Am J Clin Exp Immunol 2024;13(3):68-87
www.ajcei.us /ISSN:2164-7712/AJCEI0155457

Review Article

Assessing the anti-inflammatory effects of whole-body vibration: a meta-analysis based on pre-clinical and clinical evidences

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Received January 15, 2024; Accepted June 6, 2024; Epub June 25, 2024; Published June 30, 2024

Abstract: Background: Whole-body vibration (WBV) is a commonly used physical exercise for disease prevention and rehabilitation. Recent studies indicated the beneficial mechanism of WBV may be associated with its anti-inflammatory potential, however, its regulatory roles on different inflammatory mediators remained controversial. The aim of this study was to perform a meta-analysis to re-confirm the effects of WBV exercise on various inflammatory factors. Methods: The PubMed, EMBASE and Cochrane Library databases were searched up to September 2023 to collect all articles comparing WBV with control (or post-pre trials). The effect size was expressed as the standardized mean difference (SMD) and 95% confidence intervals (CI). Results: A total of 31 eligible studies were included, including 14 pre-clinical and 17 clinical studies. The meta-analysis of pre-clinical studies showed that compared with the control group, WBV exercise could significantly reduce the level of IL-6 (SMD: -1.03, 95% CI: -1.93, -0.13), TNF-α (SMD: -1.36, 95% CI: -2.54, -0.17) (for disease subgroup), IL-1β (SMD: -2.20, 95% CI: -3.24, -1.15), IFN-γ (SMD: -1.91, 95% CI: -2.71, -1.12), IL-4 (SMD: -0.71, 95% CI: -1.39, -0.03) and IL-17 (SMD: -1.32, 95% CI: -2.05, -0.59) overall. Pooling of clinical studies revealed WBV exercise significantly reduced the level of TNF-α (WBV vs control: SMD: -1.11, 95% CI: -2.16, -0.06; post vs pre: SMD: -1.29, 95% CI: -1.91, -0.67), CRP (SMD: -3.59, 95% CI: -6.36, -0.82, P = 0.011) and enhanced the level of IL-10 (WBV vs control: SMD: 2.90, 95% CI: 1.10, 4.71; post vs pre: SMD: 1.75, 95% CI: 0.64, 2.87) and IL-6 (SMD: 0.91, 95% CI: 0.31, 1.52) (healthy subgroup). Conclusion: WBV may be an effective prevention and rehabilitation tool for inflammatory diseases.

Keywords: Whole-body vibration, inflammation, murine models, clinical trials, meta-analysis

Introduction

Physical exercise has been widely accepted as an important non-pharmacological strategy for prevention and rehabilitation treatment of several diseases [1]. However, the adherence of conventional aerobic and resistance exercise is often low (approximately 60%) in populations due to a lack of time, motivation, companionship, access to specialized facilities and poor physical conditions (such as fragility, reduced cognitive function and motor capacity) that leads to the difficulties to perform active exercise [2, 3]. These disadvantages of conventional exercise indicate the requirement of alternative intervention approaches. Whole-body vibration (WBV) involves the exposure of the entire body to mechanical oscillations while the populations stand or sit on a vibration platform [4]. The intensity of vibrations transmitted to the populations can be regulated according to their frequency (5-60 Hz), amplitude (0.5-4 mm), acceleration (0.3 g-8 g) and durations of sessions (5-15 min per session) [4]. This kind of exercise can be assessed at home, in the local community or at rehabilitation units; requires little effort and motivation from the practitioner; needs a low exposure time and is suitable for individuals whom exercise is inconvenient. WBV is therefore suggested as a better alternative exercise. WBV had been applied for rehabilitation treatment of patients with knee osteoarthritis (OA) [5], cerebral palsy [6], metabolic syndrome [7], stroke [8], Parkinson [9] and prevention of falls and fractures in middle-aged and senior people [10, 11], the improvement

https://doi.org/10.62347/LLGY4023

effects of which were confirmed in these meta-analysis studies.

Although the beneficial mechanism of physical exercise may be complex, it may be associated with its anti-inflammatory and immunomodulatory potential [12-15]. Khosravi et al. found exercise training significantly decreased pro-inflammatory markers in cancer survivors, especially C-reactive protein [CRP: standardized mean differences (SMD): -0.5, 95% confidence intervals (CI): -0.9, -0.06, P = 0.025] and tumor necrosis factor (TNF-α: SMD: -0.3, 95% CI: -0.5, -0.06, P = 0.004) [15]. Compared with pre-treatment, TNF-α levels were found to be significantly decreased in adult individuals with multiple sclerosis after regular exercise intervention (SMD: -0.51, 95% CI: -0.91, 0.11, P = 0.01) [13]. CRP was confirmed to be reduced in knee OA patients at 6-18 weeks after regular exercise therapy [14]. These findings from meta-analyses implied WBV, as an exercise model, may also function by changing the expression and secretion of inflammation-related mediators. This hypothesis had been identified in several pre-clinical and clinical studies. For example, Kerr et al. found WBV intervention significantly reduced the levels of interleukin (IL)-6, TNF-α and interferon-γ (IFN-γ) in both female and male stroke model mice [16]. Chen et al. reported WBV treatment inhibited the increase of the IL-1β and TNF-α in the brain sections of traumatic brain injury model mice [17]. Wang et al. demonstrated that regardless of low, middle or high frequency, WBV was effective in decreasing the expression of IL-1β in an early knee OA rat model [18]. Rodriguez-Miguelez et al. detected the TNF-α protein content was lowed, while IL-10 mRNA content and protein concentration increased in the WBV training group compared with the control elderly subjects [19]. Seefried et al. found compared with the baseline value, the level of CRP was significantly lower in maintenance hemodialysis patients after WBV intervention [20]. Oh et al. reported WBV exercise for patients with nonalcoholic fatty liver disease decreased the levels of TNF-α and CRP by 50.8% and 14.5%, respectively (P < 0.05) [21]. However, some studies showed no benefit of WBV on influencing the pro-inflammatory factors IL-1β, IL-6, IL-10, IFN-γ or TNF-α [22-25]. Even, Yu et al. found low-frequency vibration promoted the production of TNF-α to increase cartilage degeneration in knee OA [26]. These results suggested the anti-inflammatory mechanisms of WBV remained inconclusive.

Herein, this study was to perform a meta-analysis of all published studies to re-confirm the effects of WBV exercise on inflammatory factors in healthy or pathological model animals or human subjects. This study may provide a theoretical basis for guiding WBV training as a promising non-pharmacological rehabilitative and prevention method, particularly for inflammatory diseases.

Materials and methods

Search strategy

This meta-analysis was conducted following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Three English electronic databases (PubMed, EMBASE and Cochrane Library) were searched from inception to September 2023. The search terms included: ("whole body vibration" OR "whole-body vibration" OR "vibration training" OR "vibration exercise" OR "vibration therapy") AND ("inflammation" OR "inflammatory" OR "inflammatory biomarkers" OR "cytokines" OR "immune cells" OR "immunity"). The systematic reviews, meta-analyses and citation lists of the identified studies were also manually checked for potential eligible articles.

Inclusion and exclusion criteria

Two authors independently performed the literature selection and a third investigator was discussed when discrepancies occurred. Articles included had to meet the population, intervention, comparators, outcomes and study design (PICOS) criteria: (1) participants: murine or human subjects (healthy or pathological); (2) intervention: the experimental group underwent WBV exercise; (3) comparison: comparing with the control group that did not carry out WBV or comparing with the pre-treatment; (4) outcomes: the percentage of immune cells or the levels and expression of inflammatory markers [such as IL-1β, IL-4, IL-6, IL-8, IL-10, IL-17, TNF-α, IFN-γ, MCP-1 (monocyte chemoattractant protein-1), sTNFR1 (soluble TNF receptor 1) and sTNFR2 (soluble TNF receptor 2)] were reported; and (5) study design: random-

ized controlled trials (RCTs), non-RCTs or uncontrolled trials (post- vs pre-intervention).

Studies were excluded if they were: (1) duplicate publications; (2) secondary research studies such as case reports, systematic review, meta-analysis, conference abstracts, letters, expert comment or protocols; (3) outcomes of interest were not measured, only detected in one study or data (mean and standard deviation) were unavailable; (4) written in a language other than English; and (5) irrelevant topics.

Data extraction and quality assessment

The data were independently extracted by two reviewers and verified by the third author. The following relevant data were extracted from each eligible study and recorded in Microsoft Excel: the first author, year of publication, country, study design, participants (age, gender, disease condition), WBV intervention (machine, frequency, amplitude, acceleration, duration), sample size, outcome data and data assay method. The data in tables and texts were collected directly and the data in figures were estimated by the GetData Graph digitizer software (version 2.26; http://getdata-graph-digitizer.com/).

The methodological quality of the included studies was assessed by two reviewers independently, based on the modified Physiotherapy Evidence Database (PEDro) scale [27]. PEDro consisted 11 items as follows: (1) eligibility criteria, (2) random allocation, (3) concealed allocation, (4) baseline comparability, (5) masked participants, (6) masked therapists, (7) masked assessors, (8) adequate follow-up, (9) intention to treat analysis, (10) between-group comparison, and (11) point estimates and variability. PEDro scores ranged from 0 to 10 points, and studies with PEDro scores higher than 5 were considered to be of high quality.

