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The impact of whole-body cryotherapy on lipid profile: A systematic review and meta-analysis

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Abstract

Purpose: Whole-body cryotherapy (WBC) is an already proven method of supportive therapy in somatic medicine. Emerging evidence suggests that WBC might exert beneficial effects on lipid profile; however, studies in this field have provided mixed findings.

Objective: We aimed to perform a systematic review and meta-analysis of studies investigating the impact of WBC on lipid profile.

Methods: Electronic databases (the MEDLINE, the ERIC, the CINAHL Complete, the International Pharmaceutical Abstracts as well as the Academic Search Ultimate and the Health Source: Nursing/Academic Edition) were searched from their inception until 25th April 2020. Meta-analysis was performed using random-effects models and Hedges g' was calculated as the effect size estimate.

Results: We identified seven eligible studies. Pooled data analysis revealed significantly lower levels of triglycerides after WBC. Sensitivity analysis also demonstrated significantly lower levels of total cholesterol and low-density lipoproteins (LDL) after removing single studies. Meta-regression analysis showed that lower baseline body mass index (BMI) was significantly associated with greater changes in the levels of total cholesterol and LDL during WBC.

Conclusions: Our findings imply that WBC may exert beneficial effects on the lipid profile in terms of lowering the levels of total cholesterol, LDL and triglycerides. Lower BMI may predict a greater improvement of lipid profile during WBC. However, caution should be taken as to the way our results are being interpreted due to low number of studies and considerable methodological heterogeneity of studies included in our meta-analysis.

Key words: whole-body cryotherapy, whole-body cryostimulation, cold air exposure, fatty acids, lipid profile, cholesterol

List of Abbreviations

AS-Ankylosing Spondylitis

BMI – Body mass index

CONT-Control Group

$GABA_A$ – Gamma-aminobutyric acid receptor

HDL - High-density lipoproteins

LDL- Low-density lipoproteins

MS-Multiple Sclerosis

TC – total cholesterol

WBC-Whole Body Cryotherapy

Introduction

Cholesterol is a sterol synthesized by various tissues. It is an essential component of human cell membranes, where it plays an important role in intercellular transport, cell signaling, and neural transmission. Cholesterol itself can impact gating of ion channels, such as nicotinic acetylcholine receptor, $GABA_A$ receptor and the inward-rectifier potassium ion channel. Furthermore, cholesterol is a precursor for synthesis of vitamin D, bile acids and all steroid hormones, such as cortisol, aldosterone as well as sex hormones[1]. There are two main types of lipoproteins involved in the transport of cholesterol. Low-density lipoproteins (LDL) transport cholesterol from the liver to peripheral tissues, while high-density lipoproteins (HDL) transport cholesterol from peripheral tissues to the liver. Apart from the measurement of LDL and HDL, routine clinical practice is also based on the assessment of triglycerides and total cholesterol levels. Triglycerides are esters of fatty acids and glycerol, which represent the main component of adipose tissue and serve as the human energy storage.

Dyslipidemia is a major death cause in the world. Over 2.6 million deaths per year worldwide - 4.5% of total deaths in Europe alone. Over 50% adults from both sexes have raised cholesterol level[2]. High cholesterol (norms of total blood cholesterol value should be below 200mg/dL) values significantly increase possibility of cardiovascular diseases and dementia. To date, various pharmacological interventions have been developed and include statins, fibrates or cholesterol absorption inhibitors. Although these interventions have been found effective, their adverse effects might outweigh the benefits. Consequently, alternative interventions might be needed in some clinical situations.

Emerging evidence indicates that whole-body cryotherapy (WBC) might be beneficial in improving the lipid profile. Importantly, WBC is a series of repeatable application (usually for 2-3 min) of extremely low temperature (below -110°C)[3] on the whole body surface to provoke positive physiological and immunological responses of the human body. Cryochambers (for 4-5 individuals) are usually divided into two compartments: entryway with temperature between -10 °C and - 60 °C and the chamber with the temperature between - 120 °C to -160 °C[4]. Cold therapy treatment is a treatment with a long tradition as first applications of extremely low temperature appeared about 5000 years ago in Egypt. It is also important to note the Japanese contribution to the development of WBC led by Toshiro in 1970s. He was the first to successfully construct a cryogenic chamber to treat rheumatoid arthritis[5].

