ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ

«ΜΟΡΙΑΚΗ & ΕΦΑΡΜΟΣΜΕΝΗ ΦΥΣΙΟΛΟΓΙΑ»

Επίδραση της άσκησης στον άξονα υποθάλαμος-υπόφυση-επινεφρίδια και το σύστημα του στρες

Παναγιώτης Τοκμακίδης

Επιβλέπων: *Γεώργιος Μαστοράκος, Καθηγητής Ιατρικής Σχολής ΕΚΠΑ*

ΑΘΗΝΑ 2020

SCHOOL OF MEDICINE

NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

GRADUATE PROGRAM IN

"MOLECULAR & APPLIED PHYSIOLOGY"

Effects of exercise on the hypothalamic-pituitary-adrenal axis and the stress system: a systematic review

Panagiotis Tokmakidis

Adviser: *Professor George Mastorakos*, *University of Athens Medical School*

ATHENS 2020

SCHOOL OF MEDICINE

NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

Master of Science in "Molecular & Applied Physiology"

The present Thesis entitled:

Effects of exercise on the hypothalamic-pituitary-adrenal axis and the stress system: a systematic review

presented by:

Panagiotis Tokmakidis

has been evaluated by the following

Thesis Committee:

Prof. G. Mastorakos, adviser of the Thesis, University of Athens Medical School

Prof. M. Koutsilieris, member of the Committee, University of Athens Medical School

Prof. D. Goulis, member of the Committee, University of Thessaloniki Medical School

ATHENS – 1ST OF JULY 2020

Abstract

The assumption that exercise can be used as a physical stress challenge with the ability to alter the stress system response in psychological stress states sets the objective of the present study. The question raised is if physical exercise can affect or even control the response to the potentially harmful socio-psychological daily stress. The approach of the issue is carried out through a systematic review of the existing randomized controlled trials (RCTs) of the literature. Hypothetically, the physical stress of exercise affects the stress system response to psychological stress, through cross-adaptation mechanisms that calibrate the stress system towards a healthier response. The focus of this systematic review is the effect of the various exercise regimens on the hypothalamic-pituitary-adrenal axis and other components of the stress system, as represented by outcome measures reflecting the stress system response to psychological stressors. Overall, the present review intended to address all available data concerning healthy individuals randomly assigned to either any form of exercise or a control condition and evaluated in comparison for any possible outcome reflecting the physiological response to psychological stress.

Key words: Stress system, Physical exercise, Nervous system, Cardiovascular system, Hypothalamic-pituitary-adrenal axis, Cortisol, Salivary a-amylase

Περίληψη (Abstract in Greek)

Η υπόθεση ότι η άσκηση μπορεί να χρησιμοποιηθεί ως μία δοκιμασία φυσικού στρες με τη δυνατότητα να αλλάξει την απόκριση του συστήματος του στρες σε καταστάσεις ψυχολογικού στρες θέτει τον στόχο της παρούσας μελέτης. Το ερώτημα που τίθεται είναι εάν η σωματική άσκηση μπορεί να επηρεάσει ή ακόμα και να ελέγξει την απόκριση στο δυνητικά επιβλαβές κοινωνικο-ψυχολογικό καθημερινό στρες. Η προσέγγιση του θέματος επιτελείται μέσω μιας συστηματικής ανασκόπησης των υφιστάμενων τυχαιοποιημένων ελεγχόμενων δοκιμών (RCTs) της βιβλιογραφίας. Υποθετικά, το φυσικό στρες της άσκησης επηρεάζει την απόκριση του συστήματος του στρες στο ψυχολογικό στρες μέσω μηχανισμών διασταυρούμενης προσαρμογής που ρυθμίζουν το σύστημα του στρες προς μια πιο υγιή απόκριση. Στο επίκεντρο αυτής της συστηματικής ανασκόπησης είναι η επίδραση των διαφόρων προγραμμάτων άσκησης στον άξονα υποθάλαμος-υπόφυση-επινεφρίδια και άλλες συνιστώσες του συστήματος του στρες, όπως αναπαριστάται από μετρήσεις εκβάσεων που αντικατοπτρίζουν την απόκριση του συστήματος του στρες σε ψυχολογικούς στρεσογόνους παράγοντες. Εν γένει, η παρούσα ανασκόπηση έγινε με σκοπό να εξεταστούν όλα τα διαθέσιμα δεδομένα αναφορικά με υγιή άτομα που κατανεμήθηκαν τυχαία είτε σε οποιαδήποτε μορφή άσκησης είτε σε κατάσταση ελέγχου και αξιολογήθηκαν συγκριτικά για οποιοδήποτε έκβαση δύναται να αντικατοπτρίζει τη φυσιολογική απόκριση στο ψυχολογικό στρες.

Λέξεις-κλειδιά: Σύστημα του στρες, Σωματική άσκηση, Νευρικό σύστημα, Καρδιαγγειακό σύστημα, Άξονας υποθάλαμος-υπόφυση-επινεφρίδια, Κορτιζόλη, α-Αμυλάση σιέλου

Table of Contents

Acknowledgments

Effort and devotion are required in order to complete a Master thesis. Daily duties are becoming more demanding and time is often hard to find. Fortunately, this attractive and difficult path becomes challenging when you meet people that open up new avenues and give you exactly what you need at the proper time; inspiration, motivation, reinforcement and their priceless assistance.

I would like to thank the adviser of my thesis, Professor George Mastorakos, who suggested such an interesting topic and gave me the directions to proceed and enjoy the pathway of my study.

I would also like to extend my gratitude to Professor Michael Koutsilieris, director of the graduate program and member of my thesis committee, who gave me the opportunity to discover the molecular aspects of Physiology all over Medicine.

My deepest acknowledgments go to my Professor Dimitrios Goulis at the Medical School of the Aristotle University of Thessaloniki who taught me how to appreciate science, guided me step by step on my thesis, and was available and willing to answer every single e-mail. Thanks to him, I was introduced to my colleague Maria Christou with whom I collaborated to conduct my thesis. Maria thanks a lot for your support, expertise and valuable advice.

In addition, I would like to express my gratitude to the secretary of the graduate program, Mrs. Xenia Gaitanari, who kept reminding us of our duties and was always there to help and endorse our efforts.

Finally, I feel the need to thank my parents for their constant encouragement and faith, and especially my father for offering his professional guidance and assistance through this path of writing that he inspired me to follow.

Abbreviations

ACTH	Adrenocorticotropic hormone
ANS	Autonomic Nervous System
ATP	Adenosine triphosphate
AUC_G	Area under the curve to the ground
AVP	Arginine vasopressin
α-MSH	Alpha-melanocyte-stimulating hormone
BMI	Body Mass Index
BP	Blood Pressure (systolic-SBP, diastolic-DBP)
BZD	Benzodiazepine
CNS	Central Nervous System
CRH	Corticotropin-releasing hormone
DASS-21	Depression, Anxiety and Stress Scales – 21 items
ECG	Electrocardiogram
FITT	Frequency, Intensity, Time-duration, Type
fMRI	Functional Magnetic Resonance Imaging
GABA	γ-aminobutyric acid
HIIT	High Intensity Interval Training
HPA axis	Hypothalamic-Pituitary-Adrenal axis
HR	Heart Rate
HRV	Heart Rate Variability
LC/NE	Locus coeruleus/norepinephrine-autonomic system
MAP	Mean Arterial Pressure
Met	Medical Subheadings terms
MIST	Montreal Imaging Stress Task
NPY	Neuropeptide Y
PA	Physical Activity
PASAT	Paced Auditory Serial Addition Test
PCr	Phosphocreatine
PFC	Prefrontal cortex (medial-mPFC, subgenual-sgPFC)
PMID	PubMed Identifier
POMC	Proopiomelanocortin
PSS	Perceived Stress Scale
RCT(s)	Randomized Controlled Trial(s)
SAM axis	Sympathetic-Adrenal-Medullary axis
SECPT	Socially Evaluated Cold-Pressor Test
TSST	Trier Social Stress Test (TSST-C for children, TSST-G for groups)
VO_2max	Maximal oxygen uptake (aerobic capacity)

Introduction

Stress is defined as the pressure, strain, weight, load, or force applied to an object, body, or the human body. Mechanically, the stress applied to a body or an object per unit area can be measured and provide its limits. Beyond these limits there is an absolute catastrophic reaction. The stress applied to the human body, however, cannot be measured and quantified with accuracy. We do not completely know our limits (difficult to test) and hopefully there is no absolute collapse beyond these limits, but rather a reserve space of reaction as evidenced by the stress system mechanisms of acute and chronic adaptation. However, when acute or chronic stress surpass controllable limits and lead to obvious stress-related sequelae (e.g., affective illnesses, psychological disorders and immunity distortion), special treatment may be required. Fortunately, the adaptive alterations elicited by certain stressful stimuli, such as the physical stress of exercise, can possibly prevent maladaptive stress responses leading to pathology.

Several studies have examined the effects of exercise on psychological stress as well as the adaptive mechanisms recruited by exercise-induced physical stress; a wide topic addressed from different perspectives through some comprehensive review articles. In 2001, *Salmon* introduced a theory to unify the effects of physical exercise on anxiety, depression and sensitivity to stress (1). In 2014, *Russell et al.* briefly explored the interaction between stress and exercise focusing on its impact on brain function (2). In 2017, *Mikkelsen et al.* underlined the positive effects of exercise on anxiety, stress and depression through mechanisms including endorphins, mitochondria, neurotransmitters and the hypothalamic-pituitary-adrenal axis (3). Recently, salivary biomarkers reflecting psychosocial stress (4), blood-brain barrier permeability (5), neuroinflammation in depressive disorders (6), and the epigenetic action of adrenal stress hormones in skeletal muscle (7), have also been studied in association with the physical stress of exercise. In addition to the stress-related benefits of physical exercise, the negative health-related effects of the lack of exercise as well as the positive health-related effects of exercise prescription in chronic diseases have also been reviewed (8, 9).

Indeed, exercise within a wide range of acceptable limits can provide beneficial stress to the human body. In other words, the physical stress of exercise has been proven to be beneficial for health. It is well known that exercise does not only improve physical fitness, but also prevents and treats many chronic and degenerative diseases. The American College of Sports Medicine in collaboration with the American Medical Society created the “Exercise is Medicine” movement, which is widespread all over the world, including Greece. Thus, the physical stress of exercise used to control the arterial blood pressure in hypertension (10), the glycemic status in type 2 diabetes (11) and the blood lipid levels in patients with coronary artery disease (12), can also be applied as an intervention that may control the response to the socio-psychological daily stress. In this regard, the duration, type and intensity of exercise should be controlled and tested for efficacy against psychological stress in order to establish efficient stress-oriented exercise interventions.

Purpose of the study

The question of how the physical stress of exercise can affect or even control the response to the socio-psychological daily stress requires a systematic approach through the existing randomized controlled trials (RCTs) of the literature. Exercise challenges the stress system and the exercise-induced alterations may calibrate the stress system towards a healthier response when encountering psychological stress. The purpose of the present systematic review is to examine the effects of exercise on the stress system response in psychological stress states, in an effort to elucidate the role of exercise as an intervention that might help healthy humans in ameliorating maladaptive stress responses.

Main entities section

Stress and the stress system

One of the most impressive aspects of human physiology is the ability of the body to keep everything in balance, constantly pursuing a state of harmony to function normally and maintain homeostasis. Anything that threatens or is even perceived as threatening this optimal body equilibrium causes a state of disharmony, which must be counteracted in order to survive. In this context, stress can be defined as a state of threatened homeostasis caused by intrinsic or extrinsic adverse forces, called stressors, and counteracted through physiological and behavioral responses elicited by an intricate neuroendocrine infrastructure, the stress system (13, 14).

However, stress is not necessarily a harmful state. On the contrary, controlled or self-driven challenges to homeostasis constitute a fundamental threat crucial for normal development and preservation of self and species, as long as a normally functioning stress system responds properly to the challenge (15). Physical exercise, for instance, may be a beneficial stressor that challenges the stress system and yield favorable adaptations. Therefore, the activation of the stress system in response to stressors of any kind increases the chances for survival by producing the appropriate behavioral and peripheral changes that improve the ability to adjust homeostasis (16, 17).

The notion of a stress system that coordinates the adaptive response to stressors was suggested in 1992 by *Chrousos* and *Gold* in *"The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis."* (16), where they describe the main components of the stress system. According to them, the stress system is principally composed of two tightly interconnected central regulators in the brain, namely the corticotropin-releasing hormone (CRH) system in the hypothalamus and the locus coeruleus/norepinephrine-autonomic (LC/NE) system in the brainstem, as well as their peripheral neuroendocrine effectors, the hypothalamic–pituitary–adrenal axis (HPA axis) and the limbs of the autonomic nervous system (ANS) respectively.

While describing the complex central effects of the CRH and LC/NE systems is beyond the scope of this review, it is important to underline some of the main effects and interactions, necessary to understand the close integration of the stress system with other central nervous system (CNS) components involved in the regulation of emotion, cognitive function and behavior (16). As such, the main central effects of the CRH and LC/NE systems are the stimulation of arousal and attention, the stimulation of the mesocorticolimbic dopaminegic system (anticipatory and reward phenomena) and the stimulation of the hypothalamic beta-endorphin system (suppression of pain sensation and analgesia). Other hypothalamic effects exerted through the catecholaminergic system are the inhibition of appetite and the activation of thermogenesis (17). Finally, of utmost importance is the reciprocal yet little direct anatomical interaction between the stress system and limbic forebrain structures, including the amygdala, hippocampus and medial prefrontal cortex (mPFC), which comprise the principal stress-regulatory limbic sites that process both psychogenic and systemic stimuli (18).

Apart from the anatomically limited and complex neural interconnections of the stress system, principally mediating the behavioral effects of stress, there is a more tangible component of the stress system consisting of its multiple neuroendocrine effectors that principally mediate the physiological effects of stress (Figure 1). Thus, from an endocrine point of view, the central main effectors of the stress system are CRH, arginine vasopressin (AVP) and the proopiomelanocortin (POMC) derived peptides alpha-melanocyte-stimulating hormone (α-MSH) and beta-endorphin, while the peripheral main effectors of the stress system are the glucocorticoids and the catecholamines norepinephrine and epinephrine (19). The release of these neuroendocrine messengers from the stress system and ultimately their action through their respective receptors in target-tissues produces a stress response phenotype affecting many aspects of human physiology, explaining why levels of stress and means of coping with stress can influence health and disease (20).

