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A Systematic Review of Randomised Control Trials Examining the Effects of Mindfulness on Stress and Anxious Symptomatology

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ABSTRACT

Anxiety is a leading source of disability worldwide and current treatment methods are not beneficial for all individuals. There is evidence that meditation has mood-enhancing properties however the biological mechanisms are largely unknown. This systematic review investigates the effects of meditation on sympathetic nervous system and hypothalamic pituitary adrenal axis activation measures. It focuses on studies collecting physiological parameters such as blood pressure, heart rate, cortisol, and peripheral cytokine expression. Overall the 23 trials reviewed trials indicate that meditation practice increases parasympathetic nervous system activation, as well as decreases anxious symptomatology in diverse populations. Further research is required to confirm these preliminary findings and facilitate implementation in clinical settings.

Keywords: Meditation; Anxi; Mood; Stress; Inflammation; Mindfulness

Abbrevation: ANS- Autonomic Nervous System; Autogenic Training- A relaxation technique involving mantras about body relaxation; BMI- Body Mass Index; BP- Blood Pressure; CAR- Cortisol Awakening Response; CRH- Corticotropin-Releasing Hormone; CRP- C-Reactive-Protein; DASS- Depression Anxiety Stress Scales; DBP- Diastolic Blood Pressure; GSR- Galvanic Skin Response; HIV- Human Immunodeficiency Virus; HPA- Hypothalamic–Pituitary–Adrenal; HR- Heart Rate; HRV- Heart Rate Variability; IgA- Immunoglobulin-A; Integrative Mind Body Training- A meditation technique involving focus on a calming mental image, slow breathing via pharynx contraction, and listening to soothing music; IL-1- Interleukin-1; IL-2- Interleukin-2; IL-10- Interleukin-10; Mindfulness- Awareness of one's moment-to-moment subjective conscious experience; Mindfulness Based Stress Reduction- A program combining mindfulness-meditation, and Hatha yoga; Mindfulness Based Cognitive Therapy- A psychological intervention based upon Cognitive Behavioural Therapy and integrating Mindfulness-Meditation; Mindfulness Based Eating Awareness- A psychological intervention based upon Mindfulness-Based-Stress-Reduction, and integrating Mindfulness-Meditation; Transcendental Meditation- A mantra meditation; Relaxation Response- A Meditation involving repetition of a simple word, phrase or activity to focus attention; Compassion Meditation- A closed eye mantra meditation where the individual thinks kind thoughts toward self and others; Theravada Meditation- A meditation technique where the individual focuses awareness of bodily sensations; Mindfulness Meditation- A Meditation practice of focused awareness on ones breath, attention to the present moment, and observing the internal state without judgment; PNS- Parasympathetic Nervous System; RCT- Randomized Control Trial; SBP- Systolic Blood Pressure; SNS- Sympathetic Nervous System; TSST- Trier Social Stress Test

INTRODUCTION

Anxious symptomatology and Stress

Anxiety is a leading source of adult disability worldwide [1]. According to a systematic review of studies from 44 countries, approximately 7.3% of the world's populations were estimated to suffer from anxiety in 2013 [2]. The aetiology of anxiety is complex and polygenetic and it is important to understand the mechanisms that contribute to its development in order to achieve the best possible treatment and prognostic outcomes.

Among other biological abnormalities, anxiety is associated with dysfunctional stress response and reactivity. Chronic stress and inflammation can contribute to the onset of anxious symptoms [3-5], and clinical anxiety is associated with an increased expression of stress induced pro-inflammatory cytokines (small cell signaling protein molecules involved in the innate immune response and inflammation) [6], that stimulate the Autonomic Nervous System (ANS) and Hypothalamic Pituitary Adrenal (HPA) axis [7]. The ANS plays a key role in stress reactivity via its two main divisions, the Sympathetic Nervous System (SNS) and the Parasympathetic Nervous

System (PNS). The SNS mobilises the body to deal with stressful or threatening situations, via control of internal muscles, organs and glands. The PNS counterbalances the SNS and returns the body to a homeostatic state after SNS activation [8]. In many cases the PNS and SNS have complementary and opposing actions. For example, the SNS increases heart rate (HR), blood pressure (BP) and HPA axis activation, which is responsible for the downstream release of the glucocorticoid hormone, cortisol (a widely used biomarker of HPA axis dysfunction), from the adrenal cortex. The PNS decreases HR, BP and cortisol release [8]. Glucocorticoid levels and the further synthesis of pro-inflammatory cytokines are normally regulated by a HPA axis negative feedback mechanism [7]. However, anxiety is characterized by dysfunctional glucocorticoid feedback inhibition, as characterised by a variety of somatic symptom patterns thought to reflect SNS activation, including hyper-secretion of Corticotropin-Releasing Hormone (CRH), HPA axis dysfunction [9,10], increased circulatory cortisol [11] as well as an increased production of pro-inflammatory cytokines [6,7,12,13]. Thus anxiety is a stress associated inflammatory condition [14,15].

Meditation is an affective Treatment for Anxious Symptomatology

Meditation has become increasingly popular as a form of stress management in Western Societies. In Australia, 17.5% of adults are reported to practice meditation [16] and in the United States approximately 7.5% of adults with a medical condition practice meditation [17]. Indeed, meta-analyses and systematic reviews indicate that various meditative practices affectively decrease anxious symptomatology in various populations [18-21]. However, the neurobiological mechanisms via which meditation exerts its mood enhancing effects are still not clearly understood.

The word meditation originates from the Latin, meditat, meaning 'contemplated', and describes a practice aimed to induce a state of consciousness to achieve a benefit or objectively acknowledge conscious content. The practice of meditation dates back to prehistoric religious practice, with the earliest written accounts dating to Hindu traditions in 1500 BCE [22]. There are numerous forms of meditation practiced today, each with unique approaches and theoretical underpinnings. Meditation practice may include the use of controlled breathing (pranayama), repetitive phrases (mantra) and visualisations. All forms of meditation however share the practice of Mindfulness, which is the awareness of one's moment-to-moment subjective conscious experience [22].

In the present systematic review, we aim to explore the effect of meditation on anxious symptomatology, the stress response and related biological changes such as endocrine, autonomic, and inflammatory measures, that are associated with anxious symptomatology. We investigate the effects of meditation on autonomic arousal measures such as HR, BP, Galvanic Skin Response (GSR), skin conductance and temperature, respiration, as well as HPA axis activation as indicated by cortisol levels [23], and markers of inflammation such as cytokines, antibodies, white blood cells, hormones and proteins.

SYSTEMATIC SEARCH STRATEGY

In the present study, we aimed to systematically review Randomised Control Trials (RCTs) investigating the effects of meditation on stress-related biological measures, in the context of anxious symptomatology. We searched PubMed and Scopus with no year restriction for articles containing the specific title word, 'meditation,' or 'mindfulness,' and the specific abstract word 'anxiety,' or 'anxious' and 'neuroendocrine,' 'immune,' 'cortisol,' 'catecholamines,' 'norepinephrine,' 'cytokine,' 'interleukin,' 'interferon,' 'tumour necrosis factor-alpha,' 'brain-derived neurotropic factor,' 'dopamine,' 'serotonin,' 'blood pressure,' or 'heart rate.' Articles reviewed were restricted to original RCTs published in English that included a population who engaged in a meditation practice, with outcome measures related to HPA axis activation or inflammation, in conjunction with a measure of anxious symptomatology. Review papers, non-randomised trials, case series, short comments and dissertations were excluded.

RESULTS

A total of 225 papers with stress-related physiological parameters were initially retrieved from PubMed and Scopus and an additional five articles we identified through other sources (searching reference lists of sourced articles), 110 of which were duplicates, leaving 120 articles. Studies were screened using title and abstract, when required full texts were accessed (n=91). Twenty-nine of these were excluded as they were review articles. A further 43 papers were excluded as they were not RCT's, 15 were excluded as they did not include a biological or anxious symptomatology related outcome, and three were excluded as they did not involve a meditation based intervention. Five additional papers were excluded, as their results have not yet been published and two were excluded, as they were not published in English. Thus, 23 RCT trials were included in the final review. The details of the search strategy are depicted in Figure 1.

