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Physiological responses to acute physical and psychosocial stress -

relation to aerobic capacity and exercise training

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Abstract

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Exercise training is an effective method to promote health and to prevent development of disease. Both physical and mental health have been shown to benefit from exercise training. It has also been speculated that physical exercise might affect responses to acute psychosocial stress. In an acute stress situation, several physiological systems respond to ensure survival and it is suggested that exercise training may influence these stress systems.

The main purpose of this thesis was to study physiological responses to acute physical and psychosocial stress and possible associations with aerobic capacity and exercise training. The thesis is based on four papers analysing data from a randomized controlled trial (RCT). The participants were healthy individuals who reported themselves as untrained at screening. The RCT included testing of acute physical and psychosocial stress. Before and after the tests, hormonal and autonomic responses were assessed. After initial testing, the participants were randomized to either an intervention- or a control group. The intervention consisted of regular aerobic exercise training conducted for six months. At follow-up, the same tests were repeated for both groups.

The main findings were that most participants showed an increase in the studied variables in response to acute stress. Aerobic capacity did not seem to have any relation to hormonal or blood pressure responses to acute psychosocial stress. Neither did the subjective perception of stress at the psychosocial stress test correlate with the actual physiological response. Due to methodological issues, it was not possible to evaluate the effects of exercise training.

Thus, in healthy individuals, the stress systems seem to respond adequately to acute stress, irrespective of level of aerobic capacity or type of stressor.

Svensk sammanfattning

Fysisk träning är ett av våra viktigaste redskap för att bibehålla hälsa, och bevisen för dess välgörande effekter är många. Flera av våra vällevnadssjukdomar är möjliga att förebygga, såsom hjärt-kärlsjukdom och diabetes typ II. Det har även spekulerats i huruvida fysisk träning kan påverka kroppens svar på akut psykosocial stress.

Stress är ett växande samhällsproblem och allt fler individer upplever ökade nivåer av stress. Våra kroppar är emellertid väl rustade för att hantera akuta stressreaktioner. Flera olika system borgar för att upprätthålla kroppens inre balans och att livsviktiga funktioner vidmakthålls.

Syftet med denna avhandling var att studera fysiologiska reaktioner på akut fysisk och psykosocial stress, och om/hur dessa relaterar till och påverkas av aerob kapacitet och fysisk träning. Genom fyra delstudier har olika aspekter av ämnet belysts. Samtliga delstudier bygger på data från en randomiserad kontrollerad studie (RCT) genomförd på Institutet för Stressmedicin i Göteborg. Vi sökte otränade och friska kvinnor och män i åldern 20 till 50 år. Studien innefattade baslinjemätningar bestående av ett maximalt uthållighetstest på ergometercykel samt ett standardiserat psykosocialt stresstest. Före och efter de båda testerna mättes hormonerna adrenokortikotropt hormon (ACTH), kortisol, dehydroepiandrosteron (DHEA) och dehydroepiandrosteronsulfat (DHEA-S). Autonoma reaktioner mättes som systoliskt och diastoliskt blodtryck samt hjärtfrekvens. Efter de inledande mätningarna randomiserades deltagarna till antingen en interventionsgrupp eller en kontrollgrupp. Interventionsgruppen skulle under ett halvår komma ingång med regelbunden konditionsträning, samtidigt som kontrollgruppen skulle fortsätta på samma aktivitetsnivå som tidigare. Efter sex månader genomfördes samma tester som vid baslinjemätningarna.

Delstudie I är en beskrivning av själva studieprotokollet, men innehåller också en metodologisk diskussion om två avgörande aspekter i genomförandet av en RCT. Den första aspekten är kopplad till ett av inklusionskriterierna, att deltagarna skulle vara otränade vid tidpunkten för inklusion. Det visade sig att konditionsvärdena (mätt vid ett maximalt konditionstest) var högre än väntat utifrån den självskattade aktivitetsnivån som rapporterats vid screeningtillfället. Den andra aspekten var den fysiologiska responsen vid akut stress, där en minskad respons var förväntad för de deltagare som genomgått

träningsinterventionen. Förutsättningarna för att kunna observera en sådan nedgång var en synlig respons vid den första mätningen, men för 13 av deltagarna kunde ingen positiv respons påvisas.

Delstudie II jämförde fysiologiska reaktioner vid akut fysisk och psykosocial stress. Den hormonella responsen samt pulsreaktionen var högre vid fysisk stress än vid psykosocial stress, medan det omvända gällde för systoliskt och diastoliskt blodtryck. Det fanns en korrelation mellan kortisolresponsen vid fysisk och psykosocial stress, det vill säga att de deltagare som reagerade med hög kortisolrespons under det fysiska testet reagerade med hög respons även under det psykosociala testet. Däremot sågs inget samband för autonoma reaktioner eller vid vilket tidpunkt högsta värdet inträffade. Inget samband kunde heller fastställas mellan hur stressande testet upplevts och storleken på den fysiologiska reaktionen.

