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Mindfulness mediates the physiological markers of stress: Systematic review and meta-analysis

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ABSTRACT

Meditation is a popular form of stress management, argued to mediate stress reactivity. However, many studies in this field commonly fail to include an active control group. Given the frequency with which people are selecting meditation as a form of self-management, it is important to validate if the practice is effective in mediating stress-reactivity using well-controlled studies. Thus, we aimed to conduct a meta-analysis investigating the neurobiological effects of meditation, including focused attention, open monitoring and automatic self-transcending subtypes, compared to an active control, on markers of stress. In the current meta-analysis and systematic review, we included randomised controlled trials comparing meditation interventions compared to an active control on physiological markers of stress. Studied outcomes include cortisol, blood pressure, heart-rate, lipids and peripheral cytokine expression. Forty-five studies were included. All meditation subtypes reduced systolic blood pressure. Focused attention meditations also reduced cortisol and open monitoring meditations also reduced heart rate. When all meditation forms were analysed together, meditation reduced cortisol, C - reactive protein, blood pressure, heart rate, triglycerides and tumour necrosis factor-alpha. Overall, meditation practice leads to decreased physiological markers of stress in a range of populations.

1. Introduction

Stress is common in modern society and is accepted as an important contributing factor to the onset of a range of illnesses, including depression and anxiety (Dantzer, 2012; Iwata et al., 2013; Masi and Brovedani, 2011; Pascoe et al., 2011). Meditation to manage stress is becoming increasingly popular in Western societies. In Australia, about 1 in 6 adults practise meditation (Xue et al., 2007) and in the United States approximately 1 in 13 adults with a medical condition practise meditation (Bertisch et al., 2009). Despite its growing popularity, the neurobiological mechanisms by which meditation may influence stress are not well understood (Pascoe and Crewther, 2016).

There are many forms of meditation and techniques have been classified in several ways (Ospina et al., 2007). A common method of classification distinguishes between open monitoring (OM) and focused attention (FA) meditation, depending on how attentional processes are directed (Chiesa and Malinowski, 2011). More recently, automatic self-transcending (AST) meditation has also be proposed as a third meditation subtype (Travis and Parim, 2017). OM or mindfulness-based meditation involves non-reactive observation of the content of ongoing experience, to become reflectively aware of cognitive and emotional patterns (Raffone and Srinivasan, 2009, 2010). In FA meditation, attention is focused and sustained on a particular object and brought back to the object when the mind has wandered. Thus, the meditator is controlling one's own attention (Cahn and Polich, 2006; Raffone and Srinivasan, 2009, 2010). AST involves a meaningless mantra that the meditator can attend to without effort or concentration, with the aim of the mantra becoming secondary and ultimately disappearing as self-awareness increases. In AST meditation the mind should be free from focus and mental effort (Travis and Shear, 2010). While OM, FA and AST classifications are useful and each of these meditation types show differences in terms of brain

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functionality (Travis and Shear, 2010), meditation classifications should not be considered to be mutually exclusive, either within a single meditation session or over a life-time of meditation practice (Travis and Shear, 2010). Most meditative techniques lie somewhere on a continuum or orthogonal axes between mindful and concentrative types (Andresen, 2000; Chambers et al., 2009; Chiesa and Malinowski, 2011; Lutz et al., 2008). Indeed, OM and FA have been described as both involving FA, which depending on the meditation type takes different directions (Lutz et al., 2008).

A recent systematic review has shown that various meditation practices influence physiological markers of stress reactivity (Pascoe and Crewther, 2016). Daily life stressors cause pathological arousal and psychological stress resulting in persistent activation of the sympathetic nervous system (SNS) and hypothalamic pituitary adrenal (HPA) axis (Nesse et al., 2016). We have shown in a systematic review that meditation appears to modulate physiological markers of stress in people experiencing depressive symptomatology, particularly when practiced for many hours with a strong focus on breathing (Pascoe and Crewther, 2016). While our review provided preliminary evidence of the beneficial effects of meditation practice on stress reactivity, no meta-analysis has been conducted. Furthermore in our review many studies failed to include an active control (AC) group, which is a significant methodological limitation in this developing filed. Thus, a meta-analysis assessing the impact of meditation on physiological markers of stress in randomised controlled trials (RCTs) with an AC group is both timely and important. In this study we aimed to conduct a meta-analysis of RCTs investigating the effects of meditation practices, including AST, FA and OM subtypes, compared to an AC, on markers of physiological stress.

2. Materials and methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2010). A prospective protocol for the systematic review was not previously published.

2.1. Criteria

Eligible studies were RCTs published in English that included a meditation intervention compared to an AC group, with outcome measures related to physiological markers of stress. Dissertations were excluded.

2.2. Search strategy

Searches were undertaken in May 2016 and updated in December 2016. Articles were obtained by searches of the electronic databases MEDLINE, AMED, CINAHL, PsycINFO, SocINDEX, PubMed, Scopus. Authors of eligible studies were contacted to request unpublished data.

2.3. Study selection

Sourced studies were imported into Covidence Online Software (https://www.covidence.org). Two independent reviewers screened studies for relevance based on titles/abstracts and later full-texts (MCP, ZJ) with disagreements resolved through discussion or by consulting a third reviewer (CFS).

2.4. Data extraction

Data were extracted using a Covidence Online Software and a pre-designed form including study design, country undertaken, aims, ethical information, studied outcomes, sample size, participant characteristics and intervention characteristics. Means (M), standard deviation (SD) and sample size (n) were extracted. Data was extracted independently by two reviewers (MCP, ZJ).

2.5. Risk of bias in individual studies and grades of recommendation, assessment, development and evaluation

The methodological quality of the included studies was independently assessed by two reviewers (MCP, MH), using Covidence Online Software. Due to the nature of the studies reviewed, blinding of participants and personnel was not assessed as it is not possible to blind the person delivering or receiving the meditation intervention. To best capture the current state and quality of research in this field, papers were not excluded based on quality assessment, and thus all eligible articles were included. Grades of Recommendation, Assessment, Development and Evaluation (GRADE), was assessed using the GRADE working group recommendations (Cochrane Collaboration, 2011).

2.6. Summary measures

For the meta-analysis we report the mean difference (MD), or the standardised mean difference (*SMD*), where the MD in each study is divided by the SD to create an index that is comparable across studies (Borenstein et al., 2009). The *SMD* was only used in place of MD when studies included in the meta-analysis used different outcome measures that could not be converted to a common scale (Borenstein et al., 2009). The Hedges' G (*g*), form of the *SMD* was used. Results using completers only were used only when intention-to-treat (ITT) results were not reported. We report the confidence interval (*CI*), the *Z*-value, *p*-value and I^2 statistic (Borenstein et al., 2009).

2.7. Data analysis

Meta-analysis was undertaken using Comprehensive Meta-Analysis Software Version 3 (CMA Version-3). The primary analysis compared the effect of the intervention compared to AC on physiological markers of stress. For the purpose of subgroup analysis, studies were classified as OM, FA or AST. A funnel plot was used to look for any publication bias. Sensitivity analyses were performed using 'one-study-removed'; results of this are only presented in text when removal of a study affected the outcome. A random-effects model was used in all analyses, weighting the studies based on the sample size/standard error. In cases when pre-post correlations were not reported in the published papers, we used a 0.5 correlation.

3. Results

3.1. Study selection

A PRISMA flow-diagram shows the selection of papers for inclusion and exclusion (Fig. 1). 2041 articles were retrieved. Of these 1273 were duplicates and a further 80 were thesis, books or conference proceedings. Ultimately 45 were included. Additional data was provided by one author (Wahbeh et al., 2016).

3.2. Study characteristics

Study specifications are listed in Table 1. Five studies compared meditation with two AC conditions (Carlson et al., 2015; Jung et al., 2015; Lipschitz et al., 2013; Oken et al., 2010; Wahbeh et al., 2016). Separate analyses including these second AC groups are reported in

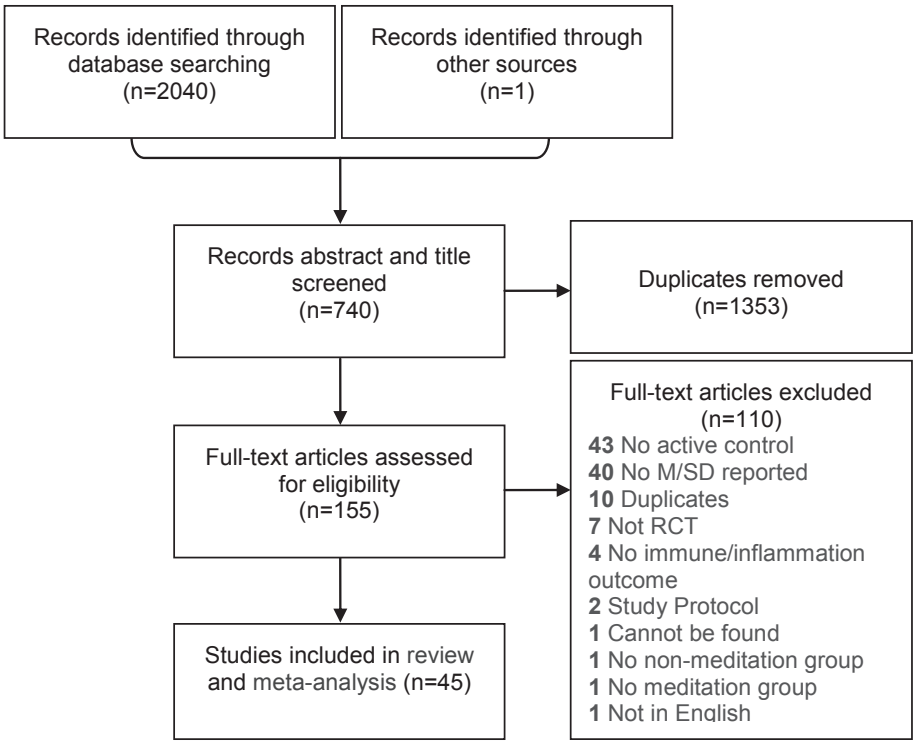

Fig. 1. Flow chart showing the retrieval process of trials included in the systematic review and meta-analysis.

supplementary data. Two studies reported outcomes on the same sample, and thus were combined into one study (Carlson et al., 2013, 2015). One study employed a crossover design and therefore only outcomes before the crossover period were included in the meta-analysis (Patel and North, 1975). Eight studies reported outcomes as mean change scores (Chacko et al., 2016; Daubenmier et al., 2016; Grant et al., 2013; Gregoski et al., 2011; Jayadevappa et al., 2007; Lavretsky et al., 2013; Patel and North, 1975; Wenneberg et al., 1997). All other studies reported outcomes as pre-post means and SD, standard error (SE) or CI within each group.

Group sample sizes ranged from 5 to 136. The interventions and AC groups in each study varied in their components, frequency and length as reported in Table 2 (template for intervention description and replication [TIDiER] table).

3.3. Classification of meditation practices

As seen in Table 1, 28 interventions were classified as OM. OM meditations include mindfulness meditation (MM) and qi gong (Travis and Shear, 2010). We classed the mindfulness program delivered by Hsiao et al. (2016)., as OM as this program included qi gong and MM (Travis and Shear, 2010). Consistent with the work of Tang et al. (2015) we classed Integrative Body-Mind Training (IBMT) as an MM and therefore as an OM. Consistent with the classification of Simkin and Black (2014), mindfulness-based interventions including mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) programs were classed as an OM. Other mindfulness-based interventions considered to be OM were the mindfulness-based intervention delivered by Daubenmier et al. (2016) as the meditation practices were modelled on the MBSR program. The mindfulness-oriented recovery enhancement (MORE) intervention delivered by Garland et al. (2014) was considered to be an OM as it was developed from MBCT.

Eight studies were classified as FA. FA meditations include Kirtan kriya (Raffone and Srinivasan, 2009; Srinivasan and Baijal, 2007; Wang et al., 2011). We also classified walking meditation as FA, as this meditation style involved concentration on the movement or position of ones arms or legs while walking (Gainey et al., 2016). The meditation intervention delivered by Curiati et al. (2005) was considered to be FA as it involved controlled breathing, body scan, and mental repetition of the word “peace,” while trying to keep away any other thoughts and concentrating on a guided image of a healthy heart. We also classed Omkar mantra meditation as FA, as it is a concentrative type of meditation involving focusing attention on a chakra while chanting a mantra, to exclude potential sources of distractions (Harinath et al., 2004). Integrated amrita meditation technique was also considered to be FA, as it involves focused breathing, focusing the mind on an internal point and chanting a mantra (Vandana et al., 2011). The mindfulness-based social and emotional learning education program delivered by Schonert-Reichl et al. (2015) was also classed as FA, as the primary mindfulness practices involved focusing on one's breathing and listening attentively to a single resonant sound.

