88. Fonda B, De Nardi M, Sarabon N. Effects of whole-body cryotherapy duration on thermal and cardiovascular response. *J Therm Biol* 2014;42:52–5.
89. Shattock MJ, Tipton MJ. 'Autonomic conflict': a different way to die during cold water immersion? *J Physiol* 2012;14:3219–30.
90. Adelson PD. Hypothermia following pediatric traumatic brain injury. *J Neurotrauma* 2009;26:429–36.

91. Kuo JR, Lo CJ, Chang CP, et al. Attenuation of brain nitrostative and oxidative damage by brain cooling during experimental traumatic brain injury. *Biomed Res Int* 2011;2011:1–8.
92. Zhao H, Chen Y. Effects of mild hypothermia therapy on the levels of glutathione in rabbit blood and cerebrospinal fluid after cardiopulmonary resuscitation. *Iran J Basic Med Sci* 2015;2:194.
93. Ikeda K, Ikeda T, Taniuchi H, et al. Comparison of whole-body cooling and selective head cooling on changes in urinary 8-hydroxy-2-deoxyguanosine levels in patients with global brain ischemia undergoing mild hypothermia therapy. *Med Sci Monit* 2012;7:CR409–14.
94. Loap S, Lathe R. Mechanism underlying tissue cryotherapy to combat obesity/overweight: triggering thermogenesis. *J Obes* 2018;2018:1–10.
95. Siqueira AF, Vieira A, Ramos GV, et al. Multiple cryotherapy applications attenuate oxidative stress following skeletal muscle injury. *Redox Rep* 2017;6:323–9.
96. Sarver DC, Sugg KB, Disser NP, et al. Local cryotherapy minimally impacts the metabolome and transcriptome of human skeletal muscle. *Sci Rep* 2017;1:2423.
97. Banfi G, Malavazos A, Iorio E, et al. Plasma oxidative stress biomarkers, nitric oxide and heat shock protein in trained elite soccer players. *Eur J Appl Physiol* 2006;96:483–6.
98. Lombardi G, Sanchis-Gomar F, Perego S, et al. Implications of exercise-induced adipo-myokines in bone metabolism. *Endocrine* 2016;2:284–305.
99. Schaap LA, Pluijm SM, Deeg DJ, et al. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am J Med* 2006;6:526–e9.
100. Imai D, Takeda R, Suzuki A, et al. Effects of skin surface cooling before exercise on lactate accumulation in cool environment. *Eur J Appl Physiol* 2018;3:551–62.
101. Kaikkonen P, Nummela A, Rusko H. Heart rate variability dynamics during early recovery after different endurance exercises. *Eur J Appl Physiol* 2007;102:79–86.
102. Melanson EL, Freedson PS. The effect of endurance training on resting heart rate variability in sedentary adult males. *Eur J Appl Physiol* 2001;5:442–9.
103. Ward MM, Mefford IN, Parker SD, et al. Epinephrine and norepinephrine responses in continuously collected human plasma to a series of stressors. *Psychosom Med* 1983;6:471–86.
104. National Institute for Health and Care Excellence. Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management. NICE guideline Date: Oct 29, 2021. Accessed 13 Jan 2022. https://www.nice.org.uk/guidance/ng206.
105. Krueger M, Costello JT, Achtzehn S, et al. Whole-body cryotherapy (−110 °C) following high-intensity intermittent exercise does not alter hormonal, inflammatory or muscle damage biomarkers in trained males. *Cytokine* 2019;113:277–84.
106. Broatch JR, Poignard M, Hausswirth C, et al. Whole-body cryotherapy does not augment adaptations to high-intensity interval training. *Sci Rep* 2019;9:1.
107. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. *J Strength Cond Res* 2010;10:2857–72.
108. Vallerand AL, Jacobs I. Rates of energy substrates utilization during human cold exposure. *Graefes Arch Clin Exp Ophthalmol* 1989;58:873–8.
109. De Nardi M, Bisio A, Guardia LD, et al. Partial-body cryostimulation increases resting energy expenditure in lean and obese women. *Int J Environ Res Public Health* 2021;8:4127.
110. Palmer BF, Clegg DJ. Non-shivering thermogenesis as a mechanism to facilitate sustainable weight loss. *Obes Rev* 2017;18:819–31.
111. Flachs P, Rossmeisl M, Kuda O, et al. Stimulation of mitochondrial oxidative capacity in white fat independent of UCP1:a key to lean phenotype. *Biochim Biophys Acta (BBA) Mol Cell Biol Lipids* 2013;1831:986–1003.
112. Pfannenberg C, Werner MK, Ripkens S, et al. Impact of age on the relationships of brown adipose tissue with sex and adiposity in humans. *Diabetes* 2010;59:1789–93.
113. Yoneshiro T, Aita S, Matsushita M, et al. Recruited brown adipose tissue as an antiobesity agent in humans. *J Clin Investig* 2013;123:3404–8.
114. Giordano A, Frontini A, Cinti S. Convertible visceral fat as a therapeutic target to curb obesity. *Nat Rev Drug Discov* 2016;6:405–24.
115. Jung RT, Shetty PS, James WPT, et al. Reduced thermogenesis in obesity. *Nat Cell Biol* 1979;279:322–3.
116. Xu Z, You W, Zhou Y, et al. Cold-induced lipid dynamics and transcriptional programs in white adipose tissue. *BMC Biol* 2019;17:1–21.
117. Piché ME, Tchernof A, Després J-P. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res* 2020;126:1477–500.
118. Ruban A, Stoenchev K, Ashrafian H, et al. Current treatments for obesity. *Clin Med* 2019;3:205–1.
119. Browning MG, Evans RK. The contribution of fat-free mass to resting energy expenditure: implications for

weight loss strategies in the treatment of adolescent obesity. *Int J Adolesc Med Health* 2015;3:241–6.

120. Costello H, Gould RL, Abrol E, et al. Systematic review and meta-analysis of the association between peripheral inflammatory cytokines and generalised anxiety disorder. *BMJ Open* 2019;7:e027925.
121. Dionisie V, Filip GA, Manea MC, et al. The anti-inflammatory role of SSRI and SNRI in the treatment of depression: a review of human and rodent research studies. *Inflammopharmacology* 2021;1:75–90.
122. Okura Y, Rikimaru T. Cold stimuli on the cheeks activate the left ventrolateral prefrontal cortex and enhance cognitive performance. *J Cogn Enhanc* 2020;2:164–75.
123. Theurot D, Dugué B, Douzi W, et al. Impact of acute partial-body cryostimulation on cognitive performance, cerebral oxygenation, and cardiac autonomic activity. *Sci Rep* 2021;1:7793.
124. *Whole Body Cryotherapy (WBC): A "Cool" Trend that Lacks*. Food and Drug Administration. Accessed 13 March 2022, https://www.fda.gov/consumers/consumer-updates/whole-body-cryotherapy-wbc-cool-trend-lacks-evidence-poses-risks
125. Tipton M, Bradford C. Moving in extreme environments: open water swimming in cold and warm water. *Extrem Physiol Med* 2014;3:1.
126. Zalewski P, Bitner A, Słomko J, et al. Whole-body cryostimulation increases parasympathetic outflow and decreases core body temperature. *J Therm Biol* 2014;45:75–80.
127. Hårdstedt M, Seiler C, Kristiansson L, et al. Swimming-induced pulmonary edema: diagnostic criteria validated by lung ultrasound. *Chest* 2020;4:1586–95.