Statistical analysis

All statistical analyses were conducted using STATA 13.0 (STATA Corporation, College Station, TX, USA). The effects of WBV interventions on each outcome were calculated as the SMD and 95% CIs. A negative effect size represented decreases in the levels of inflammatory markers after WBV exercise. The significance of the combined SMD was estimated by Z-test, with a p-value < 0.05 as the statistical threshold. The heterogeneity between studies was assessed using the χ^2 test with Cochran Q and I^2 statistic. $P < 0.1$ and $I^2 > 50\%$ indicated the presence of a considerable risk of heterogeneity and thus, a random-effects model was selected for the pooled analysis; otherwise, the fixed-effects model was applied. Subgroup analysis was performed based on country (Asian or non-Asian), participants (healthy or diseases), WBV frequency (< 20 or > 20 Hz), WBV duration (< or > one week), assay method (PCR or others) and sample source (blood, synovial fluid or tissues). Publication bias was evaluated by Egger's linear regression test. If publication bias existed ($P < 0.05$), the trim-and-fill method was then performed to correct the pooled estimate. The stability of the meta-analysis results was assessed by carrying out a leave-one-out sensitivity analysis (that is: one study was omitted each time and the effect size was then re-calculated).

Results

Search results

As shown in **Figure 1**, a total of 1647 records were initially identified through searching electronic databases. Of them, 1048 were duplicates and thus excluded. After reviewing the titles and abstracts, 555 studies were removed as they were systematic reviews (n = 17), case reports (n = 23), comments (n = 9), protocol (n = 8), without control (n = 4), and studies unrelated to our topic (n = 494, not WBV or not exploring inflammation mechanisms). The remaining 44 studies were downloaded for full reading, after which 13 of them were eliminated because of no WBV exercise (n = 2), without non-WBV control (n = 2), data unavailable (n = 5) and data only detected in single study (n = 4). Finally, 31 eligible studies were included in this meta-analysis, including 14 pre-clinical [16-18, 22, 23, 28-36] and 17 clinical (9 experiment-control [19, 24, 25, 37-42] that also contained post-pre test data and 8 post-pre [20, 21, 26, 43-47]) studies.

Study characteristics

The basic characteristics of the included studies are shown in **Tables 1** and **2**. These 14 preclinical studies [16-18, 22, 23, 28-36] were published from 2011 to 2023. All of them were

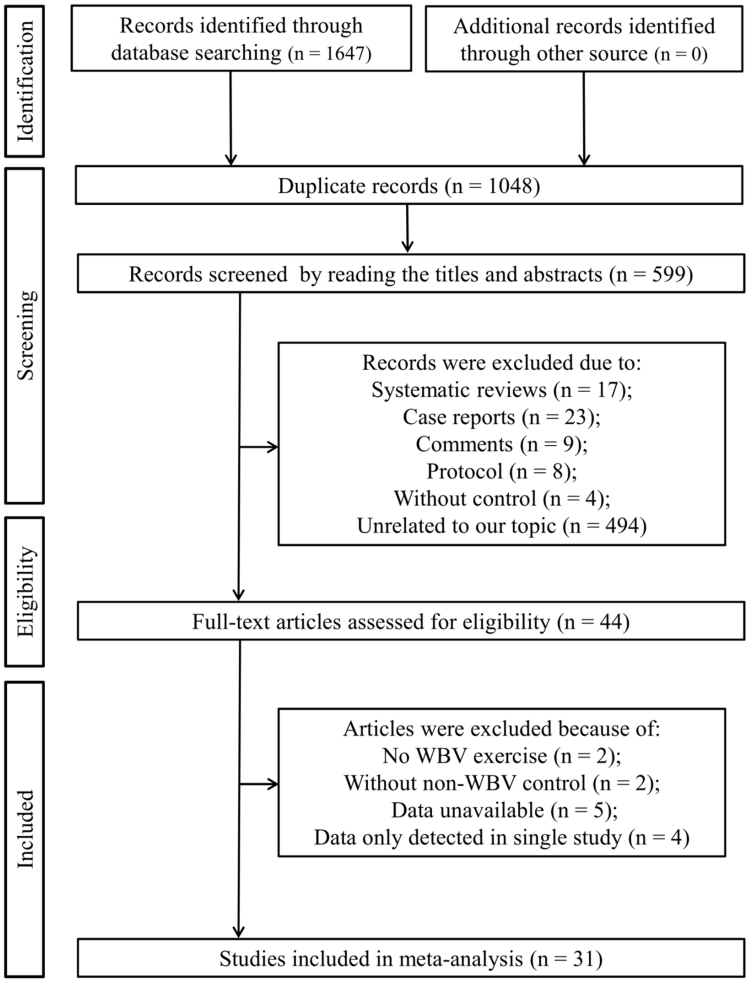

Figure 1. Flow diagram of included studies.

RCTs performed by authors of China (n = 8), Canada (n = 1), Iran (n = 1), Poland (n = 1), Thailand (n = 1) and USA (n = 2). WBV was set as a prevention tool for healthy mice/rats or a treatment approach for stroke, OA, obesity, osteoporosis, atherosclerosis, brain injury, ulcer and type 2 diabetes mellitus model mice/rats (**Table 1**). Nine clinical studies [19, 24, 25, 37-42] were control trials, including 5 RCTs and 4 non-RCTs. They were published from 2012 to 2023. Their participants were obese, knee OA, chronic obstructive pulmonary disease (COPD), depressed adolescents, premenstrual syndrome (PMS) patients, healthy students and seniors enrolled from Italy (n = 2), Brazil (n = 2), USA (n = 1), Canada (n = 1), Germany (n = 1), Sweden (n = 1) and Egypt (n = 1) (**Table 1**). Eight studies published from 2014 to 2022 only compared the outcomes between after and before WBV treatment [20, 21, 26, 43-47] (**Table 2**). Each one study evaluated the effects of WBV for patients with knee OA, interstitial lung disease, COPD, hemodialysis, fibromyalgia, nonalcoholic fatty liver disease; three studies reported the healthy or older humans. These post-pre studies were conducted in China, Germany (n = 2), Brazil (n = 1), USA (n = 1), Spain (n = 1), Brasil (n = 1) or Germany (n = 1) (**Table 2**). Inflammatory markers in blood (serum, plasma or peripheral-blood mononuclear cells), synovial fluid and various tissues were examined by PCR at mRNA levels, western blot, ELISA, enzyme-linked immunosorbent assay (ELISA), cytometric bead array (CBA), Bio-Plex assay and latex agglutination at protein levels (**Table 1**). All studies scored ≥ 5 on the PEDro scale, indicating all of them were of high quality (Table S1).

Meta-analysis of pre-clinical studies (WBV vs non-WBV)

Ten studies with 21 datasets compared the level of IL-6 between WBV exercise group and the control group that did not receive WBV (Table S2). As there was significant heterogeneity among these studies (I^2 = 80.9%, P < 0.001), a random-effects model was used. The pooled results revealed that compared with the control group, WBV exercise did not cause a significant change in the level of IL-6 (P = 0.144) (**Table 3**). However, the subgroup analysis showed WBV exercise could significantly reduce the level of IL-6 for the murine models of diseases (SMD: -1.03, 95% CI: -1.93, -0.13, P = 0.024) (**Table 3**).

Six studies with 20 datasets recorded the level of IL-1β in the WBV exercise group and the control group that did not receive WBV (Table S2). Under the random-effects model (I^2 = 90.0%, P < 0.001), the pooled results showed that compared with the control group, WBV exercise sig-

Table 1. Basic characteristics of included articles that compared WBV vs non-WBV

	Author	Year	Country	Study design	Participants	No	Intervention	Control	Source	Lab method	Outcomes
Pre-clinical	Jiang D [28]	2021	China	RCT	Male aging mice (18-month old)	12	WBV in an LD-P vertical vibration machine (f: 15 Hz; am: 2 mm; ac: 0.68 g); for 30 min/day, 6 days/week for 12 weeks	No-WBV	Gastrocnemius muscles	WB	IL-6, MCP-1
	Kerr N [16]	2022	USA	RCT	Female and male tMCAO (stroke) model rats (10-13-month old)	23	WBV in a vibration device (Soloflex) (f: 40 Hz); for 30 min/day, 5 days/week for 30 days	No-WBV	Serum	Bio-Plex assay	IL-1β, IL-4, IL-6, IL-10, IL-17, IFN-γ, TNF-α
	Sun C [29]	2015	China	RCT	Male HFD (obesity), ND rats (8-week old)	6	WBV in an LD-P vertical vibration machine (Huanzhen Machinery Limited Company) (f: 25 Hz); for 30 min/day, 6 days/week for 8 weeks	No-WBV	Adipose	WB	IL-6, TNF-α
	Pawlak M [22]	2013	Poland	RCT	Adult male rats	30	WBV for 120 min in a vibration device (Power plate) (f: 50 Hz; am: 2.5 mm; ac: 4.79 g); for 120 min/day, 5 days/week for 3 and 6 months	No-WBV	Serum	ELISA	IL-1β, IL-6, IL-10
	Wang H [30]	2023	China	RCT	Male knee OA model and sham mice (10-week old)	24	WBV in a vibration device (BodyGreen) (f: 10 Hz; am: 4 mm; ac: 0.73 g); for 20 min/day, 5 days/week for 4 weeks	No-WBV	Knee joint	PCR	IL-6, TNF-α
	Wang L [18]	2020	China	RCT	Male knee OA model rats (8-week old)	40	WBV in a customized magnetic levitation vibration platform (f: 10, 20, 40, 60 Hz; ac: 0.3 g); for 40 min/day, 5 days/week for 8 weeks	No-WBV	Distal femur	PCR, WB	IL-1β
	Tsai SH [31]	2022	China	RCT	Female OVX (osteoporosis) model mice (12-week old)	15	WBV in a vertically oscillating platform (BodyGreen) (f: 16 Hz; am: 2 mm; ac: 0.68 g); for 60 min/day, 5 days/week for 16 weeks	No-WBV	Splenocytes	ELISA	IL-4, IL-17, IFN-γ
	Wu H [32]	2018	China	RCT	ApoE$^{-/-}$ (atherosclerosis) model mice (8-week old)	8	WBV in an LD-P vertical vibration machine (Huanzhen Machinery Limited Company) (f: 15 Hz; am: 2 mm; ac: 0.68 g); for 30 min/day, 6 days/week for 12 weeks	No-WBV	Thoracic aorta	PCR, WB	IL-6
	Naghii MR [33]	2011	Iran	RCT	Male heathy rats	16	WBV in a vibration device (f: 10-50 Hz; am: 2 mm; ac: 1-10 g); 15 min, 4 days/week in the first week; 45 min, 3 days/week until day 24; 60 min, 20 days until 8 weeks	No-WBV	Plasma	ELISA	IL-6, TNF-α
	McCann MR [34]	2017	Canada	RCT	Male healthy mice (10-week-old)	18	WBV in a vibration platform (f: 45 Hz; am: 74 μm; ac: 0.3 g); for 30 min/day, 5 days/week) for 2, 4 weeks, 8 weeks	No-WBV	Thoracic IVDs	PCR	IL-1β, IL-6, TNF-α
	Wano N [35]	2021	Thailand	RCT	Male pressure ulcer model mice (8-week old)	32	WBV in a vibration platform (f: 45 Hz; ac: 0.4 g); for 30 min/day, 5 days/week) for one and two weeks	No-WBV	Wound skin tissues	ELISA	TNF-α
	Chen T [17]	2020	China	RCT	Male TBI model mice (6-8 weeks)		WBV in a vibration machine (Deca Precision Measuring Instruments)(f: 30 Hz); twice per day for 20 days	No-WBV	Brain	ELISA	IL-1β, IL-6, IL-10, TNF-α
	Chow SK [36]	2019	China	RCT	Female OVX (osteoporosis) model rats (9-month old)	48	WBV in a vibration machine (f: 35 Hz; ac: 0.3 g); for 20 min/d, 5 d/week for 1, 2, 4, 8 weeks	No-WBV	Serum	ELISA	IL-6, IL-10, TNF-α
	Weinheimer-Haus EM [23]	2014	USA	RCT	Male db/db (T2DM) model mice (12-16-week old)	24	WBV in a vibration platform (f: 45 Hz; am: 40 μm; ac: 0.4 g); for 30 min, 5 days/week for one and two weeks	No-WBV	Wound skin tissues	PCR, ELISA	IL-1β, IL-10, MCP-1, TNF-α