Delstudie III presenterade resultat från de uppföljande mätningarna, där den fysiologiska responsen på akut psykosocial stress jämfördes mellan interventions- och kontrollgruppen. I interventionsgruppen ökade konditionsvärdet signifikant (+9,5 %) jämfört med baslinjemätningen, samtidigt som konditionsvärdet i kontrollgruppen minskade (-3 %). Båda grupperna fick en minskad reaktion på stresstestet, vilket tyder på att deltagarna fått en tillvänjning till testet och/eller testsituationen. Det går därför inte att uttala sig säkert om effekterna av träningsinterventionen.

Delstudie IV innehöll tvärsnittsanalyser av DHEA och DHEA-S och dess samband med aerob kapacitet, och också hur respons i DHEA och DHEA-S på akut psykosocial stress påverkas av aerob kapacitet. Inga samband kunde dock ses.

Sammanfattningsvis kan sägas att det inte verkar finnas något samband mellan aerob kapacitet och hormonell respons vid akut fysisk och psykosocial stress. Det verkar inte heller som att upplevelsen av en stressituation är avgörande för den fysiologiska responsen. Hos friska individer ser stressystemen ut att fungera väl, oavsett vilken aerob kapacitet individen besitter. Resultat från tidigare studier har visat på varierande resultat gällande effekterna av aerob kapacitet på akuta stressreaktioner, och denna avhandling adderar således till gruppen av studier som inte kunnat påvisa samband. Fler longitudinella studier av hög kvalitet är dock önskvärda för att med säkerhet kunna fastställa resultaten i denna avhandling.

Contents

Tables and figures

Included publications and manuscripts

One paper included in this thesis has been published and is reprinted with permission from the publisher.

I. Arvidson E, Sjörs A, Gullstrand L, Börjesson M, Jonsdottir IH. Exercise training and physiological responses to acute stress: study protocol and methodological considerations from a randomized controlled study. BMJ Open Sport & Exercise Medicine 2018;4: e000393. doi:10.1136/bmjsem-2018-000393

II. Arvidson E, Sjörs A, Gullstrand L, Börjesson M, Jonsdottir IH. Physiological responses to acute physical and psychosocial stress in healthy women and men (In manuscript).

III. Arvidson E, Sjörs A, Gullstrand L, Börjesson M, Jonsdottir IH. The effects of exercise training on HPA-axis reactivity and autonomic response to acute stress – a randomized controlled study. (Submitted)

IV. Arvidson E, Börjesson M, Jonsdottir IH, Lennartsson A. DHEA and DHEA-S response to acute psychosocial stress and the relation to aerobic capacity in healthy women and men (In manuscript).

Abbreviations

ACTH	Adrenocorticotropic hormone
ANOVA	Analysis of variance
AUC_i	Area under the response curve with respect to increase
Bpm	Beats per minute
DBP	Diastolic blood pressure
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulphate
HR	Heart rate
ISM	Institute of Stress Medicine
RCT	Randomized Controlled Trial
SBP	Systolic blood pressure
TTE	Time-to-exhaustion
VO_2 peak	Peak oxygen uptake
W	Watts

Background

Exercise training is known as one of the most effective ways to promote overall health and well-being (1). Regular exercise training can contribute to the prevention and treatment of many common diseases, such as cardiovascular disease (2), diabetes type II (3, 4) and stroke (5). Exercise training has also been shown to have positive effects on mental health (6) and is used to treat mild to moderate depression (7) and long-term stress (8).

Feeling stressed has become a common part of everyday life in Western societies. In both working life and private life, the possibility of being constantly online and available is only one of many factors that probably has contributed to the increased stress levels. However, the human body is well equipped to physiologically respond to stress, which is essential for survival. Several systems act to prepare the body and mobilize energy during stressful situations. Two of the most commonly studied systems are the hypothalamic-pituitary-adrenal (HPA) axis, acting through the release of the catabolic hormone cortisol, and the autonomic nervous system (ANS), which, among other things, increases heart rate and blood pressure. Two other hormones that also respond to acute stress are dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEA-S). In contrast to the catabolic effects of cortisol, DHEA and DHEA-S have anabolic effects.

Definition of stress

What is stress?

First of all, *"stress"* is a difficult concept. The word "stress" is commonly used in everyday life, and interpretations vary considerably. But what does "stress" mean? Is there a clear definition of the word? There may actually be several answers to these questions. Outside research, stress is often understood as synonymous with having too much to do or being short of time. In this case, the cause of stress, the so-called "*stressor"*, is in focus. The stressor might be having a tight time-schedule, having too many work tasks or being in a traffic jam on the way to a meeting. Stress can also be described in terms of a feeling,

reflecting how an individual perceives a stressful situation. It can include feelings of anxiety or fear (9, 10). In research, though, the emphasis can be on physiological responses and bodily reactions to stress (11). For example, it is common to assess physiological responses to stress as hormonal reactions or cardiac reactivity (12).