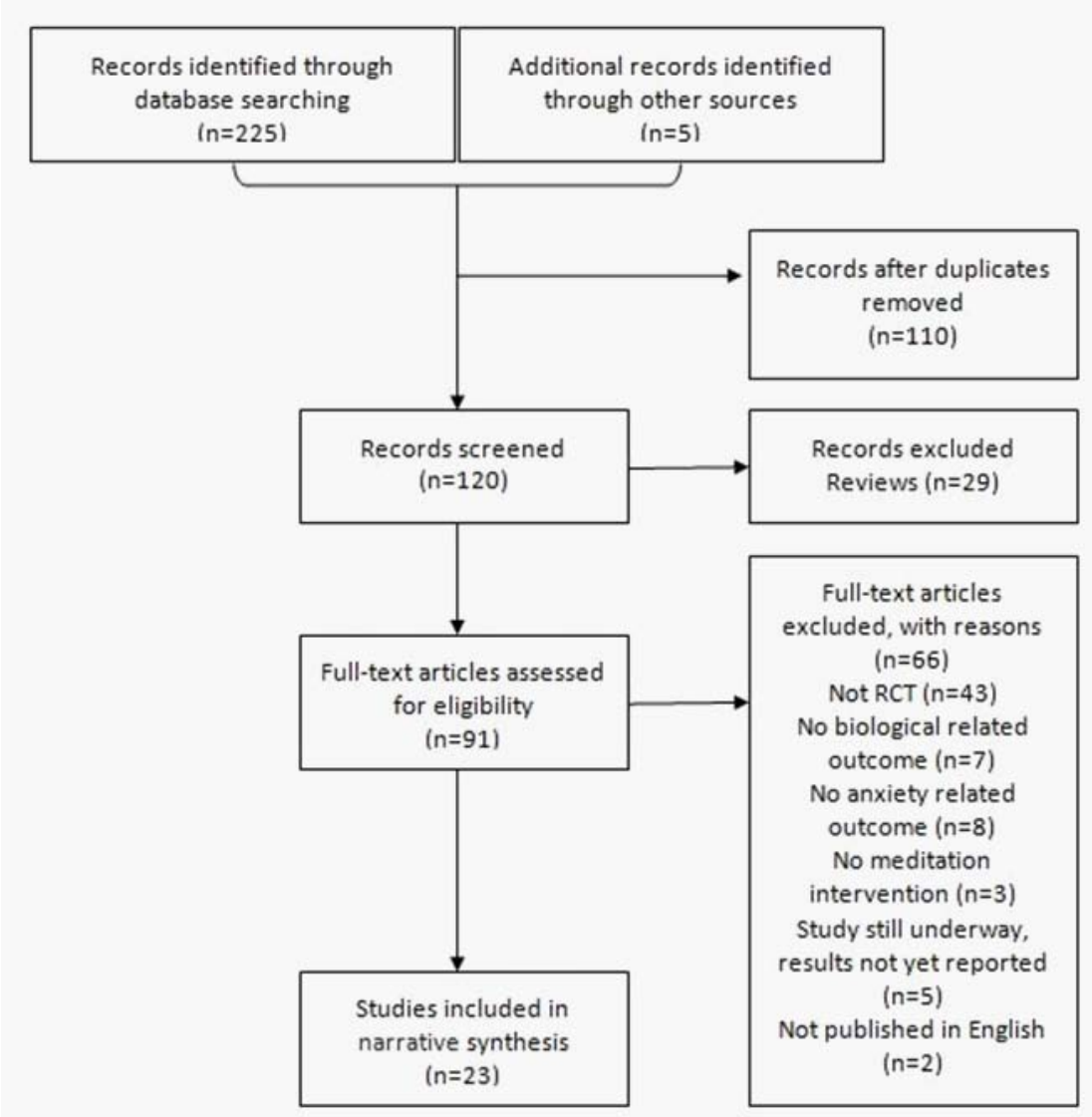

Figure 1: Flow chart showing the retrieval process of biological related trials included in the systematic review.

Characteristics of the Included Trials

Reviewed study characteristics are outlined in Table 1. Twenty-three RCTs examining the effects of meditation on biological outcomes in conjunction with anxious symptomatology have been included in this review. Twelve RCTs originated from the United States [24-35], two from China [36,37], one from Brazil [38], two from Spain [39,40], two from the United Kingdom [41,42], one from Malaysia [43], one from India [44], one from Iran [45] and one from Greece [46].

Reference	Study Location	Participants	Intervention Type	Invention Duration	Comparison Group	Inflammatory Measure	Time of Assessment	Affective/ Health Measures	Differences Between Groups	Follow up	Journal
Bahrke et al., 1978	USA	Healthy Males (n=75)	RR (n=25)	1x20mins	Exercise (n=25) Resting/ reading group (n=25)	HR, BP, skin Tb* and O^2 consum ption*	During, after and 10m post intervention	STAI	All interventions decreased anxiety. No affective or biological difference between the groups	None	Cognitive Therapy and Research
Boswell et al., 1979	USA	University Students (n=80)	TM (n=ns).	15m/2x day/ 2 weeks	Active walking/ concentration (n=ns) Progressive relaxation (n=ns). No intervention (n=ns).	HR, GSR,skin conduc tance	Post intervention (before and after final meditation)	STAI	All interventions decreased anxiety. No affective or biological difference between the groups	None	Journal of Consulting and Clinical Psychology
Chen et al., 2013	China	University (nursing) Students (n=60)	MM (n=30)	30m/day/7 days	No intervention (n=30)	HR, BP	Pre-post intervention daily for 7 days (20:00-20:30, sitting). Final score taken as M of measures	SAS, SDS	Meditation decreased anxiety and systolic blood pressure	None	Nurse Educ Today
Danuca lovet al., 2013	Brazil	Familial caregivers (n=46)	CM and Hatha yoga (n=25)	3x75m/ week/8 weeks	No-treatment (n=21)	Salivary cortisol	Pre-post invention 2x daily for 2 days at each time point (waking [between 7-8am], and 30m after waking [fasting])	BAI, BDI, LSSI	Meditation decreased anxiety, stress, cortisol, and increased mindfulness	None	Evid Based Complement Alternat Med.
Dauben mier et al, 2011	USA	Over weight/ obese women (n=39)	MBCT and MB-EAT (n=17)	1x2.5h class/ week/9 weeks plus 7h retreat in week 6 plus encouraged home practice 30m/day/6 days/week	Waitlist Control (n=20)	Salivary Cortisol, serum cortisol	Pre-post invention -Salivary cortisol 3x daily for 4 days at each time point (waking [fasting]), 30m after waking and evening)- Serum cortisol – Fasting morning samples	STAI-T, PSS, DEBQ, KIMS, BRS, WCSI DEXA	Meditation decreased anxiety and CAR	2 months	J Obes
Davidson et al., 2003	USA	Company Employees (n=48)	MBSR (n=25)	1x2.5h class/ week/8 weeks plus 7h retreat in week 6 Plus encouraged home practice 1h/ day/6 days/ week/8 weeks	Waitlist control (n=16)	Antibody titers in response to influ enza vaccine (admini stered week 8) EEG, EOG	Blood at 3-5 week (pre vaccination)and 8-9 weeks (post vaccination) EEG Pre-post 4 month follow up	PANAS, STAI-T	Meditation decreased anxiety, increased antibody titers after vaccination and left side anterior brain activation.	4 months	Psycho som Med