Clinical	Bellia A [37]	2014	Italy	RCT	Obese patients	29	WBV in a dedicated platform (Nemes Perform) (f: 30 Hz; am: 2 mm); for 20 min/day, 3 days/week for 8 weeks	No-WBV	Plasma	Latex agglutination, Lincoplex ELISA	CRP, TNF-α
	Simão AP [38]	2012	Brazil	RCT	Knee OA patients	21	WBV in a vibration device (Fitvibe) (f: 35-40 Hz; am: 4 mm; ac: 2.78-3.26 g); 3 days/week for 12 weeks	No-WBV	Plasma	ELISA	sTNFR1, sTNFR2
	Neves CDC [24]	2018	Brazil	Non-RCT	COPD patients	20	WBV in a vibration device (Fitvibe) (f: 30-40 Hz; am: 2 mm; ac: 1.45-2.25 g); for 3 min, 3 days/week for 12 weeks	No-WBV	Plasma	CBA; ELISA	IL-6, IL-8, IFN-γ; sTNFR1, sTNFR2
	Jawed Y [25]	2020	USA	Non-RCT	Healthy male humans	14	WBV in a vibration platform (Power Plate my 3) (f: 35 Hz; am: 4 mm); for 8 min	No-WBV	Plasma	ELISA	IL-6, IL-10, TNF-α
	Hazell TJ [39]	2014	Canada	Non-RCT	Healthy male students	10	WBV in a WAVE platform (Windsor) (f: 45 Hz; am: 2 mm); 15 min	No-WBV	Plasma	ELISA	IL-1β, IL-6, IL-10
	Wunram H [40]	2021	Germany	Non-RCT	Depressed adolescents	44	WBV in a vibration platform (Galileo) (f: 20 Hz; am: 2 mm); for 30 min, 3-5 days/week for 6 weeks	No-WBV	Serum	ELISA, ECLIA	TNF-α, IL-6
	Di Giminiani R [42]	2020	Italy	RCT	Healthy male sport science students	40	WBV for 24 min	No-WBV	Serum	ELISA	IL-6
	Rodriguez-Miguelez P [19]	2015	Sweden	RCT	Seniors	28	WBV in a vibration platform (Fitvibe) (f: 20-35 Hz; am: 4 mm); for 0.5-1 min/day, 2 days/week for 8 weeks	No-WBV	PBMC	PCR, WB	IL-10, TNF-α
	Shehata MM [41]	2023	Egypt	RCT	PMS woman	70	WBV in a side-oscillating WBV platform (PS-CFM001) (f: 14 Hz; am: 1 mm); for 13 min, 3 days/week for 12 weeks	No-WBV	Blood	ELISA	CRP

WBV, whole-body vibration; RCT, randomized controlled trials; tMCAO, transient middle-cerebral artery occlusion; HFD, high-fat diet; ND, normal diet; OA, osteoarthritis; OVX, ovariectomy; TBI, traumatic brain injury; T2DM, type 2 Diabetes Mellitus; COPD, chronic obstructive pulmonary disease; PMS, premenstrual syndrome; f, frequency; am, amplitude; ac, acceleration; IVD, intervertebral disc; PBMC, peripheral-blood mononuclear cells; PCR, polymerase chain reaction; WB, western blot; ELISA, enzyme-linked immunosorbent assay; CBA, cytometric bead array; IL, interleukin; CRP, C-reactive protein; TNF, tumor necrosis factor; IFN, interferon; MCP-1, monocyte chemoattractant protein-1; sTNFR1, soluble TNF receptor 1; sTNFR2, soluble TNF receptor 2.

Table 2. Basic characteristics of included articles that compared post-WBV vs pre-WBV

Author	Year	Country	Participants	No	Intervention	Source	Lab method	Outcomes
Yu PM [26]	2021	China	OA patients	4	WBV in a vibration device (Fitvibe) (f: 40 Hz; am: 2 mm); for 15 min/day, 5 days/week for 4 weeks	Synovial fluid	ELISA	TNF-α
Koczulla AR [43]	2020	Germany	ILD patients	11	WBV in a side-alternating vibration platform (Galileo) (f: increased from 6 to 26 Hz; am: 4-6 mm); for 6 min/day, 3 days/week for 8 weeks; for 9 min/day, 3 days/week for 4 weeks	Serum	NA	IL-6
Koczulla AR [43]	2020	Germany	ILD patients	16	WBV in a side-alternating vibration platform (Galileo) (f: 5 Hz; am: 4-6 mm); for 6 min/day, 3 days/week for 4 weeks	Serum	NA	
Lage VKS [44]	2018	Brazil	COPD patients and healthy humans	26	WBV in a vibration device (Fitvibe) (f: 35 Hz; am: 2 mm); for 3 min/day, 5 days/week for 4 weeks	Plasma	CBA; ELISA	IL-6, IL-8, IL-10; sTNFR1, sTNFR2
Sanni AA [47]	2022	USA	Healthy humans	40	WBV in a vibration platform (Power Plate Pro 5) (f: 30 Hz; am: 5, 2.5 mm; ac: 9 and 4.5 g); for 10 min	Plasma	ELISA	IL-6
Cristi C [45]	2014	Spain	Older adults	9	WBV in a vibration device (Fitvibe) (f: 30-45 Hz; am: 2 mm; ac: 3.6-8.1 g); for 0.5-1 min/day, 3 days/week for 9 weeks	PBMCs	PCR, WB	CRP, IL-1β, IL-6, IL-10, TNF-α
Ribeiro VGC [46]	2018	Brasil	Fibromyalgia patients and healthy humans	38	WBV in a vibration device (Fitvibe) (f: 40 Hz; am: 4 mm; ac: 2-5 g); for 320 s	Plasma	ELISA	sTNFR1, sTNFR2
Seefried L [20]	2017	Germany	Hemodialysis patients	14	WBV in a side-alternating vibration platform (Galileo) (f: 22 Hz); for 5 min in the first 4 weeks, 12.5 min during week 5-8 and 20 min in the last weeks 8-12	Plasma		CRP
Oh S [21]	2019	Japan	NAFLD patients	25	WBV in a vibration platform (Power Plate Pro-6) (f: 30-50 Hz); for 20 min, 2 days/week for 12 weeks	Plasma	ELISA	IL-6, TNF-α, CRP
Bellia A [37]	2014	Italy	Obese patients	15	WBV in a dedicated platform (Nemes Perform) (f: 30 Hz; am: 2 mm); for 20 min/day, 3 days/week for 8 weeks	Plasma	Latex agglutination, Lincoplex ELISA	CRP, TNF-α
Simão AP [38]	2012	Brazil	Knee OA patients	11	WBV in a vibration device (Fitvibe) (f: 35-40 Hz; am: 4 mm; ac: 2.78-3.26 g); 3 days/week for 12 weeks	Plasma	ELISA	sTNFR1, sTNFR2
Neves CDC [24]	2018	Brazil	COPD patients	10	WBV in a vibration device (Fitvibe) (f: 30-40 Hz; am: 2 mm; ac: 1.45-2.25 g); for 3 min, 3 days/week for 12 weeks	Plasma	CBA; ELISA	IL-6, IL-8, IFN-γ; sTNFR1, sTNFR2
Jawed Y [25]	2020	USA	Healthy male humans	14	WBV in a vibration platform (Power Plate my 3) (f: 35 Hz; am: 4 mm); for 8 min	Plasma	ELISA	IL-6, IL-10, TNF-α
Hazell TJ [39]	2014	Canada	Healthy male students	10	WBV in a WAVE platform (Windsor) (f: 45 Hz; am: 2 mm); 15 min	Plasma	ELISA	IL-1β, IL-6, IL-10
Wunram H [40]	2021	Germany	Depressed adolescents	21	WBV in a vibration platform (Galileo) (f: 20 Hz; am: 2 mm); for 30 min, 3-5 days/week for 6 weeks	Serum	ELISA, ECLIA	TNF-α, IL-6
Di Giminiani R [42]	2020	Italy	Healthy male sport science students	20	WBV for 24 min	Serum	ELISA	IL-6
Rodriguez-Miguelez P [19]	2015	Sweden	Seniors	16	WBV in a vibration platform (Fitvibe) (f: 20-35 Hz; am: 4 mm); for 0.5-1 min/day, 2 days/week for 8 weeks	PBMC, serum	PCR, WB, ELISA, IT	IL-10, TNF-α, CRP
Shehata MM [41]	2023	Egypt	PMS woman	35	WBV in a side-oscillating WBV platform (PS-CFM001) (f: 14 Hz; am: 1 mm); for 13 min, 3 days/week for 12 weeks	Blood	ELISA	CRP