But why is it necessary to define stress? Because clear definitions and common interpretations of concepts are important to ensuring clear communication in research. During the last 100 years, several scientists have tried to find a unifying definition of stress, but the word is still used differently in different research areas. The well-known stress researcher Hans Selye, who in the 1920s contributed to developing the stress concept, defined stress as

> a nonspecific response of the body to any demand made upon it.

Since then, this definition has been modified several times, often based on the orientation of the research. More recent adjustments have included additional aspects, as in Dhabhar and McEwen's 1997 definition:

> An integrated definition states that stress is a constellation of events, consisting of a stimulus (stressor), that precipitates a reaction in the brain (stress perception), that activates physiological fight or flight systems in the body (stress response)(13).

This definition considers not only the unspecified response that is central in Selye's definition but also the mental process involved. But while Selye describes a more general stress response, the later explanation more clearly relates to the instant stress response, or as it is more commonly termed, *"acute stress"*.

In everyday life, situations that can elicit an acute stress response of varying degrees might occur on a daily basis. This include public speaking, running to catch a bus, getting stuck in an elevator, and discovering that there is not enough money in one's account when trying to pay in a store. The physiological responses are often immediate, with increased heart rate and blood pressure as the most noticeable effects (14). These reactions aims to preserve *"homeostasis"*, defined as the maintenance of a steady state of body fluids, circulation, blood pressure, and a number of other variables (15). Sterling and Eyer (16) called the physiological adaptations to a new situation *"allostasis"* which they described as

> active processes by which the body responds to daily events and maintains homeostasis (16).

For the most part, acute stress reactions are not threatening to our health because of the body's physiological ability to cope with stressful situations. However, if the stressful situations are frequent and continue for a longer period, the systems might not have a chance to recover and the risk of deteriorating health increases (17, 18). This condition is often defined as *"long-term"* or *"chronic stress"* although the terms might differ depending on the research field. McEwen used the term *"allostatic overload"* to describe the condition in which the body fails to turn the systems involved on and off adequately (19). This thesis will focus on the acute stress reaction only. To learn how to prevent and treat the effects of long-term stress in patients, it is necessary to increase our understanding of how healthy individuals respond to acute stress. Theoretically, if it is possible to affect the physiological response to acute stress, it may also be possible to affect the degree of stress developed over time by reducing the pressure on the stress systems.

Stress physiological systems

Several bodily systems react to stress. The initial stress response starts in the brain, which is the central organ for the stress reaction (19). After evaluating the situation, necessary interventions are initiated (19). The allostatic processes activate many reactions, such as neuroendocrine and autonomic responses (20, 21). Here, the two main response systems will be studied, namely the HPA axis and the ANS. The thesis also includes studies of the anabolic hormones dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEA-S).

Hypothalamic Pituitary Adrenal axis

One of the most important systems involved in the acute stress reaction is the HPA-axis. The response is relatively slow compared to the autonomic nervous system in that it takes some minutes after exposure to a stressor before a response is detected. At the onset of stress, corticotropin-releasing hormone (CRH) is released from the hypothalamus, stimulating the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary into the blood. ACTH, in turn, triggers the release of cortisol from the adrenal cortex. This chain of reactions is regulated by negative feedback: that is, sufficient levels of cortisol in the blood will decrease the release of CRH in the brain (20)(see figure 1).

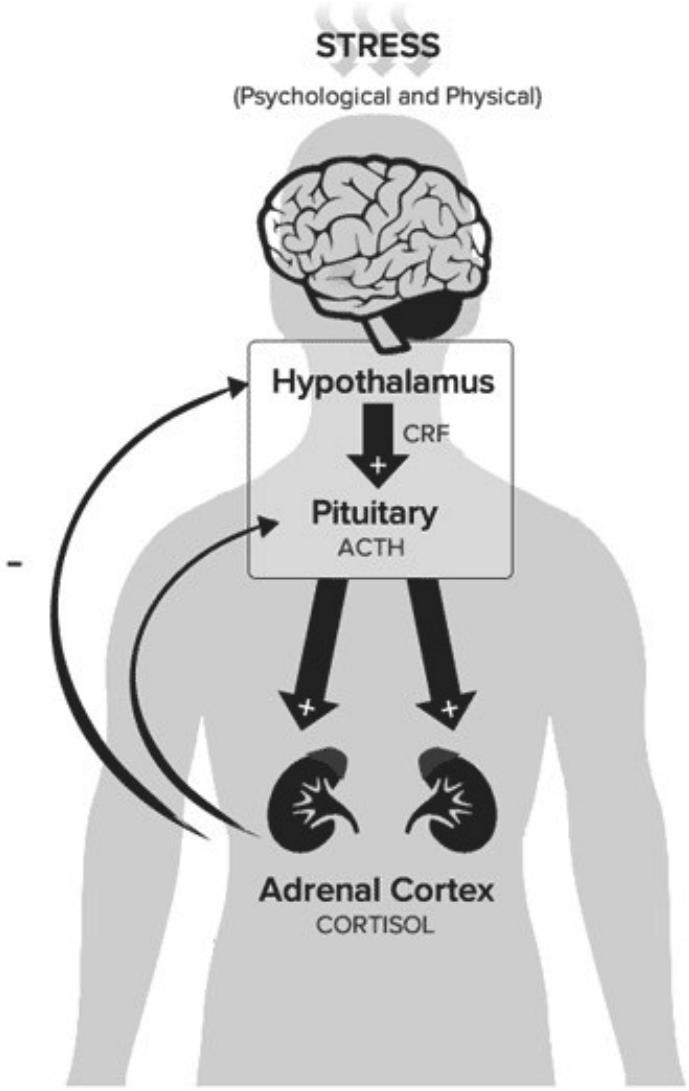
Cortisol is considered an important stress hormone due to its different features to adjust bodily functions during acute stress, in order to preserve homeostasis. The increased metabolic demands are regulated through the stimulation of gluconeogenesis (breakdown of lipids to glucose) that increases blood glucose concentrations. Cortisol also promotes mobilization of fatty acids from adipose tissues as well as the breakdown of protein to mobilize energy for the acute muscular stress reaction (22), and it is therefore defined as a catabolic hormone.