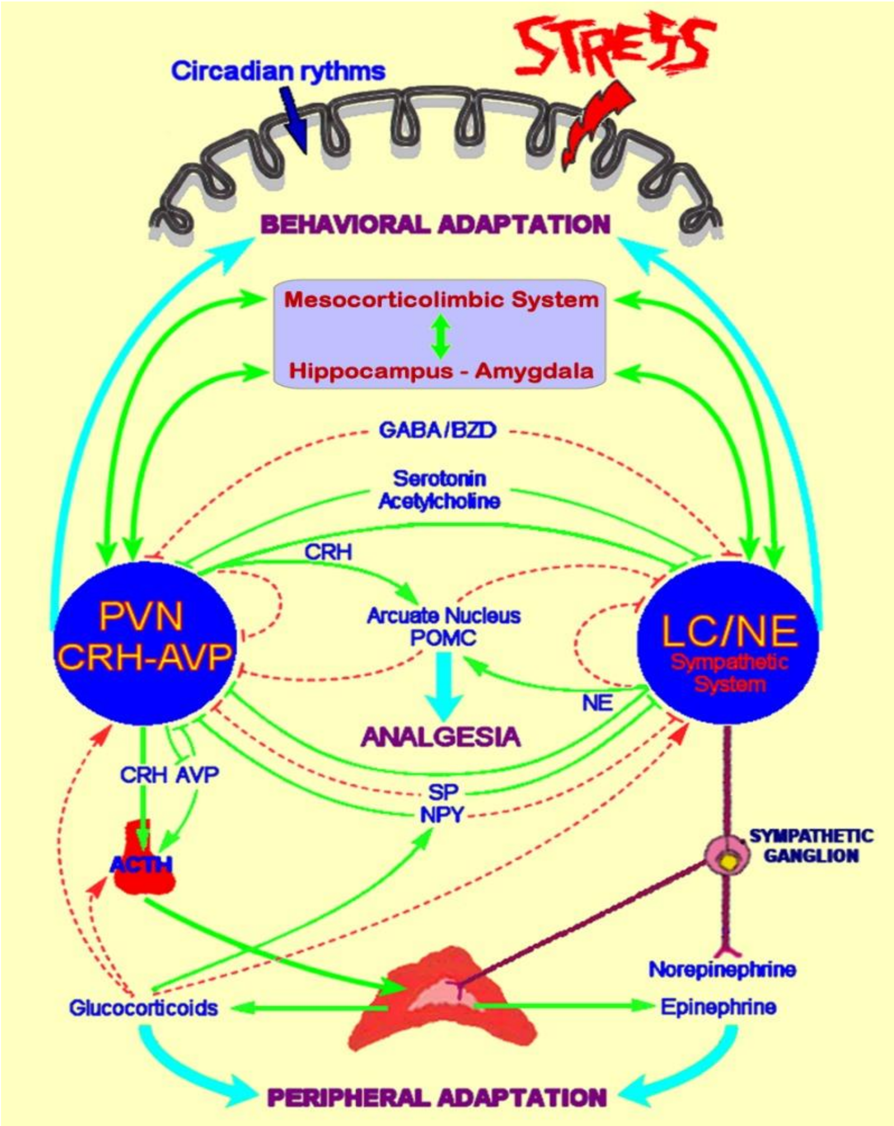

Figure 1. Presentation of the central and peripheral components of the stress system, demonstrating the functional interrelations and the relationships to other central nervous system (CNS) pathways involved in the stress response.
Figure Note: Activation is represented by solid green lines; Inhibition by dashed red lines.

CRH: corticotropin-releasing hormone
LC/NE: locus coeruleus/norepinephrine-sympathetic system
POMC: proopiomelanocortin
AVP: arginine vasopressin
GABA: γ-aminobutyric acid
BZD: benzodiazepine
ACTH: adrenocorticotropic hormone (corticotrophin)
NPY: neuropeptide Y
SP: substance P

Source from: Tsigos C, Kyrou I, Kassi E, Chrousos GP. Stress, Endocrine Physiology and Pathophysiology. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.(14)

Finally, apart from the various behavioral and physiological adaptive responses of the stress system, there are additional interactions with the axes responsible for reproduction, growth and immunity (16), as well as major inputs from the cerebral cortex and subcortical systems, the sensory organs and nerves and the endocrine and immune systems (21). To sum up, according to *Chrousos* (13), the targets of the stress system effectors include the executive and/or cognitive, reward and fear systems, the wake-sleep centers of the brain, the growth, reproductive and thyroid hormone axes, and the gastrointestinal, cardiorespiratory, metabolic and immune systems. In this context, the controllable nature of the physical stress of exercise may provide a valuable stressor for manipulating the stress system towards physiological and behavioral adaptations that favor physical and mental health.

Physical exercise and health

Exercise can be defined as a set of body movements following certain rules of intensity, duration, frequency and volume. It is important to note that the exercise output produced by muscular contractions is a physical stress challenge for the human body. Exercise affects the metabolic energy system, the neuromuscular system, the cardiovascular, respiratory and endocrine systems, the hypothalamic-pituitary-adrenal axis, microvascular circulation, cell metabolism, gene expression etc. Exercise affects either directly or indirectly all human functions, improves physical fitness and health, prevents and treats obesity, cancer, diabetes, hypertension, dementia, osteoporosis, cardiovascular and metabolic chronic diseases. Exercise has been proposed as the cornerstone of primary prevention for 35 chronic diseases (8) and can be used as a prescribed therapy for 26 of them (9).

Exercise as a stress stimulus can be controlled with the intensity and duration of exercise, whereas frequency and volume are also required for the prescription of exercise and the exercise training regimens. The intensity of exercise, however, is the most significant variable and if properly managed, can give desirable results. Overall, the intensity, duration, frequency and volume of exercise influence the internal metabolic environment and affect the body system (22) positively if properly used. These variables inseparably associated with exercise and exercise programs will be briefly described below.

Basic characteristics of exercise

Intensity of exercise

The intensity of exercise is the most important parameter of exercise training, indicates the magnitude of stress induced to the human body. Exercise-induced effects cannot be appropriately presented unless the intensity of exercise is properly described. It is generally recommended to start an exercise program with low intensity, gradually go on to moderate and finally to high intensity (9). The stress of exercise is directly dependent on the intensity of exercise. Low, moderate and high exercise intensity generate different physiological responses. Thus, based on the intensity the effects on the stress system may range from positive to negative ones. Low intensity may be used by unfit individuals or patients to begin an exercise program. Moderate intensity is safe and induces positive health-related-adaptations to the population in general. The high intensity of exercise mostly applied to professional athletes force them to work hard and often beyond safety limits. Such exercise stress may lead to muscular injuries, suppress the immune system, and induce negative health-related effects, such as suppression of the hypothalamic-pituitary-gonadal axis.

Duration of exercise

The physical condition of an individual should be taken into consideration when prescribing the duration of exercise. Unfit individuals, therefore, should avoid long duration of exercise. At the beginning of a safe exercise program, low to moderate intensity may be applied for a long time (~60 min) according to the individual’s needs. Vigorous to high intensity cannot be performed for a long time. The duration of exercise depends on intensity. For the average non-athletic population, walking exercise to exhaustion at a low to moderate intensity can last for more than an hour, running can last for about an hour, and high intensity exercise can last a few minutes or even less than a minute (utmost sprint effort for example). Such a stressful exercise is not recommended for rehabilitation programs. The longer the distance of an event, the lower the intensity (running speed, for example, at a 100 m distance cannot be compared to a 1000 m or to a 10000 m distance). When properly used during training, the high intensity of exercise, is timesaving and may produce similar or even better results. High intensity may be performed interspaced with passive recovery rest intervals or with active recovery intervals of low intensity. This constitutes the high intensity interval training (HIIT) used mostly for elite athletes and trained individuals. This training method, however, has been recently applied to patients with cardiovascular and metabolic diseases and seems to be safe and useful to clinical populations.

Frequency of exercise

The frequency of exercise is required for any training program which also includes intensity, time-duration, and type of exercise (FITT). The **FITT** acronym standing for **F**requency, **I**ntensity, **T**ime-duration, and **T**ype of exercise holds the characteristics of a training program. The frequency applied to various exercise training regimens may vary from 2 times a day for elite athletes to 2 times a week for pregnant women (23). The upper limits of exercise frequency in a weekly training program range from 4 times for pregnant women (23) to 12 times for elite athletes. The recommended frequency for the general population and patients with chronic diseases is 3 to 4 times a week. And it is advocated by different recognized scientific associations (ACSM, AHA, ADA, ESC, ECSS etc). In fact, an exercise training frequency less that 3 times a week is inadequate to induce any desirable health related physiological adaptations. The manipulation of the frequency, intensity and duration of exercise is used to attain the required training volume. Thus, the manipulation of frequency, alone or in combination with other training parameters affects the volume of exercise, induces different responses to the stress system and can be used to acquire better results.

Volume of exercise

The volume represents and combines all the characteristics of exercise. The volume of an acute exercise session combines intensity and duration of workload. The volume of a training program combines frequency, intensity, and duration of exercise. A large volume of moderate intensity and thus longer duration (at least 60 min daily) is recommended to obese and overweight individuals to control body weight and reduce body fat. In addition, evidence indicates that independent of weight loss, the large volume of physical exercise has beneficial effects on circulating lipid levels (9). Besides, an adequate exercise training volume could prevent 10 to 30% of strokes (8), and/or the magnitude of the endocrine response is relative to the volume and intensity of exercise (24). Attention is required, however, since excessive intensity or volume, or even both, may lead to undesirable physiological results including inappropriate endocrine responses (24).

Acute exercise versus chronic adaptation

Acute exercise affects the main physiological functions of the body during effort including ventilation, heart rate, blood pressure, cardiac output, and energy metabolism. In addition, the acute physiological responses are depending on the intensity of exercise. The beneficial effects on stress system reactivity and self-regulatory mechanisms against acute stress situations have recently been more reliably evaluated during acute exercise responses using salivary biomarkers (4). The acute exercise bout provides an appropriate stressor to study the regulation, integration and adaptation of the immune system (25) as well as the regulation and adaptation of the endocrine system (24). Acute exercise can be a proper model to reveal the expected specific adaptations after systematic long-term exercise.

Systematic exercise or regular chronic exercise training induces the desirable physiological health-related adaptations. To study and observe the effects of chronic exercise on the body, one can compare baseline values at the beginning of a training program with those obtained after an adequate period of training or at the end of the training exercise program. To obtain the desirable health-related adaptations the training program and mainly the intensity of exercise, applying to healthy and patient individuals, must be properly updated every 3 to 4 weeks. Nevertheless, when the applied exercise program stresses the body system beyond limits, undesirable and harmful responses may occur (24). Thus, knowledge and caution are required to obtain the desirable health related adaptations.

Aerobic versus anaerobic exercise

Aerobic exercise refers to the muscular work performed with the use of oxygen. The inspired oxygen from breathing air reaches the mitochondria within the cells and the oxygen used (cellular respiration) provide the required energy (ATP) for the physiological functions of the body. During exercise, the muscle tissue produces muscular work, and at maximal stage, oxygen requirements and metabolic energy demands surpass a 20-fold increase. Such an aerobic metabolism has been associated with maximal aerobic capacity (VO_2max) and represents cardiorespiratory fitness. Aerobic exercise has also been associated with low to moderate muscular work whereas anaerobic exercise has been associated with vigorous to maximal or supra-maximal muscular work.

Anaerobic exercise refers to the muscular work performed without oxygen. Physiologically, however, this is impossible. There is no life without oxygen. The mitochondria always provide energy (ATP) using oxygen. Thus, anaerobic exercise does not literally exist. Nevertheless, muscle cells can produce additional energy anaerobically using stored ATP, phosphocreatine (PCr) and the anaerobic part of glycolysis that produces lactate when the metabolic demands are very high. The anaerobic system contributes more to the quality, yields high power output and in a faster rate of energy produced by the aerobic metabolism. Such a metabolic process providing bursting reactions and additional muscular power has been associated with anaerobic exercise, anaerobic sprint training, and resistance training. Resistance exercise, however, constitutes a diverse strength-induced type of exercise.

Stress response and the stress syndrome

Optimal basal activity and responsiveness of the stress system are essential, not only for survival but also for some of the most fundamental aspects of everyday life, such as a sense of well-being, the successful performance of tasks and appropriate social interactions (13). Upcoming physical or psychogenic stimuli detected and interpreted by the brain as extreme or threatening, trigger the mobilization of an immediate, stereotypic, adaptive response elaborated and coordinated by the stress system when a stressor of any kind exceeds a threshold (16, 26, 27). This response, formally known as the stress response, starts with the perception of the stressful stimuli by the brain and ends up with the various behavioral and physiological adaptive changes, collectively referred to as the stress syndrome.

To maintain and re-establish homeostasis, the brain-controlled stress system must function normally both under basal conditions and under the toll of stress. Under basal conditions, an area of the mPFC clinically important in mood disorders, the subgenual prefrontal cortex (sgPFC), is pointed out as having a role in withholding the stress system response, evidently by restraining the amygdala and the two major components of the stress system, i.e. the CRH-dependent HPA axis and the LC/NE-dependent sympathetic-adrenal-medullary axis (SAM axis) of the ANS. Accordingly, during normal stress, the observed moderate diminishment in sgPFC function results in disinhibition of the restrained loci, thereby permitting activation of the stress response, phenotypically expressed as adaptive alterations appropriate for survival during a life-threatening situation (28).

The aforementioned adaptive alterations produce a stress response phenotype, described as the stress syndrome phenomenology, including the following cognitive, behavioral and physiological phenomena (14, 27-29):

- Enhanced arousal, alertness, vigilance, cognition and focused attention.
- Emerging anxiety, analgesia and loss of cognitive and affective flexibility.
- Suppression of vegetative functions redundant for immediate survival (pleasure-seeking, appetite, sleep, sexual activity, growth, reproduction).
- Adaptive redirection of energy and body resources (oxygen, nutrients) to the CNS and the stressed body sites where they are needed the most:
    - Increase in the cardiovascular tone (heart rate, blood pressure).
    - Increase in the respiratory rate.
    - Increase in intermediate metabolism (gluconeogenesis, lipolysis).
    - Insulin resistance (to provide increased glucose for the brain).

Despite the simplified approach used to describe the stress response, it should be noted that the complexity of the stress response cannot be restricted to some cortical/subcortical structures, the HPA and the SAM axes. On the contrary, different types of stressors engage different brain networks according to timing and duration of stressor exposure leading to deviations of the stress response with a variety of short- and long-term consequences (26). Of clinical importance, the dysregulation of the stress response in terms of magnitude and/or duration can disrupt homeostasis and eventually lead to many adverse effects in various physiological functions, such as growth, development, metabolism, circulation, reproduction, immunity, cognition and behavior, thereby affecting both physical and mental health (30).

Systematic review section

Study rationale

The effects of exercise on the hypothalamic-pituitary-adrenal (HPA) axis and the stress system can be viewed from two perspectives. The first perspective involves the effects of exercise as a physical stressor that elicits the stress system response. In contrast, the second involves the effects of exercise as an alleviating intervention to the stress system response elicited by a distinct stressor, antecedent or even precedent. This systematic review focused on the latter perspective, as it aimed to examine the effects of exercise on the stress system response elicited by psychological stress.

From the various stressors, psychological stress has a high impact on health and well-being, both because of its high prevalence in modern societies and the lack of effective strategies to evaluate and address its consequences on human physiology and behavior. Therefore, from a clinical point of view, interventions that would ameliorate the stress system response to psychological stressors can provide a possible means of preventing mortality, morbidity and reduction in health-related quality-of-life associated with maladaptive stress system responses elicited by psychological stress.