Whole-body cryotherapy (WBC) is an already proven method of supportive therapy in somatic medicine. Due to cold-induced analgesia, each WBC session is often followed by kinesiotherapy. Apart from rheumatism, it is used to treat neurological diseases, e.g. multiple sclerosis, chronic back pain, fibromyalgia, ankylosing spondylitis and biological rejuvenation in athletes[2]. Application of cold temperature exerts various beneficial effects on the human body, including muscle damage recovery. It activates autonomic nervous system, constricts blood vessels to improve blood circulation, and also impacts hormonal and immune responses. In addition, WBC can improve biochemical parameters in the human blood and the antioxidative system of red blood cells[6]. It has also been suggested that WBC can be used as an add-on treatment for mental disorders, mainly depression[7,8]. Moreover, WBC can activate various processes that maintain thermal homeostasis[9].

The release of catecholamines during WBC may induce liver glycogenolysis and lipolysis[9]. Low temperatures may also induce hepatic enzymes involved in the conversion of cholesterol to bile acids. Indeed, Worthmann et. al. demonstrated cold-induced conversion of cholesterol to bile acids in mice[10]. In addition, Chevalier et al. found that the gain of brown adipose tissue and increase of insulin sensitivity appear after exposure to low temperature in mice[11]. Altogether, these mechanisms may account for the beneficial effects of WBC on lipid profile alterations. However, human studies in this field have provided mixed findings. Therefore, in this study, we aimed to perform a systematic review and meta-analysis of studies investigating the effects of WBC on lipid profile.

Methods

Search strategy

Our study followed the PRISMA guidelines[12] for systematic reviews and was registered in the PROSPERO database (CRD42020157841). Two independent reviewers (J.R. and K.L.) performed an online search using the following databases: the MEDLINE, the ERIC, the CINAHL Complete, the International Pharmaceutical Abstracts as well as the Academic Search Ultimate and the Health Source: Nursing/Academic Edition (via EBSCO). The following set of keywords was used: (whole-body cryotherapy OR cryotherapy OR whole-body cryostimulation OR cryostimulation OR whole body cryotherapy OR whole body cryotherapy OR 'whole body cryostimulation' OR 'wholebody cryostimulation' or cold air or cryobiology or cryomedicine or cryochamber or cryo-cabin or cold therapy or ‘extreme cold exposition’) AND (Lipid* or Cholesterol or HDL or LDL or Triglycerides or Metabolic). Electronic databases were searched from their inception until 25th April 2020. Additionally, reference lists of eligible publications were reviewed. Any disagreements were resolved through discussion with the third reviewer (B.S.).

Eligibility criteria and data extraction

Studies were included if they met the following eligibility criteria: 1) observational studies providing lipid profile (the levels of total cholesterol, LDL, HDL and triglycerides) before and after WBC; 2) randomized controlled trials investigating the impact of WBC on lipid profile; 3) necessary data (the levels of total cholesterol, LDL, HDL and triglycerides) were available in the article or upon request (if necessary, corresponding authors were contacted). Animal model studies, studies of cell lines, case reports, non-English publications, non-original publications (commentaries, editorials, hypotheses, letters, reviews and study protocols), meta-analyses, studies addressing the impact of cryo-saunas or partial-body cryostimulation/cryotherapy were excluded. The data extracted from eligible publications included: 1) study design; 2) sociodemographic characteristics (age and sex); 3) body mass index (BMI); 4) the levels of total cholesterol, LDL, HDL and triglycerides before and after WBC, and/or the comparative intervention and 5) WBC exposure details.