Delgado et al., 2010	Spain	Female University Students with high Penn State Worry Question naire scores (n=32)	MM (n=15)	2x1h/ week/ 5weeks	PMR plus self-instruction to postpone worrying to a specific time of the day (n=17)	HR, HRV, skin conduc tance, respiration, eye blink startle, cardiac defense, Cardiac defense	Pre-post intervention, resting plus during a cued and non cued defence paradigm (using tones and images)	STAI, BDI, PANAS, SHC, TMMS-24, PSWQ	Both MM and PMR decreased anxiety, depressive symptoms, worry, HR, HRV, and respiration from baseline to post intervention MM further increased emotional comprehen sion and decreased respiration compared to PMR and reduced cardiac defence in the non-cued defence paradigm	None	Behaviour Research and Therapy
Gonzalez -Garcia et al., 2014	Spain	Patients with HIV (n=35)	MBCT (n=15)	1x2.5h class/ week/8 plus 45m/6days/ week at home practice	No intervention (n=20)	CD4 cell count HIV-RNA viral load	Baseline, week 8, week 20	BAI, BDI, PSS, NHP	MBCT decreased anxiety and depressive symptoms and at follow up increased CD4 cell count.	3 months	AIDS Behav
Hayney et al., 2014	USA	Healthy Individuals (Aged 50+) (n=149)	MBSR (n=51)	1x2.5h class/ week/8 plus 45m/day at home practice	Exercise (n=47) Waitlist control (n=51)	Antibody titers, IgA, IFNγ, IL-10 by PBMC in response to influenza vaccine (adminis tered w6)	Blood at baseline, week 9, week 18 Affective outcomes at baseline, 9 weeks, 3 months	STAI LOT PSS SF-12, BMI	There was not difference between groups on measures of anxiety, antibody response to influenza vaccine or BMI	3mth (affec tive mea sure) 6wks (anti body)	Hum Vaccin Immunother
Hidderley et al., 2004	UK	Women with Breast Cancer (n=31)	Auto genic Train ing plus home visit (n=16)	1x class/ week/2 months	Home visit (n=15)	CD4, CD8, NKC, B Cells, Neutrophils, Monocytes	Pre and post intervention	HADS	Meditation decreased anxiety but did not influence biological measures	None	Eur J Oncol Nurs
Jedel et al., 2014	USA	Women with ulcerative colitis (n=51)	MBSR (n=26)	1x2.5h class/ week/8 plus 45m/day at home practice	time/attention control (n=25)	Serum IL-6, IL-8, IL-10, CRP, ACTH, urinary cortisol, stool calprotectin	Pre and post inter vention and follow up. Urinary cortisol collected over a 24-h prior toeach study visit	STAI, BDI, PSQ, MAAS, PHCS, IBD-Q	MBSR did not affect anxiety At 12 months MBSR increased IL-10 and ACTH and decreased CRP in patients with flare ups	6 & 12 months	Digestion
Myint et al., 2011	Malaysia	University students (n=18)	Thera vada medita tion (exami nation stress) (n=6) Thera vada medita tion (no exami nation stress) (n=6)	2h/day/ 5day/ week/ 3weeks	No intervention (no examination stress)(n=6)	HR, BP, Serum Cortisol	Pre, during, post intervention BP and HR -08:00-10:00. 2x readings at 0, 5, 35 min. Final score taken as average of 2 measures Cortisol, 08:00- 08:30, 2x consecutive days	DASS	Meditation decreased anxiety in the no examination stress group but did not affect the biological measures	3 weeks	Bio medical Research

Nidich et al., 2009	USA	University Students (n=207)[a] Subgroup at risk of hyper tension (n=112)[b]	TM (n=93)[a] TM (n=48)[b]	Course taught over 3 days after wards partici pants encou raged to attend 1x 30m class x week /1month then 1x 30m class x month/ 2months plus 20m/ day home practice	Waitlist control (n=114)[a] Waitlist control (n=64)[b]	BP	Pre, post intervention (sitting) 3 x readings each time point, Final score taken as average of measures	POMS, Construc ctive Thinking Inventory	Meditation decreased anxiety Meditation decreased BP in the hypertension sub group	None	Am J Hyper tens
Pace et al., 2009	UK	Healthy Adults (n=61)	CM (n=33)	50m/2/ week/6 weeks	Health Discussion (n=28)	Plasma IL-6, cortisol, BMI	Inflammatory markers collected during TSST (14:00-17:00).	POMS	No affective or biological difference between the groups High CM practice timeassociated with lowered TSST-induced IL-6 and distress scores compared to low CM practice timeTotal CMpractice timecorrelated with TSST-induced IL-6 and distress scores	None	Psycho neuro endo crinology
Parker et al., 1978	USA	Individuals with alcohol dependence (n=30)	RR (n=10)	30m/3/ week/3 weeks	PMR (n=10) Quiet rest (n=10)	BP, HR, GSR	Pre-post assessment (8:00-10:00).	STAI	All interventions decreased anxiety and HR RR reduced SBP RR and PMR decreased DBP	None	Journal of Consul ting and Clinical Psycho logy
Parswani et al., 2013	India	Men with Coronary heart disease (n=30)	MBSR (n=15)	1x1.5h/ wee/8 weeks	Treatment as usual (n=15)	BP, BMI	Pre-post assessment and follow up.	HADS, PSS	Meditation reduced anxiety, stress, BP and BMIat post intervention and follow-up	3 months	Int J Yoga
Rosen kranz et al., 2013	USA	Healthy Adults (n=49)	MBSR (n=ns)	1x2.5h class/ week/8 weeks plus 1 full day session Plus 45-60min/ day home practice	Health Enhancement Program (n=ns)	Salivary cortisol, Blister fluid TNF-α, IL-8	Pre-post intervention and follow up Cortisol 5x daily for 3 days (waking, 30m post-waking, lunch, 15:00pm, bedtime) TSST test6x (after rest,before, after, 10, 20, 30m after TSST test)	GSI, SCL-90-R, MSC	No affective difference between the groups Meditation associated with steeper diurnal cortisol slope	4 Months	Brain Behav Immun
Seyed Alinaghi et al., 2012	Iran	Patients with HIV (n=171)	MBSR (n=85)	1x2.5h class/ week/8 weeks plus 7h retreat in week 6	Brief Education and Support Condition (n = 86)	CD4cell count in peripheral blood	Pre-post intervention and follow up	SCL-90R, MSC	Meditation loweredSCL-90R scores up to 6m,increased CD4 count up to 9m, and decreased MSCL up to12m post intervention.	3, 6, 9, 12 months	Psychosom Med

Sibinga et al., 2013	USA	School Children (n=25)	MBSR (n=ns)	50m/week/ 12weeks	Health Education (n=ns)	Salivary cortisol	Pre-post intervention and follow up Cortisol 4x daily for 2 days (waking, 60m post-waking, 14:30pm, bedtime)	MASC, SCL-90 R, COPE	Meditation decreased anxiety, rumination, trend for academia associated increases in cortisol	3 months	Prev Med
Stefanaki et al., 2015	Greece	Women with Polycystic ovary syndrome (n=38)	Mindful breathing/ diaphrag matic exercises (n=23)	30m/day/ 8weeks	No Treatment (n=15)	Salivary cortisol	Pre-post intervention 3x daily at each time point (waking [8:00], 30m post-waking [8:30], 12h post-waking [20:00])	DASS21, PSS, PCOSQ, Daily Life and General Life Satisfaction	Meditation decreased anxiety, stress, depressive symptoms andcortisol, and increased Life Satisfaction and Quality of Life	None	Stress
Taylor 1995	USA	Men with HIV (n=10)	Meditation incorpo rating PMR, EMG assisted relaxation and hypnosis (n=ns)	1h/2/week/ 10weeks	No Treatment Control (n=ns)	T cells count in peripheral blood	Pre-post intervention and follow up	STAI, POMS, Copperfield self esteem inventory	Meditation decreased anxiety and increased T cell count, self esteem and overall mood	1 month	Psychol Rep
Tang et al., 2007	China	University Students (n=40)	IMBT (n=20)	20m/day/ 5 days	Body relaxation information group (n=20)	Salivary Cortisol, Salivary IgA	Post Inter vention - Pre-post mental arithmeticstress and following 20m training session (14:00-18:00)	POMS, Raven's Matrices	Meditation decreased anxiety, depression, anger,salivary cortisol and salivaryIgA	None	Proc Natl Acad Sci
Zeidan et al., 2010	USA	University Students (n=82)	MM (n=29)	20m/ day/3days	Breathing Exercise (n=27) Waiting control (n=26)	HR, BP	Pre-post inter vention, before and after inter vention session	POMS, STAI-S	MM/breathing decreased anxiety. MM decreased HR, negative affect, and fatigue and increased SBP. Breathing decreased DBP	None	J Altern Complement Med