10 studies were classified as AST. AST practices include TM meditation (Travis and Shear, 2010). On advice from the study authors, primordial sound meditation was also considered to be an AST practice. Primordial sound meditation is derived from TM (Chopra Centre, 2017).

3.4. Risk of bias within studies and grades of recommendation, assessment, development and evaluation

In 30 studies the overall risk of bias was high and in 14 studies it was unclear (insufficient information had been provided), as presented in Table 3. On each of the domains the majority of the RCTs were rated as having a low or unclear risk of bias, which is insufficient to justify downgrading the level of evidence. In terms of population, intervention, comparison, outcomes (PICO) and applicability, we judged that the various populations included, interventions, AC group comparisons, and outcomes assessed were

Table 1
Characteristics of included studies.

Reference	Country	Setting	Study design	Participants	Intervention	Control	Time of assessment	Relevant outcome measures	Follow up	ITT	Meditation category
(Azam et al., 2016)	Canada	University	Parallel group	Students reporting recurrent headaches/ migraines (undergraduate) (age ns)	Audio-guided MM	Audio-guided MM description	Pre-post Intervention	HRV (high frequency)	None	No	OM
(Barnes et al., 2001)	USA	School	Parallel group	Students with high normal blood pressure, 15–18 years	TM	HE	Pre-post Intervention	DBP, SBP, HR (resting, stress test, ns)	None	No	AST
(Barnes et al., 2004a)	USA	School	Parallel group cluster randomisation	Students (grade 7)	MM	HE	Pre-post Intervention	DBP, SBP, HR (ambulatory)	None	Yes	OM
(Barnes et al., 2004b)	USA	School	Parallel group cluster randomisation	Students (high school) (age ns) with BP in the 85- 95th percentile	TM	HE	Pre-post Intervention, follow up	DBP, SBP, HR (ambulatory)	4 months	No	AST
(Barnes et al., 2008)	USA	School	Parallel group cluster randomisation	Students (high school, African American) with prehypertension (age ns)	MM	HE	Pre-post Intervention	DBP, SBP, HR (ambulatory), sodium (urinary)	None	No	OM
(Black et al., 2013)	USA	ns	Parallel group	Caregivers, family (dementia) (age ns)	Kirtan Kriya	Listening to music	Pre-post Intervention	Gene Regulation	None	No	FA
(Carissoli et al., 2015)	Italy	Community based	Parallel group	Healthy Individuals > 18years	MM	Listening to music	Pre-post Intervention	HR (self-collected 5×)	None	No	OM
(Carlson et al., 2015, 2013)	Canada	Cancer medical centre - multi site	Parallel group	Women with breast cancer (stage I, II, or III)	MBSR (MBCR program)	supportive-expressive therapy OR didactic stress management seminar	Pre-post Intervention	Telomere/single-copy gene ratio; cortisol (salivary 4× daily/3 days [waking, 12:00, 17:00, bedtime])	None	No	OM
(Chacko et al., 2016)	USA	Medical Centre	Parallel group	Patients who have undergone bariatric surgery 1–5 years prior to study start, weight loss plateau (<5lbs weight loss in past month), aged 18-65	MBSR, mindfulness-based eating awareness (MB-EAT)	Weight management HE	Pre-post intervention	Hs-CRP, IL-6, TNF-alpha	6 months	Yes	OM
(Chhatre et al., 2013)	USA	Community based	Parallel group	Individuals with HIV >18 years	TM	HE	Pre-post Intervention	Cortisol, norepinephrine (serum [09:00 −10:00])	None	Yes	AST
(Creswell et al., 2016)	USA	Retreat centre	Parallel group	Healthy, stressed, unemployed individuals, 24–54 years	MBSR HEM program	Relaxation retreat	Pre, follow up	IL-6 (plasma [10:00 −12:00])	4 months	No	OM
(Curiati et al., 2005)	Brazil	Hospital	Parallel group	Individuals with CHF, 76–79 years	Meditation (breathing, mantra, visualization)	Weekly meetings	Pre-post Intervention	DBP, SBP, HR (resting, ns), norepinephrine (blood [fasting])	None	No	FA
(Daubenmier et al., 2016)	USA	Community based	Parallel group	Individuals with obesity, >18 years	MB Weight loss intervention	HE, exercise, discussion, progressive muscle relaxation and cognitive-	Pre-post Intervention, follow up	DBP, SBP (resting 2×), triglyceride/ HDL ratio, CRP, FBG, HDL, LDL, triglycerides (blood [fasting])	6, 12 months	Yes	OM

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Table 1 (*continued*)

Reference	Country	Setting	Study design	Participants	Intervention	Control	Time of assessment	Relevant outcome measures	Follow up	ITT	Meditation category
						behavioural training					
(Epel et al., 2016)	USA	Retreat centre	Parallel group	Healthy women, 30–60yrs	Primordial sound meditation and yoga (ns)	Relaxation	Pre-post Intervention	TFN-a	3 wks, 10months	No	AST
(Fan et al., 2010)	China	University	Parallel group	Students (undergraduate, Chinese) (age ns)	Integrative body–mind training (IBMT)	Relaxation training	Pre-post Intervention	Immunoglobin A (salivary 1× [14:00–18:00])	None	No	OM
(Fan et al., 2014)	China	University	Parallel group	Students (undergraduate, Chinese) (age ns)	Integrative body–mind training (IBMT)	Relaxation training	Pre-post Intervention	cortisol (salivary 1× [14:00–18:00])	None	No	OM
(Gainey et al., 2016)	Thailand	University	Parallel group	Individuals with type II diabetes (age ns)	Buddhism-based walking meditation	Walking	Pre-post intervention	HR, SBP, DBP (resting), LDL, HDL, triglycerides, plasma cortisol (8 h fasting blood)	None	No	FA
(Garland et al., 2014)	USA	ns	Parallel group	Individuals with chronic pain and opioid use problems (age ns)	Mindfulness-oriented recovery enhancement (MORE)	Social support	Pre-post Intervention	HR (resting/cue inducted, ns)	None	No	OM
(Goldberg et al., 2014)	USA	ns	Parallel group	Individuals who smoke, >18 years	MBSR for smoking	CBT	Pre-post Intervention	Cortisol (hair)	None	No	OM
(Grant et al., 2013)	USA	University	Parallel group	Students (college) with a family history of hypertension >18 years	MM - from MBSR	Listening to audiobook	Pre-post Intervention	DBP, SBP, HR (resting, stress test, recovery from stress test 3×)	None	No	OM
(Gregoski et al., 2011)	USA	School	Parallel group cluster randomisation	Students (African American), grade 9	MM	Life skills training	Pre-post Intervention	DBP, SBP, HR (ambulatory), sodium (urinary)	None	No	OM
(Grossman et al., 2016)	Germany	ns	Parallel group, open-label	Individuals with fibromyalgia	MBSR	Relaxation	Pre-post intervention	Breathing frequency (breaths per min), HR (ambulatory)	2 months	Yes	OM
(Harinath et al., 2004)	India	Army unit	Parallel group	Healthy army soldiers, males, 25–35 years	Hatha yoga and Omkar mantra meditation	Physical training (army)	Pre-post Intervention	SBP, DBP, MAP (resting, ns) HR (5 min continuous)	None	No	FA
(Hayney et al., 2014)	USA	Community based	Parallel group	Healthy individuals, ≥50 years	MBSR	Exercise	Pre-post Intervention, follow up	Gene Regulation	3 months	No	OM
(Hsiao et al., 2016)	Taiwan	ns	Parallel group	Women with breast cancer completing active treatment with a partner/cohabitant aged 18-65	Mindfulness program (including qi gong and MM) plus body-mind-spirit psychotherapy	Body-mind spirit psychotherapy	Pre-post intervention	Salivary cortisol (waking up, 30 and 45 min after awakening, at 1200 h, 1700 h, and 2100 h)	5, 8, 14 months	Yes	OM
(Jayadevappa et al., 2007)	USA	ns	Parallel group	Individuals (African Americans) with CHF, ≥55 years	TM	HE	Pre-post Intervention	Brain natriuretic peptide, cortisol (plasma)	None	Yes	AST
(Jedel et al., 2014)	USA	University	Parallel group	Individuals with ulcerative colitis, inactive at recruitment, 18–70 years	MBSR	HE	Pre-post Intervention, follow up	Calprotectin (stool); cortisol (urinary); ACTH	10 months	Yes	OM

								(fasting), CRP, IL-10, IL-6, IL-8 (serum)			
(Jensen et al., 2012)	Denmark	ns	Parallel group	Students (university), <40 years	MBSR	NMSR	Pre-post Intervention	Cortisol (salivary 5× daily [waking, 15, 30, 45, 60 min after waking])	None	No	OM
(Jung et al., 2015)	Korea	Community health centres and hospitals	Parallel group cluster randomisation	Individuals with type II diabetes (age ns)	MBSR (Korean) plus HE	HE OR walking exercise plus HE	Pre-post Intervention	Cortisol (plasma [fasting]), FBG, PAI-1, t-PA (serum [fasting])	None	No	OM
(Kingston et al., 2007)	UK	University	Parallel group	Students (university) (age ns)	MM	Guided visual imagery	Pre-post Intervention	DBP, SBP, pulse (resting, ns)	None	No	OM
(Lavretsky et al., 2013)	USA	Home based	Parallel group	Caregivers (dementia) with mild-to-moderate depressive symptoms, >18 years	Kirtan kriya	Relaxation	Pre-post Intervention	Telomerase (blood mononuclear cells)	None	No	FA
(Lipschitz et al., 2013)	USA	Cancer support centre	Parallel group	Cancer survivors with sleep disturbance, 18−75 years	MBSR (excluding asana)	Sleep hygiene education OR MBB	Pre-post Intervention	A-amylase, cortisol (salivary 4× daily [waking, 30 min post waking, 12:00, 17:00, 22:00])	None	Yes	OM
(Lipschitz et al., 2015)	USA	ns	Parallel group	Cancer survivors with sleep disturbance, 18−75 years	MBSR (excluding asana)	Sleep hygiene education	Pre-post Intervention, follow up	Oxytocin (salivary 1× daily [22:00])	2 months	Yes	OM
(MacLean et al., 1997)	USA	University hospital clinical research centre	Parallel group	Healthy men (Caucasian), 18−32 years	TM	Stress education	Pre-post Intervention	Growth hormone, testosterone, thyroid-stimulating hormone (fasting serum [08:30 −09:00])	None	No	AST
(Oken et al., 2010)	USA	University	Parallel group	Caregivers, family (dementia), 45−85 years	MBCT (adapted)	Education/social control OR respite	Pre-post Intervention	Cortisol (salivary 3× daily [waking, 30 min post waking, 22:00]), CRP, HS-CRP, IL-6, TNF-a (serum)	None	No	OM
(Palta et al., 2012)	USA	Senior housing facility	Parallel group	Elderly individuals, African-American, ≥62 years	MBSR (ELDERSHINE)	Social support	Pre-post Intervention	SBP, DBP (resting 3×)	None	No	OM
(Parswani et al., 2013)	India	University hospital	Parallel group	Individuals with CHD, males, 30−65 years	MBSR (excluding asana)	HE	Pre-post Intervention, follow up	DBP, SBP (resting, ns)	3 months	No	OM
(Patel and North, 1975)	UK	Hospital	Crossover	Individuals with hypertension, <75 years	TM	Relaxation	Pre-post Intervention	SBP, DBP (resting, ns)	None	No	AST
(Paul-Labrador et al., 2006)	USA	Medical centre	Parallel group cluster randomisation	Individuals with CHD, > 18 years	TM	HE	Pre-post Intervention	DBP, SBP, MAP (resting 3×), HRV (ambulatory) HS-CRP, HDL, LDL, cholesterol, triglycerides (plasma)	None	No	AST
(Prakhinkit et al., 2014)	Thailand	University hospital	Parallel group	Individuals with mild-to-moderate depression (age ns)	Buddhism-based walking meditation	Walking	Pre-post Intervention	DBP, SBP, HR, (resting, 5 min), cortisol, CRP, HDL, LDL, cholesterol,	None	No	FA

(continued on next page)

Table 1 (*continued*)

Reference	Country	Setting	Study design	Participants	Intervention	Control	Time of assessment	Relevant outcome measures	Follow up	ITT	Meditation category
								triglycerides, IL-6, nitric oxide (fasting plasma)			
(Schonert-Reichl et al., 2015)	Canada	School	Parallel group cluster randomisation	Students (grade 4 and 5)	Mindfulness-based education program (MindUP)	Social responsibility program	Pre-post Intervention	Cortisol (salivary 3× daily [09:30, 11:30, 14:30]	None	No	FA
(Steffen and Larson, 2015)	USA	University	Parallel group	Students (undergraduate psychology) (age ns)	MM	Listening about ethical behaviours and awareness.	Pre-post Intervention	DBP, SBP (during, following stress test, 2×)	None	No	OM
(Vandana et al., 2011)	India	ns	Parallel group	Students (college) 18 –21 years	Integrated amrita meditation technique	PMR	Pre-post Intervention	Adrenaline, cortisol (plasma [fasting])	None	No	FA
(Wahbeh et al., 2016)	USA	University	Parallel group	Combat veterans with PTSD (age ns)	MM OR MM with slow breathing	Slow breathing with biofeedback OR sitting quietly	Pre-post Intervention	HR, HRV (resting, ns), cortisol (salivary 3× daily [waking, 30 min post waking, bedtime]	None	No	OM
(Wenneberg et al., 1997)	USA	University hospital and clinic	Parallel group	Healthy men (age ns)	TM	Stress education	Pre-post Intervention	DBP, SBP (ambulatory)	None	No	AST

appropriate to address the question of if meditation influences stress related physiological measures compared to AC groups in various populations. As seen in Supplementary Table 1, the GRADE of evidence was downgraded from high to low when unexplained heterogeneity was seen and the study *n* was small or there were too few studies available to accurately assess publication bias using funnel plots. When only unexplained heterogeneity was seen the GRADE of study evidence was downgraded from high to moderate.