Exercise constitutes a generally safe, easily accessible and often costless intervention that could turn out to be an efficient and pragmatic approach to prevent or at least attenuate a health problem as common as psychological stress sequelae. The proposed physiological mechanism, underlying the action of the different exercise regimens, is based on the physiological and even behavioral stress system adaptations that exercise elicits as a stressor itself. According to the cross-stressor adaptation hypothesis, the main idea behind the potential effectiveness of exercise is the hypothesis that the stress system response to the exercise stressor leads to the appropriate adaptive alterations of the stress system that will prove beneficial for encounters with stressors other than exercise, the most widely prevalent and socially relevant of which is considered to be psychological stress.

Literature review

With the expansion of the field of Medical Psychology in exercise and sports after 1980, psycho-neuroendocrine responsivity to mental stress was considered an outcome of prominent value, employing physiological and psychological measures to objectively quantify the subjective behavioral effects of regular exercise on psychological stress. However, as most exercise studies did not utilize strict control conditions or active placebo groups, the observed psychological outcomes arguably did not reflect credibly enough the effects of the exercise intervention *per se*. Indeed, alternative factors, such as expectancy of benefits, generalized treatment or attention effects, social reinforcement and history or selection bias, should always be considered as possible confounders when appraising the results of exercise trials, not accounting for these factors (31). Of additional interest, a concept of affective beneficence attributed to exercise had concurrently started to emerge based at first on associations but not causality, as evidenced by correlational studies reporting reductions in state anxiety following acute physical activity and reductions in anxiety and depression following chronic physical activity (32).

Aerobic fitness and psychosocial stress

In 1987, *Crews* and *Landers*, at their meta-analytic review of aerobic fitness and reactivity to psychosocial stressors (33), indicated that aerobically fit subjects had a reduced psychosocial stress response compared with either control group or baseline values, by combining the results of 34 studies including a total of 1449 subjects. The arousal measures (stress reactivity to psychosocial stress tasks) they used to determine possible differences between fit and unfit groups included heart rate (30 studies), systolic blood pressure (13 studies), diastolic blood pressure (17 studies), skin temperature and conductance (8 studies), changes in norepinephrine and epinephrine as well as their metabolites (4 studies), muscle tension (3 studies) and subjective self-report (9 studies). However, the meta-analysis conclusion that aerobically fit subjects show a reduced psychosocial stress response may imply but does not prove that exercise interventions will similarly result in a reduced response to psychosocial stressors.

Plasma catecholamine response

On the other hand, in 1991, *Sothmann et al.* (34) focused on the plasma catecholamine response to acute psychological stress and found no strong support for an aerobic fitness association. Hence, as evidenced by six cross-sectional studies on plasma catecholamine reactivity, they challenged the concept that a high level of aerobic fitness modifies the sympathoadrenal response to an acute psychological stressor. In addition, by expanding their research to longitudinal studies examining short-term exercise, they concluded that exercise training could modestly lower the absolute concentrations of basal circulating plasma norepinephrine, without, however, producing an adaptation in the relative plasma catecholamine change during exposure to acute psychological stress. Nevertheless, exercise training studies of short duration, despite having the advantage of promptly assessing the effects of exercise, fall short of achieving the high fitness levels examined by cross-sectional studies.

Physical activity and psychosocial well-being

In 1996, *Gauvin* and *Spence* (35), critically reviewed the evidence on the association between physical activity and psychological well-being. They raised the question whether acute and/or chronic exercise can reduce psychophysiological reactivity to psychosocial stressors. They acknowledged that acute exercise might be related to more effective responses to psychosocial stress. At the same time, they questioned the causal role of chronic exercise to the more healthful reactivity profiles observed in aerobic fitness studies. In general, they concluded that moderate quantity and quality point out to a small-to-moderate decrease in reactivity to psychosocial stressors with exercise dose suggested as the main moderator variable. Overall, the idea that physical activity is positively related to psychosocial stress reactivity was supported, although there were not enough data from high validity studies to state that exercise is the causal factor in this association.

In 2001, with the results of cross-sectional and longitudinal studies converging to support more consistently the antidepressant, anxiolytic and “anti-stress” effects of aerobic exercise training, *Salmon* attempted to provide an integrated theoretical framework for the effects of physical exercise on anxiety, depression and sensitivity to stress (1). While recognizing the unclear causality linking exercise habits to health protection from stress vulnerability, he combined interrelated evidence to develop the unifying theory that exercise training is a controllable and predictable stressor recruiting a process of stress adaptation, which confers enduring resilience to stress. Importantly, to uncover the neurochemical correlates of behavioral adaptation, he enriched his thesis with data consistent with exercise-induced adaptive changes in opioid systems as providing the link between regular exercise and reduced stress responses, mainly through opioid-mediated inhibition of noradrenergic stress responses in the CNS. In addition, contrary to the predominance of cardiovascular responses in the literature, he noticed that the HPA axis had received little attention, with the few studies in which cortisol or ACTH had been measured, showing no difference between fit and unfit subjects in response to stressor tasks. Practically, albeit tempting to consider this unifying theory an answer to the psychological benefits of exercise, it should be rather viewed as a psychobiological interpretation enabling questions about the valuable effects of exercise as a stressor if acting indeed through the process of stress adaptation.

Physiological effects of exercise as a stress model

In the context of examining the physiological effects of exercise as a stress model, in 2005, *Mastorakos et al.* described the exercise as physical stress that challenges homeostasis, leading in response to the adaptive reaction of the stress system, mediated principally by the sympathetic ANS (plus adrenal medulla) and the HPA axis (adrenal cortex) through the respective elevation of catecholamines and cortisol (36). Accordingly, adopting the assumption that the stress response is a neuroendocrine mechanism that occurs in anticipation of physical action, in 2006, *Tsatsoulis* and *Fountoulakis* (37) proposed that physical activity should be the natural means to prevent the consequences of stress. They supported their opinion with accumulating evidence documenting the beneficial effects of regular exercise in preventing or ameliorating the metabolic and psychological comorbidities induced by chronic stress. They also delved into the mechanisms of these effects, attributing the benefits of exercise both to central effects reducing sensitivity to stress and peripheral actions influencing metabolic functions, in particular, insulin sensitivity and the partitioning of fuels toward oxidation rather than storage. To sum up, these two reviews are based on the stress system's concept, the former highlights the effects of exercise on the stress system as a physical stressor, while the latter underlines the protective role of exercise on stress system dysregulation and comorbidities.

Despite the triggering theories, comprehensive interpretations and justified opinions, there was a need for a systematic review that would reliably answer the question of whether not fitness, but exercise can attenuate the stress system response to psychosocial stressors. With this reasoning, in 2006, *Hamer et al.* performed a meta-analytic systematic review of randomized controlled trials (RCTs) that examined the effect of acute exercise on blood pressure (BP) responses to psychosocial laboratory stressors (38). From the 15 RCTs that met the inclusion criteria, 10 demonstrated significant reductions in post-exercise stress-related BP responses compared with control. Interestingly, they also noticed that studies involving higher exercise doses tended to show larger effects, with the minimum dose to show a significant effect being 30 minutes at 50% VO_2max. Consequently, they provided evidence for the stress-buffering effects of exercise, but they also proposed the necessary duration and intensity of the intervention. However, they examined only acute exercise and only one parameter of the psychosocial stress response (i.e., BP); the effect of chronic exercise and/or the responses of other stress-related outcomes remained questionable.

The stress-buffering effects of exercise from a clinical perspective

Although appreciating the emerging confidence for the stress-buffering effects of exercise based on positive laboratory outcomes, from a clinical perspective, what matters are the health complaints and how to address them. To examine this aspect, in 2009, *Gerber* and *Pühse* reviewed if exercise and fitness can protect against stress-induced health complaints (39). They found that about 50% of the studies reported at least partly supportive results in that people with high exercise levels exhibited fewer health problems when they encountered stress. Inclining to support a cause-and-effect association, the causality analyses showed that stress-moderation effects had been consistently found in different samples and with different methodological approaches. Despite acknowledging that more support had resulted from cross-sectional studies, they reported that the exercise-based stress-buffer effects were also found in prospective, longitudinal and quasi-experimental investigations. Therefore, exercise and fitness could also be considered a means of protecting against health complaints induced by stress.

Recognizing the beneficial effects of exercise on psychological stress and well-being, the supporters of mind-body exercises were concurrently trying to contribute to this broad field by examining through clinical trials the effects of tai-chi, qigong and yoga. There was also the argument that these modes of exercise could be equally beneficial despite the moderate physical activity, due to their coincident mindfulness effects. Therefore, the accumulation of evidence led consecutively to the conduction of meta-analytic reviews, the most representative presented briefly below.

The effects of tai-chi on psychological well-being

To begin with, regarding tai-chi, in 2010, *Wang (Chenchen) et al.* performed a systematic review and meta-analysis on the effects of tai-chi on psychological well-being, including stress reduction, anxiety, depression and enhanced mood (40). Targeting the broad population of community-dwelling healthy participants and patients with chronic conditions, 21 out of 33 randomized and non-randomized trials supported that 1 hour to 1 year of regular tai-chi significantly increased psychological well-being. The extrapolated beneficial association between tai-chi practice and psychological health was also reinforced by seven observational studies with relatively large sample sizes. Based on their findings, they concluded that tai-chi appears to be associated with improvements in psychological well-being including reduced stress, recommending, however, the need for high-quality, well-controlled, longer randomized trials. A limitation of this review was the support of the results based not only on randomized but also non-randomized trials, not controlling for selection bias and confounding variables.

Managing stress and anxiety through qigong and yoga

Further, regarding the closely-related qigong, in 2014, *Wang (Chong-Wen) et al.* performed a systematic review and meta-analysis of RCTs on managing stress and anxiety through qigong exercise in the more narrow population of healthy adults (41). From the 7 RCTs that met the inclusion criteria, 3 RCTs suggested that qigong exercise reduced stress among healthy subjects following 1 to 3 months of qigong practice, compared to wait-list controls. Therefore, despite some encouragement from good quality evidence, the limited number of RCTs and their methodological flaws, led to the recommendation for further rigorously designed RCTs, before safe conclusions can be made.

Concluding with what is known about mind-body exercise, regarding the more popular yoga, in 2015 *Pascoe* and *Bauer* performed a systematic review of RCTs on the effects of yoga on stress measures and mood, adopting a physiology-based approach and investigating the effects of yoga on sympathetic nervous system and HPA axis regulation measures (42). They focused on studies collecting physiological parameters such as blood pressure, heart rate, cortisol, peripheral cytokine expression and/or structural and functional brain measures in regions involved in stress and mood regulation. This review's result through the synthesis of 25 RCTs was to provide preliminary evidence suggesting that yoga practice can lead to better regulation of the sympathetic nervous system and HPA axis, as well as a decrease in depressive and anxious symptoms in a range of populations. To conclude concerning mind-body exercise as a whole, further research based primarily on high-quality RCTs is needed to confirm the positive findings and facilitate the clinical implementation of these forms of exercise.

The exercise-induced glucocorticoid paradox

Before moving forward, here comes the literature to explain a paradox of physiology that may come to mind regarding the exercise-induced elevation of glucocorticoids. To address this exercise-glucocorticoid paradox, in 2017, *Chen et al.* investigated how exercise is beneficial to cognition, mood and the brain while increasing glucocorticoid levels (43). To answer this question correctly, they reviewed the evidence showing that while both chronic stress and exercise elevate basal cortisol levels through increased secretion of cortisol, the former is detrimental to cognition/memory, mood/stress coping, and brain plasticity, while the latter is beneficial. From the three preliminary answers they propose, it is essential to highlight that under regular exercise (however, not chronic stress), the elevated cortisol functions through the glucocorticoid receptors to elevate dopamine in the medial prefrontal cortex (mPFC), and the mPFC dopamine is the one essential for active coping. This may provide an answer to the paradox of the beneficial effects of exercise-induced glucocorticoid enhancement, suggesting a differentiating action of stress-induced glucocorticoids according to the triggering stressor's nature.

The influence of regular physical activity on stress reactivity

Taking into consideration the value of cortisol as a stress response outcome and the difficulty to compare responses elicited by similar but different psychosocial stressors, in 2018 *Mücke et al.* performed a systematic review on the influence of regular physical activity and fitness on stress reactivity as measured with the Trier Social Stress Test (TSST) protocol (44). With this focused approach, they found that cortisol and heart rate reactivity was attenuated by higher physical activity or better fitness in 7 of 12 studies and 4 of 9 studies, respectively. In addition, 2 of 4 studies reported smaller increases in anxiety and smaller decreases in calmness in physically active or fitter participants. Finally, 3 of 4 studies associated higher physical activity or fitness with a more favorable mood in response to the TSST. However, despite the advantage of incorporating cortisol outcomes and focusing on a single psychosocial stressor, the inclusion of cross-sectional analyses as the majority of the reviewed evidence weakens the causality of the argument that physical activity attenuates psychosocial stress response.

The effects of exercise on stress outcomes of specific age groups

Finally, despite the incessant need for robust evidence in the field, the common perception that exercise favors stress adaptation seems to stand still, permitting the focus of research on more special groups of people from the general population. Recently, *Nigdelis et al.* (45) focused on middle-aged and older women and performed a meta-analysis of 5 RCTs on the effect of programmed exercise on perceived stress, concluding that physical activity of low to moderate intensity and of at least six weeks duration, does not significantly improve perceived stress in midlife and older women. Meanwhile, *Rodriguez-Ayllon et al.* (46) focused on preschoolers, children and adolescents. They performed a meta-analytic systematic review on the role of physical activity and sedentary behavior in mental health regarding stress as part of psychological ill-being (along with depression, negative affect and psychological distress). The 12 intervention studies (3 RCTs and 9 non-RCTs) included in the meta-analysis showed a small but significant overall effect of physical activity on mental health. In contrast, longitudinal and cross-sectional studies demonstrated significant associations between physical activity and lower levels of psychological ill-being (and greater psychological well-being). In summary, with the first reviews on the effects of exercise on stress outcomes of special populations starting to emerge, the need for a systematic review examining the effects of exercise on healthy populations' stress outcomes stands as a necessity to direct further research.

Knowledge gap

Having discussed the literature's highlights to date, it is evident that plenty of research was conducted to prove the effectiveness of exercise against psychological stress. A systematic review could illustrate the gaps of existent knowledge, addressing a wide range of factors from the focused perspective of a single research question.

First, to draw firm conclusions that would address the real benefit of selecting exercise as an intervention to ameliorate the effects of psychological stress, data should come from the best study designs available, i.e., RCTs, a strategy not widely adopted by previous reviews. This approach is essential because all other study designs can complement but cannot prove a cause-and-effect association.

Second, to direct research to be clinical and involve other special populations, researchers should know what stands true for the normal healthy human. Understanding the physiological effects of exercise on healthy human individuals without considering concurrent physical or mental health variables is the core to elucidate the mechanisms of exercise before moving forward to clinical implications.