WBV, whole-body vibration; OA, osteoarthritis; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; NAFLD, nonalcoholic fatty liver disease; PMS, premenstrual syndrome; f, frequency; am, amplitude; ac, acceleration; PBMC, peripheral-blood mononuclear cells; PCR, polymerase chain reaction; WB, western blot; ELISA, enzyme-linked immunosorbent assay; ECLIA, electrochemiluminescence immunoassay; CBA, cytometric bead array; IT, immunoturbidimetric; IL, interleukin; CRP, C-reactive protein; TNF, tumor necrosis factor; IFN, interferon; sTNFR1, soluble TNF receptor 1; sTNFR2, soluble TNF receptor 2.

Table 3. Meta-analysis (pre-clinical studies: WBV vs non-WBV)

Variables			No.	SMD	95% CI	P_E-value	I^2	P_H-value	Model	Egger p
IL-6	Overall		21	-0.52	-1.21, 0.18	0.144	80.9	< 0.001	R	0.311
	Country	Asian	14	-0.38	-1.45, 0.69	0.489	85.4	< 0.001	R	
		Non-Asian	7	-0.71	-1.41, -0.01	0.048	60.0	0.020	R	
	Participants	Healthy	9	0.16	-0.88, 1.20	0.763	82.2	< 0.001	R	
		Diseases	12	-1.03	-1.93, -0.13	0.024	77.8	< 0.001	R	
	WBV frequency	< 20 Hz	5	-2.10	-4.90, 0.71	0.142	91.3	< 0.001	R	
		≥ 20 Hz	15	-0.27	-0.80, 0.25	0.304	57.4	0.003	R	
		Other	1	1.52	0.39, 2.65	0.008	-	-	R	
	Duration	≤ 1 week	1	0.56	-0.60, 1.72	0.343	-	-	R	
		> 1 week	20	-0.58	-1.31, 0.15	0.118	81.5	< 0.001	R	
	Sample source	Tissue	12	-0.82	-2.04, 0.41	0.192	84.7	< 0.001	R	
		Blood	9	-0.15	-0.84, 0.53	0.662	69.0	0.001	R	
	Assay method	PCR	6	-0.71	-2.46, 1.04	0.425	87.9	< 0.001	R	
		Other	15	-0.43	-1.17, 0.31	0.253	77.3	< 0.001	R	
IL-1β	Overall		20	-2.20	-3.24, -1.15	< 0.001	90.0	< 0.001	R	< 0.001
	Country	Asian	10	-4.40	-5.32, -3.47	< 0.001	47.5	0.047	F	
		Non-Asian	10	-0.13	-0.97, 0.72	0.770	80.2	< 0.001	R	
	Participants	Healthy	5	0.80	-0.16, 1.77	0.103	70.6	0.009	R	
		Diseases	15	-3.33	-4.54, -2.12	< 0.001	87.2	< 0.001	R	
	WBV frequency	< 20 Hz	4	-4.87	-5.90, -3.83	< 0.001	0.0	0.494	F	
		≥ 20 Hz	16	-1.47	-2.49, -0.46	0.005	88.1	< 0.001	R	
	Duration	≤ 1 week	3	-0.21	-1.17, 0.75	0.673	59.3	0.086	R	
		> 1 week	17	-2.63	-3.92, -1.33	< 0.001	90.7	< 0.001	R	
	Sample source	Tissue	16	-2.55	-3.85, -1.25	< 0.001	90.5	< 0.001	R	
		Blood	4	-0.99	-2.65, 0.67	0.242	86.6	< 0.001	R	
	Assay method	PCR	9	-2.02	-3.88, -0.16	0.033	91.9	< 0.001	R	
		Other	11	-2.39	-3.70, -1.08	< 0.001	89.0	< 0.001	R	
IL-10	Overall		11	0.11	-0.70, 0.92	0.788	78.0	< 0.001	R	0.940
	Country	Asian	6	-0.31	-1.86, 1.24	0.695	83.5	< 0.001	R	
		Non-Asian	5	0.45	-0.44, 1.33	0.323	72.3	0.006	R	
	Participants	Healthy	2	0.52	-0.12, 1.16	0.114	0.0	0.915	F	
		Diseases	9	-0.00	-1.07, 1.07	0.999	81.5	< 0.001	R	
	Duration	≤ 1 week	2	-2.06	-5.19, 1.08	0.199	88.1	0.004	R	
		> 1 week	9	0.52	-0.24, 1.28	0.179	68.2	0.001	R	
	Sample source	Tissue	3	0.40	-1.06, 1.86	0.595	65.5	0.055	R	
		Blood	8	-0.02	-1.05, 1.01	0.970	82.0	< 0.001	R	
TNF-α	Overall		20	-0.82	-1.68, 0.04	0.061	86.4	< 0.001	R	0.646
	Country	Asian	13	-0.66	-1.93, 0.62	0.310	89.7	< 0.001	R	
		Non-Asian	7	-0.94	-1.93, 0.05	0.063	74.1	0.001	R	
	Participants	Healthy	6	0.12	-0.58, 0.83	0.720	44.2	0.111	F	
		Diseases	14	-1.36	-2.54, -0.17	0.025	88.8	< 0.001	R	
	WBV frequency	< 20 Hz	2	-1.56	-3.53, 0.41	0.121	74.5	0.047	R	
		≥ 20 Hz	17	-0.76	-1.78, 0.26	0.144	87.9	< 0.001	R	
		Other	1	0.00	-0.98, 0.98	1.000	-	-	R	
	Duration	≤ 1 week	4	-1.42	-4.15, 1.32	0.310	93.9	< 0.001	R	
		> 1 week	16	-0.68	-1.55, 0.19	0.126	82.9	< 0.001	R	
	Sample source	Tissue	13	-1.09	-2.28, 0.10	0.073	87.5	< 0.001	R	
		Blood	7	-0.27	-1.34, 0.80	0.622	79.8	< 0.001	R	
	Assay method	PCR	7	-0.61	-1.38, 0.15	0.118	61.9	0.015	R	
		Other	13	-0.84	-2.19, 0.52	0.227	90.2	< 0.001	R	

IFN-γ	Overall	3	-1.91	-2.71, -1.12	< 0.001	0.0	0.968	F	0.786
IL-4	Overall	3	-0.71	-1.39, -0.03	0.040	34.2	0.219	F	0.982
IL-17	Overall	3	-1.32	-2.05, -0.59	< 0.001	33.9	0.220	F	0.250
MCP-1	Overall	2	-0.97	-11.74, 9.81	0.861	97.4	< 0.001	R	-

IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; MCP-1, monocyte chemoattractant protein-1; SMD, standardized mean difference; CI, confidence interval; F, fixed-effects; R, random-effects; P_H-value, significance for heterogeneity; P_E-value, significance for effects.

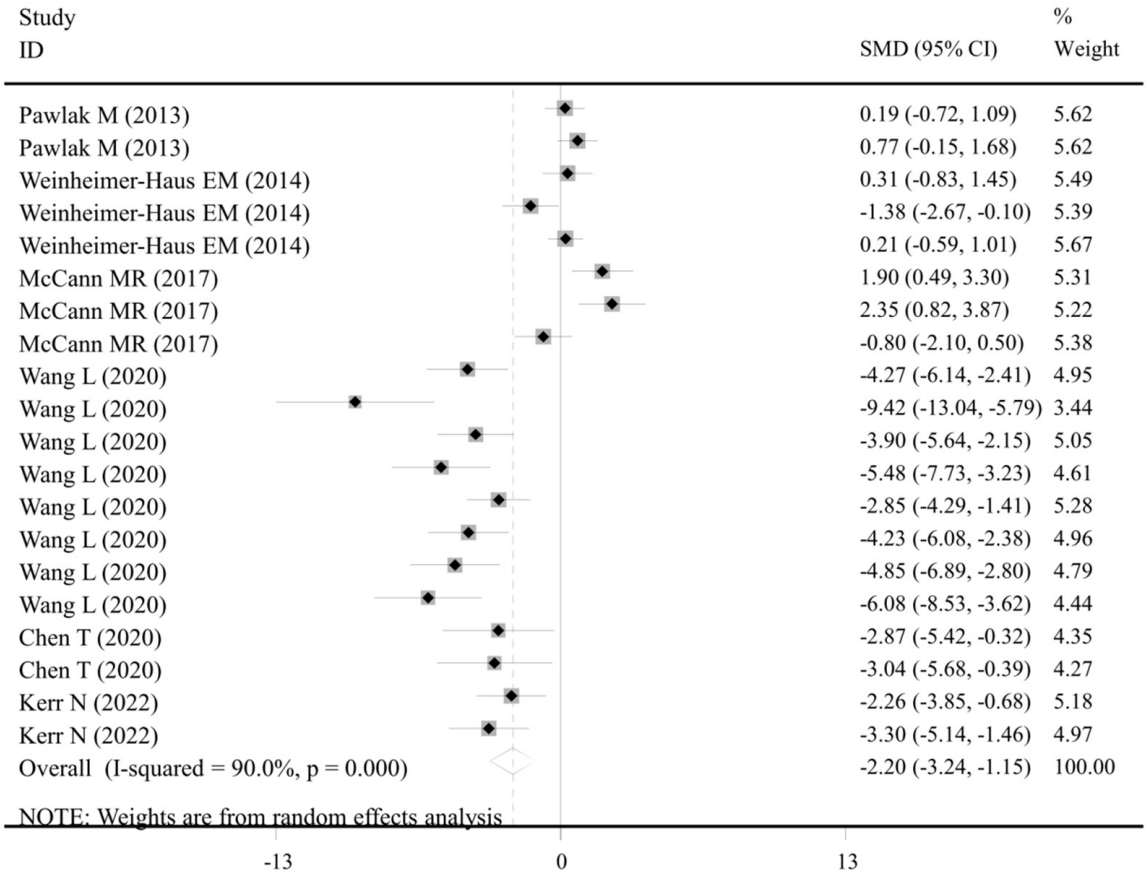

Figure 2. Forest plot of the effects of WBV exercise on interleukin-1β levels. Data were from pre-clinical studies comparing WBV with controls (overall). WBV, whole-body vibration; SMD, standardized mean difference; CI, confidence interval.