The levels of cortisol vary throughout the day in a circadian rhythm, with the lowest level seen during the night, the highest level before awakening and declining levels throughout the day. During stressful events or acute exercise, the levels rise and the time to recover is dependent on the duration and intensity of the stressor, which also determines the magnitude of the cortisol response (22). Seasonal variations have been observed indicating higher levels of salivary cortisol on awakening during winter and lower levels in the late summer (23, 24). However, the populations in these studies were small, and the studies included no information whether acute cortisol responses during the day were also affected. Thus, more studies are needed to confirm the results.

Prolonged activation of the HPA-axis, without enough recovery time, has been shown to lead to heightened basal levels of hair cortisol (25, 26). Elevated cortisol levels are thought to have neurotoxic effects, especially in a part of the brain called the hippocampus, which is important for learning and cognition (19, 27).

Figure 1.

Schematic picture of the hypothalamic-pituitary-adrenal axis



CRF: Corticotrophin releasing hormone, ACTH: Adrenocorticotrophic hormone

Autonomic nervous system

The ANS is largely controlled by areas in the spinal cord, brain stem and hypothalamus, and it controls subconscious functions in visceral organs (21). In contrast to the HPA-axis, communicating through the bloodstream, the ANS sends signals through afferent and efferent nerves, which results in a much more rapid response compared to the HPA-axis. When the ANS responds to a stressor, it acts through activation of the adrenal medulla and the sympathetic and parasympathetic nervous systems (28). The sympathetic activation in response to acute stress, also referred to as the "fight-and-flight" response, has the capability to respond within seconds of the emergence of a stressor. It increases heart rate, blood pressure and frequency of breathing (20), and also redistributes blood from the general circulation and gastrointestinal areas to the muscles. Additionally, the coagulation capacity in the blood increases in case of potential damage and blood loss. These actions prepare the body to either fight against or flee from the potential danger (21). The parasympathetic nervous system can act through a "playing dead" or "freeze" reaction to avoid attention (14).

Allostatic overload in the ANS often depends on increased activity in the sympathetic nervous system with a simultaneous decrease in parasympathetic activity (19). This might lead to insufficient recovery in the affected organs, such as the heart and blood vessels. Long-term stress has been associated with an increased risk of developing hypertension and stroke (29, 30).

Dehydroepiandrosterone

DHEA and DHEA-S are, in contrast to cortisol, endogenous anabolic steroid hormones released from the adrenal cortex, also in response to ACTH. They act as precursors of testosterone and oestrogen and have been shown to have anti-glucocorticoid and neuroprotective effects (31). DHEA and DHEA-S also play an important role for nerve growth and are suggested to have both anti-oxidative and anti-inflammatory properties (32). One anabolic effect of DHEA and DHEA-S is an increase in the synthesis of protein.

Unlike DHEA, no circadian rhythm is seen for DHEA-S, probably because of its larger quantities and slower clearance rate (33). DHEA and DHEA-S are the most abundant hormones in the body, highly dependent on sex and age, with men having higher levels than women (34). The highest levels are seen in

early adulthood; thereafter, they decline every year and are only at 20 % of peak values by the ages of 65-70 years.

It has previously been shown that prolonged stress leads to decreased levels of DHEA-S, and to attenuated levels of DHEA-S in response to acute psychosocial stress (35, 36).

Different types of stressors

It is important to distinguish not only between acute and long-term stress, but also between different types of stressors. The general perception of "stress" often emphasizes the mental aspect. However, stressors can be of several origins. In this thesis, two types of stressors will be studied: psychosocial and physical stressors. Both types of stressors elicit a reaction of the stress systems and the physiological reactions share many similarities, although the physical demands often diverge.

Psychosocial stress

In 2015, Kogler et al. defined psychosocial stress as follows:

> Psychosocial stress is induced by situations of social threat including social evaluation, social exclusion and achievement situations claiming goal-directed performance (37).