3.5. Meta-analysis

3.5.1. Blood cortisol

The assessment of cortisol (Fig. 2) was conducted using SMD. Cortisol was measured at post-intervention in three studies using AST meditation forms compared to HE, and no effect was found, $Z = -0.59$, $p = 0.55$, $I^2 = 0$. The three studies using FA meditation significantly reduced cortisol, $Z = -2.84$, $p < 0.01$, $I^2 = 8.44$. Only one OM-based study assessed cortisol. When all seven studies were analysed together a medium effect of meditation was found, $Z = -2.92$, $p < 0.01$, $I^2 = 0$. Meta-analysis of salivary cortisol was not reported given that blood cortisol was available.

3.5.2. Immune outcomes

3.5.2.1. C-reactive protein (CRP). High sensitivity (h-s) CRP was measured in four studies (Fig. 3) and CRP was measured in two studies at post-intervention and one study at 10 months post-intervention (Jedel et al., 2014). The correlation between CRP and h-s CRP is 0.98 (Helal et al., 2012; Rifai et al., 2006). Two studies used ITT analysis (Chacko et al., 2016; Daubenmier et al., 2016). CRP was measured in five studies using OM meditation forms compared to AC, and no effect was found, $Z = -1.39$, $p = 0.17$, $I^2 = 0$. Only one AST and FA study assessed CRP. When all meditation forms were analysed together, a small effect was found, $Z = -2.00$, $p = 0.045$, $I^2 = 0$, which did not withstand one-study removed analysis (see supplementary data).

3.5.2.2. Norepinephrine. Norepinephrine was measured in two studies at post-intervention and assessed using SMD (supplementary Fig. 1). No subgroup analysis based on meditation classification was conducted as one study used FA meditation and the other AST. When both studies were analysed together, no effect of meditation compared to AC was found, $Z = -1.54$, $p = 0.12$, $I^2 = 44.84$.

3.5.2.3. Interleukin 6 (IL-6). IL-6 was measured using MD and assessed in five studies (Fig. 4), two at post-intervention (Oken et al., 2010; Prakhinkit et al., 2014), one at 2 months (Chacko et al., 2016), one at 4 months (Creswell et al., 2016) and one at 10 months post-intervention (Jedel et al., 2014) ($n = 123$). Two studies used ITT analysis (Chacko et al., 2016; Creswell et al., 2016). IL-6 was measured in four studies using OM meditation forms compared to AC, and no effect was found, $Z = -1.39$, $p = 0.16$, $I^2 = 0$. Only one study assessed IL-6 using FA and none assessed IL-6 using AST. When all meditation forms were analysed together there was similarly no effect resulting from meditation, $Z = -1.02$, $p = 0.31$, $I^2 = 5.65$. Subgroup analysis using collection time points found no variance between studies assessing IL-6 at post-intervention $I^2 = 0$, indicating that the observed variance likely resulted from different collection time points following the intervention.

3.5.2.4. Tumour necrosis factor-alpha (TNF-α). TNF-α was measured in three studies at post-intervention (Fig. 4) and assessed using MD. In two studies that used OM there was no difference compared to AC, $Z = -1.67$, $p = 0.10$, $I^2 = 0$. When all three studies were analysed together, meditation was found to decrease TNF-α by 0.21 pg/mL,

Table 2
Template for intervention description and replication table describing characteristics of the interventions.

Reference	Intervention	Control	Personnel delivering treatment	Individual/ group	Mode of delivery	Duration frequency
(Azam et al., 2016)	MM: "Participants were asked to remain seated in a relaxed and upright manner with eyes closed. A 10 m audio recording was played featuring mindfulness instructions which emphasized bringing attention to sensations while breathing and re-focusing on breathing sensations once there was awareness of thoughts, feelings, bodily sensations, and/or external stimuli. The instructions were recorded by a clinical psychologist and experienced MM instructor"	Mindfulness Meditation Description (MMD): "Participants were seated identically as in the MM condition (including eyes closed). They were played 10 m audio description of historical and scientific information about mindfulness meditation. During this recording, there were no instructions on practicing mindfulness or breathing"	I & C: clinical psychologist and experienced MM instructor	Group	In person	MM & MMD: 1 day (10 m audio recording)
(Barnes et al., 2001)	TM: "Practiced while sitting comfortably with eyes closed. Origin in the ancient Vedic approach to health, and does not require changes in personal belief, lifestyle, or philosophy. No effort toward intentionally altering physiological processes. TM technique includes an introductory lecture to discuss the benefits and mechanics, then a brief personal interview and a personal instruction session, and three follow-up meetings of 1−2hrs in small groups over the next 3 days"	"The group was presented with lifestyle education sessions based in part on the National Institutes of Health guidelines on lowering BP through weight loss, diet (reducing fat and sodium intake), and increasing physical activity"	Not specified	I: Individual; C: Group	In person	I: 2mo 2 × 15 m/ day; C: 1 h/wk/7wk
(Barnes et al., 2004a)	MM	"Sessions on prevention of high BP and CVD risk factor reduction including information and instructions on lowering BP through weight loss, diet (reducing fat and sodium intake), and increasing physical activity (ie, daily 20 m walks after school)"	Science teacher	Group	In person	3mo - 20 m/wk PLUS home practice 20 m/day
(Barnes et al., 2004b)	TM	"Lifestyle education sessions based on lowering BP through weight management, diet (increasing fruit and vegetable consumption and reducing caloric, fat and sodium intake) and increasing physical activity"	Teacher	I: Individual; C: group	In person	4mo - I: 15 m/ 2xday; C: 15 m/ 5xwk
(Barnes et al., 2008)	MM	"Sessions on preventing high blood pressure using guidelines for adolescents. This instruction included information on lowering blood pressure through weight loss, diet (reducing fat and sodium intake), and physical activity"	Classroom teacher	Group	In person	3mo - I: 10 m/ 2xday; C: 20 m/wk
(Black et al., 2013)	Kirtan Kriya: "Yogic meditation chanting practice that progresses through 1 m of silently focusing inwards on the mind and body in the present moment, 11 m of mudras or repetitive finger movements while chanting "Saa, Taa, Naa, Maa," meaning "Birth, Life, Death, and Rebirth" that are chanted first aloud, gradually softening into a whisper, and then silently. The meditation practice is completed with deep breathing and the visualization of light"	"The RM protocol requested participants to relax in a quiet place with their eyes closed while listening to relaxing instrumental music provided to them on an audio CD"	CD	Individual	CD	8wks - 12 m/day
(Carissoli et al., 2015)	"MM delivered through a smartphone app, translated from the 3 m Breathing Space Meditation. The participant is invited to sit quietly in a comfortable location where he/she can devote full attention to imagine a beautiful mountain"	"Music control group "Music listeners had to use their mobile device to listen to two pieces of relaxing music (chosen from a proposed list) per day, while doing nothing else"	Smart phone	Individual	Smart phone	18d - 2 × 15 m/day
(Carlson et al., 2015, 2013)	"The intervention consists of three primary components: 1) theoretical material related to relaxation, meditation, and the body-mind connection; 2) experiential practice of meditation during the group meetings and home-based practice; and 3) group process focused on problem solving	"The SET program encourages openness and emotional expression, with an aim toward developing a mutual support system among members as well as improving interactions with family and treating physicians. Through group discussion, SET also aims to facilitate coping skills and to detoxify negative	Clinical psychologist & a nurse trained in MBSR or SET; C2 Social worker	Group	In person	I:/90 m/wk/8wk PLUS 1 × 6hr retreat; C1(SET): 12 90 m/w/12wks (Both total 18 h);

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Table 2 (*continued*)

Reference	Intervention	Control	Personnel delivering treatment	Individual/ group	Mode of delivery	Duration frequency
	related to impediments to effective practice, practical day-to-day applications of mindfulness, and supportive interaction between group members (Speca et al., 2000)"	emotions surrounding mortality" OR "A 1-day (6hr) didactic SMS"				C2(SMS) single 6 h session
(Chacko et al., 2016)	MBBT: "The intervention integrated mindfulness with adapted versions of traditional behavioural strategies for obesity. The structure of the intervention was adapted from the established MBSR course. We also incorporated elements from MB-EAT. We did not include explicit calorie and exercise goals since our target was not intensive weight loss but rather long-term weight maintenance. Sessions began with formal mindfulness practice, followed by group sharing on the week's experience, and ended with a didactic portion covering a behavioural concept or skill taught from the perspective of mindfulness"	Weight management counselling: "Participants assigned to the standard intervention received an individualized counselling session. Participants spoke privately to the dietician about their efforts in weight management. The dietician provided guidance on nutrition, exercise and lifestyle strategies tailored to post-surgical patients. This intervention was chosen as a control to mirror the usual nutrition standard-of-care that bariatric patients receive annually post-surgery"	I: Qualified mindfulness instructor	Group	In person	MBBT: 10 wks, 90 min class per week plus home practice plus 4 h retreat. C: 1 h session
(Chhatre et al., 2013)	TM	"The HE course addressed more in-depth nutritional information than generally is provided in HIV care. Participants were asked to engage in an activity, e.g., reading, twice a day for home practice"	I: certified instructor; C: nurse	Group	In person	6 mo - 2 h/5xwk/ 1wk then 2xmo/ 3mo then 1xmo/ 3mo PLUS home practice 40 m/day
(Creswell et al., 2016)	"Mindful eating exercise and body scan meditation after gentle stretching. Meditation included sitting, walking meditation, and mindful movement and meditation on various objects of attention, such as breath sensations, body sensations, sounds, moods or emotions, and thoughts and the spaces between thoughts. Participants were asked to notice pleasant and unpleasant events and record their physical sensations, moods or emotions. Discussions included exploration of pleasant and unpleasant events, stress and stress physiology, reacting and responding to stress, life challenges, plans for meeting unemployment and job-seeking stress with mindfulness"	Imagery exercises focused on visualizing a stream and later a comfortable and safe place. Participants worked in pairs to develop scripts for pleasant, relaxing place imagery, and guided one another in this exercise. Discussions included exercise for stress management, nutrition. Participants engaged in stretches led using counting or joke-telling in order to avoid the development of body awareness and acceptance. Stress and health, hobbies and interests were topics for discussion. Participants used drawing to explore their own social circles of support. Imagery exercises included reflecting on the future and where participants imagined themselves being in five years"	Not specified	Group	In person	3d/retreat
(Curiati et al., 2005)	"Listening at home, in a seated position, about the practice of meditation, divided into three 10 m stages. The first one controlled breathing, with deep and slow breaths. The aims of this technique were to reduce breathing rate and to learn how to mobilize in sequence. The breathing was followed by a kind of body scan, from head to pelvis. The second stage included mental repetition of the word "peace," gently trying to keep away any other thoughts. The breathing rhythm was spontaneous, with no breathing control. The third stage consisted of concentrating on a guided image of a healthy heart"	"The control group had a weekly meeting, which included talking about stress"	Not specified	Group & Individual	In person	12 wks - I: Single 2 h session then 1xwk PLUS home practice 30 m/ 2xday; C: 1xwk
(Daubenmier et al., 2016)	"The dietary component recommended healthy food and modest calorie reduction. The exercise component emphasized increasing daily activity and moderate-intensity exercise. Participants learned formal MM practices including sitting meditation and yoga postures drawn from MBSR. Guided meditations on mindfulness of thoughts and emotions and didactic information about the stress response were	"The dietary component recommended healthy food choices that emphasized modest calorie reduction (typically 500 kcal/day), including decreasing calorie-dense nutrient-poor foods, decreasing simple carbohydrates and substituting whole grains, and increasing consumption of fresh fruits and vegetables, healthy oils, and proteins. The exercise component emphasized increasing daily activity and moderate-	I: mindfulness meditation instructors and co-led by the same registered dietician; C: registered dietician	Group	In person	5.5mo - 2–2.5 h/ 1xwk/16wks then 1xbi-wk/6wks then 1xwk/1wk PLUS single 6.5 h session