Quality assessment

Quality assessment of eligible articles was performed according to the method for evaluating primary research papers proposed by Kmet et al.[13]. This checklist was developed to assess the following methodological aspects: 1) sufficient description of objective question; 2) study design; 3) methods of group and source selection; 4) sufficient description of subject characteristics; 5) if interventional and random allocation was possible and described; 6) if interventional and blinding of investigators was possible and reported; 6) if interventional and blinding of subjects was possible and reported; 7) measures of an outcome; 8) if sample size was appropriate; 9) analytic methods (estimation of variance for the main results, inclusion of confounding factors); 10) appropriate report of results and 11) if conclusions were supported by the results. All items of the checklist were assessed by two independent raters according to the following scores: 0 - no, 1- partial, 2 - yes or N/A (not considered in the overall score).

Statistics

Standardized mean differences (Hedges' g) calculated for differences between follow-up and baseline levels of total cholesterol, LDL, HDL and triglycerides represented primary outcome measures. Additionally, standardized mean differences were calculated to compare mean changes in the levels of total cholesterol, LDL, HDL and triglycerides in participants receiving WBC and those undergoing the control intervention. Heterogeneity was evaluated using the Cochran Q test and the I^2 statistics. A leave-one-out sensitivity analysis was performed to investigate whether any single study accounted for heterogeneity. Random-effects models were selected due to anticipated heterogeneity. Meta-regression analysis was performed to investigate whether mean age, BMI, duration of WBC and quality assessment score were associated with effect size estimates. Assessment of publication bias was not performed due to low number of studies (< 10). Results were considered statistically significant if the p-value was < 0.05. Analyses were conducted using the STATISTICA software, version 12.5.

Results

Out of 956 publication records identified, 7 studies were finally included in systematic review and meta-analysis (Figure 1). General characteristics of these studies were provided in Table 1. These studies represented data from 189 adult participants (159 males and 30 females, mean age ranged between 21.7 and 45.9 years). There were 30 women and 159 men involved in total. All studies were conducted in Poland. Two studies involved college-aged men[6,14]. Overall, four studies involved healthy subjects, in which two studies enrolled professional athletes[6,15]. Three studies recruited adults with physical illnesses - one study was conducted on obese and overweight participants [16], another one on patients with ankylosing spondylitis[4] and the third one on involved people with multiple sclerosis diagnosis[17]. The majority of studies represented observational studies[6,15–17] while three studies were randomized control trials[4,14,18]. Across seven studies, there were some differences in the temperature applied during WBC. Four studies applied -120°C, two studies used -130°C and one study was based on -110°C[14]. In the last one, WBC was applied twice a day while in one study WBC was applied every second day[6]. In majority of the studies WBC was performed day by day without weekends (5 days per week). The quality score assessment of included studies ranged between 70 to 95 %.

Total cholesterol

Pooled data analysis revealed no significant changes in the levels of total cholesterol during WBC (Table 2, Supplementary Figure 1). However, sensitivity analysis revealed that changes in the levels of total cholesterol during WBC appeared to be significant (g = -0.31, 95%CI = -0.53 - -0.08, p = 0.008) after removing one study [16]. Meta-regression analysis demonstrated a significant positive correlation between baseline BMI and effect size estimates for changes in the levels of total cholesterol (Table 3). No significant differences in the change of total cholesterol between individuals receiving WBC and those receiving the control intervention were found (Table 2, Supplementary Figure 2). Heterogeneity was significant in the analysis comparing changes in the levels of total cholesterol between participants receiving WBC and those assigned to control interventions (Table 2).

Low-density lipoproteins

Pooled data analysis demonstrated no significant changes in the levels of LDL during WBC (Table 2, Supplementary Figure 3). These changes were significant (g = -0.38, 95%CI = -0.70 - -0.06, p = 0.018) after removing the study by Lubkowska et al.[16]. Similarly, this difference appeared to be significant (g = -0.35, 95%CI = -0.68 - -0.02, p = 0.037) after removing the treatment arm with five WBC sessions from the study by Lubkowska et al.[15]. Meta-regression analysis revealed a significant positive correlation between baseline BMI and effect size estimates for changes in the levels of LDL (Table 3). No significant differences in the change of LDL levels between individuals receiving WBC and those receiving the control intervention were found (Table 2, Supplementary Figure 4). Heterogeneity was significant in all analyses (Table 2).