Third, exercise is not synonymous with fitness. Every intervention recruiting the mechanisms of physical activity regardless of its fitness effects should be considered along with its unique characteristics to highlight the possible differential effects of the various exercise interventions. This may help to point out some characteristics of exercise that should be taken into account when considering its “prescription”, acknowledging how diverse this intervention can be.

Fourth, the comparator should ideally be a placebo group or an attention control condition. However, any other control group cannot be excluded as long as the usual clinical comparison regarding exercise is not “exercise versus some other intervention”, but “exercise versus no exercise”. Blinding is not possible for the participant when comparing the intervention of exercise to any control condition.

Last but not least, stress cannot be represented by a single outcome, but rather every possible outcome used to assess psychological stress should be examined to form a clear picture of the effects of exercise on every aspect of the stress system, an approach partially adopted by previous literature.

Aim

The present systematic review aimed to address all the available data coming from RCTs conducted on healthy individuals randomly allocated either to any form of exercise or to a control condition and evaluated for every possible outcome that could be used to assess the stress system response to psychological stressors.

- Study design: RCTs
- Population: healthy
- Intervention: exercise
- Comparator: no exercise
- Outcome: psychological stress response phenotype

Materials and Methods

The present systematic review has the following characteristics:

1. Sensitive eligibility criteria, without date or language restrictions.
2. Online database searches followed by references search.
3. Specific search strategies limited by database filters.
4. Study selection by two independent reviewers, cross-checked by a supervisor.
5. Data extraction by the author, only for predefined variables in a prespecified form.
6. Qualitative synthesis (description) of the principal summary measures.

The conduction of this systematic review started in March 2020. The protocol was discussed among the researchers, setting the aim to investigate if intervening to humans with exercise compared to no exercise will result in psychological stress response outcomes of interest. The study was planned to start from PubMed by finding the search string that will answer timely to the research question. In the process, the search string was expanded to involve other databases, too. A specific search string was finally adopted, complemented by a scrutinizing references search. To follow a methodologically refined approach, a second reviewer was involved in the process of study selection. A "trial and error" process was adopted, without a predefined well-written protocol from the beginning of the study, allowing for adjustments and refinements.

The initial eligibility criteria set to define the literature were:

- Study design: randomized controlled trials
- Population: human individuals with an intact stress system
- Intervention: exercise
- Comparator: no exercise
- Outcome: any stress system measure assessing psychological stress
- Report characteristics: published reports without date restrictions

The initial search string formed to sensitively identify the relevant literature was:

[exercise OR train OR athlete OR exertion OR gym OR sports OR workout OR "physical activity" OR conditioning] AND [stress OR HPA OR "HPA axis" OR hypothalam* OR pituitary OR hypophys* OR adrenal OR CRH OR corticotropin OR CRF OR AVP OR ADH OR vasopressin OR antidiuretic OR ACTH OR adrenocorticotrop* OR PRL OR prolactin OR cortisol OR glucocorticoid OR epinephrine OR adrenaline OR norepinephrine OR noradrenaline OR catecholamines OR sympathetic OR autonom* OR "locus ceruleus" OR IL-6 OR interleukin OR TNF OR cytokine OR IL-1] AND [RCT OR trial OR randomi* OR controlled]*

- *No filters: 1,935,625 results*
- *Filter "Humans": 1,512,738 results*
- *Filter "Title/Abstract": 1,344,174 results*
- *Filters "Humans" & "Title/Abstract": 945,260 results*

Finally, a specific search string was adopted:

"Exercise"[Mesh] AND "Stress, Psychological"[Mesh]

- *Filter "Randomized Controlled Trial": 242 results*

Both reviewers proceeded by screening the titles of the 242 reports in collaboration so as to familiarize with the subject and ensure that we adopt a similar approach when assessing the records for eligibility. This screening process led to 137 eligible reports. Continuing according to the methodological rules, 137 reports were reviewed independently through abstracts screening and we ended up with 65 eligible reports. Trying to be more attentive with the initial eligibility criteria, an eligibility form was utilized for the selected abstracts and we concluded that from the 65 reports, 31 could be included for further full-text screening, while 19 were unclear and 16 were excluded.

With the generality of the initial eligibility criteria proving problematic, it was decided to further specify them, before selecting which reports qualify for full-text screening:

- Study design: RCTs, including crossover RCTs (until the point of crossover).
- Population: healthy human individuals of any age or sex, including individuals without a stated health problem, i.e., not clearly reported as healthy but without any sign of impaired physical or mental health (unhealthy populations should be excluded, because the diseases are very different, and the populations cannot be directly compared).
- Intervention: physical exercise of any type, duration or intensity (either a training program or an acute session), including walking and physically demanding forms of mind-body exercise (mind-body exercise should be included because it is still exercise, which can be analyzed as a subgroup different from “classic” exercise).
- Comparator: no-exercise control group or placebo exercise control group (not physically demanding light exercise designed to serve as a placebo comparator to the exercise intervention), excluding comparison with other interventions (comparators other than control conditions should be excluded, because the differences between “exercise versus control” and “exercise versus other intervention” are expected to be quite wide; these two types of comparisons cannot be mixed).
- Outcome: any measure used to assess the adaptation of the stress system response after exercise as long as it reflects the response to psychological stressors and not to the physical stressor of exercise; psychological stress response phenotype assessed at three levels:
  1. Brain
     a. perceived stress (questionnaires or scales)
     b. fMRI changes and other measures reflecting brain response
  2. ANS/sympathoadrenal response
     a. cardiovascular measures (BP, heart rate, heart rate variability) and other measures reflecting the sympathetic ANS response

      b. catecholamines and other measures reflecting their response (serum, urinary, salivary)
   3. HPA axis response
      a. cortisol and other measures reflecting the HPA axis response (serum, urinary, salivary).
- Report characteristics: published reports and trial registries without applying any date or language filters (although considering that if reviewed studies would require full-text screening in a different language than the ones spoken by the reviewers, we may later apply some language restrictions).

By applying these specific eligibility criteria, 28 reports were finally selected based on their abstract for further full-text screening. Both reviewers, independently assessed the full texts for eligibility ending up with 9 included reports, 8 unclear reports and 11 excluded reports. The study characteristics of these reports (population, intervention, comparator, outcome, comments concerning other eligibility details) were clearly stated in a formulated document along with the reasons for considering them as unclear or excluded. The supervisor cross-checked the aforementioned documents agreeing with the included and excluded reports and proposing as a solution for the 8 unclear reports to include 6 and exclude 2, with reasons. Therefore, for all 13 excluded reports the reasons for exclusion were stated with clear justifications and there were no other than non-eligibility. The remaining 15 reports were selected as eligible for inclusion in qualitative synthesis.

Having stated the eligibility criteria, the search was expanded beyond PubMed, by incorporating additional reports included in the databases of Scopus and Central. Part of the scope was to delve into the "grey literature" as well (materials and research produced by organizations outside of the traditional commercial or academic publishing and distribution channels).

Moving forward to the next step, the PubMed search string was transcribed to corresponding ones to search for the same terms in Central and Scopus. Reminding that the PubMed search string had been based on MeSH terms (Medical

SubHeadings), an attempt was made to form similar search strings for searching Central and Scopus. A filter for RCTs was not available and was not used in Central, proving that additional reports were in fact retrieved from PubMed, but were not indexed in PubMed as RCTs, explaining the failure to detect them in the first place. Accordingly, in Scopus an attempt was made to form a search string that would represent as closely as possible the one used in PubMed (i.e., limiting the search to RCTs).

The final search strings across the three electronic databases were as follows:

1. PubMed: *("Exercise"[Mesh] OR exercis*) AND ("Stress, Psychological"[Mesh] OR "psychologic* stress*") applying the filter "Randomized Controlled Trial"*
2. Central: *([mh exercise] or exercis*) and ([mh "stress, psychological"] or "psychologic* stress*") and random**
3. Scopus: *exercis* AND "psychologic* stress*" AND SUBJAREA(MEDI)AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (EXACTKEYWORD,"Randomized Controlled Trial"))*

The above search strings as applied on the 30th of March of 2020, led respectively to:

1. PubMed: *532 results*
2. Central: *569 trials*
3. Scopus: *551 results*

Overall, 1652 records were identified through the database searching (532 + 569 + 551). These records included also the 242 records that had been previously identified in PubMed during the first search with MeSH terms only.

At this point, it had to be ensured that there was no other ongoing systematic review with the same objective. Therefore, the online database PROSPERO (international prospective register of systematic reviews) was searched. One similar ongoing systematic review (ID: CRD42020138173) was detected, entitled "Physical exercise as a means of reducing mental stress: a systematic review and meta-analysis", by *Haag et al.* (47), registered in February 2020. In accordance with the present systematic review, this one includes RCTs examining the "exercise versus no exercise" comparison, but focuses on mentally stressed adults, a population that we excluded. Concisely, the aim of *Haag et al.* (47) was to examine exercise as an intervention that may reduce the mental stress of a mentally stressed population, while the aim of the present review was to examine exercise as an intervention that may prevent maladaptive responses to psychological stress in a healthy population.

Having identified 1410 records across the different databases, duplicates had to be removed. For this purpose, the records were separated in those with PubMed Identifier (PMID) and those without it:

1. PubMed: 532 – 242 = 290 records (all with PMID)
2. Central: 569records (533 with PMID, 36 without PMID)
    a. retrieved from PubMed: 533 records (all 533 with PMID)
    b. retrieved only from Embase: 4 records (all 4 without PMID)
    c. retrieved from "clinicaltrials.gov": 32 records (all 32 without PMID)
3. Scopus: 551 records (489 with PMID, 62 without PMID)

Overall, the numbers of records with PMID and without PMID were:

- With PMID: 290 + 533 + 489 = 1312
- Without PMID: 36 + 62 = 98

At first, the 1312 records with PMID were checked for duplicates either in between or with the initial 242 records by using the "Stata" (software for statistics and data science). The "Stata" software retrieved 731 records with PMID (additional to the initial 242); thus, the number of duplicates with exported PMID was 581 (1312 – 731).

Afterwards, the 98 records without PMID (4 from Embase, 32 from "clinicaltrials.gov" and 62 from Scopus) had to be checked. The 32 records from "clinicaltrials.gov" were registered clinical trials (part of "grey literature"), and as such, are not expected to have PMID. On the other hand, the 4 records from Embase and the 62 records from Scopus may have PMID, possibly not exported due to database attribution limitations. The titles of these records were checked through PubMed search, leading to the following results:

- Embase: 3 out of 4 records had PMID and all 3 were manually confirmed as duplicates, while the remaining 1 record was a conference paper without PMID published later in a journal with PMID (not duplicate).
- Scopus: 40 out of 62 records had PMID and 3 were manually confirmed as duplicates (40 – 3 = 37 non-duplicates with PMID), while the remaining 22 records without PMID were not duplicates.
- Overall number of duplicates: 6 (3 from Embase, 3 from Scopus).

Therefore, the total number of duplicates was 587 (581 + 6). Consequently, after removing the duplicates, the total number of records was 1065 (1652 – 587). Having already screened 242 records, the number of records needed to screen was 823 (1065 – 242).

The 823 records had the following distribution:

- Retrieved through "Stata": 731 (all with PMID)
- Retrieved from Embase: 1 (with PMID)
- Retrieved from Scopus: 59 (37 with PMID, 22 without PMID)
- Retrieved from "clinicaltrial.gov": 32 (all without PMID)

Both reviewers screened the 823 records independently, first at the level of titles and then at the level of abstracts.

The screening of the titles resulted in:

- Records with PMID: 142 eligible titles
    - "Stata": 131
    - Embase: 1
    - Scopus: 10

- Records without PMID: 22 eligible titles
  - Scopus: 9
  - “clinicaltrials.gov”: 13

The screening of the abstracts resulted in:

- Records with PMID: 39 eligible abstracts
  - “Stata”: 35
  - Embase: 1
  - Scopus: 3
- Records without PMID: 2 eligible abstracts
  - Scopus: 2
  - “clinicaltrials.gov”: 0

Therefore, 41 full-texts were assessed for eligibility (39 + 2), in addition to the 28 full-texts previously assessed during our first search in PubMed. Overall, from the 1065 records identified through database searching after removing duplicates, titles and abstracts screening resulted in a total of 69 full-text articles (28 + 41) qualifying to eligibility assessment. This means that the screening process resulted in the exclusion of 996 records (1065 – 69). The reasons for exclusion during the screening process were no other than non-eligibility, as determined independently and through agreement by both reviewers. However, the reasons for exclusion were not reported for these 996 excluded records, as there is no such requirement for records excluded by screening according to the “PRISMA statement” rules we followed (48).

Correspondingly, the reasons for excluding a full-text article out of the 69 totally assessed were clearly stated.

In order to proceed cautiously with the eligibility assessment of the 41 full-texts, an eligibility form with the characteristics of each study (population, intervention, comparator, outcome, comments concerning other eligibility details) was constructed, similar to the one used for the eligibility assessment of the initially retrieved 28 full-texts. Both reviewers independently assessed the 41 full texts; after cross-checking and discussing the disagreements, the following studies were considered eligible:

- 8 studies included (all with PMID)
- 5 studies unclear (4 with PMID, 1 without PMID), with the reasons stated
- 28 studies excluded (27 with PMID, 1 without PMID), with the reasons stated

The supervisor of the review cross-checked these results, accompanied by the eligibility form, and recommended additionally excluding 4 out of the 5 unclear studies based on the stated reasons. Two of these studies were considered unclear due to employing tai-chi as the exercise intervention. Tai-chi, despite regarded as a form of mind-body exercise, did not seem to involve physical activity of significant intensity. On the other hand, two other studies intervening with qigong (closely-related form of mind-body exercise) were included because the particular sets of qigong employed in these studies involved physical activity of significant intensity (49-54).