	introduced. Mindful eating components included guided meditations, discussion to teach mindful eating practices of paying attention to physical sensations of hunger, stomach fullness, taste satisfaction, and food cravings; use of mini-meditations before meals. Mindful walking was taught using principles from Chi Walking which emphasizes posture and alignment and awareness of internal and external sensations while walking"	intensity exercise, primarily through walking, and strength training. The control group had additional nutrition and physical activity information, strength training with exercise bands, discussion of societal issues concerning weight loss, snacks, and home activities. The control also included progressive muscle relaxation and cognitive-behavioural training"				
(Epel et al., 2016)	Meditation retreat providing training in meditation (primordial sound meditation, which is similar to mantra meditation), foundations of yoga, and sutra, with the aim of promoting inner calm, expanded awareness of one's body, breath, and self, and life-transforming skills	Vacation Group with an afternoon lecture on health behaviors each day for 1.5 h and an optional activity in the morning, such as a leisurely walk	I: MD and qualified instructors; C: ns	Group	In person	1wk retreat
(Fan et al., 2010)	IBMT: "IBMT involves several body−mind techniques including body relaxation, mental imagery and mindfulness training, accompanied with selected background music. The method emphasizes no effort to control thoughts and achievement of a state of restful alertness that allows a high degree of awareness of body, breathing and external instructions"	"RT involves the relaxing of different muscle groups over the face, head, shoulders, arms, legs, chest, back and abdomen, guided by a tutor and CD. With eyes closed and in a sequential pattern, one is forced to concentrate on the sensation of relaxation, such as the feelings of warmth and heaviness"	Qualified instructors	Group	In person	4 wks, 20−30 m/day
(Fan et al., 2014)	IBMT	RT	Qualified instructors	Group	In person	4 wks, 20 m/day
(Gainey et al., 2016)	WM: "In phase 1 (wk 1−6), 50−60% maximum HR and phase 2 (wk 7−12), 60−70% maximum HR. The sessions consisted of 10 m warm-up and general static stretching, 30 m workout and 10 m cool-down and general static stretching. Exercise intensity was confirmed using heart rate monitors and performed on the treadmill. The subjects performed walking on the treadmill while concentrating on foot stepping. The subjects had to voice "Budd" and "Dha" while setting each foot on the floor. The goal was to practice mindfulness while walking"	Exercise training program: "Phase 1 (wk 1−6), conducted at 50−60% maximum HR, phase 2 (wk 7−12), conducted at 60−70% maximum HR. The sessions consisted of a 10 m warm-up and general static stretching, followed by 30 m workout and 10 m cool-down and general static stretching. Intensity was confirmed by using the heart rate monitors and performed on the treadmill. The training program started with 12 types of stretching as warm-up and ended with another stretching as cool-down"	Not specified	Group	In person	WM & C: 12 weeks, 3 × 50 min session per week
(Garland et al., 2014)	"Training in mindfulness, cognitive reappraisal, and savouring skills. Participants were taught a savouring practice, which involved using mindfulness to intentionally orient and sustain attention on the sensory features of a pleasant experience or object while attending to and appreciating any positive emotions arising in response to the pleasant event"	"Facilitated discussion and disclosure of emotions on topics pertinent to chronic pain and long-term opioid use. This support group format was based on the evidence-based Matrix Model intensive outpatient treatment manual. Support group participants were asked to engage in 15 m of journaling a day on chronic pain-related themes at home"	I: Master's level social worker with mindfulness training; C: master's level clinical social worker	Group	In person	8 wks- 2 h/wk PLUS home practice 15 m/day
(Goldberg et al., 2014)	"MBSR taught to participants in the usual manner with some differences: subjects entered the intervention with the purpose of smoking cessation; a quit date was provided, addiction questionnaires and carbon monoxide testing was performed, and course instructions focused on how one might apply mindfulness to craving and withdrawal symptoms. Subjects were encouraged not to focus on smoking cessation as a "goal" for the intervention, instead to direct their intention toward developing a mindful orientation toward their lives"	"Based on the American Lung Association Clinics The basic American Lung Association clinic format. In-depth discussion of the general health effects of smoking, coping strategies for urges to smoke. Quit Day occurred at this third session. Benefits of quitting were reiterated and possible withdrawal symptoms discussed. The remaining sessions focused upon maintenance. Discussion included relaxation techniques, exercise or physical fitnessprograms, avoiding weight gain, and coping with tension. Session 7 was a celebration and awards were given to everyone who completed the program"	I: MBSR instructor; C: not specified	Group	In person	8 wks - 1xwk (duration not specified) PLUS (I only) home practice 45 m/6× wk
(Grant et al., 2013)	MM	"Listened to the beginning portion of an audiobook, Harry Potter and the Sorcerer's Stone"	Not specified	Group	In person	1day (duration not specified)
(Gregoski et al., 2011)	MM	"Group discussions, passive and active modelling, behavioural rehearsal, feedback, reinforcement, and	Health education teachers	Group	In person	

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Table 2 (*continued*)

Reference	Intervention	Control	Personnel delivering treatment	Individual/ group	Mode of delivery	Duration frequency
		behavioural homework assignments. The components provided training in problem-solving skills, reflective listening, conflict resolution, and anger management to enhance social skills, assertiveness, and personal and social competence"				3mo - MM: 10 m/ 2xday; LST: 50 m/ wk
(Grossman et al., 2016)	MBSR: "Each session covered specific exercises and topics within the context of mindfulness practice and training. These included various types of formal mindfulness practice, mindful awareness of dynamic yoga postures, and mindfulness during stressful situations, and social interactions. The all-day retreat included a combination of previously used and newly introduced mindfulness exercises. Pre-post intervention personal interviews were conducted to help patients formulate realistic individual goals for the intervention. Post intervention interviews addressed participants' personal experiences during the course and assessed the degree to which pre treatment goals had been met"	Relaxation and physical therapy: "The active control intervention was planned to control for the nonspecific aspects of the MBSR curriculum. Equivalent amounts of social support and weekly topical educational discussions were provided. Use PMR training, and fibromyalgia-specific gentle stretching exercises served as counterparts for mindfulness and yoga elements of the MBSR curriculum. Patients received compact discs with instructions for daily exercises. Pre-post intervention interviews were given by individual instructors using the same protocol as with the MBSR group"	MBSR: certified counsellor with MBSR training with experience in teaching fibromyalgia patients; C: psychologists	Group	In person	MBSR: 8 wks, 2.5hr session per week plus 1 × 7.5hr session per week plus daily home practice 45 −60 min. C: 2.5hr session per week plus daily home practice 45 −60 min.
(Harinath et al., 2004)	"Yogic asanas 45 m, pranayama 15 m/morning, preparatory yogic postures15 m, pranayama 15 m, and meditation 30 m/evening. Posture of each asana was maintained for 2 m, shavasana practiced for 2 m after completing four asanas. During morning hours subjects practiced Bhastrika/Bhrahmari pranayama. In the evening they performed Sheetali, Sheetkari, Bhrahmari, and Nadi Shodhan pranayama. The ratio of inhalation, retention, and exhalation of breath in Nadi Shodhan pranayam was 1:2:2. The pranayama and meditation were performed in padmasan (sitting) posture. During meditation the subjects were asked to concentrate on the Agya Chakra presumably located near the prefrontal area and then on Sahasrar Chakra near the location of pineal gland for each breath of expiration while they chanted "OM" in a soft voice"	"Routine army physical training exercise daily. These exercises consisted of body flexibility exercises for 40 m and slow running for 20 m during morning hours and games for 1 h in the evening"	I: qualified yoga instructor	Group	In person	3 mo/1 h/2xday
(Hayney et al., 2014)	MBSR〃MM including body scan, a supine meditation, gentle Hatha Yoga practiced with mindful awareness of the body, a sitting meditation with mindfulness of breath, body, feelings, thoughts, emotions, and choiceless awareness. A walking Meditation, awareness of pleasant and unpleasant events, breathing, routine activities, interpersonal communications and daily home assignments including a minimum of 45 m/day of formal mindfulness practice and 5–15 m of informal practice. Individual and group dialogue and inquiry oriented around home assignments, including an exploration of hindrances to mindfulness and development"	"Borg's Rating of Perceived Exertion was used to guide participants toward moderate intensity, sustained exercise, with a target rating of 12–16 points on the 6 –20 point scale"	I: Trained in program; C: senior exercise physiology staff	Group	In person	8 wks - 2.5 h/wk PLUS home practice 45 m/day
(Hsiao et al., 2016)	CSG with Mindfulness: "CSG aimed to enhance the capacity of both breast cancer survivors and their partners to cope with stress and their marital relationships. In addition to body-mind-spirit holistic psychotherapy, the control group received; CSG was developed based on family resilience therapy and	"ISP was developed based on body-mind-spirit holistic psychotherapy. Telephone consultations provided information on how to prevent breast cancer recurrence including a healthy lifestyle and holistic empowerment strategies to cope with stress. Survivors received both ISP and their cortisol reports	Principal researcher trained in psychotherapy and mindfulness	I: Group, C: Individual	I: In person, C: phone	I: 8 weeks - 120 min session per week. C:5/6 phone calls of 30–60 min duration

	mindfulness-based therapy to form a mindfulness-incorporated couples support group. A number of couples-focused mindfulness activities, including mindful breathing, guided imagery, individual and interactive meditation with loving kindness, such as a dyadic eye-gazing exercise and a mindful touching exercise, were applied in our group. For example, they practiced breathing in, I am aware of my self-worth. Breathing out, I send my love and caring to my partner, and they sit facing each other with one silently observing his/her partner while the other closed his/her eyes. Couples were invited to share verbally with others about their experiences of emotions, body responses, images, or memories after practice. Couples were guided to quietly focus on giving and receiving a neck and shoulder massage and then discuss their experiences of body sensations"	for each measurement time during the telephone calls; the partners received their cortisol reports only in the mail. Their partners were to learn about how to improve their cortisol responses from survivors. A total of five telephone calls lasting 30–60 m each were provided when survivors completed outcome measures at each study time point"				
(Jayadevappa et al., 2007)	"TM and participants were instructed to maintain a daily diary of their intervention compliance, change in food habits, and other usual activities"	"Educational sessions based on educational modules from the 2002 education program of the Heart Failure Society of America. Participants were instructed to listen to music or read. Participants were instructed to maintain a daily diary of their intervention compliance, change in food habits, and other usual activities"	I: certified instructor; C: nurse	Group	In person	6mo - 90 m/day/7 days, then bi wk/ 3mo, then 1xmo/ 3mo PLUS home practice 20 m/day
(Jedel et al., 2014)	MBSR	"The focus of the course was mind/body medicine and was comprised of lectures and videos. Course topics included the effect of stress on physical and psychological health, the physiology of the 'flight-or-fight response', the effect of stress on sleep, and stress and special populations. Homework comprised of articles that supplemented the course content"	I: physician with MBSR expertise; C: clinical psychologist	Group	In person	8 wks - I: 2–2.5 h/ 1× wk PLUS home practice 45 m/6× wk; C: 1× wk PLUS homework, (duration not specified).
(Jensen et al., 2012)	MBSR	"Guided relaxations, during which participants were lying down with their eyes closed. NMSR did not train the non-judgmental attitude through accepting whatever bodily sensations were experienced or through psycho-education on the presumed value of this attitude. Each course included asana, grounding exercises, and 20 m of circulatory training. A central strategy was to increase participants' body consciousness, helping them to become aware of ways to relax during stress"	MBSR: psychologist & experienced mindfulness instructor; NMSR: authorized psychomotrician	Group	In person	8 wks - I: 2.5 h/1× wk PLUS home practice 1 h/day PLUS 7 h retreat; C: 2.5 h/1× wk PLUS home practice 1 h/ day
(Jung et al., 2015)	"K-MBSR program based on an audio-CD, which facilitated mindful walking, eating, and breathing and silent sitting meditation. Each week focused on a different subject: Orientation of the program; The characteristic of mindfulness; From acting to being; The power of breathing; Mindfulness breathing; Staying present; Mindfulness hatha yoga; The day of mindfulness; Your own meditation way"	"Specific topics included diet, exercise, stress management, foot care, hypoglycaemic medications, hypoglycaemia symptoms and management strategies, and potential complications. Lectures were the main instructional method used. Participants answered closed-ended questions concerning the main theme and shared their experiences during the educational program" OR ″Walking exercise: The walking technique used included holding the head high, looking forward, moving the shoulders naturally, keeping the back straight, swinging the arms freely with a slight bend at the elbow, and walking smoothly by rolling each foot from heel to toe"	I: nurse training in K-MBSR; C: not specified	Group	In person	8 wks - I: 60 –120 m/wk PLUS home practice; C: 1× wk (meeting), 1× wk (telephone interview) 30 –60 m/3–4x wk
(Kingston et al., 2007)	MM	"GVI sessions were divided between introducing GVI, practicing GVI, and reflective discussion. Each GVI practice began by centring participants with 2 min of	I: clinical psychologist & psychiatrist; C:	Group	In person	3 wks - I: 2 h/wk/ PLUS home practice 20 m/day; C: 2 h/w/