High-Density Lipoproteins

There were no significant changes in the levels of HDL during WBC in the pooled data analysis. (Table 2, Supplementary Figure 5). These changes remained insignificant even after removing single studies. Meta-regression analysis revealed no significant moderators of effect size estimates (Table 3). No significant differences in the change of HDL levels between individuals receiving WBC and those receiving the control intervention were found (Table 2, Supplementary Figure 6). Heterogeneity was significant in all analyses (Table 2).

Triglycerides

There were significantly lower levels of triglycerides after WBC compared to the baseline levels (Table 2, Supplementary Figure 7). However, after removing the study by Stanek et al.[18] or single WBC treatment arms (10 or 20 WBC sessions) from the study by Lubkowska et al.[15], this effect size estimate was insignificant. No significant moderators of effect size estimates were found. Moreover, no significant differences in the change of triglycerides levels between individuals receiving WBC and those assigned to the control intervention were observed (Table 2, Supplementary Figure 8). Heterogeneity was significant in the pooled analysis of changes in the levels of triglycerides during WBC, and insignificant in the pooled analysis comparing changes in the levels of triglycerides during WBC and control interventions (Table 2).

Discussion

Results of our systematic review and meta-analysis do not provide unequivocal conclusions regarding the efficacy of WBC in terms of improving lipid profile, mainly due to low number of studies and methodological heterogeneity. However, sensitivity and meta-regression analyses suggest that beneficial effects of WBC, with respect to improving lipid profile, may appear in certain populations. Indeed, we found that higher baseline BMI might be associated with a greater potential of WBC to improve lipid profile concerning total cholesterol levels as well as LDL levels. The reduction of total cholesterol and LDL levels after WBC sessions was significant after excluding the study by Lubkowska et al.[16], where overweight and obese men were enrolled. Moreover, a reduction of LDL levels remained significant after excluding the treatment arm with the lowest frequency of WBC exposure (5 sessions) from another study by Lubkowska et al.[15].

The significant reduction of triglycerides was also observed after WBC sessions. However, these findings appeared to be insignificant after excluding the study by Stanek et al.[18] and two treatment arms from the study by Lubkowska et al.[15]. It has to be stressed that Stanek et al.[18] enrolled healthy women who obtained kinesiotherapy session after each WBC. In turn, excluded treatment arms from the study by Lubkowska et al.[15] were based on participants who received more intense WBC treatment with 10 and 20 WBC sessions.

It is also important to note that there were no significant differences in the change of total cholesterol, LDL, HDL as well as triglycerides between participants after WBC and from control groups. However, it should be emphasized that only 3 randomized studies were included, and in all of them, control groups received active intervention in the form of kinesiotherapy applied daily. O'Donovan et al.[19] in the randomized control trial of 64 men found that significant changes of lipid profile can be observed in the high-intensity exercise group. According to the review by Mann et al. [20], healthy participants are able to maintain low levels of LDL and triglycerides together with high levels of HDL being physically active at least 30 minutes daily, 5 days a week. For participants with dyslipidemia, achieving LDL reduction and HDL increase required an increase in this level of activity by progressing to 85% of Heart Rate max combined with moderate- to high intensity resistance training at 75-85% repetition maximum. Systematic reviews by Fikenzer et al.[21] and Mann et al.[20] showed that aerobic exercise reduces elevated levels of total cholesterol, triglycerides and LDL and increases the level of HDL in clinical and non-clinical populations. In final conclusions of the review comparing high intensity with middle intensity exercises, Mann et al.[20] stressed that only increase of HDL levels could be achieved despite of intensity. Therefore, it is of great importance for future studies in this field to include a placebo intervention that might be based on exposure to temperatures that do not have a cryogenic effect.