BAI-Becks Anxiety Inventory; BDI-Becks Depression Inventory; BP-Blood Pressure; BRS – Body Responsiveness Scale; CAR- Cortisol Awakening Response; Cope – Cope Inventory; CM – Compassion Meditation; DEXA - X-ray absorptiometry; EEG-electroencephalography; EMG – Electromyography; CRP - C-reactive protein; DASS-21- Depression Anxiety Stress Scales; DEBQ - Dutch Eating Behaviour Questionnaire; EOG- Electrooculography; GSI - Global Severity Index; GSR-Galvanic Skin Response; HADS - Hospital Anxiety and Depression Scale; HR-Heart Rate; HRV – Heart Rate Variability; IBDQ-Inflammatory Bowel Disease Quality of Life Questionnaire; IgA - Immunoglobulin A; IL-6- Interleukin-6; IL-8- interleukin IL-8; IL-10- interleukin 10;IMBT-Integrative body–mind training; KIMS – Kentucky Inventory of Mindfulness Skills; LOT-Life Orientation Test; LSSI-Lipp's Stress Symptoms Inventory for Adults; OCDS-Obsessive Compulsive Drinking Scale; PCOSQ --Polycystic Ovary Syndrome Health-Related Quality Of Life Questionnaire; PMR - Progressive Muscle Relaxation; MAAS - Mindful Attention Awareness Scale; MASC -Multidimensional Anxiety Scale For Children; MBCT – Mindfulness based Cognitive Therapy; MBEAT- Mindfulness-Based Eating Awareness; MBSR - Mindfulness-Based Stress Reduction; MSC - Medical Symptoms Checklist; MM-Mindfulness Meditation; NKC – Natural Killer Cells; PANAS – Positive and Negative Affect Schedule; NS- Not specified; PBMC - Peripheral Blood Mononuclear Cells; PHCS-The Perceived Health Competence Scale; POMS - Profile of Mood States; PSS- Perceived Stress Scale; PMR – Progressive Muscle Relaxation; PSQ-Perceived Stress Questionnaire; PSWQ-Penn State Worry Questionnaire; RR-Relaxation Response; SAS-Self-Rating Anxiety Scale; SCL-90-R- Symptom Checklist-90-Revised; SDS- Self-Rating Depression Scale;SF-12-Medical Outcomes Study Short Form; SHC- Subjective Health Complaints; STAI-T-Spielberger State-Trait Anxiety Inventory Trait Version; STAI-S- State-Trait Anxiety Inventory - State Version; TM-Transcendental Meditation; TMMS-24-Trait Meta-Mood Scale; NHP-Nottingham Health Profile; TNF-α- Tumour necrosis factor alpha; TSST - Trier Social Stress Test; WCSI-Wheaton Chronic Stress Inventory; * not tested in exercise group.

The studied populations were heterogeneous across trials, fourteen studies included healthy individuals [24,27,28,34,41], including University students [25,30,33,36,37,43], University students experiencing high levels of worry [39], school children [32] and familial caregivers [38]. One trial involved overweight/obese women [26], three involved individuals diagnosed with Human Immunodeficiency Virus (HIV) [35,45]. Four trials focused on individuals with medical conditions such as cancer, coronary heart disease, ulcerative colitis or polycystic ovary syndrome [29,42,44,46] and one studied individuals with alcohol dependence [31].

Mindfulness-Based-Stress-Reduction, a program developed by Jon Kabat-Zinn which combines Mindfulness-Meditation (described below), and Hatha yoga (yoga asanas or physical postures), was the most common intervention and was used in seven trials [27-29,32,34,44,45]. Three trials employed Mindfulness-Meditation, which focuses on drawing attention to the present moment, and observing the internal state without judgment. Individuals sit with eyes closed and focus on awareness of the breath, such as the sensation of breath moving through the nostrils and the rise and fall of the abdomen while breathing in and out [33,36,39]. One study involved mindful breathing and diaphragmatic breathing exercises to manage stress [46]. One trial used a combination of Mindfulness-Based-Cognitive-Therapy (a psychological intervention based upon Cognitive Behavioural Therapy and integrating Mindfulness-Meditation [as described above]) and Mindfulness-Based-Eating-Awareness (founded by Dr. Jean Kristeller and based upon Mindfulness-Based-Stress-Reduction [as described above]) [26]. Another study employed Mindfulness-Based-Cognitive-Therapy only [40]. Two studies used Transcendental-Meditation, a mantra meditation introduced in India in the 1950s by the guru Maharishi Mahesh Yogi, which involves sitting with the eyes closed and silently repeating a mantra for the duration of the practice. The mantra is intended as a vehicle to allow the individual's attention to travel to a less active state [25,30]. Two studies used Relaxation-Response, which is derived from Transcendental-Meditation and was described by Dr. Benson in 1975. Relaxation-Response involves repetition of a simple word, phrase or activity to focus attention, as well as a passive attitude [24,31]. Two studies used Compassion-Meditation, which focuses on being compassionate towards self and others. This meditation is performed with eyes closed and begins by focusing attention and breath on the heart centre and on kind feelings toward self, followed by the recital of a traditional phase. The individual then focuses kind feelings toward others; beginning with those close, followed by those with which they have hostile relations, while repeating the same phrase [38,41]. One study employed Autogenic-Training, a relaxation technique performed in a comfortable position where the individual repeats six phrases to relax the body (my arms/legs are heavy and warm, my heartbeat is calm and strong, my breathing is calm and relaxed, etc.) and developed by Johannes Heinrich Schultz in the 1930's [42]. One study used Theravada-Meditation, from a branch of Buddhism and consisting of Samatha and Vispassna, which focuses on concentration, calming and insight, where the individual sits with closed eyes and focuses attention awareness of specific bodily sensations [43]. One trial employed a meditative program incorporating progressive

muscle relaxation (tensing up particular muscles, and then relaxing them in a systematic fashion throughout the entire body, i.e. right hand and forearm, then right upper arm etc.), self hypnosis and electromyography assisted relaxation [37]. Finally, one study used Integrative-Mind-Body-Training, a less common form of meditation, developed by in the 1990s by Prof. Yi-Yuan Tang, that involves concentrating on a calming mental image, maintaining the body in a relaxed sitting/standing physical state (i.e. lotus position) and breathing slowly via contraction of the pharynx, while listening to soothing music [37].

The most common stress-related biological measures (n=9 studies) were autonomic arousal measures including BP, HR, skin conductance, galvanic skin response and respiration [24,25,30,31,33,36,39,43,44]. Heart rate variability (HRV) was measured in one study as an indicator of ANS function and cardiovascular response [39]. Increased HRV is interpreted to indicate greater PNS activity and a healthy balance between the SNS and PNS [8]. The steroid hormone cortisol was assessed in nine trials [26,29,32,34,37,38,41,43,46]. Antibodies or antibody response was measured in three studies [27,28,37]. Cytokines were measured in four trials [28,29,34,41]. Three studies measured white blood cells [35,42,45]. The acute phase protein, C Reactive Protein (CRP), adrenocorticotropic hormone and the neutrophil protein, Calprotectin, were measured in one study [29]. One study measured brain electrical activity using electroencephalography and electrooculography [27]. Some other relevant health related measures included body Mass Index (BMI) [26,41,44] health symptoms and complaints [28,29,34,39,45,46] and health competence [29].

As outlined in Table 1, all trials included some measure of anxious symptomatology. Other studied outcomes included depressive symptoms [29,30,32-39,41-46] affect [27,39], stress or perceived stress [26,28,29,38,44,46], worry [39], coping behaviour [32], eating behaviour [26], quality of life [46], mindfulness (awareness of ones moment-to-moment, subjective conscious experience) [26,29], self esteem [35], optimism [28] and mental ability and constructive thinking [30,37].

Findings of the Included Trials

Cortisol outcomes

Waking salivary cortisol: Six of the reviewed studies assessed salivary cortisol. Findings of the reviewed trials suggest that meditation is associated with decreased salivary levels of cortisol. In familial caregivers, Danucalov et al., reported that Compassion-Meditation in conjunction with hatha yoga was associated with a decrease in salivary waking cortisol, anxious symptomatology, depressive symptomatology, and self perceived stress after eight weeks of practice, compared to a non-treatment control group [38].

Stefanaki et al., similarly found that mindful breathing/ diaphragmatic exercises decreased waking cortisol, and 30 min post-waking cortisol, depressive symptoms and self perceived stress,

when compared to the no treatment control group. In this study, cortisol was collected at multiple time points throughout the day and collection time was recorded, however salivary cortisol samples were only collected on one day at both baseline and post intervention [46]. As various factors such as medications [47,48], smoking [49], blood in the saliva [50] and eating and drinking substances with low pH can artificially affect cortisol levels [51], it is important to collect salivary measures at several time points over several days, in clinical research.

Rosenkranz et al., investigated the effect of eight weeks of Mindfulness-Based-Stress-Reduction on both cortisol diurnal rhythms and in response to a Trier Social Stress Test (TSST), in 49 community dwelling healthy adults. Consistent with the finding of Danucalov et al., and Stefanaki et al., Mindfulness-Based-Stress-Reduction was associated with a steeper cortisol slope, however did not appear to influence self reported measures of anxious symptomatology. It is important to note that in this study the sample size of the treatment groups was not specified [34].