This definition includes the mental strain experienced in social interactions, especially in socially demanding situations. Psychosocial stress has been evaluated with several different methods, including the Montreal Imaging Stress Task, developed to study responses in the brain with functional magnetic resonance imaging or positron emission tomography (38), and the Trier Social Stress Test (TSST)(39), which is used in this study (see description of the test in the Methods section, p. 38). In the Results and Discussion sections of this thesis, descriptions of reactions to acute "psychosocial stress" are referring to responses to the TSST.

Physical stress

Physical stress can be triggered by a number of factors, for example a cold pressure test (40) or electric foot shock (used on animals) (41). In this thesis, acute physical stress is elicited using an exercise test performed to exhaustion. The most prominent difference between psychosocial and physical stress is the

bodily demands, among them metabolic requirements. During exercise, the muscles and tissues need to be supplied with oxygen and nutrients to maintain homeostasis. This is executed by the release of hormones that, in turn, increase the heart rate to provide the working muscles with energy and increase breathing to meet the demands of oxygen supply (42). Throughout this thesis, "physical stress" refers to responses to an acute exercise bout.

Aerobic capacity

Aerobic capacity can be defined as:

> the maximal amount of physiological work that an individual can do as measured by oxygen consumption. It is determined by a combination of aging and cardiovascular conditioning and is associated with the efficiency of oxygen extraction from the tissue (43).

Aerobic capacity is ideally assessed as peak oxygen uptake (VO_2 peak) (44), achieved by an exercise test that includes gradual increase in resistance and is performed to exhaustion (45).

Another plausible method to assess aerobic capacity is to use submaximal tests and estimate a peak value (46, 47). However, a submaximal test can never be as reliable as a peak performance test, and often overestimate the values compared to maximal testing (46, 47).

Exercise training

It is possible to improve aerobic capacity through regular aerobic exercise training. According to the World Health Organization (WHO), *"exercise training"* is a subcategory of the overarching concept *"physical activity"*. Physical activity is defined as

> any bodily movement produced by skeletal muscles that requires energy expenditure- including activities undertaken when working, playing, carrying out household chores, travelling, and engaging in recreational pursuits (48).

Exercise training, on the other hand, is described as activity that is

> planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness (48).

It is common to distinguish between "aerobic" exercise, which aims to increase oxygen uptake, and "resistance" exercise, which focuses on improving in

muscular strength. Aerobic and resistance exercise have been shown to affect the body differently (15, 49). In this thesis, "exercise training" refers to aerobic exercise only.

Regular exercise training leads to physiological adjustments that occur on several levels. One example is cellular adaptations that increase biosynthesis and storage of essential neurotransmitters such as epinephrine and norepinephrine. Other adaptations include changes in neural communication and functional adaptations in "end-organs" such as the heart or the muscles. For example, one effect of aerobic exercise is increased oxidative capacity in the muscles due to enlarged mitochondrial volume and increased utilization of free fatty acids. This adaptation results in increased endurance and more effective use of energy (42). Other adaptations are increased wall thickness and heart volume, improved cardiac output, increased VO_2 peak and increased blood supply to the heart itself. Due to increased vagal activity, decreased sympathetic activity and increased heart size, a decreased resting heart rate is seen as well as lower heart rate at submaximal work as a result of aerobic exercise training of sufficient intensity and duration (42).

The cross-stressor adaptation hypothesis

It is believed that physiological adaptations to exercise training may also affect reactions to psychosocial stress. The so called "cross-stressor adaptation hypothesis" is a theory originally described by Sothman et al. (50) in the mid-1990s. Since then, a number of studies addressing this theory have emerged, but no consensus has been reached yet, and the hypothesis has not been fully confirmed. Their hypothesis is based on the idea of the stress response as non-specific, causing similar actions in the stress systems independent of the origin of the stressor. They suggest that the physiological adaptations that are seen after regular exercise, would also be seen in responses to psychosocial stress.

An important result of an adaptation is that it may lower the physiological "cost" for a response, that is, the total physiological arousal might be weaker. According to the hypothesis, exercise training will increase coordination between the different systems to diminish the risk of disturbed homeostasis. During acute exercise, a decreased HPA-axis and ANS response has been observed at a given work load in trained individuals compared to untrained individuals (42, 51). If these adaptations are transferable to non-exercise

stressors, it would be beneficial in every-day life when commonly recurring stressors might put great pressure on the individual. However, the mechanisms behind the plausible effects are yet not fully known.

Summary of previous studies of the cross-stressor adaptation hypothesis

Although the paper defining the cross-stressor adaptation hypothesis was published in 1996, the plausible connections between physical and psychosocial stress were studied many years earlier. The first review of articles studying the effects of exercise training and aerobic capacity in response to psychosocial stress was a meta-analysis by Crews and Landers, published in 1987 (52). The paper comprised 34 studies, including both published and unpublished work. Outcome measures were heart rate, blood pressure, temperature, hormonal changes and subjective assessment. The stressors used were categorized as cognitive performance, physical performance, active physical performance and passive response, which imply a great diversity of both stressors and evaluative methods. Heart rate was the only variable assessed in all studies and was therefore used as a comparable factor of arousal achieved at the stress tests. An increase in heart rate above or below 30 beats per minute (bpm) was classified as a high and low response, respectively. The authors concluded that exercise training resulted in a lower response to psychosocial stress. However, in 24 of the 34 studies, the stress test caused a low response in heart rate (lower than 30 bpm), which raises questions of the adequacy of the stress tests. Also, the heterogeneity in the different stressors and outcomes leads to doubts about the authors conclusions.