There are various mechanisms that might underline the beneficial effects of WBC on lipid profile. The study by Vallerand et al. revealed that the human body exposed to cold reacts by increasing its lipid metabolism[22]. It has also been demonstrated that brown adipose tissue plays a major role in the metabolism of triglycerides. Moreover, Yizhen et al.[23] found that brown adipose tissue produces heat by breaking down triglycerides stored in the intercellular lipid droplets during exposure to cold temperature in order to maintain stable temperature in mice[23].

The reviewed and analyzed study protocols differed - especially in exposure temperature and WBC devices used in the studies. One study applied temperature of -110°C[14], four studies applied temperature of -120°C[4,6,16,18] and two applied temperature of -130°C[15,17]. Moreover, experimental groups differed in gender, age and anthropometric characteristics. Only two studies (out of seven) enrolled women[15,17], one study engaged participants with multiple sclerosis[17], one with ankylosing spondylitis[4] and another one - overweight and obese participants[16]. Four among seven studies had fitness program or kinesiotherapy session included in the protocols[4,14,16,18].

It should also be mentioned that the improvement of lipid profile after WBC may be connected with lowering of the inflammatory state, especially in patients with ankylosing spondylitis. Inflammatory response of tissues to WBC is identified with decrease in serum C-reactive protein and seromucoid concentration[24] , as well as with the increased concentrations of anti-inflammatory cytokines[25] .

Our meta-analysis is characterized by some important limitations that need to be discussed. Firstly, the number of eligible studies was relatively low, and thus we were unable to perform additional subgroup analyses. Included studies varied in terms of participants' characteristics, WBC parameters and protocols, additional physical activity afterwards as well as the use of control interventions. A limited number of studies did not allow to test the hypothesis whether various parameters of WBC impact the extent of lipid profile improvement. At this point, it should be noted that only three studies represented randomized control trials. Finally, all studies were performed within Polish populations. Therefore, generalizability of our findings might be limited.

In summary, our findings may lead to cautious conclusions that WBC sessions can be expected to improve lipid profile in healthy participants (based on reported BMI) when using protocols including at least 10 sessions followed by kinesiotherapy. However, randomized control trials including various clinical populations, control interventions and larger samples are still needed to provide unequivocal conclusions. The results of reviewed studies are very promising, and show that WBC is a field of medicine worth exploring in further studies. This is of particular importance as dyslipidemia is considered a civilization disease. Presented results show that WBC can be effective in supporting the treatment of lipid disorders, which are among the most important risk factors of civilization diseases, such as circulatory system diseases and chronic liver diseases.

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Figure 1. Selection of studies.