nificantly inhibited the level of IL-1β (SMD: -2.20, 95% CI: -3.24, -1.15, P < 0.001) (**Table 3**; **Figure 2**). The subgroup analysis confirmed that WBV frequency and IL-6 assay methods did not influence the inhibition effect of WBV exercise on IL-6 (all still significant), but long-term WBV exercise (> one week) may be more effective for disease control (**Table 3**).

Five studies with 11 datasets measured the level of IL-10 in the WBV and non-WBV groups (Table S2). Under the random-effects model (I^2 = 78.0%, P < 0.001), the combined results showed no significant difference in the level of IL-10 between two groups (P = 0.788) (**Table 3**). The subgroup analysis also confirmed that WBV exercise had no effect on IL-10 (P > 0.05) (**Table 3**).

Nine studies with 20 datasets examined the level of TNF-α in murine which underwent WBV or not (Table S2). The meta-analysis with a random-effects model (I^2 = 86.4%, P < 0.001) showed WBV exercise only induced a borderline statistically significant improvement in TNF-α (SMD: -0.82, 95% CI: -1.68, 0.04, P = 0.061)

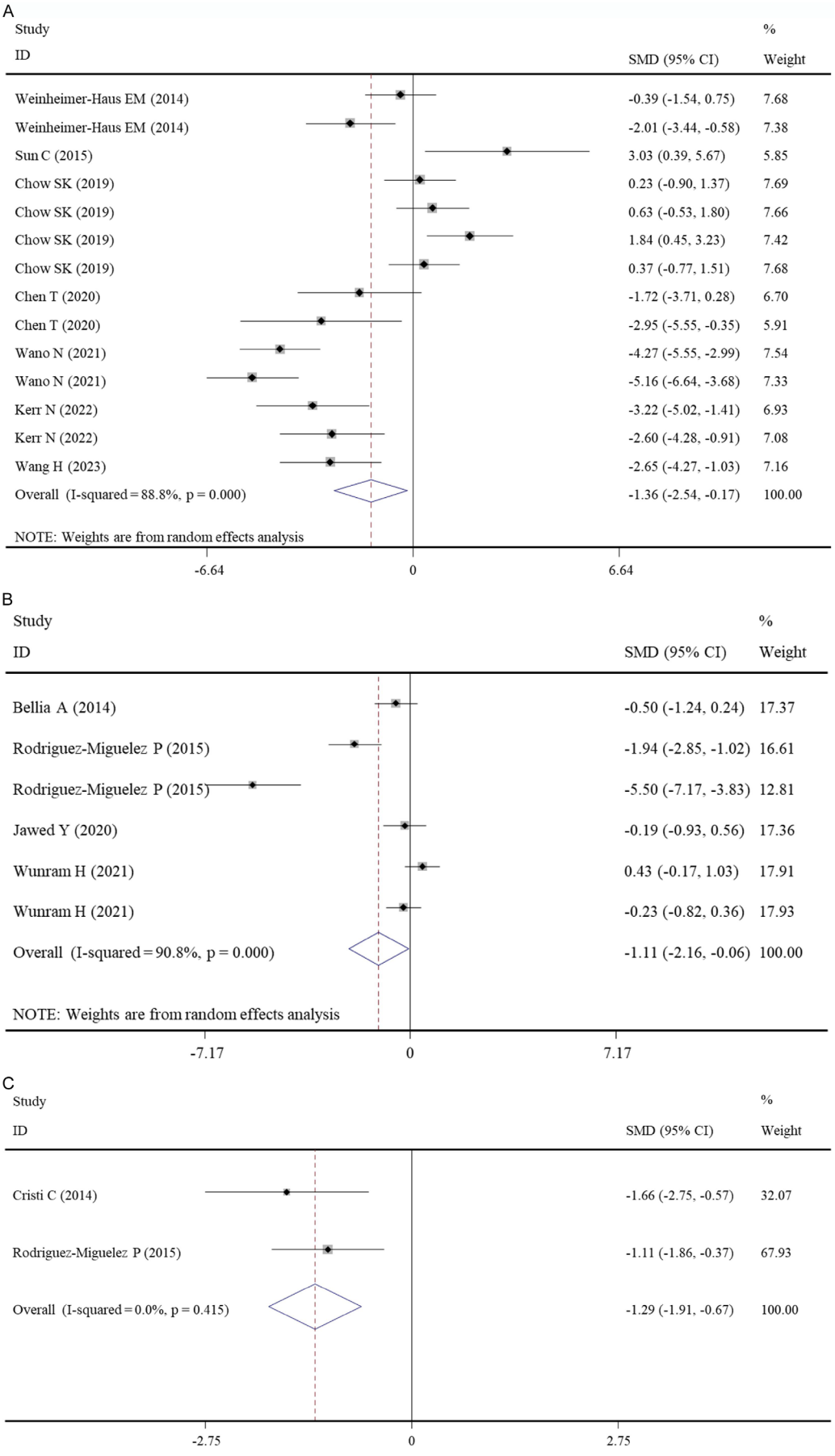
A
Study
ID
SMD (95% CI)
%
Weight
Weinheimer-Haus EM (2014) -0.39 (-1.54, 0.75) 7.68
Weinheimer-Haus EM (2014) -2.01 (-3.44, -0.58) 7.38
Sun C (2015) 3.03 (0.39, 5.67) 5.85
Chow SK (2019) 0.23 (-0.90, 1.37) 7.69
Chow SK (2019) 0.63 (-0.53, 1.80) 7.66
Chow SK (2019) 1.84 (0.45, 3.23) 7.42
Chow SK (2019) 0.37 (-0.77, 1.51) 7.68
Chen T (2020) -1.72 (-3.71, 0.28) 6.70
Chen T (2020) -2.95 (-5.55, -0.35) 5.91
Wano N (2021) -4.27 (-5.55, -2.99) 7.54
Wano N (2021) -5.16 (-6.64, -3.68) 7.33
Kerr N (2022) -3.22 (-5.02, -1.41) 6.93
Kerr N (2022) -2.60 (-4.28, -0.91) 7.08
Wang H (2023) -2.65 (-4.27, -1.03) 7.16
Overall (I-squared = 88.8%, p = 0.000) -1.36 (-2.54, -0.17) 100.00
NOTE: Weights are from random effects analysis
-6.64
0
6.64
B
Study
ID
SMD (95% CI)
%
Weight
Bellia A (2014) -0.50 (-1.24, 0.24) 17.37
Rodriguez-Miguelez P (2015) -1.94 (-2.85, -1.02) 16.61
Rodriguez-Miguelez P (2015) -5.50 (-7.17, -3.83) 12.81
Jawed Y (2020) -0.19 (-0.93, 0.56) 17.36
Wunram H (2021) 0.43 (-0.17, 1.03) 17.91
Wunram H (2021) -0.23 (-0.82, 0.36) 17.93
Overall (I-squared = 90.8%, p = 0.000) -1.11 (-2.16, -0.06) 100.00
NOTE: Weights are from random effects analysis
-7.17
0
7.17
C
Study
ID
SMD (95% CI)
%
Weight
Cristi C (2014) -1.66 (-2.75, -0.57) 32.07
Rodriguez-Miguelez P (2015) -1.11 (-1.86, -0.37) 67.93
Overall (I-squared = 0.0%, p = 0.415) -1.29 (-1.91, -0.67) 100.00
-2.75
0
2.75

Figure 3. Forest plot of the effects of WBV exercise on tumor necrosis factor-α levels. A. Data from pre-clinical studies comparing WBV exercise with controls (subgroup, disease models); B. Data from clinical studies comparing WBV exercise with control (overall); C. Data from clinical studies comparing post- with pre-WBV exercise (subgroup, PCR assay). WBV, whole-body vibration; SMD, standardized mean difference; CI, confidence interval.