One study measured daytime cortisol. Tang et al., tested salivary cortisol in response to a mental arithmetic stress task, in healthy University students who had engaged in either five days of Integrative-Mind-Body-Training or body relaxation training. Participants in the Integrative-Mind-Body-Training groups showed a lower cortisol response to the arithmetic stress task and overall lower anxious symptomatology, depressive symptoms, anger, and fatigue. However, baseline cortisol levels in response to stress and prior to Integrative-Mind-Body-Training training were not assessed. Cortisol samples were only assessed after participants had engaged in either five days of Integrative-Mind-Body-Training training or the body relaxation information control group [37]. Daubenmier et al., found no significant changes in the cortisol slope or Cortisol Awakening Response (CAR) [characterised by a rise in cortisol upon awakening, generally reaching its peak during the initial 30-45 mins. after waking] [52]) in overweight and obese individuals who practiced nine weeks of Mindfulness-Based-Stress-Reduction, compared to a waitlist-control group. However, in the subgroup of obese participants (n=10), Mindfulness-Based-Stress-Reduction was associated with reduced CAR and maintained body weight, while participants in the waitlist control condition (n=8) had no change in CAR response and showed an increase in body weight. Mindfulness-Based-Stress-Reduction was further associated with decreased anxious symptomatology and increased mindfulness [26]. These results suggest that meditation more affectively mediates cortisol levels in individuals with obesity associated altered cortisol metabolism [53], than in individuals without. A limitation of this trial is that the particular wake up time of individual participants was not stated. Early waking time has been associated with heightened CAR, and thus controlling for wake time when assessing CAR is an important consideration [54]. However, CAR has been shown to be reasonably stable across consecutive days and the samples were collected at the same time intervals after wake time for two consecutive days [55].

Conversely, Sibinga et al. found that 12 weeks of Mindfulness-Based-Stress-Reduction did not significantly decrease overall daily cortisol (collected at waking, 60 mins. post-waking,

14:30, bedtime), but did decrease anxious symptomatology and rumination in school children. However, due to a lack of consent and school absences, the final sample size for cortisol collection was n=25 (original group sizes in this study were Mindfulness-Based-Stress-Reduction=22 and Health-Education=19). The authors did not specify from how many children in each of the intervention groups' cortisol was collected. However, given the small sample size, this study was likely underpowered [32]. Five of the six reviewed studies reported that meditation practices influenced levels of salivary cortisol. Thus, at this stage it appears that meditation lowers morning and daytime cortisol levels in some populations.

Serum cortisol: Only two reviewed trials collected serum cortisol. Additional to collecting salivary cortisol, as discussed above, Daubenmier et al., assessed morning serum cortisol levels after nine weeks of Mindfulness-Based-Stress-Reduction in overweight/obese participants. In this trial, Mindfulness-Based-Stress-Reduction was not associated with a change in serum cortisol, but was associated with decreased anxious symptomatology and increased mindfulness [26].

Myint et al., similarly found no difference in morning serum cortisol levels in University students trained for three weeks in Theravada-Meditation, compared to students in a no intervention group. However, there were only six participants per group in this study, and thus it was likely underpowered. Student trained in Theravada-Meditation were seen to have lower Depression Anxiety Stress Scales (DASS) scores at three weeks after completing the intervention, than students in the no intervention group, but only when not exposed to examination stress [43]. Thus, these two studies indicate that meditation practice does not influence serum cortisol levels.

Plasma cortisol: Pace et al., collected plasma cortisol from 61 healthy adults assigned to either six weeks of Compassion-Meditation or health-discussion, during a TSST. In this study plasma cortisol levels during the TSST did not differ between the two groups. Affective measures such as anxiety and depression scores similarly did not differ between the groups. Similar to the study by Tang et al., a major limitation of this trial is that baseline cortisol levels in response to stress and prior to Compassion-Meditation training were not collected. The authors only collected cortisol samples post training, thus the influence of characteristics such as baseline stress reactivity are unknown [41]. Given the limited evidence thus far and the possible methodological shortcomings in the trial by Pace et al., it is unclear at this stage if meditation practice affects plasma cortisol levels.

Urinary cortisol: Only one trial investigated urinary cortisol. In 51 women with ulcerative colitis, Jedel et al., reported no effect resulting from eight weeks of Mindfulness-Based-Stress-Reduction on urinary cortisol levels, in non-flare and flare-up participants, compared to individuals in a time/attention control condition [29]. Thus, according to the limited evidence thus far, it appears that Mindfulness-Based-Stress-Reduction does not influence urinary cortisol levels.

Autonomic measures

There is evidence for a beneficial effect of meditation on stress-related autonomic measures such as BP and HR. In healthy University nursing students, Chen et al., demonstrated that seven days of Mindfulness-Meditation decreased anxious symptomatology, and Systolic BP (SBP), when compared to a no-intervention control group [36].

Delgado et al., similarly showed that both a five-week Mindfulness-Meditation intervention and a progressive-muscle-relaxation intervention decreased HR and HRV, during meditation or relaxation, compared to when participants were resting or during self-induced worry periods. These results were found in female University students with high scores on the Penn State Worry Questionnaire. Both interventions decreased anxiety and depressive symptoms, and individuals in the Mindfulness-Meditation intervention showed increased emotional comprehension and respiration while meditating, compared to the individuals in the progressive-muscle-relaxation group, while relaxing. Finally, during a non-cued defence paradigm, meditation was seen to decrease cardiac defence compared to relaxation [39].

In a trial by Nidich et al., three months of Transcendental-Meditation decreased BP, psychological distress including anxious symptomatology, and improved coping ability, in University students at risk of hypertension, compared to a waitlist control group. In University students not at risk of hypertension, Transcendental-Meditation was similarly seen to decrease psychological distress, including anxious symptomatology and improve coping ability, but not to influence BP [30].

Parker et al., similarly showed that relaxation-response, progressive-muscle-relaxation and quiet rest decreased HR and anxiety in a small study involving 30 men with alcohol dependence. Relaxation-response, progressive-muscle-relaxation and quiet rest could arguably all be categorized as meditative practices, as all incorporate aspects of mindfulness. Therefore, it is not surprising that all three interventions decreased anxious symptoms and HR. Relaxation-response further decreased SBP while both relaxation-response and progressive-muscle-relaxation decreased Diastolic BP (DBP), indicating that relaxation-response and progressive-muscle-relaxation are more effective than quiet rest alone in mediating autonomic arousal [31].

In a sample of 30 males with coronary heart disease, Parswani et al., further reported that BP, anxiety symptoms, depressive symptoms, perceived stress, and BMI were decreased after eight weeks of Mindfulness-Based-Stress-Reduction, and at three-month follow-up, compared to a treatment-as-usual control group [44].

Finally, Zeidan et al., showed that in a sample of 82 healthy University students, that three days of Mindfulness-Meditation or breathing exercises was associated with decreased anxious symptomatology during examination period, as compared to a no treatment control group [33]. Mindfulness-Meditation further decreased HR, negative affect, fatigue, and interestingly increased SBP, while breathing exercises were seen to decrease DBP. The authors failed to discuss

possible reasons as to why Mindfulness-Meditation may have increased SBP. This curious result is inconsistent with the finding that Mindfulness-Meditation was associated with decreased HR, and might suggest that Mindfulness-Meditation increased autonomic arousal [33].

Three of the reviewed trials found no effect of meditation on autonomic measures. In a trial by Bahrke et al., a single 20 minute session of Relaxation-Response was not associated with any change in HR, BP, skin temperature or oxygen consumption, compared to a single 20 minute session of exercise or rest, in healthy males [24]. Arguably, the single 20 minute meditation intervention used in this trial was too short to result in significant biological changes.

In 80 University students, Boswell et al., demonstrated that two weeks of Transcendental-Meditation was not associated with a decrease in HR, skin conductance, GSR or anxious symptomatology, compared to an active walking/concentration, progressive relaxation or no intervention control group [25]. Again in this study, the intervention duration was only two weeks, which may have been too short to result in significant changes.

Finally, in a trial involving University students trained for three weeks in Theravada-Meditation, and either exposed or not exposed to exam stress, Myint et al., reported that meditation had no effect on HR or BP, compared to students in a no intervention group. As highlighted earlier however, this trial only consisted of six participants per group, and therefore was likely underpowered [43]. Thus, overall the trials reviewed suggest that more long-term meditation practices influence autonomic measures such as HR and BP.

In the trials reviewed meditation was seen to decrease anxious symptoms and influence autonomic arousal measures in healthy University students [33,36,39], University students at risk of hypertension [30], men with coronary heart disease [44] and in individuals with alcohol dependence [31]. Therefore, meditation appears to reduce anxious symptomatology associated with a number of sources, such as severe medical conditions (i.e. heart disease), or psychosocial stress, such as exam stress.

Immune changes

Antibodies: Three studies investigated the effects of meditation on antibodies (proteins that identify and neutralise pathogens in the body) response/levels, and report mixed results. In a trial involving 48 healthy company employees, Davidson et al., demonstrated that an eight-week Mindfulness-Based-Stress-Reduction program reduced the production of antibodies in response to influenza vaccine, as well as decreased anxiety symptoms and increased left side anterior brain activation, compared to a waitlist control group. Changes in brain electrical activity persisted at four months follow up [27].