Therefore, the eligibility assessment of the 41 full-text articles resulted in:

- 9 studies included (all with PMID)
- 32 studies excluded (30 with PMID, 2 without PMID), with the reasons stated

Therefore, 9 studies additional to the initial 15 were included in the qualitative synthesis. Overall, the eligibility assessment of a total of 69 full-text articles resulted in:

- 24 studies included (15 + 9)
- 45 studies excluded (13 + 32), with reasons

A screening of the references of the 24 included studies was performed. This process, which was independently performed by the two reviewers, led to 137 suitable reference titles, requiring further screening:

- Duplicates of previously assessed articles: 6

- Not found: 2
- Not humans: 2
- Not RCTs: 80
- Not eligible population: 3
- Not eligible comparison: 15
- Not eligible outcome: 9
- Not excluded: 20

Having excluded 109 references through screening (2 + 80 + 3 + 15 + 9) out of 129 after removing the duplicates (137 – 6 = 131) and those not found (131– 2 = 129), a full-text eligibility assessment was performed for 20 references that could not be excluded by screening, using an eligibility form containing the study characteristics. An independent assessment resulted in:

- 11 included studies
- 4 unclear studies, with the reasons stated
- 5 excluded studies, with the reasons stated

Discussing these results with the supervisor of the review resulted in:

- 15 studies included, leading to a total of 39 for qualitative synthesis (24 + 15)
- 5 studies excluded, leading to a total of 50 excluded with reasons (45 + 5)

In conclusion, the study selection process (databases and references) resulted in (see Figure 2) the following:

- Records identified through database searching: 1652 (587 duplicates)
- Records identified through references searching: 137 (6 duplicates)
- Records after duplicates removed: 1196 (1065 + 131)
- Records screened: 1194 (1065 + 129)
- Records excluded through screening: 1105 (996 + 109)
- Full-text articles assessed for eligibility: 89 (69 + 20)
- Full-text articles excluded, with reasons: 50 (45 + 5)
- Studies included in qualitative synthesis: 39 (24 + 15

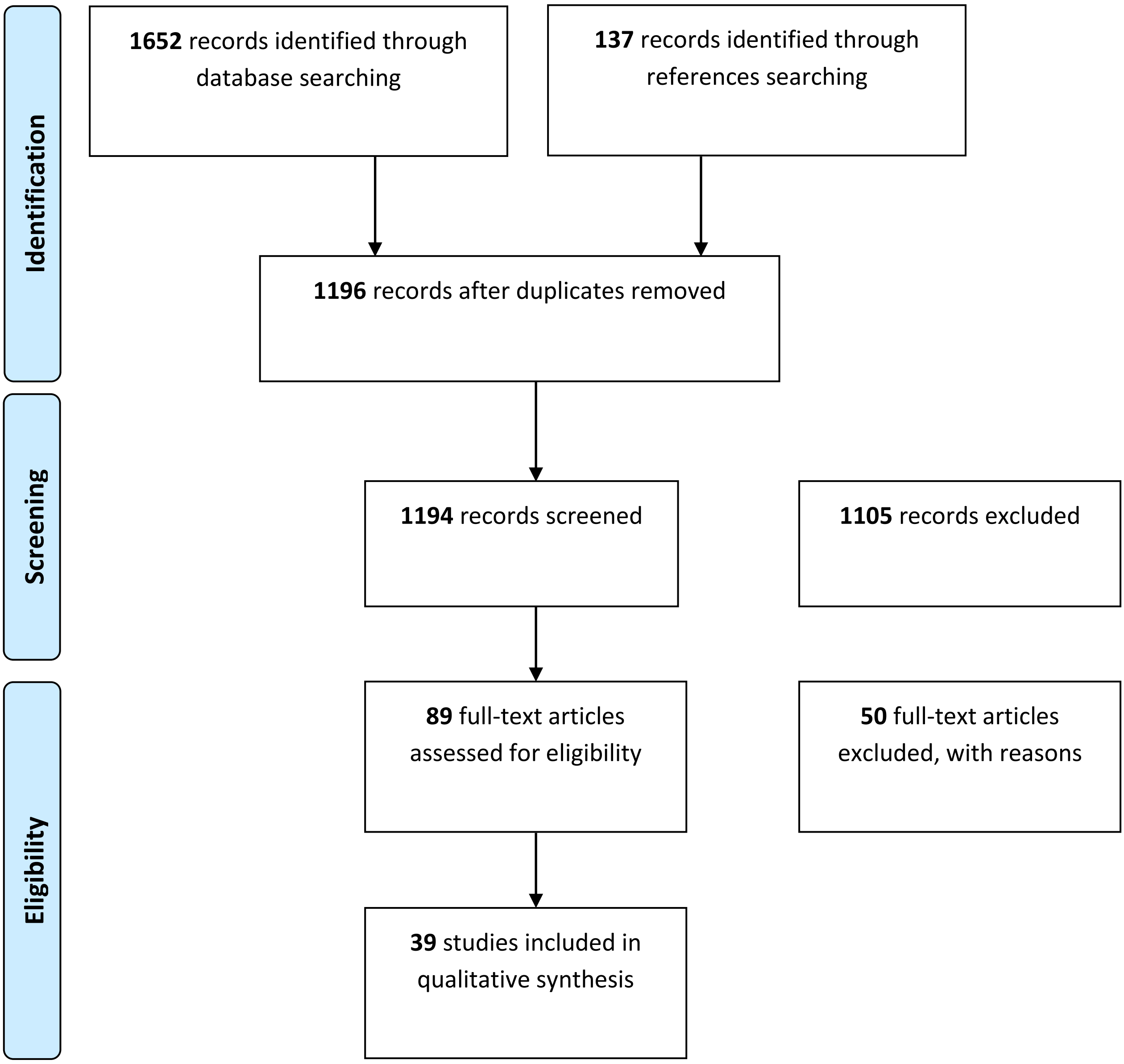

Figure 2. Study selection flow-diagram (according to the "PRISMA statement") (48)

Having selected 39 studies answering to the research question, no additional records were searched for in the "grey literature", limiting the search for unpublished studies only to the already excluded 32 registered trials from "clinicaltrials.gov".

During the process of eligibility assessment, predefined variables regarding study characteristics were collected in a prespecified eligibility form. Therefore, for the process of data collection the same form was used enriched with parameters defining the duration and type of exercise. The variables of this prespecified form, constituting the substrate for data collection, were the following:

- Identifier
    - PMID
    - DOI (if PMID unavailable)
- Population
    - Male/female/both (possible postpartum status if female)
    - Age
    - BMI (Body mass index)
    - Medical history
        - physical health
        - mental health
        - medications intake
        - psychotherapy
        - smoking
        - substance abuse
        - injury pain
        - recent operation
- Exercise duration
    - Acute
    - Short-term
    - Chronic
- Exercise type
    - Aerobic
    - Resistance
    - Interval
    - Leisure
    - Mind-body
    - Combined

- Comparator
    - Versus acute exercise
        - placebo control (light exercise)
        - attention control (watching, reading, meditation, body measurements, ergometer sitting, other sedentary activity)
        - assessment-only control
    - Versus short-term exercise
        - assessment-only control
    - Versus chronic exercise
        - attention control (meditation, music program, group meeting, relaxation training, watching TV)
        - waiting-list control
        - assessment-only control
- Outcome
    - Endocrine
        - salivary cortisol
        - blood cortisol
        - urinary catecholamines
    - Cardiovascular
        - blood pressure
        - heart rate
        - heart rate variability
    - CNS
        - fMRI changes
    - ANS
        - salivary α-amylase
    - Subjective
        - perceived stress scale
        - subjective/perceived stress rating
        - stress mood state
        - subjective arousal level

- Psychological stressor
  - Mental/cognitive
    - mental arithmetic
    - difficult tests
    - ECG quiz
    - Stroop task
    - Raven's progressive matrices
    - mirror star-tracing task
    - block design
    - digit span
    - bolt head maze
    - PASAT mental arithmetic
    - digits backward test
    - fine motor task
    - passive responding
    - reaction time task
  - Emotional
    - stressful film
  - Psychosocial
    - (public) speech task
    - losing against a female competitor (for a male participant)
    - handling a lit cigarette (for a temporarily abstinent smoker)
    - Trier Social Stress Test for Groups (TSST-G)
    - Trier Social Stress Test for Children (TSST-C)
    - Montreal Imaging Stress Task (MIST)
  - Physical-mental
    - Socially Evaluated Cold-Pressor Test (SECPT)
  - Real-life
    - academic examination period (for a student)
  - Job-related
    - simulated fire scene response (for a firefighter)

Results

The extracted data were heterogeneous, suggesting that many RCTs provided data not directly comparable to other RCTs. The two main factors contributing to this heterogeneity were the wide variety of stress outcomes and exercise interventions.

Exercise, based on duration, was acute (minutes), chronic (weeks to months) or short-term (days to weeks). In addition, different types of exercise act through different physiological mechanisms; thus, their effects on the stress system response should differ. To enable comparisons, exercise was classified as follows:

- Duration
    - Acute (exercise session)
    - Chronic (exercise program of considerable duration)
    - Short-term (exercise program lasting 2 weeks)
- Type
    - Aerobic
    - Resistance/anaerobic
    - Interval
    - Leisure
    - Mind-body
    - Combined

The studies examining the stress response to a defined psychological stressor were synthesized separately from the studies not employing a psychological stressor. These distinct syntheses of results were not compared. The terms used to classify these distinct results are the following:

- Reactivity: assessment of the change in reaction to a psychological stressor
- Recovery: assessment of the change after reaction to a psychological stressor
- Alleviation: assessment of the change in basal status, not related to a stressor

The results are presented separately for the different outcomes of interest, following an exercise-based order for the qualitative synthesis of every outcome:

- Endocrine outcomes: salivary cortisol, blood cortisol, urinary catecholamines
- Cardiovascular outcomes: blood pressure, heart rate, heart rate variability
- Other ANS outcomes: salivary α-amylase
- CNS outcomes: fMRI changes
- Subjective outcomes: perceived stress scale, subjective/perceived stress rating, stress mood state, subjective arousal level

Endocrine outcomes

From the 39 RCTs, 11 reported endocrine outcomes:

- Salivary cortisol: 10 RCTs
  - reactivity: 8
  - recovery: 2
  - alleviation: 3
- Plasma cortisol: 1 RCT
  - alleviation: 1
- Urinary catecholamines: 1 RCT
  - recovery: 1

The duration and type of exercise in 11 RCTs assessing endocrine outcomes were:

- Acute (20-60 min): 7 RCTs
  - Aerobic: 4 interventions
    - walking
      - 20 min
        - *No difference in salivary cortisol reactivity (but a small decrease trending significance)*
          - *real-life stressor: driving*
          - *20 healthy adult drivers: crossover*
          - *moderate-to-vigorous walking*
          - *attention control: watching TV (55)*

- 60 min
  - *No difference in salivary cortisol recovery*
    - *mental/emotional stressors*
    - *96 healthy tai-chi practitioners*
    - *brisk walking (after stressors)*
    - *attention control conditions*
      - *tai-chi practice*
      - *tai-chi meditation*
      - *neutral reading (54)*

- cycling
  - 30 min
    - *No significant effects on salivary cortisol reactivity peak levels, but decreased activation slope of salivary cortisol*
      - *psychosocial stressor: TSST-G*
      - *84 male adults (high or low active)*
      - *moderate-to-high intensity cycling*
      - *placebo exercise control: stretching (4)*
- walking/running
  - 30 min
    - *Reduced salivary cortisol responsivity*
      - *psychosocial stressor: MIST*
      - *36 young men (20-30 yr)*
      - *moderate intensity exercise*
      - *placebo exercise control: stretching (56)*
- playful/running/stairs
  - 30 min
    - *No difference in the salivary cortisol responsivity mean levels, but significantly*

different salivary cortisol responsivity time course with an average decrease over time

- *psychosocial stressor: TSST-C*
- *26 normal weight children (7-11 yr)*
- *moderate intensity exercise*
- *attention control: sedentary activity (57)*

- Leisure: 1 intervention
  - walking:
    - 40 ± 5 min
      - *Lower salivary cortisol levels (alleviation) after walking in nature (but not walking in gym), during the exam period (no differences during the no-exam period)*
        - *no stressor, but stressful exam time*
        - *90 healthy university students*
        - *nature walking*
        - *attention control: watching nature (58)*
- Mind-body: 1 intervention
  - yoga
    - 30 min
      - *Lower salivary cortisol responsivity*
        - *mental stressor: PASAT arithmetic*
        - *24 healthy young adults: crossover*
        - *hatha yoga*
        - *attention control: watching TV (59)*

- Chronic (10 w – 4 mo): 4 RCTs
  - Mind-body: 1 intervention
    - qigong
      - 10 w: 2 sessions per week lasting 45 min
        - *Reduction in salivary cortisol (alleviation)*

- ➢ *no stressor, but 1^{st} year students*
- ➢ *34 nursing and midwifery students*
- ➢ *self-healing qigong*
- ➢ *assessment-only control (49)*

- o Aerobic: 2 interventions
  - ▪ walking/running
    - – 12 w: 2 sessions per week lasting 60 min
      - ❖ *Reduced salivary cortisol AUC_G responsivity (but, no significant difference from the relaxation training attention control)*
        - ➢ *psychosocial stressor: TSST-G*
        - ➢ *96 healthy male office workers*
        - ➢ *HR-controlled running outdoors*
        - ➢ *waiting-list control (60)*
  - ▪ running/jumping/climbing/aerobics/soccer/basketball
    - – 4 mo: self-chosen frequency; 90-150 min per week
      - ❖ *No effect on urinary catecholamine excretion responsivity*
        - ➢ *mental stressors: reaction time tasks*
        - ➢ *38 untrained men: crossover*
        - ➢ *intensity at 70% of maximal capacity*
        - ➢ *waiting-list control (61)*
- o Combined (aerobic/strength/mind-body): 1 intervention
  - ▪ aerobics/strengthening/yoga
    - – 12 w: 3 sessions per week lasting 50-60 min
      - ❖ *No difference (alleviation) in plasma cortisol*
        - ➢ *no stressor, but postpartum period*
        - ➢ *healthy postpartum women*
        - ➢ *low-impact exercise*
        - ➢ *assessment-only control (62)*

Cardiovascular outcomes

From the 39 included RCTs, 29 reported cardiovascular outcomes:

- blood pressure (BP): 20 RCTs
  - responsivity: 20
  - recovery: 1
  - alleviation: not eligible (basal BP change does not safely reflect stress)
- heart rate (HR): 26 RCTs
  - responsivity: 26
  - recovery: 1
  - alleviation: not eligible (basal HR change does not safely reflect stress)
- heart rate variability (HRV): 8 RCTs
  - responsivity: 5
  - recovery: 1
  - alleviation: 4 (basal HRV change can safely reflect stress)

The duration and type of exercise in 29 RCTs assessing cardiovascular outcomes are:

- Acute (10-45 min): 15 RCTs
  - Aerobic: 4 interventions
    - walking
      - 15 min
        - *Reduced BP (SBP, DBP) responsivity*
          - *mental and psychosocial stressors*
            - *Stroop task (SBP, DBP)*
            - *speech task (SBP, DBP)*
            - *lit cigarette handling (SBP)*
          - *60 temporarily abstinent smokers*
          - *brisk walking*
          - *assessment-only control: sitting quietly (63)*

- 20 min
  - *No difference in BP responsivity (but elevated HR responsivity and reduced HRV)*
    - *real-life stressor: driving*
    - *20 healthy adult drivers: crossover*
    - *moderate-to-vigorous walking*
    - *attention control: watching TV (55)*

- running
  - graded exercise test
    - *Lower mean BP responsivity for accurate feedback participants (but low-performance feedback removed buffering effect of exercise)*
      - *mental and psychosocial stressors*
        - *mental arithmetic*
        - *Stroop task*
        - *speech task*
      - *40 competitive endurance athletes*
      - *maximal intensity exercise*
      - *attention control: body measurements (64)*
- cycling
  - 10 min
    - *No effects on HR responsivity*
      - *mental stressor: digits backward test*
      - *57 healthy female psychology students*
      - *light-to-moderate intensity exercise*
      - *assessment-only control: sitting quietly (65)*
  - 20 min (4 RCTs)
    - *No effect on cardiovascular responsivity; BP, HR*
      - *mental stressor*
        - *pre-exercise: digits backward*