Table 4. Meta-analysis (clinical studies: WBV vs non-WBV)

Variables			No.	SMD	95% CI	P_E-value	I^2	P_H-value	Model	Egger p
IL-6	Overall		10	0.06	-0.32, 0.45	0.751	64.2	0.003	R	0.118
	Participants	Healthy	7	-0.08	-0.54, 0.38	0.736	63.1	0.013	R	
		Diseases	3	0.38	-0.24, 1.00	0.229	59.2	0.086	R	
	WBV frequency	≥ 20 Hz	7	0.03	-0.37, 0.44	0.877	49.9	0.063	F	
		NA	3	0.16	-0.79, 1.10	0.746	84.8	0.001	R	
	Duration	≤ 1 week	3	0.38	-0.24, 1.00	0.229	59.2	0.086	R	
		> 1 week	7	-0.08	-0.54, 0.38	0.736	63.1	0.013	R	
IL-10	Overall		6	2.90	1.10, 4.71	0.002	93.7	< 0.001	R	0.002
	Duration	≤ 1 week	4	0.65	0.22, 1.09	0.003	0.0	0.525	F	
		> 1 week	2	10.19	2.16, 18.22	0.013	92.4	< 0.001	R	
	Assay method	PCR	5	1.97	0.36, 3.57	0.017	91.6	< 0.001	R	
		Other	1	6.29	4.42, 8.16	< 0.001	-	-	R	
TNF-α	Overall		6	-1.11	-2.16, -0.06	0.038	90.8	< 0.001	R	0.003
	Participants	Healthy	3	-2.43	-4.90, 0.04	0.054	94.2	< 0.001	R	
		Diseases	3	-0.07	-0.61, 0.47	0.793	52.6	0.121	R	
	Duration	≤ 1 week	1	-0.19	-0.93, 0.56	0.625	-	-	R	
		> 1 week	5	-1.35	-2.64, -0.06	0.041	92.6	< 0.001	R	
	Assay method	PCR	1	-1.94	-2.85, -1.02	< 0.001	-	-	R	
		Other	5	-0.93	-2.05, 0.18	0.101	90.8	< 0.001	R	
CRP	Overall		2	-5.08	-14.82, 4.66	0.307	99.0	< 0.001	R	-
sTNFR1	Overall		2	0.94	-1.22, 3.10	0.393	89.5	< 0.001	R	-
sTNFR2	Overall		2	0.22	-0.69, 1.14	0.630	53.2	0.144	R	-
IL-1β	Overall		3	-0.04	-0.55, 0.47	0.879	0.0	0.984	F	0.063

IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; sTNFR1, soluble TNF receptor 1; sTNFR2, soluble TNF receptor 2; SMD, standardized mean difference; CI, confidence interval; F, fixed-effects; R, random-effects; P_H-value, significance for heterogeneity; P_E-value, significance for effects.

(**Table 3**). The subgroup analysis found that WBV exercise may be particularly suitable for disease models to reduce their TNF-α levels (SMD: -1.36, 95% CI: -2.54, -0.17, P = 0.025) (**Table 3**; **Figure 3A**).

Two studies provided the data of IFN-γ, IL-4, IL-17 and MCP-1 in two groups. The pooled results concluded that compared with the control group, WBV exercise significantly suppressed the level of IFN-γ (SMD: -1.91, 95% CI: -2.71, -1.12, P < 0.001), IL-4 (SMD: -0.71, 95% CI: -1.39, -0.03, P = 0.04), IL-17 (SMD: -1.32, 95% CI: -2.05, -0.59, P < 0.001), but had not effect on MCP-1 (P > 0.05) (**Table 3**). Subgroup analysis was not performed for them because of too few articles included.

Meta-analysis of clinical studies (WBV vs non-WBV)

Five studies with 10 datasets investigated the differences of IL-6 in people undergoing WBV exercise or not (Table S2). Findings from the random-effect model (I^2 = 64.2%, P = 0.003) showed that the level of IL-6 was not statistically different between these two groups (P = 0.751). This non-significant result was also demonstrated in all subgroups (P > 0.05) (**Table 4**).

Three studies with 6 datasets measured the level of IL-10 in the WBV and non-WBV groups (Table S2). Under the random-effects model (I^2

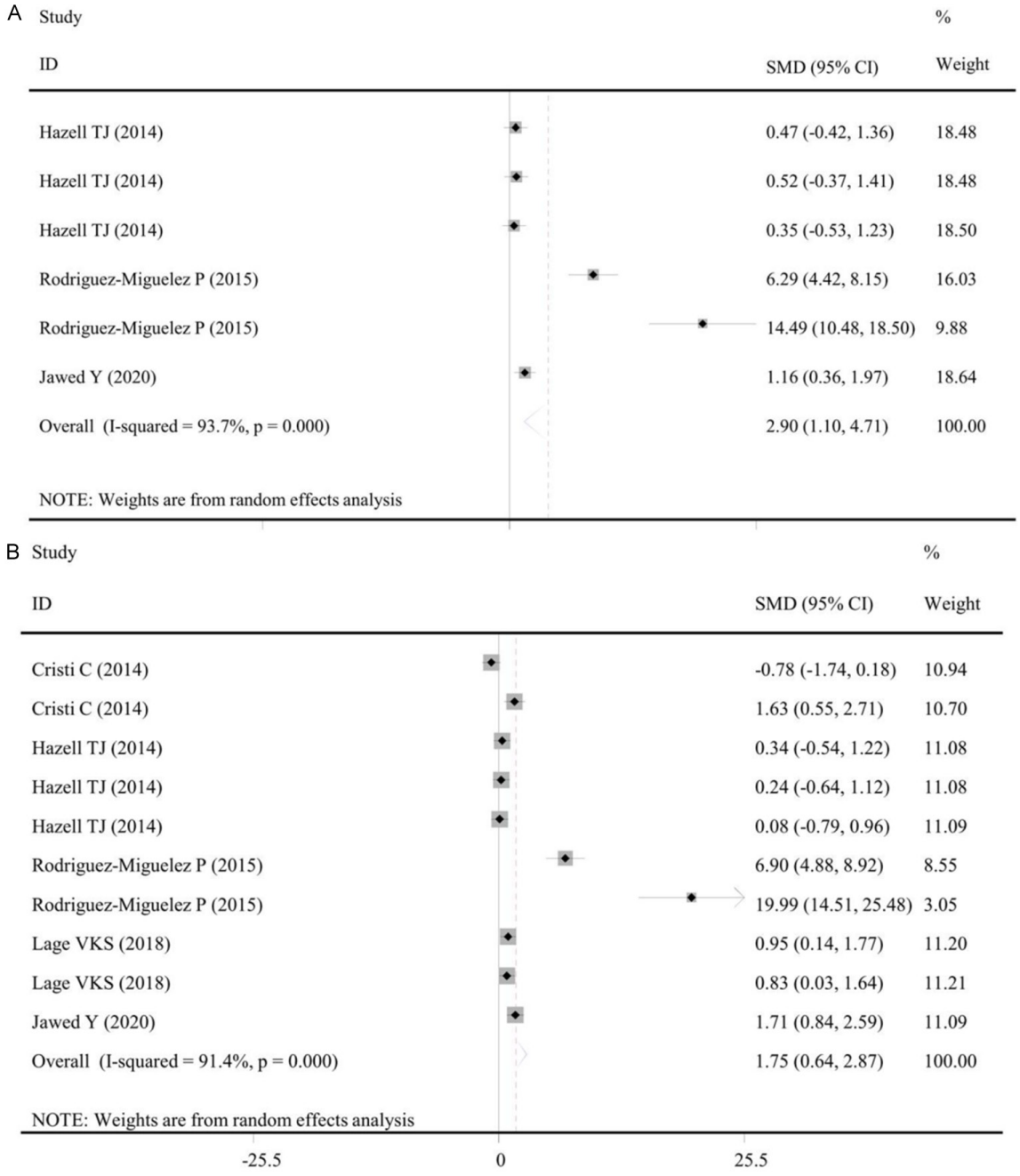

Figure 4. Forest plot of the effects of WBV exercise on interleukin-10 levels. A. Data from clinical studies comparing WBV exercise with control (overall); B. Data from clinical studies comparing post- with pre-WBV exercise (overall). WBV, whole-body vibration; SMD, standardized mean difference; CI, confidence interval.

= 93.7%, P < 0.001), the pooled results showed WBV exercise significantly enhanced the level of IL-10 compared with controls (SMD: 2.90, 95% CI: 1.10, 4.71, P = 0.002) (**Table 4**; **Figure 4A**), which also confirmed in all subgroups (**Table 4**).

Four studies with 6 datasets examined the level of TNF-α in individuals which underwent WBV or not (Table S2). The meta-analysis with a random-effects model (I^2 = 86.4%, P < 0.001) showed in comparison with control, WBV exercise significantly reduced the level of TNF-α (SMD: -1.11, 95% CI: -2.16, -0.06, P = 0.038) (**Table 4**; **Figure 3B**). The subgroup analysis found that WBV exercise may be more effective when it lasted for more than one week (P < 0.05) (**Table 3**).