This is inconstant with the finding of Hayney et al., who showed that in 149 healthy individuals aged 50+, that eight weeks of Mindfulness-Based-Stress-Reduction was not associated with changes in antibody response to influenza vaccine, measures of anxious symptomatology or BMI,

compared to individuals in an exercise or waitlist condition. The authors suggested that perhaps none of the immune measures were further improved by exercise or Mindfulness-Based-Stress-Reduction, due to the robust immunization responses shown by most participants [28]. However the timing of the assessment may also contribute the lack of differences seen between groups. Both Davidson et al., and Hayney et al., used an influenza vaccine and engaged healthy individuals, however these trials differed in terms of when they assessed antibody response following influenza vaccine. Davidson et al., assessed antibody response at zero to one week after vaccination, while Hayney et al., assessed antibody response three and 12 weeks after immunisation. Thus, it likely that in the trial by Hayney et al., that antibody levels were measured too long after immunisation to reflect the more acute immune response induced by the vaccine. Additionally, as the study by involved Hayney et al., involved individuals who were 50+, it is possible that a number of participants were experiencing menopause, which is associated with a decline in ovarian function and increased pro-inflammatory cytokine activity [56], which would not have been present among the participants in the study Davidson et al., where participants had an average age of 36 years.

In a study by Tang et al., University students who engaged in five days of Integrative-Mind-Body-Training showed higher levels of salivary levels of the antibody Immunoglobulin-A (IgA), in response to a mental arithmetic stress task, compared individuals in a relaxation group. The result was only seen after engaging in a 20 mins. Integrative-Mind-Body-Training training session immediately post stress test, compared to a 20 mins. relaxation session immediately post stress [37].

T cells: Four studies reported the effects of meditation on T cell counts. Seyed Alinaghi et al., assessed CD4+ T lymphocytes in peripheral blood from 171 adults diagnosed with HIV and assigned to either eight weeks of Mindfulness-Based-Stress-Reduction or Health-Education. Mindfulness-Based-Stress-Reduction was seen to be associated with lower levels of psychological distress up until six months post intervention, increased CD4 count up until nine months post intervention and decreased medical symptoms up until 12 months post intervention [45].

Taylor et al., similarly reported that in a trial involving 10 HIV positive males, a meditation program consisting of progressive-muscle-relaxation, self hypnosis, and electromyography assisted bio-feedback, increased T cell count in peripheral blood samples and self esteem, and decreased state and trait anxiety, after 10 weeks of practice, compared to individuals in a no treatment control group [35].

Gonzalez-Garcia et al., further reported that eight weeks of Mindfulness-Based-Cognitive-Therapy increased CD4 cell counts in peripheral blood samples of men diagnosed with HIV, at three months follow up, compared to individuals in a no intervention control group. Mindfulness-Based-Cognitive-Therapy further decreased anxious and depressive symptoms and perceived stress, and increased quality of life. There was however no differences between the groups in the percentage of patients with undetectable HIV-RNA viral load [40].

In a sample of 31 women with breast cancer, Hidderley et al., reported that two months of Autogenic Training decreased B and T cell counts, compared to individuals in a home visit control group. However the authors reported that this effect was only seen in a subset of women considered to have achieved a meditative state (n=7), compared to the original group size of n=16. The authors describe the patients as having reached a meditative state once they show altered facial features, the jaw line dropping and the mouth open. This arbitrary and subjective assessment regarding the mediative state of participants lacks scientific rigour, and selecting only seven of the original 16 participants for further analysis can arguably be interpreted as data cherry picking, thus the reported results of this study should be interpreted with caution [42]. Overall three of the four trials reviewed suggest that meditation practice influence T cell counts, while the remaining study lacks sufficient methodological rigour.

Cytokines, proteins and hormones: The reviewed trials indicate that meditation influences peripheral cytokine levels. In a trial involving 51 women with ulcerative colitis, Jedel et al., demonstrated that eight weeks of Mindfulness-Based-Stress-Reduction increased IL-10 and ACTH and decreased CRP in patients with ulcerative colitis flare ups, compared to individuals in a time/attention control condition. Mindfulness-Based-Stress-Reduction did not influence affective outcomes, levels of stool calprotectin at the time of flare-up, or IL-6 and IL-8 in individuals with and without flare-ups. The authors interpreted these results to suggest that Mindfulness-Based-Stress-Reduction might be affective for individuals with high stress reactivity during periods of ulcerative colitis remission [29].

Pace et al., collected plasma IL-6 from 61 healthy adults assigned to either six weeks of Compassion-Meditation or health-discussion, and then exposed to a laboratory TSST. There was no difference between groups in IL-6 levels in response to the TSST. The authors did report a correlation between increased meditation practice and decreased TSST-induced IL-6. The authors further reported and that individuals whose total meditation practice time was above the group median had lower TSST-induced IL-6 and distress scores than individuals whose total meditation practice time was below the median, suggesting that only high levels of engagement in compassion-meditation may mediate stress-induced immune and affective responses [41].

In 49 community dwelling healthy adults, Rosenkranz et al., reported no difference in blister fluid levels of IL-8 and TNF-α (induced by skin application of capsaicin), between individuals after eight weeks of Mindfulness-Based-Stress-Reduction or a health enhancement program [34].

These results are inconstant with the finding of Hayney et al., who reported that eight weeks of Mindfulness-Based-Stress-Reduction was not associated with changes in Interferon-Gamma (IFNγ) or IL-10 after influenza immunization, in 149 healthy individuals, compared to individuals in an exercise or waitlist condition. However, as earlier discussed, this study likely collected blood samples too long after immunisation to reflect the more acute immune response induced by the influenza vaccine.

Differences in Meditation Forms and Studied Populations on Arousal

The reviewed trials varied greatly in terms of meditation practiced, studied populations and biological outcomes assessed. In most of the trials employing Mindfulness-Based-Stress-Reduction [27-29,34,45] individuals practiced for a similar amount of time, being least 2.5 hours a week for eight weeks, and in all but one trial [45] were encouraged to practice at home for at least a further 315 mins week. In all trials but one [38], Mindfulness-Based-Stress-Reduction was seen to influence the biological measures collected, including antibody titers [27], cytokines [29], cortisol [34] and white blood cells [45]. Two trials involved healthy adults [28,34] and two involved individuals with health conditions, being ulcerative colitis [29] or HIV [45].

Individuals practiced Mindfulness-Based-Stress-Reduction for less than 2.5 hours a week in only two trials. In the study by Parswani et al., men with coronary heart disease practiced for 90mins. a week for eight weeks, and Mindfulness-Based-Stress-Reduction was still seen to decrease BP [44]. In the trial by Sibinga et al., however, healthy school children only practiced for 50 mins. a week over 12 weeks and Mindfulness-Based-Stress-Reduction was not seen to influence salivary cortisol [32]. Thus the biological effects of Mindfulness-Based-Stress-Reduction appear to be affective in diverse populations but only in individuals who practice at least 90 mins. a week.

All of the three reviewed trials that used Mindfulness-Meditation demonstrated that the practice resulted in changes in autonomic measures [33,36,39]. These studies involved University students, and showed that Mindfulness-Meditation decreased SBP [33,36], HR, HRV and respiration [33,39]. Thus, it appears that Mindfulness-Meditation affectively mediates autonomic arousal in healthy individuals and in individuals with a chronic health condition. One study employed mindful breathing/diaphragmatic exercises in women with polycystic ovary syndrome and showed that the practice decreased salivary cortisol [46].

One of two trials using Relaxation-Response found no effect of the practice on HR, BP, skin temperature or oxygen consumption, but only required participants to engage in a single 20min. session [24]. In the study by Parker et al., however, where participants practiced for 90mins. a week for 3 weeks, Relaxation-Response reduced SBP and both Relaxation-Response and progressive-muscle-relaxation decreased DBP [31].

One trial employed Mindfulness-Based-Cognitive-Therapy plus Mindfulness-Based-Eating-Awareness [26] while another used Mindfulness-Based-Cognitive-Therapy alone [40]. Both of these trials involved individuals with ongoing health problems, being obesity [26] and HIV respectively [40], and demonstrated that Mindfulness-Based-Cognitive-Therapy was associated with decreased CAR [26], or increased CD4 cell count [40]. In both of these studies, individuals practiced for at least 2.5 hours a week for eight weeks, and were encouraged to practice at home for a further 210-315mins. a week. Thus the meditation dose was quite high.