- *post-exercise: mental arithmetic*
- *80 male/female college students (<35 yr)*
- *moderate intensity exercise*
- *assessment-only control (66)*
- *Blunted cardiovascular responsivity; BP, HR*
  - *mental stressor: mental arithmetic*
  - *20 male medical/research students*
  - *high intensity exercise (not low)*
  - *assessment-only control (67)*
- *Lower BP (SBP, DBP) responsivity (not HR)*
  - *psychosocial and mental stressor*
    - *speech task (SBP)*
    - *mental arithmetic (DBP)*
  - *48 young men (20-35 yr)*
  - *high intensity exercise (not moderate)*
  - *placebo exercise control: light pedaling (68)*
- *Attenuated cardiovascular responsivity; BP, HR*
  - *psychosocial stressor: public speaking*
  - *40 male/female university students*
  - *high intensity postprandial exercise*
  - *assessment-only control (69)*

- 30 min
  - *Attenuated cardiovascular responsivity; SBP, HR*
    - *mental stressor: Stroop task*
    - *12 moderately active males: crossover*
    - *submaximal intensity exercise*
    - *attention control: reading, conversation (70)*
- 40 min
  - *Lower BP (DBP, MAP, but not SBP) responsivity*
    - *mental stressor: Stroop task*

- *40 low to moderately fit women*
- *exercise intensity at 70% of HR reserve*
- *attention control: sitting on ergometer (71)*

- playful/running/stairs
  - 30 min
    - *No difference in mean BP responsivity, but higher HR responsivity*
      - *psychosocial stressor: TSST-C*
      - *50 children 7-11 yr; 24 overweight/obese*
      - *moderate intensity exercise*
      - *attention control: sedentary activity (57)*

- Interval: 1 intervention
  - cycling
    - 20 min
      - *Dampened cardiovascular responsivity; BP, HR*
        - *psychosocial stressor: speech task*
        - *28 children 8-12 yr (BMI < 85^{th} %)*
        - *30 s exercise at 60% of HR reserve*
        - *attention control: watching TV (72)*

- Leisure: 1 intervention
  - walking
    - 21-22 min
      - *Lower cardiovascular responsivity; SBP, HR*
        - *mental stressor: Stroop task*
        - *40 school children 10-14 yr*
        - *simulated self-paced walking to school*
        - *attention control: sedentary commute (73)*
    - 40 ± 5 min
      - *No differences in HR (and HRV) responsivity*
        - *physical-mental stressor: SECPT*

                - *90 healthy university students*
                - *walking in nature or walking in gym*
                - *attention control: watching nature (58)*
    - Mind-body: 1 intervention
        - yoga
            - 30 min
                - *No difference in BP or HR responsivity (but accelerated BP recovery)*
                    - *mental stressor: PASAT arithmetic*
                    - *24 healthy young adults: crossover*
                    - *hatha yoga*
                    - *attention control: watching TV (59)*
- Chronic (6 w – 6 mo): 12 RCTs
    - Aerobic: 8 interventions
        - running
            - 20 w: 2 sessions per week lasting 30 min + 3 min/w
                - *Higher HRV and reduced HR "responsivity" (assessment during a lasting real-life stressor)*
                    - *stressor: academic examination period*
                    - *61 inactive male students*
                    - *progressively increased intensity*
                    - *waiting-list control (74)*
        - cycling
            - 8 w: 3 sessions per week for 40 min
                - *No difference in BP or HR responsivity*
                    - *mental stressors*
                        - ✓ *Stroop task*
                        - ✓ *mental arithmetic*
                    - *24 healthy unfit college students*
                    - *moderate intensity exercise*
                    - *assessment-only control (75)*
            - 10 w: 3 sessions per week lasting 30 min

- ❖ *Reduced cardiovascular responsivity; SBP, HR*
  - ➢ *mental-psychosocial stressor*
    - ✓ *criterion motor task (superiority)*
    - ✓ *losing from a woman competitor*
    - ✓ *unpleasant feedback information*
  - ➢ *60 unfit male university students*
  - ➢ *exercise intensity at a HR of 170 bpm*
  - ➢ *attention control*
    - ✓ *progressive relaxation training*
    - ✓ *group meetings (76)*

- ▪ rowing
  - − 16 w: 4 sessions per week lasting 40 min
    - ❖ *Lower cardiovascular responsivity: BP, HR*
      - ➢ *job-related stressor: simulated fire scene*
      - ➢ *53 healthy active fire fighters*
      - ➢ *low-to-moderate ± higher intensity*
      - ➢ *assessment only control: normal lifestyle (77)*
- ▪ walking/running
  - − 12 w: 2 sessions per week lasting 60 min
    - ❖ *Reduced HR and HRV responsivity*
      - ➢ *psychosocial stressor: TSST-G*
      - ➢ *96 healthy male office workers*
      - ➢ *HR-controlled running outdoors*
      - ➢ *waiting-list control (60)*
  - − 6 mo: 5 sessions per week lasting 40-62 min
    - ❖ *No reduced cardiovascular responsivity; BP, HR*
      - ➢ *mental stressor: mental arithmetic*
      - ➢ *83 sedentary middle-aged employees*
      - ➢ *moderate intensity exercise*
      - ➢ *assessment-only control (78)*

- running/calisthenics
  - 10 w: ≥3 sessions per week lasting 60 min
    - *No difference in HR responsivity*
      - *mental stressors*
        - *mental arithmetic*
        - *ECG quiz*
        - *Stroop task*
      - *23 untrained males (20-30 yr)*
      - *progressively more vigorous activity*
      - *waiting-list control: habitual PA patterns (79)*
- walking/running/cycling
  - *8 w: 3 sessions per week lasting 20-30 min*
    - *Reduced HR responsivity (but BP unaffected)*
      - *mental stressors*
        - *passive responding*
        - *push-button Stroop task*
        - *verbal Stroop task*
      - *40 sedentary middle-aged males*
      - *moderate intensity exercise*
      - *assessment-only control (80)*
- running/cycling/swimming/rowing/stairs
  - 6 w: 3-5 sessions per week lasting 20-45 min
    - *Lower cardiovascular responsivity; SBP, HR*
      - *mental stressor: mental arithmetic*
      - *30 healthy sedentary young employees*
      - *exercise intensity at 70-85 % of HR_{max}*
      - *assessment-only control (81)*
- running/jumping/climbing/aerobics/soccer/basketball
  - 4 mo: self-chosen frequency of 90-150 min per week
    - *No effect on cardiovascular responsivity; BP, HR*
      - *mental stressors: reaction time tasks*

- ➢ *38 untrained men: crossover*
- ➢ *intensity at 70% of maximal capacity*
- ➢ *waiting-list control (61)*

- Resistance/anaerobic: 1 intervention
  - weight-training/cycling
    - 10 w: ≥3 sessions per week lasting 60 min
      - ❖ *No difference in HR responsivity*
        - ➢ *mental stressors*
          - ✓ *mental arithmetic*
          - ✓ *ECG quiz*
          - ✓ *Stroop task*
        - ➢ *23 untrained males (20-30 yr)*
        - ➢ *progressively more vigorous activity*
        - ➢ *waiting-list control: habitual PA patterns (79)*
- Mind-body: 1 intervention
  - yoga
    - 12 w: 1 session per week lasting 60 min
      - ❖ *Increase in HRV at 6 and 12 w; alleviation effect*
        - ➢ *no stressor, but work-related stress*
        - ➢ *60 mental health professionals*
        - ➢ *breathing, meditation, stretching*
        - ➢ *attention control: tea-time watching TV (82)*
- Combined (aerobic/strength): 1 intervention
  - running/stairs/strengthening/flexibility
    - 12 w: 3 sessions per week lasting 60 min
      - ❖ *No difference in HR responsivity (but faster HR recovery)*
        - ➢ *mental and psychosocial stressors*
          - ✓ *mental arithmetic*
          - ✓ *fine motor task*

                - ✓ *speech task*
            - ➢ *89 healthy psychology students*
            - ➢ *exercise intensity progressive increase*
            - ➢ *waiting-list control: attended seminars (83)*

- Short-term (2 w): 2 RCTs
    - Interval: 3 interventions
        - sprint
            - 2 w: 3 sessions per week lasting 12-24 min
                - ❖ *Improvement in HR complexity; HRV alleviation*
                    - ➢ *neither stressor nor stressed*
                    - ➢ *109 healthy young university students*
                    - ➢ *high intensity interval training (HIIT)*
                    - ➢ *assessment only control (84)*
        - [sprint] or [resistance] or [resistance and sprint]
            - 2 w: 3 sessions per week lasting 13 min
                - ❖ *No effect on HRV (no alleviation effect)*
                    - ➢ *neither stressor nor stressed*
                    - ➢ *30 young physically active healthy adults*
                    - ➢ *high intensity interval training (HIIT)*
                    - ➢ *assessment only control: normal lifestyle (85)*

Central Nervous System outcomes

From the 39 included RCTs, 1 reported CNS outcomes:

- fMRI changes: 1 RCT
    - responsivity: 1

The duration and type of exercise in 1 RCT assessing fMRI changes are:

- Acute (30 min): 1 RCT

- Aerobic: 1 intervention
  - walking/running
    - 30 min
      - *Higher bilateral hippocampus/parahippocampal gyrus activity (sustained fMRI signal) and lower (right dorsolateral and dorsomedial) prefrontal cortex (PFC) activity (sustained fMRI signal)*
        - *psychosocial stressor: MIST*
        - *36 right-handed young men (20-30 yr)*
        - *moderate intensity exercise*
        - *placebo exercise control: stretching (56)*

Autonomic Nervous System outcomes

From the 39 included RCTs, 2 reported other ANS outcomes:

- salivary α-amylase: 2 RCTs
  - responsivity: 2

The duration and type of exercise in 2 RCTs assessing salivary α-amylase are:

- Acute (30 min): 2 RCTs
  - Aerobic: 2 interventions
    - Cycling
      - 30 min
        - *No significant effect on salivary α-amylase responsivity peak level, but decreased activation slope of salivary α-amylase*
          - *psychosocial stressor: TSST-G*
          - *84 male adults (18-30 yr)*
          - *moderate-to-high intensity cycling*
          - *placebo exercise control: stretching (4)*
    - walking/running

- 30 min
  - *No difference in salivary α-amylase responsivity*
    - *psychosocial stressor: MIST*
    - *36 young men (20-30 yr)*
    - *moderate intensity exercise*
    - *placebo exercise control: stretching (56)*

Subjective outcomes

From the 39 included RCTs, 9 reported subjective outcomes:

- Perceived Stress Scale (PSS): 4 RCTs
  - responsivity/recovery: not applicable
  - alleviation: 3
- subjective/perceived stress rating: 4 RCTs
  - responsivity: 3
  - alleviation: 2
- stress mood state: 1 RCT
  - responsivity/recovery: not applicable
  - alleviation: 1
- subjective arousal level: 1 RCT
  - responsivity: 1

The duration and type of exercise in 9 RCTs assessing subjective outcomes are:

- Acute (20-30 min): 3 RCTs
  - Leisure: 1 intervention
    - walking
      - 21-22 min
        - *Lower perceived stress rating responsivity (perceived stress 10-point Likert scale)*
          - *mental stressor: Stroop task*
          - *40 school children 10-14 yr*

- *simulated self-paced walking to school*
- *attention control: sedentary commute (73)*

- Aerobic: 2 interventions
  - Cycling
    - 20 min
      - *Unaffected subjective stress rating responsivity (subjective stress rating scales)*
        - *mental stressor: mental arithmetic*
        - *30 male medical/research students*
        - *high intensity exercise (not low)*
        - *assessment-only control (67)*
  - walking/running
    - 30 min
      - *No differences with regard to subjective stress rating responsivity (subjective stress numerical analogous scale)*
        - *psychosocial stressor: MIST*
        - *36 young men (20-30 yr)*
        - *moderate intensity exercise*
        - *placebo exercise control: stretching (56)*

- Chronic (6 w – 12 mo): 6 RCTs
  - Aerobic: 2 interventions
    - walking/running
      - 6 mo: 5 sessions per week lasting 40-62 min
        - *No significant change over time on perceived stress rating (perceived stress 11-point Likert scale); no alleviation effect*
          - *neither stressor nor stressed*
          - *120 sedentary middle-aged employees*
          - *moderate intensity home-based exercise*
          - *assessment-only control (86)*

- 12 mo: 3 sessions per week lasting 60 min
  - *Lower PSS scores and improvements in perceived stress rating (perceived stress 10-point Likert scale); alleviation effect*
    - *neither stressor nor stressed*
    - *357 sedentary older adults (50-65 yr)*
    - *higher or lower intensity exercise*
      - *higher-intensity group-based*
      - *higher-intensity home-based*
      - *lower-intensity home-based*
    - *assessment-only control (87)*

- running/calisthenics
  - 10 w: ≥3 sessions per week lasting 60 min
    - *Unchanged subjective arousal level responsivity*
      - *mental stressors*
        - *mental arithmetic*
        - *ECG quiz*
        - *Stroop task*
      - *23 untrained males (20-30 yr)*
      - *progressively more vigorous activity*
      - *waiting-list control: habitual PA patterns (79)*

- Resistance/anaerobic: 1 intervention
  - weight-training/cycling
    - 10 w: ≥3 sessions per week lasting 60 min
      - *Unchanged subjective arousal level responsivity*
        - *mental stressors*
          - *mental arithmetic*
          - *ECG quiz*
          - *Stroop task*
        - *23 untrained males (20-30 yr)*
        - *progressively more vigorous activity*

- *waiting-list control: habitual PA patterns (79)*

- Mind-body: 1 intervention
  - qigong
    - 6 w: 2 sessions per week lasting 60 min
      - *Reduction of PSS score; alleviation effect*
        - *no stressor, but work-related stress*
        - *50 hospital staff employees*
        - *"The Basic Eight" qigong set*
        - *waiting-list control (50)*
    - 10 w: 2 sessions per week lasting 45 min
      - *Improvement in stress mood state (Depression, Anxiety, and Stress Questionnaire: DASS-21 stress score); alleviation effect*
        - *no stressor, but 1st year students*
        - *34 nursing and midwifery students*
        - *self-healing qigong*
        - *assessment-only control (49)*
- Aerobic/mind-body: 1 intervention
  - gymnastics/yoga
    - 12 w: ≥3 sessions per week lasting 15 min
      - *Improvement in PSS score; alleviation effect*
        - *no stressor, but postpartum period*
        - *140 postnatal women*
        - *yoga movements and music into a DVD*
        - *assessment-only control: routine care (88)*

Discussion

The main hypothesis of the present systematic review assumed that a manageable exercise stress can affect the socio-psychological stress in our everyday life. This hypothesis is supported by adequate studies although the evidence from physiological biomarkers, such as cortisol, require more research. To begin with, exercise is not a single stimulus or intervention and can only be compared between studies by using some broad classifications. The exercise interventions were all unique in terms of exercise characteristics (FITT: frequency, intensity, time-duration, type). One basic classification that was followed was the separation of exercise to acute (exercise session), chronic (exercise program of considerable duration) and short-term (exercise program lasting only 2 weeks).