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Table 2 (*continued*)

Reference	Intervention	Control	Personnel delivering treatment	Individual/ group	Mode of delivery	Duration frequency
		guided deep breathing. Participants were then encouraged to evoke mental images of the scenes described by the group trainer (e.g., walking through a garden)"	clinical psychologist			2wks PLUS home practice 20 m/day
(Lavretsky et al., 2013)	Kirtan Kriya	"The relaxation group were asked to relax in a quiet place with their eyes closed while listening to the instrumental music on the relaxation CD"	CD	Individual	CD	8 wks - 12 m/day
(Lipschitz et al., 2013)	MBSR (excluding asana)	SHE: "Participants were informed about ways to change their daily activities and evening habits to improve their sleep. Topics discussed included: What would cause my insomnia? When should I speak with my doctor about my sleep disturbance? What behavioural changes would help me to get a better night's sleep? What activities to avoid to get a better night's sleep? Medications used for sleep problems? Participants could ask questions and the group discussed their sleep issues" MBB: "Training included identifying the underlying source of sleep problems from an MBB perspective; awareness exercises to reduce daytime stress; addressing sleep issues pertinent to cancer survivors; and practicing MBB on a daily basis. Participants were provided a MBB published book, which they were encouraged to read and practice MBB techniques and exercises"	I: clinical social worker, experienced MBSR instructor; C: clinical social worker	Group	In person	3 wks - 2 h/wk
(Lipschitz et al., 2015)	MBSR (excluding asana)	SHE OR MBB	Clinical social worker	Group	In person	3 wks - 2 h/wk
(MacLean et al., 1997)	TM	"Topics included 'Recognizing Stress in One's Life' and 'How to Effectively Deal with and Reduce the Impact of Stress' as well as lessons in time management. Daily entry of experiences into a diary as a control for the daily attention to practice of the TM program"	I: qualified instructor; C: counselling instructor	Group	In person	4mo 1× class (duration ns) PLUS home practice 15 −20 m/day
(Oken et al., 2010)	"Didactic instruction and discussion concerning stress, relaxation, meditation, and mind−body interaction; instruction and practice in meditation and other mindfulness exercises; and group discussion and problem-solving regarding successes and difficulties in exercises and applying in daily life. A seated meditation, beginning with awareness of breathing and expanding to include awareness of body sensations and cognitive and emotional experience. Mindful awareness was encouraged during routine daily activities. Also practiced a brief meditative exercise, of mindfully attending to a troubling situation and responses to it, shifting focus of attention to the breath, and then returning attention to the troubling situation in a calmer and less reactive mood"	Education Class: "Subjects completed weekly assignments consisting of daily reading from The Caregiver Help-book and carrying out of action plans generated by the subject. Non-didactic, social interaction time was limited to 15 ms. The patient for whom the participant is caring for was provided with respite care during the classes" Respite Care only: "The third group of caregivers was provided with respite care. The time for respite care during the week was chosen by the caregiver"	I: clinical psychologist trained in MBSR & MBCT; C: trained teacher	Group; Respite - Individual	In person	7wks - 90 m/wk PLUS home practice; Respite: 7 wks - 3 h/wk
(Palta et al., 2012)	"The sessions consisted of an opening meditation, sharing of successes, a review of home practices, a lesson to practice and apply mindfulness skills to self-care and interpersonal relationships, a guided breath meditation, a closing meditation, an invitation to do specific home practices, and a healthy fruit-and-vegetable snack"	"To initiate communication among participants, the research assistants provided pre-planned conversation starters that mirrored the topics in the intervention group. Following the session, participants were offered a fruit-and vegetable snack identical to the foods served to the intervention group"	I: an interventionist trained in MBSR; C: research assistant	Group	In person	8wks - 90 m/wk
(Parswani et al., 2013)			Not specified	Group	In person	

	"Patients in both the groups were given health education about CHD and its management. The MBSR therapeutic program included training in different variants of mindfulness meditation such as body scan meditation, sitting meditation, mindful walking, mindful eating, 3-min breathing space, mastery and pleasure activities and cognitive restructuring"	"Patients in both the groups were given health education about CHD and its management. Patients in the TAU group did not receive any further sessions after the health education session"				8wks - 30 m home practice/day I: 1 h/wk; C: single session (duration ns)
(Patel and North, 1975)	TM	General relaxation (not specified)	Not specified	Group	In person	6wks - 30 m/2xwk
(Paul-Labrador et al., 2006)	TM	"Lectures and discussions included CHD risk factors and the impact of stress, diet, and exercise on CHD".	Professional Health educators	Group	In person	16wks - 90 m/2xwk/4wks then 90 m/wk/12wks
(Prakhinkit et al., 2014)	"In this practice, each step is taken after each breath. The program was divided into two phases, (wk 1–6) mild intensity and (wk 7–12) moderate intensity. Program included 11 common stretching exercises. Walking exercises were perfomred while rhythmically swinging both arms and voicing "Budd" with arm swing up and "Dha" with arm swing down and instructed to practice mindfulness. In phase 2, the training workload was increased by subjects holding a 500 mL water bottle in each hand"	"Walking was divided into two phases, (weeks 1–6) mild intensity (20%–39% individually determined heart rate reserve) and (weeks 7–12) moderate intensity (40%–50% heart rate reserve). The program included 11 common stretching exercises performed during warm-up and cool-down stages"	Investigators	Group	In person	12wks - 20 m/3xwk then 30 m/3xwk
(Schonert-Reichl et al., 2015)	"Focusing on one's breathing and attentive listening to a single resonant sound, includes lessons that promote executive functions, self-regulation, social –emotional understanding, and positive mood. Lessons that involve performing acts of kindness for one another and collectively engaging in community service learning activities. Aimed at changing the ecology of the classroom environment to one in which belonging, caring, collaboration, and understanding others is emphasized to create a positive classroom milieu"	"The framework includes a common set of expectations for the development of students along four categories: contributing to classroom and school community, valuing diversity and defending human rights, and practicing democratic rights and responsibilities"	Classroom teacher	Group	In person	12wks - I: 45 m/wk PLUS 3 m/day; C: Not specified
(Steffen and Larson, 2015)	MM	"Passive listening to tracks focusing on awareness of the environment and the importance of ethical behaviours. The specific tracks were Awareness, A Sixth Sense, and An Ethical Foundation"	CD	Group	In person	single 15 m session
(Vandana et al., 2011)	"Relaxation exercises/yogic postures and breathing exercises which draw attention to the way one breathes and prompt a more complete breathing. Throughout the process awareness is the main component. One is encouraged to be aware of all the subtleties of each of the steps. One part in particular focuses on the flow of breath while focusing the mind on an internal point, rather than on a physical object outside. Belief in a spiritual master and chanting the mantra given by the master is recommended. Only the first class is guided"	"Based upon the practice of tensing or tightening one muscle group at a time followed by a relaxation phase with release of the tension. PMR involves a physical and mental component. With the eyes closed and in a sequential pattern, a tension is given to a muscle group purposefully for approximately 10sec and then released for 20sec before continuing with the next muscle group. The whole PMR session takes approximately 30 m"	I: teachers approved by the Mata Amritanandamayi Math; C: physiotherapist	Group	In person	8mo - I: 28 m/day; C: 30 m/day
(Wahbeh et al., 2016)	MM OR MM + Slow Breathing: "Mindful awareness of the breath with an intention to slow the breath. Participants sat upright and attempted to focus their attention on the breath as it passed the opening of the nostrils and created movement in the abdomen or chest and naturally slow their breath as they consciously observed their breathing"	Slow breathing "There were no instructional scripts. Participants used a breathing device designed to reduce respiratory rate" Sitting Quietly: "Activities included making jewellery, tying flies, reading magazines or books, doing crossword puzzles, playing solitaire, and observing nature"	Trained research Assistant	Group	In person	6wks - MM, MM + SB, SB: 20 m/wk PLUS home practice 20 m/day; SQ: 20 m/day.
(Wenneberg et al., 1997)	TM	"Topics included how to recognize stress in one's life and how to deal with and reduce the impact of stress, as well as lessons in time management. Home practice consisted of keeping a diary about their experiences of the stress education program"	I: qualified instructor; C: psychologist	Group	In person	14-16wks - 15–20 m/2xday

Table 3
Risk of bias assessment for included studies.

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
(Azam et al., 2016)	L	L	UC	H	UC	L
(Barnes et al., 2001)	UC	UC	UC	UC	UC	UC
(Barnes et al., 2004a)	H	UC	L	L	UC	H
(Barnes et al., 2004b)	UC	UC	UC	H	UC	L
(Barnes et al., 2008)	H	UC	UC	H	UC	H
(Black et al., 2013)	L	UC	H	L	UC	L
(Carissoli et al., 2015)	UC	UC	UC	UC	H	H
(Carlson et al., 2015, 2013)	L	L	L	L	H	L
(Chacko et al., 2016)	L	L	L	L	L	L
(Chhatre et al., 2013)	UC	UC	L	L	UC	H
(Creswell et al., 2016)	L	L	L	L	H	UC
(Curiati et al., 2005)	UC	UC	UC	H	UC	H
(Daubenmier et al., 2016)	L	L	H	L	H	H
(Epel et al., 2016)	L	L	H	UC	UC	L
(Fan et al., 2010)	UC	UC	UC	L	UC	L
(Fan et al., 2014)	UC	UC	UC	UC	UC	H
(Gainey et al., 2016)	L	UC	UC	H	UC	H
(Garland et al., 2014)	L	L	UC	H	UC	UC
(Goldberg et al., 2014)	UC	UC	UC	H	UC	L
(Grant et al., 2013)	UC	UC	UC	UC	L	H
(Gregoski et al., 2011)	H	UC	UC	UC	UC	H
(Grossman et al., 2016)	UC	UC	L	L	L	H
(Harinath et al., 2004)	L	UC	UC	UC	UC	UC
(Hayney et al., 2014)	L	L	L	UC	L	L
(Hsiao et al., 2016)	L	L	UC	L	UC	L
(Jayadevappa et al., 2007)	L	L	L	L	UC	L
(Jedel et al., 2014)	L	L	L	L	L	H
(Jensen et al., 2012)	UC	UC	L	L	UC	UC
(Jung et al., 2015)	H	L	L	H	UC	L
(Kingston et al., 2007)	L	L	L	UC	UC	UC
(Lavretsky et al., 2013)	L	L	UC	UC	UC	H
(Lipschitz et al., 2013)	L	UC	UC	L	UC	L
(Lipschitz et al., 2015)	UC	UC	UC	UC	UC	H
(MacLean et al., 1997)	UC	L	L	H	H	H
(Oken et al., 2010)	UC	L	L	UC	UC	L
(Palta et al., 2012)	UC	UC	UC	L	UC	H
(Parswani et al., 2013)	L	UC	UC	H	UC	H
(Patel and North, 1975)	UC	UC	L	L	UC	UC
(Paul-Labrador et al., 2006)	L	L	L	H	UC	H
(Prakhinkit et al., 2014)	L	UC	UC	H	UC	L
(Schonert-Reichl et al., 2015)	L	L	L	L	UC	H
(Steffen and Larson, 2015)	UC	UC	UC	L	UC	L
(Vandana et al., 2011)	L	UC	UC	UC	UC	L
(Wahbeh et al., 2016)	L	UC	L	UC	UC	UC
(Wenneberg et al., 1997)	UC	UC	L	H	UC	L

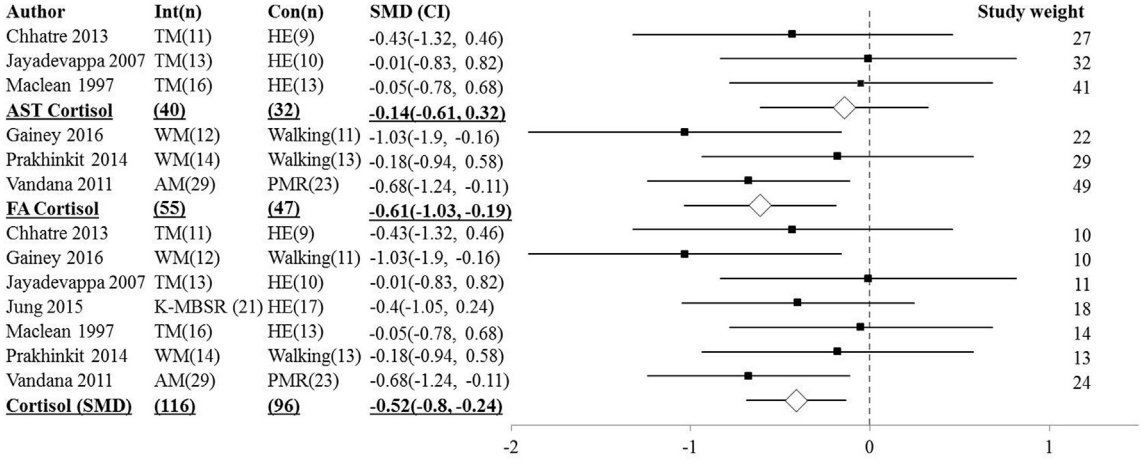

Fig. 2. Forest plot of meditation interventions on blood cortisol. AM = Amrita meditation; AST = Automatic self-transcending; Con = Control group; FA=Focused attention; HE = health education, Int = Intervention; K-MBSR=Korean mindfulness based stress reduction; PMR=Progressive muscle relaxation; SE=Stress education; SMD=Standardised mean difference, TM = Transcendental meditation; WM=Walking meditation.