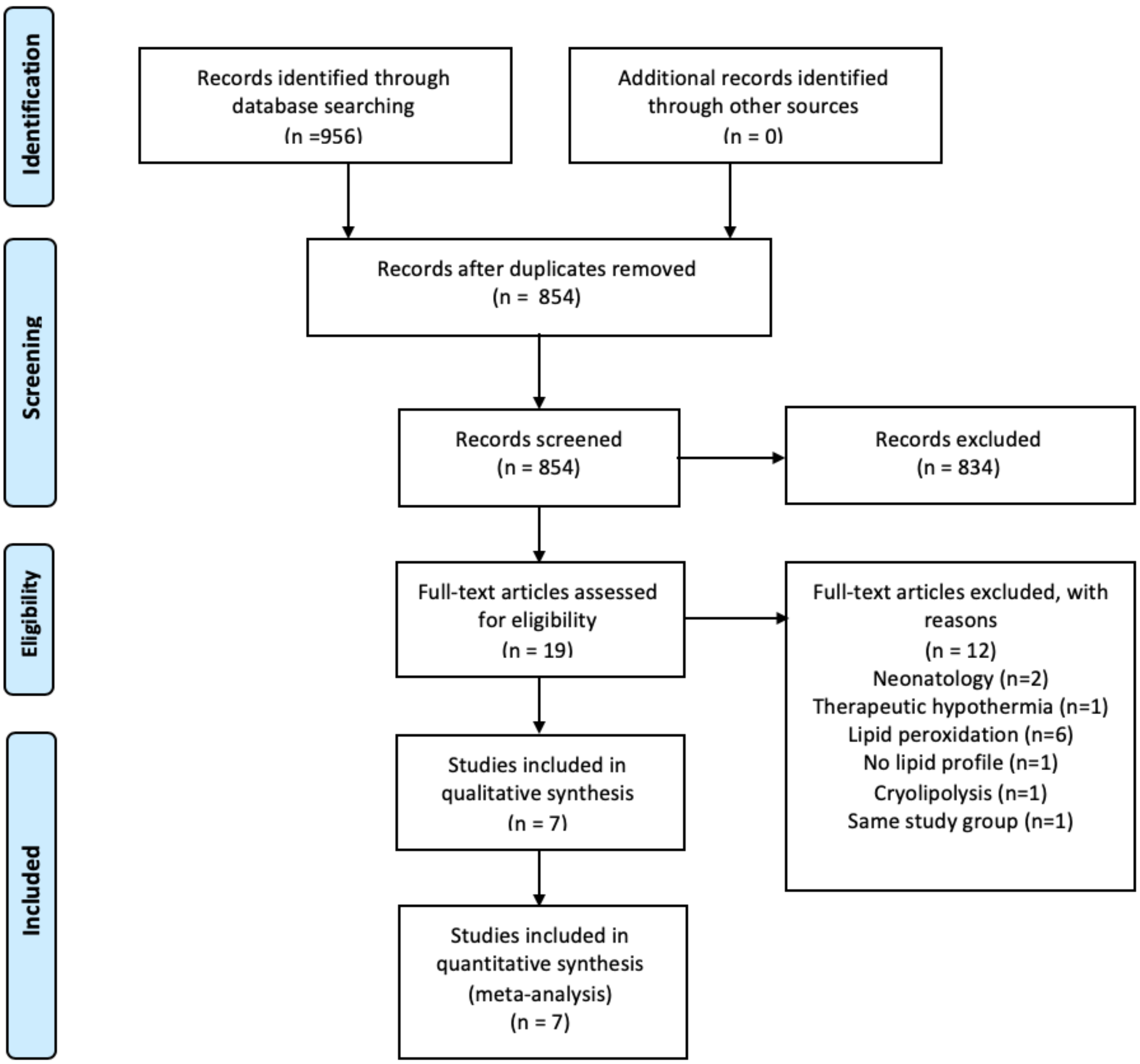

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Table 1. General characteristics of studies included in systematic review and meta-analysis

Authors (year)	**Study design**	**Population (mean age ± SD)**	**Men (%)**	**Procedure & temperature**	**Quality score (%)**
Bryczkowska et al. (2018)	Observational study	30 women with MS (45.6 ± 12.4)	0	30 WBC sessions (3-min a day) Temp: -130°C	84
Kępińska et al. (2016)	Observational study	10 men athletes (22.1±.1.9)	100	12 WBC sessions (3-min a day), every 2nd day for 4 weeks Temp: -120°C	86
Lubkowska et al. (2015)	Observational study	30 overweight and obese men (40 ± 4.0)	100	20 WBC sessions (3-min a day) after 1-month fitness program repeated in the last month of the 6-month study (typical diet) Temp: -120°C	95
Lubkowska et al. (2010)	Observational study	69 men 1st group n=10 (26± 2.5) 2nd group n=39 (31.7±7.9) 3rd group n=20 (34 ± 5.7)	100	1st group - 5 daily WBC sessions (3-min a day) 2nd group - 10 daily WBC sessions 3rd group - 20 daily WBC sessions Temp: -130°C	89
Stanek et al. (2019)	RCT	32 healthy men CONT, n=16 (45.94±1.24) WBC, n=16 (45.63± 1.5)	0	1st group - 10 daily WBC sessions (3-min a day) with a subsequent 60-min kinesiotherapy 2nd group - 10 days of 60-min kinesiotherapy Temp: -120°C	91
Stanek et al. (2018)	RCT	32 men with AS CONT, n=16 (45.94 ± 1.24) WBC, n= 16 (46.63 ± 1.5)	100	1st group - 10 daily WBC sessions (3-min a day) with a subsequent 60-min kinesiotherapy 2nd group - 10 days of 60-min kinesiotherapy Temp: -120°C	93
Ziemann et al. (2014)	RCT	18 men WBC, n = 9 (21.7 ± 0.9) CONT, n = 9 (22.0 ± 2.0)	100	10 WBC sessions (3-min twice a day) after performing the step up/down exercise Temp: -110°C	70