Moreover, some types of exercise such as leisure walking and mind-body exercise may recruit additional mechanisms to buffer stress in comparison to the classic exercise interventions. For example, the potential benefit of mind-body exercise cannot be solely attributed to physical activity, but meditation and other mindfulness techniques may contribute importantly to the effect of the intervention. Accordingly, a leisure walk may affect stress through attention effects related to the surrounding environment (e.g., walking in nature). In an effort to enable comparisons between RCTs employing similar types of exercise, the type of exercise was classified in six categories (i.e., aerobic, resistance/anaerobic, interval, leisure, mind-body, combined). However, the exercise interventions were widely heterogeneous with the exception of cycling for 20 minutes. it was the only intervention studied by as many as 4 RCTs which showed a similarity but presented differences in exercise intensity and study characteristics. In addition, it is important to note that the intensity of exercise is the most powerful parameter and affects every single physiological response (metabolic, respiratory, cardiovascular, neuromuscular, hormonal etc.) of the body. Even identical exercise programs with different intensities produce completely different stress responses.

On the same wavelength, stress cannot be assessed by a single outcome since each and every outcome which reflects psychological stress may adapt differently to the physical stress of exercise. Stress-related outcomes were various, but some were the same across the different RCTs. Thus, it is possible to draw conclusions for every single outcome used to assess stress, acknowledging, however, that the stress-related outcomes may be assessed with different methodological approaches across the various RCTs. The most widely represented outcomes were cardiovascular by a total of 29 RCTs (20 RCTs reporting BP, 26 RCTs reporting HR, 8 RCTs reporting HRV). Only 1 RCT reported CNS outcomes (i.e., fMRI changes), while other than cardiovascular ANS outcomes (i.e., salivary α-amylase) were studied by only 2 RCTs. Regarding endocrine outcomes, salivary cortisol was adequately represented (7 RCTs), while plasma cortisol and urinary catecholamines were only studied by 1 RCT each. Subjective outcomes were sufficiently represented by a total of 9 RCTs (4 reported PSS, 4 subjective/perceived stress rating, 1 stress mood state, 1 subjective arousal level). However, it should be noted that the present review was designed to obtain results from RCTs using the term "psychological stress" in their text, other possibly eligible RCTs measuring the above outcomes without referring to psychological stress may have been omitted during database search.

All in all, the variety of exercise interventions and stress-related outcomes did not permit the quantitative synthesis of the obtained data. Therefore, a qualitative synthesis based on the study characteristics of the included RCTs (stress-related outcomes, stressor or no stressor, type of stressor, population, possible crossover study design, exercise intervention characteristics, comparator) was followed. The focus of synthesis was placed separately on every stress-related outcome, allowing some safe conclusions to emerge before expanding the findings to psychological stress as a whole. Therefore, the main findings of every outcome are summarized first, followed by the discussion of some limitations, in order to conclude with a general interpretation of the various stress-related results.

Main findings

Brain and nervous system activity reaction

The question of how the body reacts to exercise stress challenges researchers to study the brain functional reaction in association with psychosocial stress. The stress response starts from the perception of the stressful stimuli by the brain. To examine the stress-buffering effects of exercise on CNS responses, Zschucke et al., (56), applied the fMRI system to detect brain metabolic activity through blood flow and oxygen consumption before and after 30 min of moderate intensity of exercise running/walking) in trained and untrained men (56). The results of this well-designed RCT study revealed higher bilateral hippocampus/parahippocampal gyrus activity and lower (right dorsolateral and dorsomedial) prefrontal cortex activity. These observations, combined with salivary cortisol (HPA axis), suggest that the stress-buffering effect of exercise generates negative bio-feedback mechanisms dampening the everyday psychosocial stress. Lower cortisol levels were observed in individuals with higher fitness. In addition, exercise-related-changes in cortisol and α-amylase levels were comparable between fit and sedentary individuals (56).

Salivary α-amylase, a useful stress-related biomarker of ANS activity, has been used to examine the effects of exercise on psychosocial stress. Two RCTs (4, 56) used similar duration (30 min) but different intensity and mode of exercise (moderate-to-high intensity cycling and moderate running/walking). Compared to the control group, no significant effects on salivary α-amylase responsivity were observed neither for cycling nor for running/walking. Nevertheless, the higher intensity of cycling displayed a decreased activation slope of salivary α-amylase (4). It is known that even the intensity of exercise alone, irrespective of the mode, can change many of the physiological and ANS responses which affect psychosocial stress. In addition, no significant effect on urinary catecholamine exertion responsivity was reported in untrained men after four months of training (61). The intervention program, however, allowed a self-selected weekly frequency ranging from 90 to 150 min at an intensity of about 70% of the “maximal capacity” and included aerobic activities, running, jumping, climbing, soccer, basketball (61). Probably a more consistent training intervention program would have provided different outcomes on the psychophysiological reactivity.

Plasma and salivary cortisol

Alterations in plasma or salivary cortisol are often used as biochemical markers of stress and salivary cortisol is considered a legitimate index. When exercise is used as a controllable stressor against the sustained everyday stress, the increased levels of circulating cortisol may be attenuated, and this may affect the physiological regulatory network of the body. Responses on plasma or salivary cortisol, however, are not always in agreement. Exercise as an anti-stress factor varies. The mode, duration, intensity, or combination of different kinds of exercise affect the physiological response in cortisol levels. When combining the mind-body approach with yoga, aerobic and strength exercise for 12 weeks in healthy postpartum women, no differences were observed in plasma cortisol (62).

Salivary cortisol which was applied as a more feasible and reliable biochemical marker of stress, revealed no difference in responsivity after 20 min of walking (55) and no differences in recovery after 60 min of walking (54). When increasing the intensity, however, by using cycling exercise for 30 min, a decreased activation in the slope of cortisol response was observed (4). In addition, a relief of stress associated with the reduced responsivity in salivary cortisol was obtained with the higher intensity of 30 min running/walking (56). Following a similar running/walking intervention program for 12 weeks, the relief of stress was physiologically denoted with the reduced area under the curve responsivity of salivary cortisol (60). Although no effects were observed on responsivity after 30 min of playful/running/stairs activity, it decreased with the passage of time (57). Even moderate exercise of leisure walking during stressful situations (exam period) offers alleviation after walking in nature (58). Furthermore, when mind and body are involved in activities such as yoga or qigong it is difficult to evaluate if the influence on HPA axis and alleviation of cortisol responsivity (59, 49) are driven by exercising the body or by meditating with the mind.

Cardiovascular responses

Cardiovascular responses such as blood pressure and heart rate are applicable, easily obtained, and more sensitive to various stressors. From the selected 39 RCT studies, 74% (29 studies) reported cardiovascular measurements. In these studies, 90% reported heart rate measurements, 69% blood pressure, and 28% heart rate variability. The sensitivity response to the experimental protocols was very high. The acute aerobic exercise of 15 min brisk walking reduced BP responsivity (63), whereas in another study, 20 min of moderate to vigorous walking revealed no significant differences in BP responsivity but elevated HR responsivity and reduced HRV (55). 10 min of high to moderate cycling intensity is not sufficient to induce proper effects on HR responsivity. Even 20 min of moderate cycling intensity failed to affect the cardiovascular responsivity of BP and HR (66). 20 min of high cycling intensity, however, reduced BP and HR responsivity (67, 68, 69). When the duration of cycling exercise was increased to 30 or 40 min, moderate intensity attenuated BP and HR (70, 71).

Reports on chronic aerobic training exercise ranged from 6 weeks to 6 months. 20 weeks of running (2 sessions per week, each session lasting 30 min), with progressively increased intensity revealed higher HRV and reduced HR responsivity of real-life stressors (74). Furthermore, no differences in BP and HR were observed following cycling training for 8 weeks (3 sessions per week for 40 min) at moderate intensity (75). When intensity was set at a HR of 170 bpm, however, BP and HR responsivity was obtained (76). Moreover, rowing training for 16 weeks, (4 sessions per week, each session lasting 40 min), with intensity ranging from light to high, reduced BP and HR responsivity (77).

The results of popular and practical modes of exercise such as walking/running are not always in agreement. Six months of walking/running, 5 sessions per week lasting 40 to 60 min, in sedentary middle-aged employees at moderate intensity failed to show changes in BP and HR responsivity (78). Healthy male office workers, however, following the same mode of exercise of 12 weeks, 2 sessions per week lasting 6 min, with controlled HR running intensity, reduced HR and HRV responsivity (60). It seems that the exercise intensity based on the controlled HR provides more desirable results. The running/calisthenics training intervention of 10 weeks, using 3 or more than 3 sessions per week, lasting 60 min, increased intensity progressively to more vigorous activity but failed to display HR responsivity in young untrained men (79). When combining running and calisthenics, the question is whether priority was given to hemodynamic adaptations or to body appearance. Even activities focusing on hemodynamics such as walking/running/cycling at moderate intensity induce HR but not BP responsivity (80). When intensity was increased at 70-85% of HRmax, young employees who took up running/cycling/swimming/rowing/stair-climbing for 6 weeks (3-5 sessions per week lasting 20-45 min), reduced BP and HR responsivity (81).

Mind and body yoga intervention for 12 weeks, (1 session per week lasting 60 min), increased HRV and yielded alleviation effects (82). The combined strength and aerobic training for 12 weeks, 3 sessions per week and lasting 60 min revealed no differences in HR responsivity but faster HR recovery (83). Short-term of 2-week high intensity interval training, (3 sessions per week lasting 12-24 min) was applied in healthy young university students (84) and healthy young physically active individuals (85). The university students showed alleviation in HRV and improvement in HR complexity whereas active individuals failed to present HRV or alleviation effect. Obviously the physically active individuals cannot be compared with the university students. Many details may explain the variation of the results. The mind and body intervention can be hardly compared with the combined strength and aerobic intervention. The classification of the studies and the extraction of data need special attention to reach a valid conclusion.

Subjective stress evaluation

People can talk and provide information. This could be valuable sometimes during different experimental conditions. Among the selected studies, 4 used perceived stress scale, another 4 used subjective perceived stress rating, 1 study used stress mood state and another 1 subjective arousal level. Acute exercise, 20 to 30 min, prompted different results. Self-paced walking of 22 min decreased perceived stress rating responsivity obtained with the 10-point Likert scale (73). In contrast, 20 min of high intensity cycling (67) and 30 min moderate intensity walking/running (56) failed to affect the subjective stress rating responsivity.

Chronic intervention of 6 months walking/running, (5 session per week, 40-60 min), at moderate intensity revealed non-significant change on perceived stress rating (86). Using a similar mode of exercise with higher intensity for 12 months, (3 sessions per week, lasting 60 min), presented improvement in perceived stress rating and alleviation effects (87). Mind and body intervention such as qigong and yoga yielded alleviation effects (49, 50, 88). Furthermore, 6 weeks of qigong, (2 sessions per week, lasting 60 min) induced reduction of perceived stress scale scores (50) and 10 weeks (2 sessions per week, 45 min) improved the stress mood state (49). In addition, gymnastics /yoga (12 weeks with 3 or more than 3 sessions per week lasting 15 min) improved the perceived stress scale score. The question whether mind or body influence experimental results awaits to be answered.

Limitations of the study

Although the present systematic review observed the exercise effects on the stress system collecting information from physiological markers such as cortisol, a-amylase, cardiovascular responses and subjective evaluation, a steady conclusion cannot be reached, mainly because of the nature of exercise stimulus which cannot be simply accepted as a comparable factor among the various RCT reports. Indeed, aerobic exercise is the opposite of anaerobic exercise, strength exercise is completely different from leisure exercise activities and the mind and body combination cannot be compared with the different modes of combined exercise. Swimming, cycling, running, walking may be better compared when the intensity is presented with physiologically accepted values (e.g. %VO2max or %HRmax). The general terms of light, moderate, vigorous, or high do correspond accurately to the intensity of the exercise program (can be differently appraised by different authors). These limitations should not be overlooked when exercise is taken as a physiological stress stimulus among various studies.

Besides, the methodological limitations of collecting the proper studies and treating them appropriately should be acknowledged and reported for the reader. Thus, the limitations of the study are listed below:

- The eligibility criteria, not clear from the start, were sealed in the process.
- We slightly searched for “grey literature” and we did not contact any authors.
- We did not have a written review protocol, neither did we register our study.
- Our search strings were based on database filters, limiting their sensitivity.
- During the first PubMed search, we did not screen the titles independently.
- Data collection was performed only by the author and not by two reviewers.
- Data were not extracted with a distinct process, but while assessing eligibility.
- Any processes for confirming data from investigators were not followed.
- Risk of bias in individual studies was not assessed and not used in synthesis.
- Data extraction have not been performed yet for the present report.

Conclusion

One can take the time to enjoy exercise in order to cope with daily stress. The present systematic review presented adequate data that support the hypothesis of the study. Even though there is no full agreement, there is evidence which supports that exercise can be a beneficial stressor against the psychosocial everyday stress. Cortisol and α-amylase responded better when intensity was higher. Intensity also influenced the cardiovascular responses and subjective evaluation.

Exercise can be used as a buffering stressor against psychosocial stress. Even though the type of exercise may play a significant role, the intensity of exercise seems to be most important parameter. More research is required, however, to acquire the proper exercise intensity along with the appropriate duration and frequency. There is no study that has examined the stress response to different exercise intensities. Based on the selected studies, exercise intensity above moderate and close to vigorous yielded better results.

Further research on the dose-response approach using different modes of exercise may provide more information about the proper exercise program. Attention should also be paid to other specific aspects of an exercise intervention program such as frequency and mode of exercise. A standardized exercise program testing different intensities may reveal the appropriate stress system response that a healthy individual needs in order to cope better with the encountered psychosocial daily stressors.

References

1. Salmon P. Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. Clin Psychol Rev. 2001;21(1):33-61.

2. Russell VA, Zigmond MJ, Dimatelis JJ, Daniels WM, Mabandla MV. The interaction between stress and exercise, and its impact on brain function. Metab Brain Dis. 2014;29(2):255-60.

3. Mikkelsen K, Stojanovska L, Polenakovic M, Bosevski M, Apostolopoulos V. Exercise and mental health. Maturitas. 2017;106:48-56.

4. Wunsch K, Wurst R, von Dawans B, Strahler J, Kasten N, Fuchs R. Habitual and acute exercise effects on salivary biomarkers in response to psychosocial stress. Psychoneuroendocrinology. 2019;106:216-25.

5. Malkiewicz MA, Szarmach A, Sabisz A, Cubala WJ, Szurowska E, Winklewski PJ. Blood-brain barrier permeability and physical exercise. J Neuroinflammation. 2019;16(1):15.

6. Ignacio ZM, da Silva RS, Plissari ME, Quevedo J, Reus GZ. Physical Exercise and Neuroinflammation in Major Depressive Disorder. Mol Neurobiol. 2019;56(12):8323-35.

7. Steiner JL, Johnson BR, Hickner RC, Ormsbee MJ, Williamson DL, Gordon BS. Adrenal stress hormone action in skeletal muscle during exercise training: An old dog with new tricks? Acta Physiol (Oxf). 2020:e13522.

8. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol. 2012;2(2):1143-211.

9. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports. 2015;25 Suppl 3:1-72.