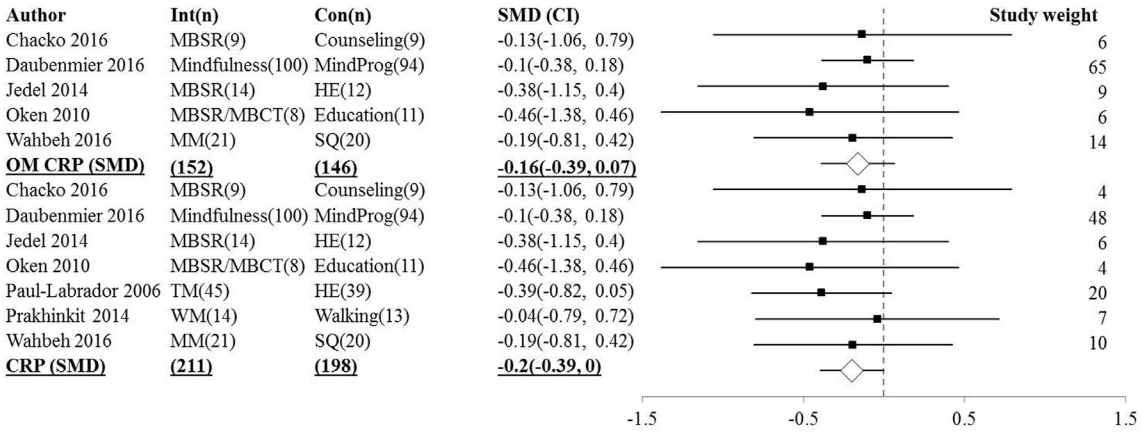

Fig. 3. Forest plot of meditation interventions on c-reactive protein. CBT=Cognitive behavioural therapy; Con = Control group; CRP=C-reactive protein; E = Education; HE = health education, Int = Intervention; K-MBSR=Korean mindfulness based stress reduction; MBCT = Mindfulness based cognitive therapy; MBSR = Mindfulness based stress reduction; MM = Mindfulness meditation; OM=Open monitoring; MindProg = Mindfulness program with Education, cognitive behavioural therapy, progressive muscle relation and social support; PMR=Progressive muscle relaxation; SE=Stress education; SMD=Standardised mean difference, SS=Social support; SQ=Sitting quietly; TM = Transcendental meditation; WM=Walking meditation.

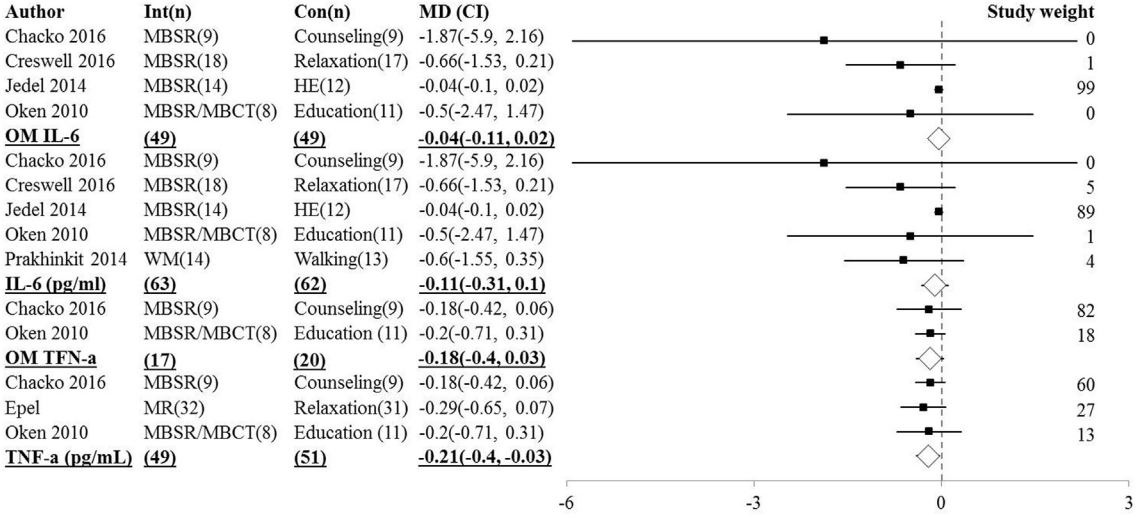

Fig. 4. Forest plot of meditation interventions on interleukin-6 and tumour necrosis factor-alpha. Con = Control group; HE = health education, IL-6 = Interleukin 6; Int = Intervention; MBCT = Mindfulness based cognitive therapy; MBSR = Mindfulness based stress reduction; MR = Meditation retreat; OM=Open Monitoring; TNF-α = Tumour necrosis factor alpha.

$Z = -2.25$, $p = 0.02$, $I^2 = 0$.

3.5.3. Autonomic measures

3.5.3.1. Blood pressure (BP). Resting DBP and SPB were assessed using MD at post-intervention (Figs. 5 and 6). Two studies used ITT analysis (Barnes et al., 2004a; Daubenmier et al., 2016). Resting SBP was measured in three studies using AST meditation and was found to decrease SBP by 8.97 mm of mercury (mmHg) compared to AC, $Z = -3.11$, $p < 0.01$, $I^2 = 40.07$. Resting SBP was measured in three studies using FA meditation and was found to decrease SBP by 5.55 mmHg, $Z = -0.45$, $p = 0.03$, $I^2 = 0$. Resting SBP was measured in five studies using OM meditation did not decrease SBP, $Z = -1.71$, $p = 0.09$, $I^2 = 36.65$. When all studies were analysed together, meditation decreased SBP by 5.37 mmHg, $Z = -3.66$, $p < 0.01$, $I^2 = 34.84$.

None of the meditation subtypes were found to decrease resting DBP as shown in Fig. 6 (AST, $Z = -1.72$, $p = 0.08$, $I^2 = 81.02$; FA, $Z = -1.74$, $p = 0.08$, $I^2 = 42.43$; OM, $Z = -1.03$, $p = 0.30$, $I^2 = 0$). When all meditation forms we analysed together, meditation was found to decrease resting DBP by 2.96 mmHg compared to AC, $Z = -2.75$, $p = 0.01$, $I^2 = 57.08$.

Ambulatory DBP and SBP was measured in five studies at post-intervention (Fig. 7), with 4 measuring 24hr BP and one measuring from 13:00–22:00 (Wenneberg et al., 1997). Only one study used ITT analysis (Cohen et al., 2016).

Neither AST nor OM was found to decrease ambulatory DBP compared to health education (AST, $Z = -1.68$, $p = 0.09$, $I^2 = 0$; OM, $Z = -1.68$, $p = 0.09$, $I^2 = 0$). When all meditation forms were analysed together, meditation decreased ambulatory DBP by 1.63 mmHg, $Z = -2.31$, $p = 0.02$, $I^2 = 0$.

AST did not decrease ambulatory SBP however OM did by 2.33 mmHg, $Z = -2.31$, $p = 0.02$, $I^2 = 0$. When all meditation forms were analysed together, meditation similarly reduced SBP, $Z = -2.15$, $p = 0.01$, $I^2 = 0$. Removal of the study by Barnes et al. (2004a) resulted in a p value of 0.057.

Three studies assessed DBP and SBP during a stress test (supplementary Fig. 2) (Barnes et al., 2001; Steffen and Larson, 2015) [social stress test]; (Grant et al., 2013) [cold pressor]. For

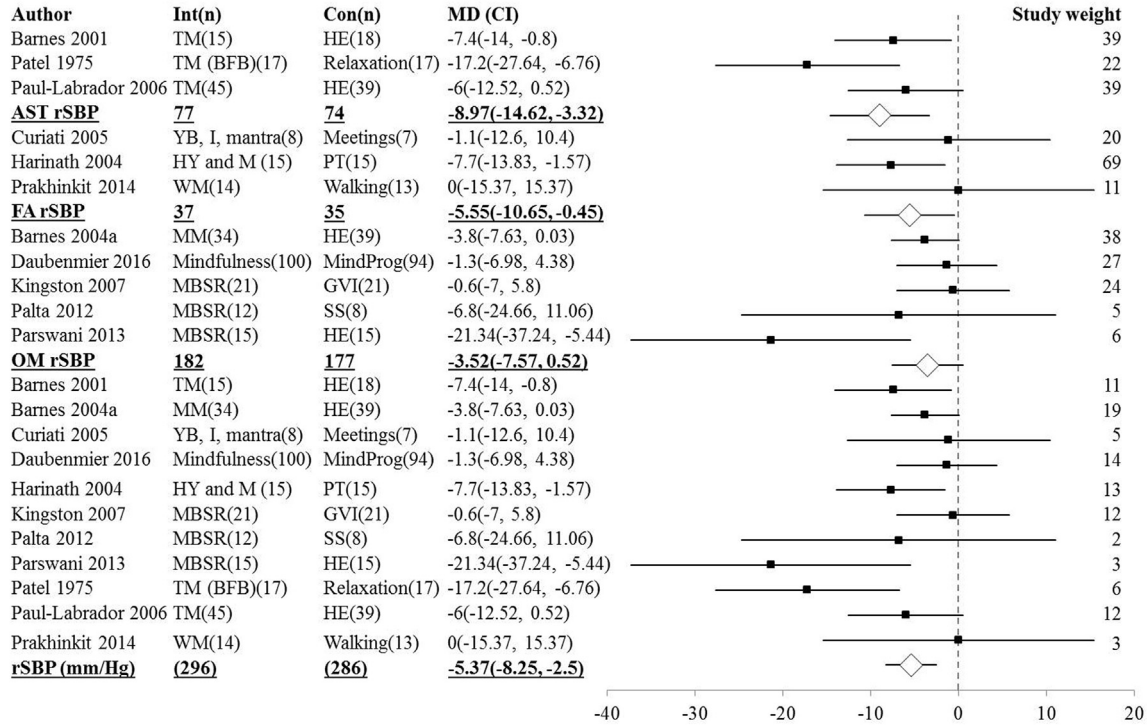

Fig. 5. Forest plot of meditation interventions on resting systolic blood pressure. AST = Automatic self-transcending; BFB=Biofeedback; Con = Control group; FA=Focused Attention; GVI = Guided visual imagery; HY=Hatha yoga; HE = health education, I=Imagery; Int = Intervention; L = learning; M = Meditation; MBSR = Mindfulness based stress reduction; MM = Mindfulness meditation; OM=Open monitoring; Re=Reading; PMR=Progressive muscle relaxation; rSBP = Resting systolic blood pressure; PT=Physical training; SS=Social support; SQ=Sitting quietly; TM = Transcendental meditation; Mm/Hg = Millimetres of mercury; MindProg = Mindfulness program with Education, cognitive behavioural therapy, progressive muscle relation and social support; WM=Walking meditation; YB=Yoga breathing.