Another review, also published before Sothman et al. presented their hypothesis, reported a conclusion that was opposite to the meta-analysis above (53). The authors used the term "fitness" to distinguish between individuals with high or low aerobic capacity and questioned the absence of a clear definition of fitness in earlier studies. Also, they claimed that, to be valid, fitness must be assessed using a VO_2 peak test, which precluded several studies from comparative analyses. They concluded that it was not possible to predict the physiological response to acute psychosocial stress based on the individual's

level of fitness. They also questioned the comparison of response to physical and psychosocial stressors, given the different mechanisms involved.

In 2006, Jackson and Dishman published a review including a meta-regression analysis of 73 studies of both cross-sectional and longitudinal design (54). The aim of the review was to study the influence of cardiorespiratory fitness, defined as VO_2 peak, on cardiovascular responses to acute psychosocial stress. In cross-sectional studies, the VO_2 peak was between 40 and 59 mL/kg/min. In the studies that included an exercise training intervention the VO_2 peak was between 35 and 42 mL/kg/min, with an average increase of approximately 13 % following the intervention. The results revealed a slightly higher cardiovascular reactivity in individuals with higher cardiorespiratory fitness, but the effects were smaller in studies where fitness was measured using a VO_2 peak test than in studies using submaximal testing. There were also smaller effects in better controlled studies.

The same year, a meta-analysis by Forcier et al. was published, studying the effects of physical fitness on cardiovascular reactivity (55). The 33 included studies compared fit (high initial fitness, objectively measured as resting HR, VO_2 peak or treadmill tests) and unfit (low initial fitness) participants and their responses to psychosocial stressors. Stress reactivity was measured as at least 5 bpm increase in heart rate or at least 5 mmHg increase in blood pressure. Nineteen of the studies induced a reactivity of less than 10 mmHg or bpm, while 14 resulted in reactivity of more than 10. The authors concluded that fitness had a significant effect on heart rate and systolic blood pressure reactivity, and on heart rate recovery after psychosocial stress. However, as with the study by Crews and Landers, it is reasonable to question a stress test inducing an increase in heart rate or blood pressure less than 10 bpm or mmHg. Moreover, only a few of the longitudinal studies included a non-training control group, which makes it difficult to assume that the results are an effect of exercise training alone.

The most recent review found was published in 2018 (56). The review evaluated effects of exercise training and cardiovascular fitness on physiological responses to acute laboratory stress, measured with the Trier Social Stress Test (TSST; for a description, see the Methods section). The main outcome measures were cortisol, heart rate and psychological stress reactivity. Physical activity and fitness were measured both objectively and subjectively. Seven out of twelve studies reported attenuated responses in cortisol, and 4 out of 9 showed lower reactivity in heart rate, in groups performing a greater amount of

physical activity or with higher levels of fitness. In contrast to the review by Jackson and Dishman (54), which found smaller effects if fitness was objectively measured, this study reported the opposite finding. In light of previous reviews and meta-analyses, the use of the same test to elicit stress increases the comparability between studies. However, like many of the earlier studies, it is problematic that physical activity and fitness are measured and defined differently across studies.

Only one RCT has been found examining the cross-stressor adaptation hypothesis for both HPA-axis and ANS responses. Klaperski et al (57) conducted an exercise training intervention study, comparing 12 weeks of aerobic exercise to relaxation training or a control situation. The result showed a reduced response in cortisol in the exercise training group compared to the control group, but no significant differences could be seen compared to the relaxation training group. However, although the exercise training group increased their level of exercise training, the level of daily activities was reduced. At the same time, the relaxation group increased both the level of exercise and level of daily activities, potentially influencing the results.

No reviews, meta-analyses or studies were found that explore the cross-stressor adaptation hypothesis addressing the influence of DHEA and DHEA-S, although the anabolic effects might constitute a role in the theory.

In summary, results from earlier reviews and meta-analyses are not unequivocal. The support for the cross-stressor adaptation hypothesis is therefore not clear, but taking into account the methodological diversity in study designs over the years, this is perhaps not so surprising. The only RCT found confirmed the hypothesis, but the unclear results regarding the relaxation group makes the interpretations unsure. Thus, further studies are needed, especially in the form of well performed RCT: s, elucidating the plausible role of exercise training on affecting the acute physiological stress response.

Aims

The overall aim of this thesis was to study, from different perspectives, physiological reactions to acute physical and psychosocial stress in healthy women and men.

Aims for each paper:

Paper I: To describe the protocol of an RCT designed to explore the effect of exercise training in physiological reactions to acute psychosocial stress. The aim was also to discuss relevant methodological issues related to conducting an exercise intervention study with acute stress responses as outcome measures.