Table 5. Meta-analysis (clinical studies: post-WBV vs pre-WBV)

Variables			No.	SMD	95% CI	P_E-value	I^2	P_H-value	Model	Egger p
IL-6	Overall		25	0.91	0.31, 1.52	0.003	93.2	< 0.001	R	< 0.001
	Country	Asian	1	-0.40	-0.96, 0.16	0.163	-	-	R	
		Non-Asian	24	0.97	0.34, 1.61	0.003	93.3	< 0.001	R	
	Participants	Healthy	18	1.33	0.47, 2.20	0.002	94.6	< 0.001	R	
		Diseases	7	-0.12	-0.42, 0.18	0.428	24.9	0.239	F	
	WBV frequency	< 20 Hz	1	-0.29	-0.98, 0.41	0.421	-	-	R	
		≥ 20 Hz	20	0.75	0.11, 1.40	0.022	92.6	< 0.001	R	
		NA	4	2.09	-0.31, 4.49	0.088	96.5	< 0.001	R	
	Duration	≤ 1 week	17	1.40	0.52, 2.28	0.002	94.7	< 0.001	R	
		> 1 week	8	-0.10	-0.52, 0.32	0.641	60.2	0.014	R	
	Assay method	PCR	1	1.36	0.33, 2.40	0.010	-	-	R	
		Other	22	1.00	0.32, 1.68	0.004	93.9	< 0.001	R	
		NA	2	-0.19	-0.73, 0.34	0.480	0.0	0.681	F	
IL-1β	Overall		5	0.39	-0.23, 1.01	0.216	54.4	0.067	R	0.021
	Duration	≤ 1 week	3	0.13	-0.38, 0.64	0.616	0.0	0.713	F	
		> 1 week	2	0.90	-0.92, 2.71	0.332	83.9	0.013	R	
	Assay method	PCR	1	1.85	0.73, 2.97	0.001	-	-	F	
		Other	4	0.10	-0.35, 0.55	0.661	0.0	0.865	F	
CRP	Overall		8	-1.81	-3.97, 0.35	0.100	97.6	< 0.001	R	0.286
	Country	Asian	1	-1.53	-2.16, -0.89	< 0.001	-	-	R	
		Non-Asian	7	-1.87	-4.55, 0.81	0.172	97.9	< 0.001	R	
	Participants	Healthy	3	1.15	-1.75, 4.06	0.437	95.2	< 0.001	R	
		Diseases	5	-3.59	-6.36, -0.82	0.011	98.0	< 0.001	R	
	WBV frequency	< 20 Hz	2	-8.40	-9.45, -7.35	< 0.001	0.0	1.000	F	
		≥ 20 Hz	6	0.29	-1.09, 1.66	0.683	93.6	< 0.001	R	
	Assay method	PCR	1	1.85	0.73, 2.98	0.001	-	-	R	
		Other	6	-2.69	-5.56, 0.20	0.068	98.1	< 0.001	R	
		NA	1	-0.36	-1.10, 0.39	0.350	-	-	R	
IL-10	Overall		10	1.75	0.64, 2.87	0.002	91.4	< 0.001	R	0.001
	Participants	Healthy	9	1.95	0.67, 3.23	0.003	92.3	< 0.001		
		Diseases	1	0.95	0.14, 1.77	0.022	-	-		
	Duration	≤ 1 week	6	0.70	0.23, 1.18	0.004	45.6	0.102	R	
		> 1 week	4	5.87	1.55, 10.20	0.008	96.8	< 0.001	R	
	Assay method	PCR	2	3.01	-4.52, 10.53	0.433	97.8	< 0.001	R	
		Other	8	1.36	0.35, 2.38	0.009	88.1	< 0.001	R	
TNF-α	Overall		11	-0.02	-1.31, 1.27	0.974	95.4	< 0.001	R	0.898
	Country	Asian	2	-0.37	-9.37, 8.63	0.936	97.2	< 0.001	R	
		Non-Asian	9	0.16	-1.01, 1.32	0.791	94.1	< 0.001	R	
	Participants	Healthy	7	-0.62	-2.84, 1.61	0.588	96.9	< 0.001	R	
		Diseases	4	0.61	-0.23, 1.45	0.157	76.0	0.006	R	
	Duration	≤ 1 week	1	-0.19	-1.58, 1.19	< 0.001	-	-	R	
		> 1 week	10	1.65	0.78, 2.52	0.786	95.5	< 0.001	R	
	Sample source	Synovial fluid	1	4.32	1.51, 7.12	0.003	-	-	R	
		Blood	9	-0.33	-1.65, 0.98	0.619	95.7	< 0.001	R	
	Assay method	PCR	2	-1.29	-1.91, -0.67	< 0.001	0.0	0.415	F	
		Other	9	-0.84	-2.19, 0.52	0.696	96.0	< 0.001	R	

sTNFR1	Overall		6	-0.04	-1.94, 1.86	0.969	95.9	< 0.001	R	0.888
	Participants	Healthy	2	2.51	-1.69, 6.70	0.242	96.9	< 0.001	R	
		Diseases	4	-1.28	-3.23, 0.76	0.217	94.6	< 0.001	R	
	Duration	≤ 1 week	4	0.22	-2.64, 3.07	0.882	97.2	< 0.001	R	
		> 1 week	2	-0.53	-2.85, 1.78	0.650	91.6	0.001	R	
sTNFR2	Overall		6	0.22	-1.31, 1.74	0.781	94.4	< 0.001	R	0.210
	Participants	Healthy	2	-0.86	-2.83, 1.10	0.388	92.3	< 0.001	R	
		Diseases	4	0.79	-1.46, 3.03	0.491	95.4	< 0.001	R	
	Duration	≤ 1 week	4	0.22	-2.64, 3.07	0.882	97.2	< 0.001	R	
		> 1 week	2	-0.53	-2.85, 1.78	0.650	91.6	0.001	R	
IL-8	Overall		3	-0.05	-0.51, 0.42	0.850	0.0	0.378	F	0.951

IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; sTNFR1, soluble TNF receptor 1; sTNFR2, soluble TNF receptor 2; SMD, standardized mean difference; CI, confidence interval; F, fixed-effects; R, random-effects; P_H-value, significance for heterogeneity; P_E-value, significance for effects.

Two and three datasets respectively analyzed the data of CRP, sTNFR1, sTNFR2, and IL-1β between two groups. The meta-analysis identified no statistically significant differences in these four inflammatory mediators between two groups (P > 0.05) (**Table 4**). Subgroup analysis was not performed for them because of too few articles included.

Meta-analysis of clinical studies (post-WBV vs pre-WBV)

Ten studies with 25 datasets compared the level of IL-6 in populations before and after WBV exercise (Table S2). Surprisingly, the pooled analysis showed that WBV exercise increased the level of IL-6 compared with pre-treatment (SMD: 0.91, 95% CI: 0.31, 1.52, P = 0.003) (**Table 5**). This significant result was also demonstrated in several subgroups (Non-Asian country, healthy participants, WBV frequency ≥ 20 Hz, duration ≤ 1 week and assay by PCR, WB and ELISA; P < 0.05) (**Table 5**).

Two studies with 5 datasets measured the level of IL-1β in populations before and after WBV exercise (Table S2). The pooled results showed WBV exercise did not have effects on the level of IL-1β (P = 0.216) (**Table 5**), which also confirmed in subgroup analyses (**Table 5**).

Four studies with 6 datasets examined the level of CRP in populations before and after WBV exercise (Table S2). The overall meta-analysis did not detect a significant difference (P = 0.100), but the subgroup analysis indicated compared with the baseline value, the level of CRP in populations with diseases was significantly decreased after WBV exercise (SMD: -3.59, 95% CI: -6.36, -0.82, P = 0.011) (**Table 5**; **Figure 5**).

Five studies with 10 datasets recorded the level of IL-10 in populations before and after WBV exercise (Table S2). Under the random-effects model (I^2 = 91.4%, P < 0.001), the pooled results showed the level of IL-10 in the populations undergoing WBV exercise was significantly higher than that before treatment (SMD: 1.75, 95% CI: 0.64, 2.87, P = 0.002) (**Table 5**; **Figure 4B**), which also confirmed in all subgroups (**Table 5**). This significant result was also demonstrated in several subgroups (Non-Asian country, healthy participants, WBV frequency ≥ 20 Hz, duration ≤ 1 week and assay by PCR, WB and ELISA; P < 0.05) (**Table 5**).

Seven studies with 11 datasets examined the level of TNF-α in individuals before and after WBV exercise (Table S2). Although the overall meta-analysis indicated the level of TNF-α was not significantly changed following WBV exercise (P > 0.05) (**Table 5**), the subgroup analysis found that WBV exercise may reduce the expression of TNF-α at mRNA level (SMD: -1.29, 95% CI: -1.91, -0.67, P < 0.001) (**Table 5**; **Figure 3C**).

Four studies with 6 datasets investigated the difference of sTNFR1 and sTNFR2 between before and after WBV exercise. Both of the overall and subgroup meta-analyses did not identify statistically significant differences in these two indicators between before and after WBV exercise (P > 0.05) (**Table 5**).

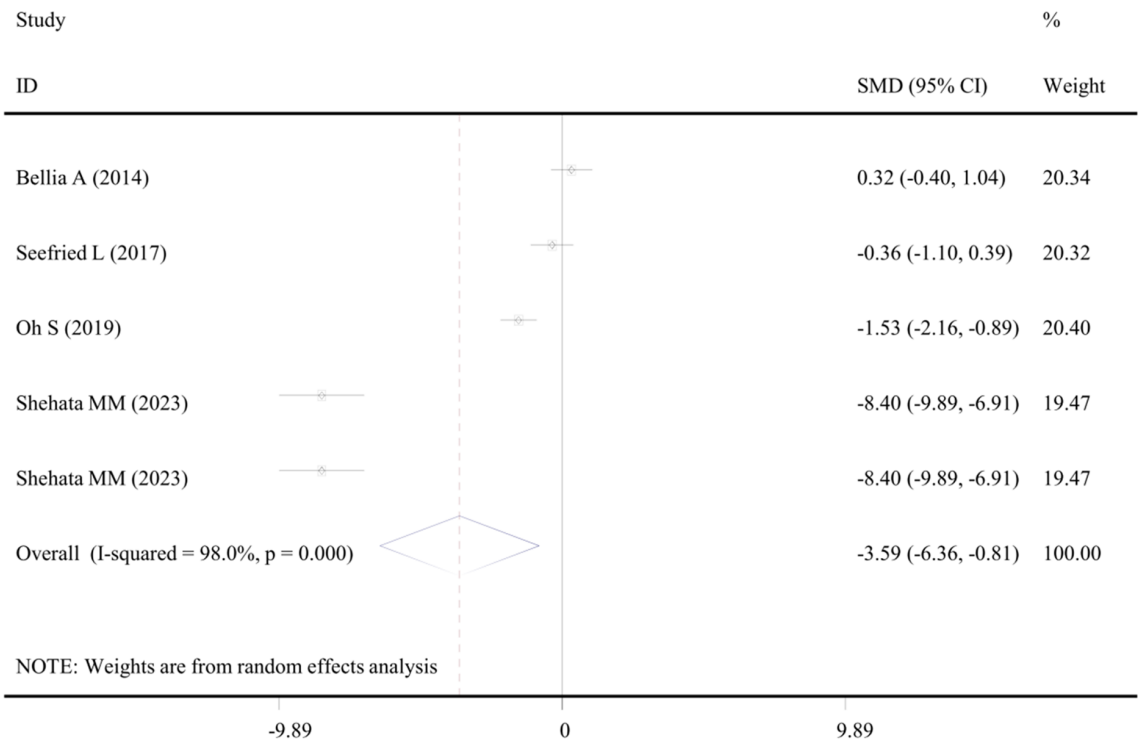

Figure 5. Forest plot of the effects of WBV exercise on C-reactive protein levels. Data were from clinical studies comparing post- with pre-WBV exercise (disease subgroup). WBV, whole-body vibration; SMD, standardized mean difference; CI, confidence interval.