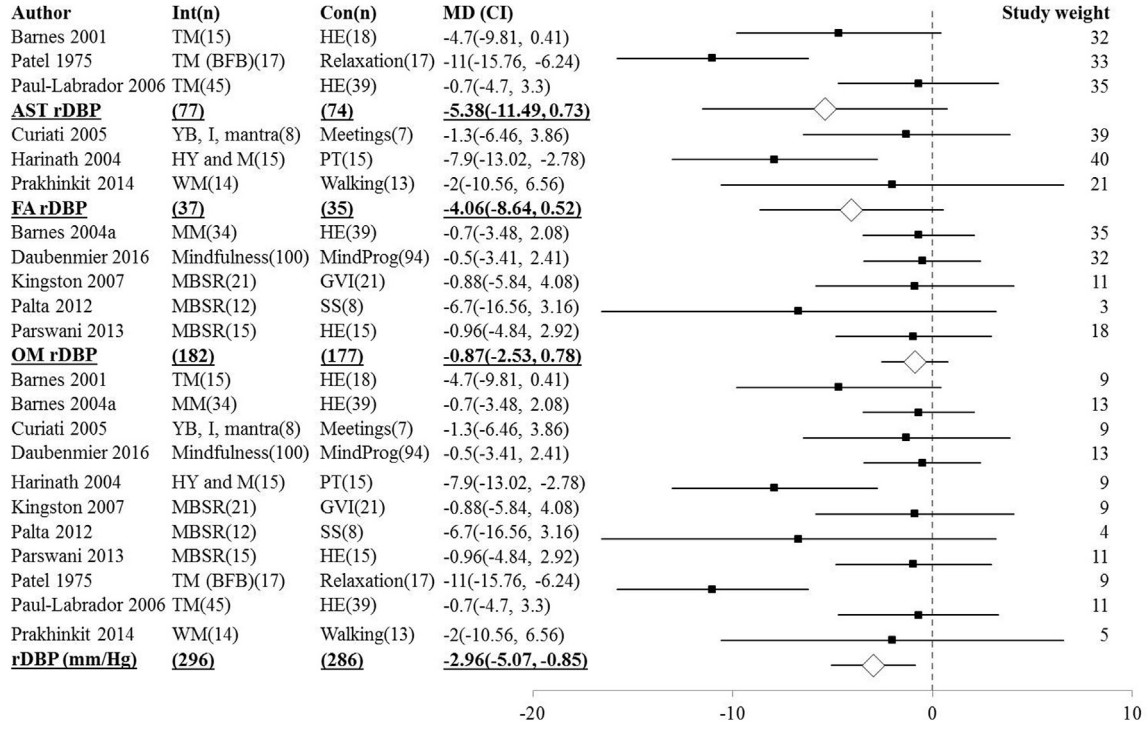

Fig. 6. Forest plot of meditation interventions on resting diastolic blood pressure. AST = Automatic self-transcending; BFB=Biofeedback; Con = Control group; FA=Focused attention; GVI = Guided visual imagery; HY=Hatha yoga; HE = health education, I=Imagery; Int = Intervention; L = learning; M = Meditation; MBSR = Mindfulness based stress reduction; MM = Mindfulness meditation; OM=Open monitoring; rDBP = Resting Diastolic blood pressure; Re=Reading; PMR=Progressive muscle relaxation; PT=Physical training; SS=Social support; SQ=Sitting quietly; TM = Transcendental meditation; Mm/Hg = Millimetres of mercury; MindProg = Mindfulness program with Education, cognitive behavioural therapy, progressive muscle relation and social support; WM=Walking meditation; YB=Yoga breathing.

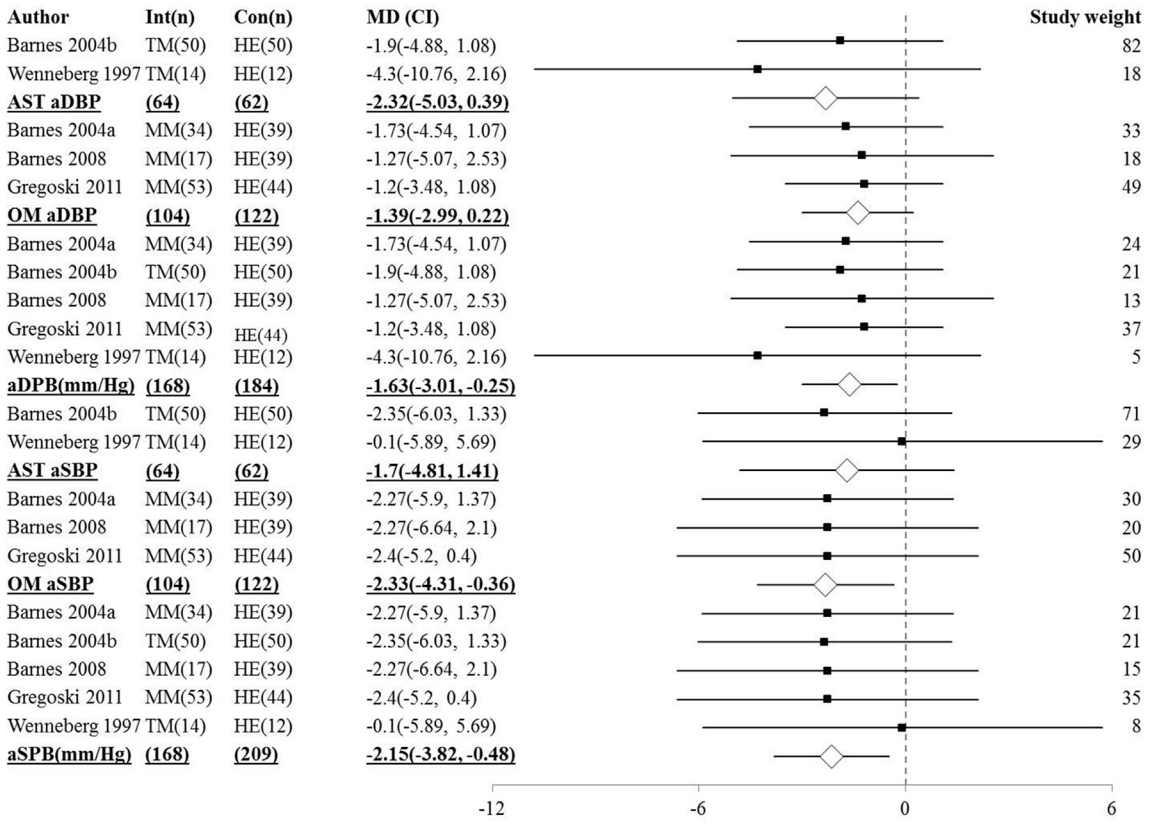

Fig. 7. Forest plot of meditation interventions on ambulatory blood pressure. a = ambulatory; AST = Automatic self-transcending; BAM=Breathing awareness meditation; BLS=Botvin LifeSkills Training; Con = Control group; HE = health education; Int = Intervention; MM = Mindfulness meditation; Mm/Hg = Millimetres of Mercury; OM=Open monitoring; SE=Stress education; SMD=Standardised mean difference; st = Stress test; TM = Transcendental meditation.

DBP no effect was found in the two studies that used an OM form of meditation, $Z = -0.86$, $p = 0.39$, $I^2 = 0$. No effect on DBP was found when all three studies were analysed together, $Z = -0.80$, $p = 0.43$, $I^2 = 0$.

For SBP, the two studies that used OM meditation decreased SBP by 5.43 mmHg, $Z = -1.98$, $p = 0.05$, $I^2 = 0$. There was similarly a decrease in SBP when all three studies were analysed together $Z = -2.59$, $p = 0.01$, $I^2 = 0$. Removal of the study by Steffen and Larson (2015) resulted in a non-significant p value of 0.12. Only one AST study assessed BP during a test.

3.5.3.2. Heart rate (HR). Heart rate was assessed using MD at post intervention (Fig. 8). One study used ITT analysis (Barnes et al., 2004a). OM meditation decreased resting HR by 3.11BPM, $Z = -2.01$, $p = 0.04$, $I^2 = 0$. FA had no effect, $Z = -1.86$, $p = 0.06$, $I^2 = 0$ and only one AST study assessed resting HR (Barnes et al., 2001). When all studies were analysed together, participants in the meditation group had a resting HR 3.37BPM slower than those in the AC group, $Z = -2.77$, $p = 0.01$, $I^2 = 0$.

Ambulatory HR (24hr) was measured in five studies at post-intervention (Fig. 8). Only one study used ITT analysis (Barnes et al., 2004a). OM did not decrease ambulatory HR, $Z = -1.44$, $p = 0.15$, $I^2 = 0$. Only one AST study assessed ambulatory HR. When all studies were analysed together, meditation similarly did not decrease ambulatory HR, $Z = -1.81$, $p = 0.07$, $I^2 = 0$.

3.5.3.3. Heart rate variability-high frequency (HRV-hf). HRV-hf was measured in three studies at post-intervention (supplementary Fig. 3). One study used ITT analysis (Chacko et al., 2016). Two studies measured ambulatory 24hr HRV (Grossman et al., 2016; Paul-Labrador et al., 2006) while the third study measured resting HRV-hf (Azam et al., 2016). There was no effect of OM meditation in two studies, $Z = -1.12$, $p = 0.26$, $I^2 = 78.89$. Only one AST study assessed HRV-hf. Similarly, no effect of meditation was found when all three studies were analysed together, $Z = -0.82$, $p = 0.41$, $I^2 = 72.11$.

3.5.4. Lipids

Triglycerides, HDL and LDL were measured in four studies at post-intervention using SMD (Fig. 9). One study used ITT analysis (Daubenmier et al., 2016). Only one OM and AST study assessed lipids. Two studies used FA meditation and found no effect of meditation on triglycerides, $Z = -1.16$, $p = 0.25$, $I^2 = 0$. An effect of the intervention was found on triglycerides when all studies were analysed together, $Z = -2.24$, $p = 0.03$, $I^2 = 0$. Removal of the study by Daubenmier et al. (2016), which was largely responsible for the effect, resulted in a non-significant p value of 0.25. FA meditation had no effect on HDL, $Z = 1.33$, $p = 0.18$, $I^2 = 0$, cholesterol, $Z = -0.45$, $p = 0.66$, $I^2 = 0$, or LDL, $Z = -0.67$, $p = 0.50$, $I^2 = 0$. No effect of meditation was seen on HDL, LDL or cholesterol when all studies were analysed together (HDL, $Z = 0.95$, $p = 0.34$, $I^2 = 0$; LDL, $Z = -0.95$, $p = 0.34$, $I^2 = 0$; Cholesterol, Z=-0.36, $p = 0.72$, $I^2 = 0$).

3.5.5. Fasting blood glucose (FBG)

FBG at post intervention was assessed using MD in three studies (supplementary Fig. 4) (Daubenmier et al., 2016; Gainey et al., 2016; Jedel et al., 2014). No effect was found in the two studies using OM, $Z = -0.61$, $p = 0.54$, $I^2 = 0$ or when all three studies were analysed