Abbreviations: WBC-Whole Body Cryotherapy; CONT-Control Group; AS-Ankylosing Spondylitis; MS-Multiple Sclerosis

Table 2. Pooled analysis of lipid profile alterations during WBC.

Outcome	k	Meta-analysis			Heterogeneity analysis		
		g	95%CI	p	I^2	Q	P(Q)
TC – after WBC vs. baseline	9	-0.23	-0.52 – 0.06	0.126	46.10%	14.85	0.060
LDL – after WBC vs. baseline	9	-0.30	-0.61 – 0.01	0.054	51.92%	16.64	**0.034**
HDL – after WBC vs. baseline	9	-0.05	-0.37 – 0.27	0.763	55.11%	17.82	**0.026**
TG – after WBC vs. baseline	9	-0.41	-0.77 - -0.04	**0.028**	64.54%	22.56	**0.004**
ΔTC – WBC vs. control intervention	3	-1.58	-3.39 – 0.24	0.088	91.67%	24.02	**< 0.001**
ΔLDL – WBC vs. control intervention	3	-2.12	-4.27 – 0.02	0.052	93.25%	29.64	**< 0.001**
ΔHDL – WBC vs. control intervention	3	0.72	-0.86 – 2.29	0.371	90.58%	21.24	**< 0.001**
ΔTG – WBC vs. control intervention	3	-0.22	-0.95 – 0.52	0.566	64.97%	5.71	0.058

Significant results ($p < 0.05$) were marked with bold characters

k refers to the number of comparisons

Abbreviations: HDL – high density lipoproteins, LDL – low density lipoproteins, TC – total cholesterol, TG – triglycerides, WBC – whole-body cryotherapy

Table 3. Meta-regression analysis of changes in the levels of lipids during WBC.

	Moderator	k	β	95%CI	p	Adj. R^2
TC	Age	9	0.01	-0.03 – 0.04	0.633	
	Number of WBC sessions	9	0.03	-0.01 – 0.06	0.129	30.85%
	Quality of study	9	0.03	-0.02 – 0.08	0.190	16.25%
	BMI	8	0.17	0.07 – 0.27	**< 0.001**	100%
LDL	Age	9	-0.01	-0.05 – 0.02	0.483	
	Number of WBC sessions	9	0.02	-0.02 – 0.06	0.301	
	Quality of study	9	0.02	-0.04 – 0.07	0.540	
	BMI	8	0.15	0.04 – 0.26	**0.010**	80.71%
HDL	Age	9	0.01	-0.03 – 0.04	0.699	
	Number of WBC sessions	9	0.03	-0.01 – 0.07	0.056	50.11%
	Quality of study	9	-0.03	-0.08 – 0.02	0.213	29.31%
	BMI	8	-0.03	-0.13 – 0.06	0.494	
TG	Age	9	-0.03	-0.07 – 0.01	0.150	
	Number of WBC sessions	9	-0.01	-0.05 – 0.05	0.947	
	Quality of study	9	-0.03	-0.09 – 0.03	0.313	
	BMI	8	0.11	-0.08 – 0.29	0.256	

Significant moderators ($p < 0.05$) were marked with bold characters

k refers to the number of comparisons

Abbreviations: HDL – high density lipoproteins, LDL – low density lipoproteins, TC – total cholesterol, TG – triglycerides, WBC – whole-body cryotherapy