10. Moraes-Silva IC, Mostarda CT, Silva-Filho AC, Irigoyen MC. Hypertension and Exercise Training: Evidence from Clinical Studies. Adv Exp Med Biol. 2017;1000:65-84.

11. Tokmakidis SP, Touvra AM, Douda HT, Smilios I, Kotsa K, Volaklis KA. Training, detraining, and retraining effects on glycemic control and physical fitness in women with type 2 diabetes. Horm Metab Res. 2014;46(13):974-9.

12. Volaklis KA, Spassis AT, Tokmakidis SP. Land versus water exercise in patients with coronary artery disease: effects on body composition, blood lipids, and physical fitness. Am Heart J. 2007;154(3):560 e1-6.

13. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009;5(7):374-81.

14. Tsigos C, Kyrou I, Kassi E, Chrousos GP. Stress, Endocrine Physiology and Pathophysiology. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.

Copyright © 2000-2020, MDText.com, Inc.; 2000.

15. Stratakis CA, Gold PW, Chrousos GP. Neuroendocrinology of stress: implications for growth and development. Horm Res. 1995;43(4):162-7.

16. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. Jama. 1992;267(9):1244-52.

17. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002;53(4):865-71.

18. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci. 2009;10(6):397-409.

19. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol. 2005;67:259-84.

20. Johnson EO, Kamilaris TC, Chrousos GP, Gold PW. Mechanisms of stress: a dynamic overview of hormonal and behavioral homeostasis. Neurosci Biobehav Rev. 1992;16(2):115-30.

21. Torpy DJ, Chrousos GP. The three-way interactions between the hypothalamic-pituitary-adrenal and gonadal axes and the immune system. Baillieres Clin Rheumatol. 1996;10(2):181-98.

22. Ament W, Verkerke GJ. Exercise and fatigue. Sports Med. 2009;39(5):389-422.

23. Savvaki D, Taousani E, Goulis DG, Tsirou E, Voziki E, Douda H, et al. Guidelines for exercise during normal pregnancy and gestational diabetes: a review of international recommendations. Hormones (Athens). 2018;17(4):521-9.

24. Hackney AC, Lane AR. Exercise and the Regulation of Endocrine Hormones. Prog Mol Biol Transl Sci. 2015;135:293-311.

25. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev. 2000;80(3):1055-81.

26. Godoy LD, Rossignoli MT, Delfino-Pereira P, Garcia-Cairasco N, de Lima Umeoka EH. A Comprehensive Overview on Stress Neurobiology: Basic Concepts and Clinical Implications. Front Behav Neurosci. 2018;12:127.

27. Habib KE, Gold PW, Chrousos GP. Neuroendocrinology of stress. Endocrinol Metab Clin North Am. 2001;30(3):695-728; vii-viii.

28. Gold PW. The organization of the stress system and its dysregulation in depressive illness. Mol Psychiatry. 2015;20(1):32-47.

29. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Mol Psychiatry. 2002;7(3):254-75.

30. Nicolaides NC, Kyratzi E, Lamprokostopoulou A, Chrousos GP, Charmandari E. Stress, the stress system and the role of glucocorticoids. Neuroimmunomodulation. 2015;22(1-2):6-19.

31. Dishman RK. Medical psychology in exercise and sport. Med Clin North Am. 1985;69(1):123-43.

32. Morgan WP. Affective beneficence of vigorous physical activity. Med Sci Sports Exerc. 1985;17(1):94-100.

33. Crews DJ, Landers DM. A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. Med Sci Sports Exerc. 1987;19(5 Suppl):S114-20.

34. Sothmann MS, Hart BA, Horn TS. Plasma catecholamine response to acute psychological stress in humans: relation to aerobic fitness and exercise training. Med Sci Sports Exerc. 1991;23(7):860-7.

35. Gauvin L, Spence JC. Physical activity and psychological well-being: knowledge base, current issues, and caveats. Nutr Rev. 1996;54(4 Pt 2):S53-65.

36. Mastorakos G, Pavlatou M, Diamanti-Kandarakis E, Chrousos GP. Exercise and the stress system. Hormones (Athens). 2005;4(2):73-89.

37. Tsatsoulis A, Fountoulakis S. The protective role of exercise on stress system dysregulation and comorbidities. Ann N Y Acad Sci. 2006;1083:196-213.

38. Hamer M, Taylor A, Steptoe A. The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. Biol Psychol. 2006;71(2):183-90.

39. Gerber M, Pühse U. Review article: do exercise and fitness protect against stress-induced health complaints? A review of the literature. Scand J Public Health. 2009;37(8):801-19.

40. Wang C, Bannuru R, Ramel J, Kupelnick B, Scott T, Schmid CH. Tai Chi on psychological well-being: systematic review and meta-analysis. BMC Complement Altern Med. 2010;10:23.

41. Wang CW, Chan CH, Ho RT, Chan JS, Ng SM, Chan CL. Managing stress and anxiety through qigong exercise in healthy adults: a systematic review and meta-analysis of randomized controlled trials. BMC Complement Altern Med. 2014;14:8.

42. Pascoe MC, Bauer IE. A systematic review of randomised control trials on the effects of yoga on stress measures and mood. J Psychiatr Res. 2015;68:270-82.

43. Chen C, Nakagawa S, An Y, Ito K, Kitaichi Y, Kusumi I. The exercise-glucocorticoid paradox: How exercise is beneficial to cognition, mood, and the brain while increasing glucocorticoid levels. Front Neuroendocrinol. 2017;44:83-102.

44. Mücke M, Ludyga S, Colledge F, Gerber M. Influence of Regular Physical Activity and Fitness on Stress Reactivity as Measured with the Trier Social Stress Test Protocol: A Systematic Review. Sports Med. 2018;48(11):2607-22.

45. Nigdelis MP, Martínez-Domínguez SJ, Goulis DG, Pérez-López FR. Effect of programmed exercise on perceived stress in middle-aged and old women: A meta-analysis of randomized trials. Maturitas. 2018;114:1-8.

46. Rodriguez-Ayllon M, Cadenas-Sánchez C, Estévez-López F, Muñoz NE, Mora-Gonzalez J, Migueles JH, et al. Role of Physical Activity and Sedentary Behavior in the Mental Health of Preschoolers, Children and Adolescents: A Systematic Review and Meta-Analysis. Sports Med. 2019;49(9):1383-410.

47. Fabiana Haag ASBEFLDT. Physical exercise as a means of reducing mental stress: a systematic review with meta-analysis.

48. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.

49. Chan ES, Koh D, Teo YC, Hj Tamin R, Lim A, Fredericks S. Biochemical and psychometric evaluation of Self-Healing Qigong as a stress reduction tool among first year nursing and midwifery students. Complement Ther Clin Pract. 2013;19(4):179-83.

50. Griffith JM, Hasley JP, Liu H, Severn DG, Conner LH, Adler LE. Qigong stress reduction in hospital staff. J Altern Complement Med. 2008;14(8):939-45.

51. Jahnke R, Larkey L, Rogers C, Etnier J, Lin F. A comprehensive review of health benefits of qigong and tai chi. Am J Health Promot. 2010;24(6):e1-e25.

52. Nedeljkovic M, Ausfeld-Hafter B, Streitberger K, Seiler R, Wirtz PH. Taiji practice attenuates psychobiological stress reactivity--a randomized controlled trial in healthy subjects. Psychoneuroendocrinology. 2012;37(8):1171-80.

53. Robert-McComb JJ, Chyu M-C, Tacón A, Norman R. The effects of tai chi on measures of stress and coping style. Focus on Alternative and Complementary Therapies. 2015;20(2):89-96.

54. Jin P. Efficacy of Tai Chi, brisk walking, meditation, and reading in reducing mental and emotional stress. J Psychosom Res. 1992;36(4):361-70.

55. Antoun M, Ding D, Bohn-Goldbaum EE, Michael S, Edwards KM. Driving in an urban environment, the stress response and effects of exercise. Ergonomics. 2018;61(9):1273-81.

56. Zschucke E, Renneberg B, Dimeo F, Wustenberg T, Strohle A. The stress-buffering effect of acute exercise: Evidence for HPA axis negative feedback. Psychoneuroendocrinology. 2015;51:414-25.

57. Messerli-Burgy N, Horsch A, Schindler C, Boichat A, Kriemler S, Munsch S, et al. Influence of Acute Physical Activity on Stress Reactivity in Obese and Normal Weight Children: A Randomized Controlled Trial. Obes Facts. 2019;12(1):115-30.

58. Olafsdottir G, Cloke P, Schulz A, van Dyck Z, Eysteinsson T, Thorleifsdottir B, et al. Health Benefits of Walking in Nature: A Randomized Controlled Study Under Conditions of Real-Life Stress. Environment and Behavior. 2018;52(3):248-74.

59. Benvenutti MJ, Alves EDS, Michael S, Ding D, Stamatakis E, Edwards KM. A single session of hatha yoga improves stress reactivity and recovery after an acute psychological stress task-A counterbalanced, randomized-crossover trial in healthy individuals. Complement Ther Med. 2017;35:120-6.

60. Klaperski S, von Dawans B, Heinrichs M, Fuchs R. Effects of a 12-week endurance training program on the physiological response to psychosocial stress in men: a randomized controlled trial. J Behav Med. 2014;37(6):1118-33.

61. de Geus EJ, van Doornen LJ, Orlebeke JF. Regular exercise and aerobic fitness in relation to psychological make-up and physiological stress reactivity. Psychosom Med. 1993;55(4):347-63.

62. Zourladani A, Zafrakas M, Chatzigiannis B, Papasozomenou P, Vavilis D, Matziari C. The effect of physical exercise on postpartum fitness, hormone and lipid levels: a randomized controlled trial in primiparous, lactating women. Arch Gynecol Obstet. 2015;291(3):525-30.

63. Taylor A, Katomeri M. Effects of a brisk walk on blood pressure responses to the Stroop, a speech task and a smoking cue among temporarily abstinent smokers. Psychopharmacology (Berl). 2006;184(2):247-53.

64. Bartholomew JB. Stress reactivity after maximal exercise: the effect of manipulated performance feedback in endurance athletes. J Sports Sci. 2000;18(11):893-9.

65. Roth DL, Bachtler SD, Fillingim RB. Acute emotional and cardiovascular effects of stressful mental work during aerobic exercise. Psychophysiology. 1990;27(6):694-701.

66. Roth DL. Acute emotional and psychophysiological effects of aerobic exercise. Psychophysiology. 1989;26(5):593-602.

67. Roy M, Steptoe A. The inhibition of cardiovascular responses to mental stress following aerobic exercise. Psychophysiology. 1991;28(6):689-700.

68. Steptoe A, Kearsley N, Walters N. Cardiovascular activity during mental stress following vigorous exercise in sportsmen and inactive men. Psychophysiology. 1993;30(3):245-52.

69. Faulk KE, Bartholomew JB. The moderating effect of physical activity on cardiovascular reactivity following single fat feedings. Psychophysiology. 2012;49(1):145-9.

70. Probst M, Bulbulian R, Knapp C. Hemodynamic responses to the stroop and cold pressor tests after submaximal cycling exercise in normotensive males. Physiol Behav. 1997;62(6):1283-90.

71. Hobson ML, Rejeski WJ. Does the Dose of Acute Exercise Mediate Psychophysiological Responses to Mental Stress? 1993;15(1):77.

72. Roemmich JN, Lambiase M, Salvy SJ, Horvath PJ. Protective effect of interval exercise on psychophysiological stress reactivity in children. Psychophysiology. 2009;46(4):852-61.

73. Lambiase MJ, Barry HM, Roemmich JN. Effect of a simulated active commute to school on cardiovascular stress reactivity. Med Sci Sports Exerc. 2010;42(8):1609-16.

74. von Haaren B, Ottenbacher J, Muenz J, Neumann R, Boes K, Ebner-Priemer U. Does a 20-week aerobic exercise training programme increase our capabilities to buffer real-life stressors? A randomized, controlled trial using ambulatory assessment. Eur J Appl Physiol. 2016;116(2):383-94.

75. Kubitz KA, Landers DM. The Effects of Aerobic Training on Cardiovascular Responses to Mental Stress: An Examination of Underlying Mechanisms. 1993;15(3):326.

76. Anshel MH. Effect of chronic aerobic exercise and progressive relaxation on motor performance and affect following acute stress. Behav Med. 1996;21(4):186-96.

77. Throne LC, Bartholomew JB, Craig J, Farrar RP. Stress Reactivity in Fire Fighters: An Exercise Intervention. International Journal of Stress Management. 2000;7(4):235-46.

78. Albright CL, King AC, Taylor CB, Haskell WL. Effect of a six-month aerobic exercise training program on cardiovascular responsivity in healthy middle-aged adults. J Psychosom Res. 1992;36(1):25-36.

79. Sinyor D, Golden M, Steinert Y, Seraganian P. Experimental manipulation of aerobic fitness and the response to psychosocial stress: heart rate and self-report measures. Psychosom Med. 1986;48(5):324-37.

80. Stein PK, Boutcher SH. The effect of participation in an exercise training program on cardiovascular reactivity in sedentary middle-aged males. Int J Psychophysiol. 1992;13(3):215-23.

81. Spalding TW, Lyon LA, Steel DH, Hatfield BD. Aerobic exercise training and cardiovascular reactivity to psychological stress in sedentary young normotensive men and women. Psychophysiology. 2004;41(4):552-62.

82. Lin SL, Huang CY, Shiu SP, Yeh SH. Effects of Yoga on Stress, Stress Adaption, and Heart Rate Variability Among Mental Health Professionals--A Randomized Controlled Trial. Worldviews Evid Based Nurs. 2015;12(4):236-45.

83. Calvo MG, Szabo A, Capafons J. Anxiety and heart rate under psychological stress: The effects of exercise-training. Anxiety Stress Coping. 1996;9(4):321-37.

84. de Sousa AFM, Medeiros AR, Benitez-Flores S, Del Rosso S, Stults-Kolehmainen M, Boullosa DA. Improvements in Attention and Cardiac Autonomic Modulation After a 2-Weeks Sprint Interval Training Program: A Fidelity Approach. Front Physiol. 2018;9:241.

85. Benitez-Flores S, Medeiros AR, Voltarelli FA, Iglesias-Soler E, Doma K, Simoes HG, et al. Combined effects of very short "all out" efforts during sprint and resistance training on physical and physiological adaptations after 2 weeks of training. Eur J Appl Physiol. 2019;119(6):1337-51.

86. King AC, Taylor CB, Haskell WL, DeBusk RF. Influence of regular aerobic exercise on psychological health: a randomized, controlled trial of healthy middle-aged adults. Health Psychol. 1989;8(3):305-24.

87. King AC, Taylor CB, Haskell WL. Effects of differing intensities and formats of 12 months of exercise training on psychological outcomes in older adults. Health Psychol. 1993;12(4):292-300.

88. Yang CL, Chen CH. Effectiveness of aerobic gymnastic exercise on stress, fatigue, and sleep quality during postpartum: A pilot randomized controlled trial. Int J Nurs Stud. 2018;77:1-7.