Two studies with 3 datasets analyzed the change of IL-8 before and after WBV exercise. The meta-analysis identified the level of IL-8 was not significantly altered after WBV exercise (P = 0.850) (**Table 5**).

Publication bias and sensitivity analyses

Egger's test was performed to determine the potential publication bias. The results showed that there were significant publication bias in the analysis of IL-1β with the pre-clinical studies (P < 0.001), IL-10 (P = 0.002), TNF-α (P = 0.003) with the WBV vs non-WBV clinical studies, IL-6 (P < 0.001), IL-1β (P = 0.021) and IL-10 (P = 0.001) with the post-WBV vs pre-WBV clinical studies. After filling the missing data using the trim-and-fill method to adjust publication bias, the SMD of IL-1β and TNF-α were not changed; the SMD for IL-6 (0.74, 95% CI: 0.11, 1.37) was slightly changed, but the result remained significant (P = 0.02); the level of IL-10 (WBV vs non-WBV: SMD: 1.52, 95% CI: 3.61, -0.56, P = 0.152; post- vs pre-WBV: SMD: 0.63, 95% CI: -0.74, 2.00, P = 0.370) was found not to be significantly increased. These findings indicated the caution to use IL-10 changes to explain the function mechanisms of WBV exercise. However, the sensitivity analyses demonstrated our results on IL-10 were stable (**Figure 6**).

Discussion

Although a recent study had linked the inflammatory biomarker responses and WBV [48], this only preliminarily reviewed four individual clinical studies. To the best of our knowledge, our study was the first meta-analysis of all published pre-clinical (14) and clinical (17) articles to comprehensively investigate the effects of WBV exercise on the levels of various inflammatory mediators. The significant results from our study can be summarized in the following five points: 1) meta-analysis of pre-clinical studies showed compared with controls, WBV exercise significantly reduced IL-1β, IFN-γ, IL-4 and IL-17 levels in murine models; 2) meta-analysis of pre-clinical and clinical studies showed in comparison with controls or pre-intervention, WBV exercise had significant effects on inhibiting TNF-α levels; 3) meta-analysis of clinical stud-

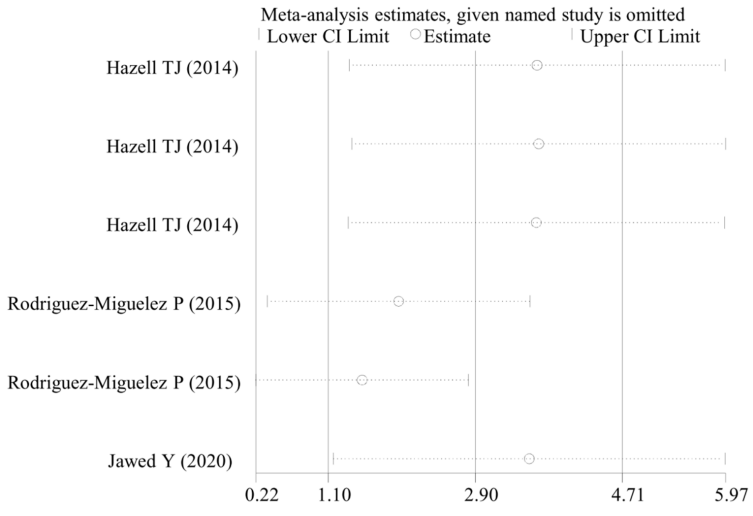

Figure 6. Sensitivity analysis for IL-10. CI, confidence interval.

ies showed relative to controls or pre-intervention, WBV exercise enhanced IL-10 levels; 4) IL-6 was found to be decreased in disease murine models by WBV exercise compared with control, while was observed to be increased from pre- to post-WBV intervention; and 5) WBV exercise resulted in significant decreases in CRP for patients from pre- to post-intervention.

TNF-α was reported to be located in the upstream of the cytokine cascade [49]. TNF-α activated mitogen-activated protein kinase, p38, and nuclear factor kappa B signaling pathways and then induced the expression of other inflammatory mediators, such as IL-1β, IL-6, IL-8, CRP and MCP-1 [50-52]. Thus, upregulation of TNF-α was a very critical step contributing to the development of various inflammation-related diseases, including stroke [53], obesity [54], OA [55], depression [56] and NAFLD [57]. Inactivating or blocking TNF-α was considered as the main target in the treatment of these inflammation-related diseases [58]. In line with this hypothesis, several studies found WBV lowered the levels of TNF-α as well as its downstream (IL-1β and CRP) and alleviated the symptoms [21, 37]. This hypothesis was also confirmed in our meta-analysis of both pre-clinical and clinical studies and previous studies that focused on other exercise interventions [13, 15].

IL-6 was analyzed in both pre-clinical and clinical studies. It decreased in pre-clinical RCT, but no change in clinical control studies and even increased in post-pre-clinical studies. These differences may be attributed to two aspects: 1) most of participants in clinical studies were healthy. IL-6 was also proved to stimulate growth and proliferation of normal cells [59]. Thus, the increase in IL-6 levels by WBV may be a protective inflammatory pathway to prevent the development of apoptotic diseases; 2) only one session of WBV exercise (< 30 min) was performed in several clinical studies [25, 39], while multiple bouts of WBV exercise [22, 28, 29, 32] were applied in animal studies. Thus, the non-significant change in IL-6 levels may be due to the low effectiveness of short-term WBV exercise.

The present meta-analysis has some limitations. First, the number of included studies was relative small for several inflammatory mediators, particularly IL-1β of clinical trials which may be the reasons to lead to a significant decrease by WBV in animal studies, but not in clinical trials. Although IFN-γ, IL-4 and IL-17 were found to be significantly decreased by WBV, only three datasets were included and thus the conclusion remained dubious. The effects of WBV on immune cells (e.g. Treg [60], lymphocytes [61]) could not be analyzed because only one study reported them. Second, the study heterogeneity existed for analysis of most of indicators and could not be removed by the subgroup analysis, which may also influence the reliability of our conclusion. Third, some data were extracted with the GetData Digitizer, which may be slightly different from the actual data. Thus, more experiments (particularly RCT clinical trials) should be performed to confirm the anti-inflammatory effects of WBV exercise.

Conclusion

This present meta-analysis based on the available pre-clinic and clinical evidence suggests that WBV exercise may mainly function by reducing the levels of pro-inflammatory IL-1β, TNF-α, CRP and enhancing the level of anti-inflammatory IL-10. It regulation roles on IL-6

may be different for healthy populations and patients.

Acknowledgements

This study was supported by the program of Shanghai Science and Technology Committee (Grant Nos. 22Y11912100, 20S31905600) and Geriatric Rehabilitation-Nursing Innovation Center Project of Shanghai Sanda University (No. 2023-14).

Disclosure of conflict of interest

None.

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Table S1. Quality assessment of the included studies based on the PEDro scale

Study	Year	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Masked participants	Masked therapists	Masked assessors	Adequate follow-up	Intention to treat analysis	Between-group statistical comparison	Point estimates and variability	Total score
Jiang D	2021	*	*	*	*				*		*	*	7
Kerr N	2022	*	*	*	*						*	*	6
Yu PM	2021	*	*						*		*	*	5
Sun C	2015	*	*	*	*				*		*	*	7
Pawlak M	2013	*	*	*	*				*		*	*	7
Wang H	2023	*	*		*						*	*	5
Wang L	2020	*	*	*	*				*		*	*	7
Tsai SH	2022	*	*	*	*				*		*	*	7
Wu H	2018	*	*	*	*				*		*	*	7
Koczulla AR	2020	*	*	*							*	*	6
Lage VKS	2018	*			*						*	*	4
Sanni AA	2022	*	*	*	*						*	*	6
Bellia A	2014	*	*	*	*				*		*	*	7
Cristi C	2014	*			*				*		*	*	5
Simão AP	2012	*	*	*	*				*		*	*	7
Ribeiro VGC	2018	*			*				*		*	*	5
Neves CDC	2018	*			*			*	*		*	*	6
Jawed Y	2020	*			*				*		*	*	5
Naghii MR	2011	*	*	*	*				*		*	*	7
Hazell TJ	2014	*			*				*		*	*	5
Wunram H	2021	*	*	*	*				*	*	*	*	8
Di Giminiani R	2020	*	*	*	*						*	*	6
Seefried L	2017	*			*				*		*	*	5
McCann MR	2015	*	*	*	*				*		*	*	7
Rodriguez-Miguelez P	2021	*	*	*	*				*		*	*	7
Wano N	2020	*	*	*	*						*	*	6
Chen T	2019	*	*	*	*						*	*	6
Chow SK	2023	*	*	*	*				*		*	*	7
Shehata MM	2019	*	*	*	*				*		*	*	7
Oh S	2014	*			*				*		*	*	5
Weinheimer-Haus EM	2014	*	*	*	*						*	*	6