Paper II: To study the physiological reactions to acute physical and psychosocial stress in terms of HPA-axis response and autonomic reactions in women and men. The paper also aimed to study differences and/or associations between the responses to physical and psychosocial stress, and whether the responses correlated to perceived stress.

Paper III: To study the effects of a six-month exercise training intervention on HPA-axis response and autonomic reactions to acute psychosocial stress in healthy but untrained individuals.

Paper IV: To study physiological responses to acute psychosocial stress in women and men, focusing on levels of DHEA and DHEA-S. The aim was also to study whether aerobic capacity correlated to levels of DHEA and DHEA-S.

Methods

Table 1.

Overview of methods and number of participants for each included paper

	Number of participants	Study design	Measurements
Paper I	119	study protocol/ cross sectional	VO_2 peak, ACTH, cortisol
Paper II	119	cross sectional	ACTH, cortisol, BP, HR, perceived stress
Paper III	81	RCT, longitudinal	VO_2 peak, TTE, ACTH, cortisol, BP, HR
Paper IV	88	cross sectional	VO_2 peak, DHEA, DHEA-S, cortisol

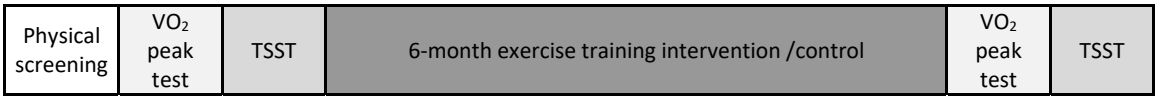
VO_2 peak: peak oxygen uptake, ACTH: adrenocorticotropic hormone, BP: blood pressure, HR: heart rate, DHEA: dehydroepiandrosterone, DHEA-S: dehydroepiandrosterone sulphate, RCT: randomized controlled trial, TTE: time-to-exhaustion

Study design

This thesis is based on an RCT, called "Acute Stress and exercise Training Intervention" (ASTI). The study was conducted at the Institute of Stress Medicine (ISM) in Gothenburg, Sweden, from 2013 to 2016 and registered at clinicaltrials.gov, ID NCT02051127. The aim of the RCT was to explore the effects of exercise training on physiological responses to acute psychosocial stress. Only selected parts of the original study are included in this thesis. The participants went through a physical stress test (VO_2 peak test) and a psychosocial stress test (TSST) and were then randomized to either an intervention group, which performed aerobic exercise training during the intervention period, or a control group. Six months later, both groups were followed up using the same procedures as at baseline (see details below) (Figure 2).

Figure 2.

Flow through the AST-study



VO_2 peak: peak oxygen uptake, TSST: Trier Social Stress Test

Study procedures

The study protocol was extensive and required considerable resources. The planning of the study began in 2012, and the actual testing started in spring 2013 as a small pilot study that included eight participants. In the autumn of the same year the original study started. The testing periods were divided into several "test weeks". Once a month (excluding January, June, July and December) a group of 8-12 participants were tested. The groups were generally a mix of participants performing either baseline- or follow-up measurements. In total, there were 28 test weeks from April 2013 to April 2016, with the last follow-up in October 2016.

Every participant made at least five visits during the study (see table 2). The first visit was a physical screening. Individuals considered eligible for the study were then booked for the second visit.

Table 2.

Activities at the five visits for each participant during the study.

Visit 1	**Visit 2**	**Visit 3**	**Intervention**	**Visit 4**	**Visit 5**
App. 30 min	*App. 4 h*	*App. 2.5 h*	*6 months*	*App. 4 h*	*App. 2.5 h*
Screening	Questionnaires	TSST	Exercise or	Questionnaires	TSST
BP, ECG,	Cognitive tests		control group	Cognitive tests	
blood tests	Vo2 peak test			Vo2 peak test	

BP: blood pressure, ECG: electrocardiography, TSST: Trier Social Stress Test, VO_2 peak: Peak oxygen uptake

Visits 2 and 4

The second and fourth visits took place at the Centre for Health and Performance, University of Gothenburg. At the start of the second visit, participants were given verbal and written information about the study and they were invited to ask questions. A written informed consent form was signed by each participant and the researcher. At both visit 2 and visit 4, a standardized meal was served containing controlled amounts of protein (15 g), carbohydrates (65 g) and fat (20 g). All meals were frozen ready meals (from e.g. Findus and Felix), and all participants were served the same amount of food. After lunch, each participant was taken to a quiet room to perform a computerized cognitive test, which took approximately 30 minutes to complete. Thereafter the participant was shown to a room outside the test lab and met the nurses who would take the samples. The participant filled out questionnaires and was prepared for the physical stress test. A peripheral venous catheter (BD Venflon Pro, Becton Dickinson Infusion Therapy, USA) was inserted in an antecubital vein by a nurse, and an automatic blood pressure cuff was put on.