Biological outcomes were available for two studies investigating the effects of Compassion-

Meditation. One Compassion-Meditation and hatha yoga based study by Danucalov et al., showed a change in salivary cortisol [38] while the Pace et al., study used only Compassion-Meditation and reported no change in plasma cortisol or IL-6 [41]. These two trials both involved healthy adults, although the familial caregivers in the study by Danucalov et al., were arguably living with higher stress levels. In the trial by Danucalov et al., however individuals practiced for 225mins. a week for eight weeks, while in the trial by Pace et al., individuals practiced only 100mins. a week for six weeks. Thus, again there appears to be a dose related effect where individuals who practice meditation for a longer duration show more changes in measures of autonomic arousal. Indeed, in the study by Pace et al., more hours of compassion-meditation practice was associated with lowered TSST-induced IL-6 and distress scores, compared to low compassion-meditation practice time, and the total compassion-meditation practice time correlated with TSST-induced IL-6 and distress scores [41]. Thus, these studies suggest that the dose of meditation practice is likely an important mediating factor in terms of modulation of the SNS.

Biological outcomes were available for only two studies investigating the effects of Transcendental-Meditation, both of which involved University students and found no effect of meditation on BP, HR, GSR or skin conductance [25,30]. In a subset of the study by Nidich et al., involving hypertensive University students, Transcendental-Meditation decreased BP. Thus, it is possible that Transcendental-Meditation does not affectively mediate SNS activity in healthy individuals. However, there are too few studies available to draw conclusions in this regard.

The one study that used Autogenic-Training found no effect of the practice on white blood cell counts and authors did not specify the duration of each session [42]. The one study involving Theravada-Meditation found no effect of the practice on HR, BP, or serum cortisol, when practiced for 2h/day, for three weeks by University students, suggesting that Theravada-Meditation is not as affective at mediating the SNS as some other forms of meditation.

Only one study employed Integrative-Mind-Body-Training in University students [37] and another employed a meditation program incorporating progressive-muscle-relaxation, electromyography assisted relaxation and hypnosis, in men with HIV [35]. These studies found the practices to have effects on white blood cell count [35] and salivary cortisol and IgA [37]. In the study by Taylor et al., the meditation program was practiced for 2h/week for 10 weeks [35]. However, in the study by Tang et al., Integrative-Mind-Body-Training was only practiced for 100mins. over five days, and was still reported to lower salivary cortisol and salivary IgA in response to mental arithmetic stress, compared to Body-Relaxation [37].

DISCUSSION

Overall, the studies reviewed provide preliminary evidence that various forms of meditation practice, particularly Mindfulness-Meditation, Mindfulness-Based-Stress-Reduction, and Mindfulness-Based-Cognitive-Therapy, and to a lesser degree Integrative-Mind-Body-Training

and mindful breathing/diaphragmatic exercises, are associated with biological changes including cortisol levels, SNS activation, decreased stress and negative affect in a range of populations. Programs involving more hours of meditation practice per week seem to be more affective than those with fewer hours.

Interestingly, in each of the affective meditation programs, Mindfulness-Meditation or focus on breathing was a key component. In Mindfulness-Meditation the individuals focuses awareness of the breath, such as the sensation of breath moving through the nostrils and the rise and fall of the abdomen. In Integrative-Mind-Body-Training the individual focuses on breathing slowly via contraction of the pharynx. This differs to some of the other forms of meditation studied, such as Transcendental-Meditation, Autogenic-Training or Theravada-meditation, which were not seen to influence the biological outcomes studies. While Transcendental-Meditation, Autogenic-Training and Theravada-meditation incorporate some breathing awareness and techniques, they focus largely on mantra, visualisations, or muscle relaxation. Thus, focus on breathing awareness and control may be an important factor mediating the biological effects of meditation in the context of anxious symptomatology. Indeed, breathing is one of the actions of the ANS that individuals can control, and activation of the PNS and homeostatic state is characterised by calm, relaxed breathing [57].

Additionally, the population studied and source of stress, such as medical, chronic self-induced stress, or response to an acute exam problem, must also be considered. The stress related to the experience of having a chronic medical condition has far more degrees of complexity, such as acceptance and grieving, compared to the stress that might be experienced by University students who are preparing for exams, or by healthy individuals facing high levels of daily stress. In the present study meditation was seen to decrease anxious symptoms and influence the biological outcomes measured in both healthy individuals [27,33,36,37,39] and in individuals with a chronic health condition, such as polycystic ovary syndrome [46], HIV [35,40,45], or coronary heart disease [44]. However, there was one study in woman with breast cancer where meditation was seen to decrease anxious symptoms but not influence the biological outcomes studied [42] and another involving women with ulcerative colitis where meditation influenced the biological outcomes studies but not anxious symptoms [29]. Most of the reviewed studies suggest that meditation is likely useful to individuals with a chronic health condition, in spite of the complex nature of the stress and anxious symptoms associated with living with ongoing health issues. However there are too few trials identified in the present review to draw definitive conclusions.

CONCLUSIONS

Meditation is commonly practiced by individuals to manage anxious symptomatology and is promoted as an affective management for anxious symptoms by various government and health organisations, including the National Health Services in Britain [58], the Department of Health in Australia [59], and the National Institute of Health in the United States [60]. Mindfulness

and meditative techniques have become widely used in psychological interventions such as Mindfulness-Based-Cognitive-Therapy [61]. Some individuals may find meditation appealing as it allows them actively engage in the management of their symptoms and can be utilised at all times. Meditation may also not be perceived as 'artificially' effecting biochemical processes, as pharmaceutical interventions may be.

Despite the growing popularity of meditation, its neurobiological effects are still not clearly understood. Many of the reviewed trials in the current systematic review are characterised by small sample size, no follow up or lack methodological rigour. Despite these limitations, the large majority of the studies provide some evidence that meditation is associated with biological changes in BP, HR, cortisol or cytokine levels, particularly those with many hours of practice and focus on breathing. It is therefore plausible that meditation may affect mood via SNS and HPA activity. Further studies are required in order to confirm the preliminary findings that meditation appears to influence the stress response.

References

1. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013; 382: 1575-1586.
2. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med. 2013; 43: 897-910.
3. Masi G, Brovedani P. The hippocampus, neurotrophic factors and depression: possible implications for the pharmacotherapy of depression. CNS Drugs. 2011; 25: 913-931.
4. Dantzer R1. Depression and inflammation: an intricate relationship. Biol Psychiatry. 2012; 71: 4-5.
5. Pascoe MC, Crewther SG, Carey LM, Crewther DP. Inflammation and depression: why poststroke depression may be the norm and not the exception. Int J Stroke. 2011; 6: 128-135.
6. Salim S, Chugh G, Asghar M. Inflammation in anxiety. Adv Protein Chem Struct Biol. 2012; 88: 1-25.
7. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Ann N Y Acad Sci. 2012; 1261: 55-63.
8. Buijs RM. The autonomic nervous system: a balancing act. Handb Clin Neurol. 2013; 117: 1-11.
9. Boyer P. Do anxiety and depression have a common pathophysiological mechanism? Acta Psychiatr Scand Suppl. 2000; : 24-29.
10. Roy-Byrne PP, Uhde TW, Post RM, Gallucci W, Chrousos GP. The corticotropin-releasing hormone stimulation test in patients with panic disorder. Am J Psychiatry. 1986; 143: 896-899.
11. Olson KL, Marc DT, Grude LA, McManus CJ, Kellermann GH. The Hypothalamic-Pituitary-Adrenal Axis. In: R Klatz, Goldman R, editors. The Actions of the Central Nervous System and Potential Biomarkers, in Anti-Aging Therapeutics Volume XIII. Chicago: American Academy of Anti-Aging Medicine. 2011; 91-100.
12. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000; 21: 55-89.
13. King SL, Hegadoren KM. Stress hormones: how do they measure up? Biol Res Nurs. 2002; 4: 92-103.
14. 14. Moylan, S., et al. Exercising the worry away: how inflammation, oxidative and nitrogen stress mediates the beneficial effect of physical activity on anxiety disorder symptoms and behaviours. Neurosci Biobehav Rev. 2013; 37: 573-584.
15. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2014; 53: 23-34.
16. Xue CC, Zhang AL, Lin V, Da Costa C, Story DF. Complementary and alternative medicine use in Australia: a national population-based survey. J Altern Complement Med. 2007; 13: 643-650.
17. Bertisch SM, Wee CC, Phillips RS, McCarthy EP. Alternative mind-body therapies used by adults with medical conditions. J Psychosom Res. 2009; 66: 511-519.

18. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol. 2010; 78: 169-183.

19. Manzoni GM, Pagnini F, Castelnuovo G, Molinari E. Relaxation training for anxiety: a ten-years systematic review with meta-analysis. BMC Psychiatry. 2008; 8: 41.

20. Goyal M, Singh S, Sibinga EM2, Gould NF3, Rowland-Seymour A1. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med. 2014; 174: 357-368.

21. Chen KW, Berger CC, Manheimer E, Forde D, Magidson J. Meditative therapies for reducing anxiety: a systematic review and meta-analysis of randomized controlled trials. Depress Anxiety. 2012; 29: 545-562.

22. Lating GEJ. Meditation, in a Clinical Guide to the Treatment of the Human Stress Response. D Meichenbaum, Editor. Berlin: Springer. 2002; 199-214.

23. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006; 27: 24-31.

24. Bahrke MS, WP Morgan. Anxiety reduction following exercise and meditation. Cognitive Therapy and Research. 1978; 2: 323-333.

25. Boswell PC, Murray EJ. Effects of meditation on psychological and physiological measures of anxiety. J Consult Clin Psychol. 1979; 47: 606-607.

26. Jennifer Daubenmier, Jean Kristeller, Frederick M Hecht, Nicole Maninger, Margaret Kuwata, et al. Mindfulness Intervention for Stress Eating to Reduce Cortisol and Abdominal Fat among Overweight and Obese Women: An Exploratory Randomized Controlled Study. J Obes. 2011.

27. Davidson RJ, Kabat-Zinn J, Schumacher J, Rosenkranz M, Muller D. Alterations in brain and immune function produced by mindfulness meditation. Psychosom Med. 2003; 65: 564-570.

28. Hayney MS, Coe CL, Muller D, Obasi CN, Backonja U, et al. Age and psychological influences on immune responses to trivalent inactivated influenza vaccine in the meditation or exercise for preventing acute respiratory infection (MEPARI) trial. Hum Vaccin Immunother. 2014; 10: 83-91.

29. Jedel S, Hoffman A, Merriman P, Swanson B, Voigt R, et al. A randomized controlled trial of mindfulness-based stress reduction to prevent flare-up in patients with inactive ulcerative colitis. Digestion. 2014; 89: 142-155.

30. Nidich SI, Rainforth MV, Haaga DA, Hagelin J, Salerno JW,, et al. A randomized controlled trial on effects of the Transcendental Meditation program on blood pressure, psychological distress, and coping in young adults. Am J Hypertens. 2009; 22: 1326-1331.

31. Parker JC, Gilbert GS, Thoreson RW. Reduction of autonomic arousal in alcoholics: a comparison of relaxation and meditation techniques. J Consult Clin Psychol. 1978; 46: 879-886.

32. Sibinga EM, Perry-Parrish C, Chung SE, Johnson SB, Smith M. School-based mindfulness instruction for urban male youth: a small randomized controlled trial. Prev Med. 2013; 57: 799-801.

33. Zeidan F, Johnson SK, Gordon NS, Goolkasian P. Effects of brief and sham mindfulness meditation on mood and cardiovascular variables. J Altern Complement Med. 2010; 16: 867-873.

34. Rosenkranz MA, Davidson RJ, Maccoon DG, Sheridan JF, Kalin NH. A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. Brain Behav Immun. 2013; 27: 174-184.

35. Taylor DN. Effects of a behavioral stress-management program on anxiety, mood, self-esteem, and T-cell count in HIV positive men. Psychol Rep. 1995; 76: 451-457.

36. Chen Y, Yang X, Wang L, Zhang X. A randomized controlled trial of the effects of brief mindfulness meditation on anxiety symptoms and systolic blood pressure in Chinese nursing students. Nurse Educ Today. 2013; 33: 1166-1172.

37. Tang YY, Ma Y, Wang J, Fan Y, Feng S. Short-term meditation training improves attention and self-regulation. Proc Natl Acad Sci U S A. 2007; 104: 17152-17156.

38. Danucalov MA, Kozasa EH, Ribas KT, Galduróz JC, Garcia MC. A yoga and compassion meditation program reduces stress in familial caregivers of Alzheimer's disease patients. Evid Based Complement Alternat Med. 2013; 2013: 513149.

39. Delgado LC, Guerra P, Perakakis P, Vera MN, Reyes del Paso G. Treating chronic worry: Psychological and physiological effects of a training programme based on mindfulness. Behav Res Ther. 2010; 48: 873-882.

40. Gonzalez-Garcia M, Ferrer MJ, Borras X, Muñoz-Moreno JA, Miranda C, et al. Effectiveness of mindfulness-based cognitive therapy on the quality of life, emotional status, and CD4 cell count of patients aging with HIV infection. AIDS and Behavior. 2014; 18: 676-685.

41. Pace TW, Negi LT, Adame DD, Cole SP, Sivilli TI. Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. Psychoneuroendocrinology. 2009; 34: 87-98.

42. Hidderley M, M Holt. A pilot randomized trial assessing the effects of autogenic training in early stage cancer patients in relation to psychological status and immune system responses. Eur J Oncol Nurs. 2004; 8: 61-65.

43. Myint K, Choy KL, Su TT, Lam SK. The effect of short-term practice of mindfulness meditation in alleviating stress in university students. Biomedical Research. 2011; 22: 165-171.

44. Parswani MJ, MP Sharma, S Iyengar. Mindfulness-based stress reduction program in coronary heart disease: A randomized control trial. Int J Yoga. 2013; 6: 111-117.

45. SeyedAlinaghi S, Jam S, Foroughi M, Imani A, Mohraz M, et al. Randomized controlled trial of mindfulness-based stress reduction delivered to human immunodeficiency virus-positive patients in Iran: effects on CD4(+) T lymphocyte count and medical and psychological symptoms. Psychosom Med. 2012; 74: 620-627.

46. Stefanaki C, Bacopoulou F, Livadas S, Kandaraki A, Karachalios A, et al. Impact of a mindfulness stress management program on stress, anxiety, depression and quality of life in women with polycystic ovary syndrome: a randomized controlled trial. Stress. 2015. 18: 57-66.

47. Poll EM, Kreitschmann-Andermahr I, Langejuergen Y, Stanzel S, Gilsbach JM. Saliva collection method affects predictability of serum cortisol. Clin Chim Acta. 2007; 382: 15-19.

48. Granger DA, Hibel LC, Fortunato CK, Kapelewski CH. Medication effects on salivary cortisol: tactics and strategy to minimize impact in behavioral and developmental science. Psychoneuroendocrinology. 2009; 34: 1437-1448.

49. Badrick E, Kirschbaum C, Kumari M. The relationship between smoking status and cortisol secretion. J Clin Endocrinol Metab. 2007; 92: 819-824.

50. Ashman SB, Dawson G, Panagiotides H, Yamada E, Wilkinson CW. Stress hormone levels of children of depressed mothers. Dev Psychopathol. 2002; 14: 333-349.

51. IM Goodyer, J Herbert, PME Altham, J Pearson, SM Secher, et al. Adrenal secretion during major depression in 8- to 16-year-olds.1. Altered diurnal rhythms in salivary cortisol and dehydroepiandrosterone (DHEA) at presentation. Psychological Medicine. 1996; 26: 245-256.

52. Clow A, Thorn L, Evans P, Hucklebridge F. The awakening cortisol response: methodological issues and significance. Stress. 2004; 7: 29-37.

53. Björntorp P, Rosmond R. Obesity and cortisol. Nutrition. 2000; 16: 924-936.

54. Kudielka BM, C Kirschbaum. Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. Psychoneuroendocrinology. 2003; 28: 35-47.

55. Edwards S, Clow A, Evans P, Hucklebridge F. Exploration of the awakening cortisol response in relation to diurnal cortisol secretory activity. Life Sci. 2001; 68: 2093-2103.

56. Pfeilschifter J, Köditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity after menopause. Endocr Rev. 2002; 23: 90-119.

57. JÃ¤nig W. Autonomic Nervous System. In: R Schmidt, G Thews, editors. Human Physiology. Berlin Heidelberg: Springer. 1989; 333-370.

58. Services NH. Mindfulness for mental wellbeing. GOV.UK. 2014.

59. Health Do. Anxiety Disorders. Do Health, Editor. Victoria: Australian Government. 2010.

60. Health NCfCaI. Meditation: What You Need To Know. NIo Health, Editor. US Department of Health & Human Services. 2014.

61. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol. 2010; 78: 169-183.