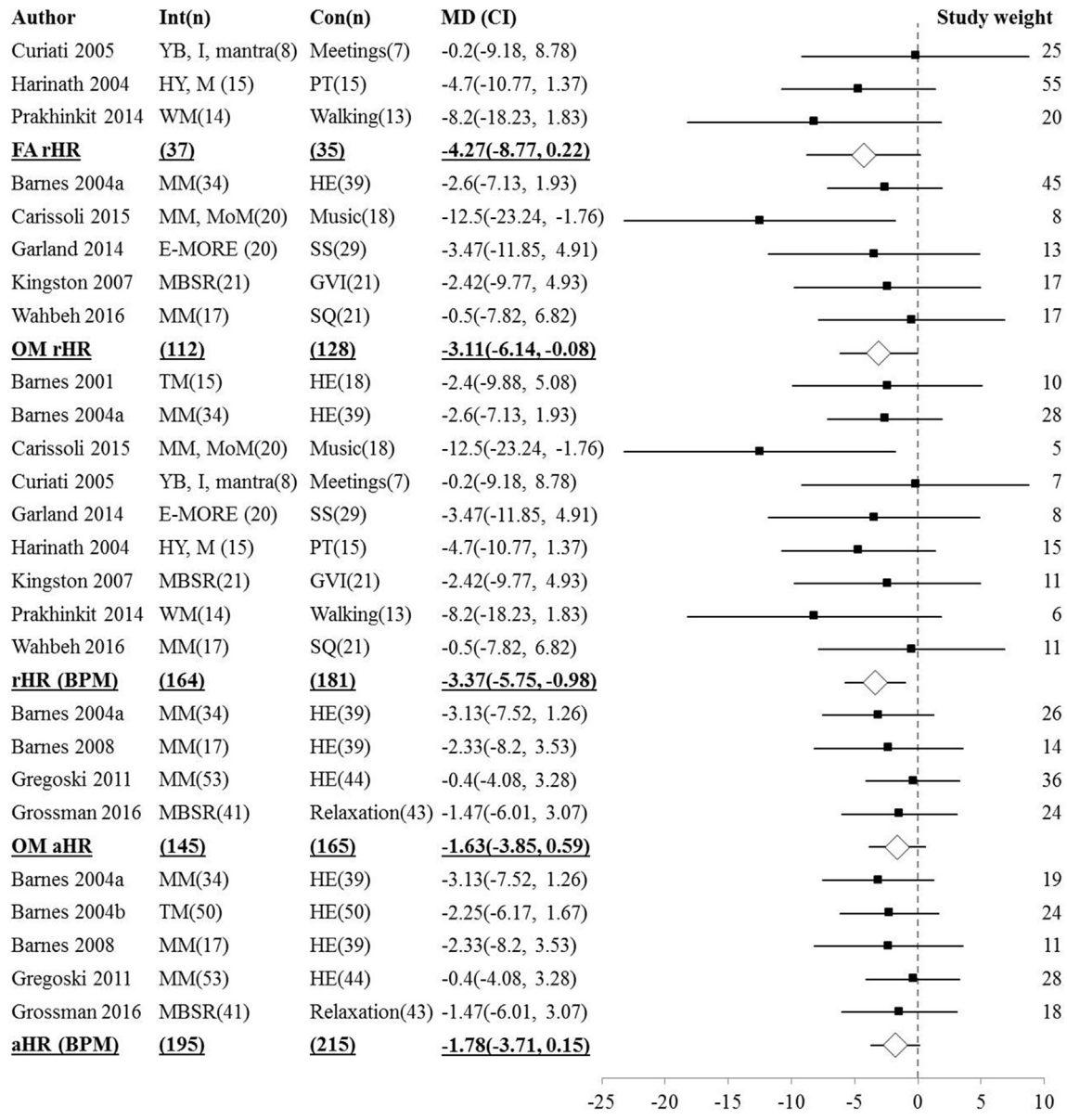

Fig. 8. Forest plot of meditation interventions on resting and ambulatory heart rate. a = ambulatory; BAM=Breathing awareness meditation; BLS= Botvin lifeSkills training; Con = Control group; E-MORE = E Mindfulness oriented recovery enhancement; FA=Focused attention; GVI = Guided visual imagery; HE = health education; HR=Heart rate; HY=Hatha yoga; I=Imagery; Int = Intervention; MBSR = Mindfulness based stress reduction; M = Meditation; MM = Mindfulness meditation; MoM=Mountain meditation; OM=Open monitoring; PT=Physical training; SE=Stress education; SS=Social support; r = Resting; TM = Transcendental meditation; WM=Walking meditation; YB=Yoga breathing.

together, $Z = -0.62$, $p = 0.54$, $I^2 = 0$. Only one FA study assessed cholesterol.

4. Discussion

We conducted a meta-analysis of RCTs investigating the effects of meditation, including AST, FA and OM subtypes, compared to an AC on markers of physiological stress. We included 45 studies which examined the relationship between meditation and cortisol, HR, BP, cytokine and lipid levels. Lipids were included as high cholesterol levels are associated with the accumulation of cholesterol in macrophages and other immune cells, which promotes inflammation (Tall and Yvan-Charvet, 2015), and as individuals with chronic inflammatory diseases show a changed lipid profile (Feingold and Grunfeld, 2000).

4.1. Meditations effects according to classification

AST meditations reduced resting SBP. FA meditations reduced blood cortisol, and resting SBP. OM meditations reduced ambulatory SBP, SBP following a stress test and resting HR. These results indicate that AST, FA and OM influence stress-related physiological measures. The effect of OM on resting HR, ambulatory SBP, and stress test-related DBP were assessed as providing moderate level evidence. The effect of FA on blood cortisol and resting SBP and of AST on resting SBP received a GRADE assessment of low level evidence.

The level of evidence was also considered to be low or moderate where no effect of a meditation subtype was found, including resting SBP and HRV-hf. The primary reason for downgrading the GRADE of evidence was the limited number of studies included in

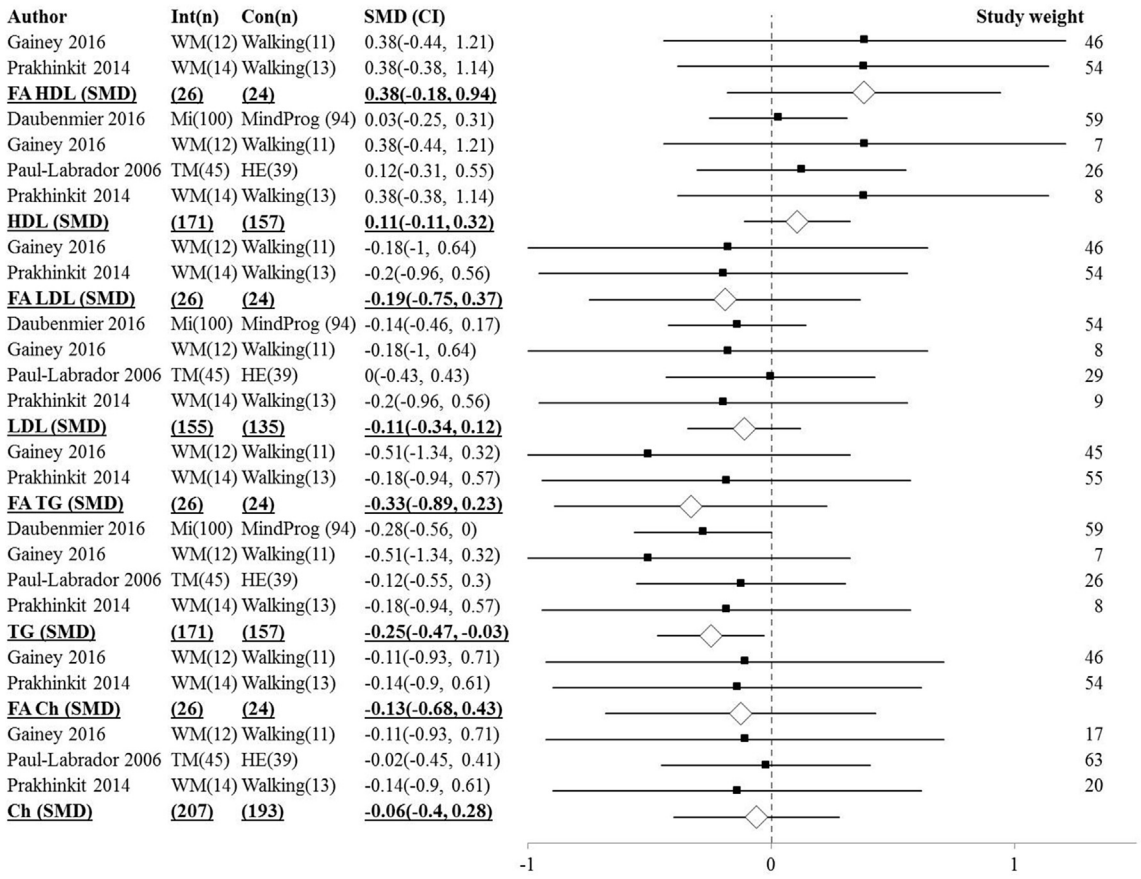

Fig. 9. Forest plot of meditation interventions on lipids. Ch = Cholesterol; Con = control; FA=Focused attention; HE = health education; HDL=High density lipoprotein; Int = Intervention; L = Learning; LDL = Low density lipoprotein; MindProg = Mindfulness program with Education, cognitive behavioural therapy, progressive muscle relation and social support; Mi = Mindfulness; MM = Mindfulness meditation; Mo=Mountain meditation; SMD = standardised mean difference; PT=Physical training; Re=Reading; TC = Thi chi; TG = Triglycerides; TM = Transcendental meditation; WM=Walking meditation.

the analysis, small associated sample sizes and too few studies to accurately assess publication bias. Based on these limitations, we suggest that research is lacking regarding the effect of meditation subtypes on stress-related physiological effects and that further research should be conducted in this area. While this meta-analysis provides preliminary evidence that AST meditations reduce resting SBP, FA meditations reduce blood cortisol, and resting SBP and OM meditations reduce ambulatory SBP, SBP following a stress test and resting HR, further research needs to be conducted to support or refute these findings.

It is not surprising that meditation subtypes were seen to have differing effects on physiological markers of stress. Meditation subtypes are associated with different pattern of brain functionality. OM meditations are associated with an electroencephalogram (EEG) delta band of 5–8 Hz and MM practices reduce activity in the default mode network (DMN) (Tomasino et al., 2012, 2014), a functionally connected group of brain nodes including the medial prefrontal cortex (mPFC), anterior and posterior cingulate cortices (ACC, PCC), precuneus (PCU), inferior parietal cortex (IPC), and lateral temporal cortex (Raichle et al., 2001; Raichle and Snyder, 2007). FA meditations are associated with an EEG Gamma band (30–50 Hz) and Beta2 band (20–30 Hz) (Travis and Shear, 2010). AST meditations are associated with an EEG band of Alpha1 activity (8–10 Hz) and activation in the DMN (Travis and Shear, 2010). Given the known differences of meditation subtypes on brain functionality, it would be valuable to better explore the unique effects of meditation subtypes on physiological markers of stress in future research.

4.2. Meditations effects not according to classification

When all meditation subtypes were analysed together, meditation interventions reduced blood cortisol, CRP, resting and ambulatory BP as well as SBP following a stress test, resting HR, triglycerides and TNF-α. The effect of meditation on cortisol and resting HR was considered to be high level evidence. The effect of meditation on CRP, TNF-α, BP and triglycerides was considered to be moderate level evidence. Although different meditation forms were analysed together, heterogeneity between study effects were seen only for resting BP, HRV-hf and IL-6 and the GRADE of evidence for these outcomes was downgraded accordingly.

The populations included in the current meta-analysis are diverse, indicating that the observed effects of meditation are not limited to a specific population. The effects of meditation on SNS, HPA activity and lipids seen in this study do not appear to be mediated by relaxation effects, as thirteen studies (see Table 1) used relaxation techniques such as PMR as the AC.

4.3. Comparison of effects between meditation subtypes and analysis of all meditation types

For CRP, ambulatory and resting DBP, triglycerides and TNF-α, there was no effect of any of the meditation subtypes, but there was an effect when all subtypes were analysed together. In the case of

TNF-α and triglycerides, there were only two studies included when these outcomes were analysed according to meditation subtype and the level of evidence was considered to be low. For ambulatory and resting DBP the level of evidence was considered to be moderate, however only two and three studies were included in the subtype analysis. Therefore the results of these subgroup analyses should be considered preliminary. For resting DBP and CRP, five studies of OM found no effect, which was considered moderate level evidence, indicating that the observed effects seen when all subtypes were analysed together may result from those few studies using AST or FA medication forms.

4.4. Clinical significance

The physiological outcomes assessed in this meta-analysis are markers of SNS activation, which is responsible for the mobilisation of the body in situations of stress, to 'fight-or-flight' the stressor. While this is an adaptive response in situations of imminent stress, daily life stressors associated with modern life can cause pathological arousal and psychological stress (Nesse et al., 2016), which similarly results in activation of the SNS and HPA axis in the absence of a physical threat. The results of our meta-analysis demonstrate the meditation interventions decrease activation of the SNS, as indicated by physiological changes such as decreased cortisol, HR, BP and cytokine levels, in RCTs with an AC. This is an important finding as prolonged stress and hyperactivity of the HPA axis is associated with the onset of debilitating clinical illnesses such as anxiety and depression (Iwata et al., 2013; Ventriglio et al., 2015) and thus meditation may protect against mood disorders by regulating stress reactivity and inflammation.

4.5. Strengths and limitations

The major strength of this meta-analysis is that it is the first to report the immune-modulating effects of meditation in well-controlled studies, in that it includes only RCTs with an AC group. The major limitation is that many of the included studies do not include a follow-up period. Therefore the longevity of the observed effects is unknown. Of note, we classed a number of studies as having a high risk of bias; however, we would suggest that this is a general issue in scientific publishing standards (Franco et al., 2014; Macleod et al., 2015).

4.6. Conclusion

Meditation is a popular form of stress management in Western societies; however, the precise mechanisms of the practice on stress are still not well understood. This meta-analysis of RCTs is the first to demonstrate that meditation is associated with reduced physiological markers of stress, as demonstrated by decreased BP, cortisol, HR and cytokine levels, compared to an AC, namely relaxation, exercise or education.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2017.08.004.

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