Two hours after the lunch was ingested the first blood sample was drawn (-10 minutes) and the participant entered the test lab to perform the VO_2 peak test. The participant was provided with a pulse sensor and was informed of the test procedures. After a five-minute warm-up on the bicycle, a tight mask was put on to collect expired gases during the test. Some degree of discomfort was experienced by most of the participants, but the mask had to sit tight in order to avoid air leakage. When the equipment was calibrated and the participant was ready to start, the second sample was drawn (-0 minutes), the blood pressure cuff was turned off and the test started (for a description of the test protocol, see page 37).

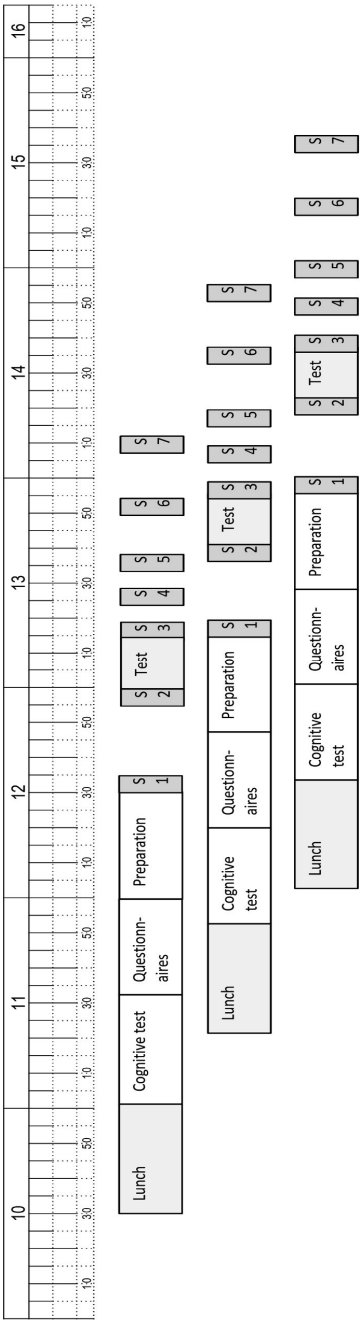
Directly after the test, the participant was released from the mask and sat down on a chair when the third (+0 minutes) sample was drawn and the blood pressure cuff was turned on again. Several participants had slight vertigo some minutes after the test and were therefore supervised by the nurses taking the samples. The participant rested for one hour in a sitting position while the remaining samples were taken (10-, 20-, 40- and 60-minutes post-test). They were allowed to drink water, but no other intake of food or beverages was permitted. Following the last sample, the nurse removed the inserted catheter and supplied the participant with a frozen ready meal that was to be eaten before the stress test scheduled for the following week.

Two to three participants were booked for each test day. To manage the logistics for personnel and use of the test rooms, the time for arrival was set to 45 minutes between participants (protocol for the logistics are shown in figure 3). On most of the testing days, three personnel were in place.

Samples that were to be cold spun were put on ice and taken care of immediately. Samples that were to be centrifuged at room temperature were taken care of after the last participant had completed the samplings.

Figure 3.

Overview of logistics for the physical stress test, a testing day including three participants



S 1-7: time point for samplings 1-7

Visits 3 and 5

On the testing days for the TSST, the participants had ingested their lunch before arrival, again two hours before the test was scheduled to start. The vein catheter was inserted by the nurse directly on arrival, and the participant had a short rest before the first blood sample was drawn (-10 minutes). After the second sample (-0 minutes), the participant started the test (for a description of the test protocol, see page 38).

The samplings after the stress test followed the same protocol as after the physical stress test (+0-, 10-, 20-, 40- and 60 minutes post-test). Following the TSST sampling procedures at the third visit, the participants were randomized. Each participant, regardless of whether he or she was randomized to the intervention- or the control group, received information on what was to take place during the time between baseline measures and follow-up. Participants randomized to the intervention group booked time for a group meeting the week after the stress test. At that meeting, the research staff gave the participants information about the intervention, handed out pulse watches and gave instructions on how to use the watch and the training log. The participants also received information on the positive effects of exercise training and a voucher giving them access to the training centres during the intervention period. Participants randomized to the control group were asked to maintain their current level of physical activity.

At the last visit (visit 5), all participants were thanked for their participation. Participants in the control group were invited to a motivational group meeting the week after the test. They received information on the positive effects of exercise training and a 12-month voucher to a training centre and were introduced to the same training log as the intervention group.

Preparations between the test weeks

In the time between the test weeks, data and results from the tests were entered in SPSS, and protocols for the coming tests were prepared. Labels for all the tubes for sampling (28 for each participant) and micro tubes for storing of samples (72 for each participant) were printed. Medical journals and questionnaires were prepared for new participants, and physical screenings were done for potential participants. Additionally, participants randomized to the intervention group got started on their exercise training.

Participants

The participants were healthy volunteers, 20 to 50 years of age, both women and men, with a self-reported sedentary lifestyle, working or studying at least 50 % of full time and living in the Gothenburg area. Participants were recruited through two local newspapers, notice boards around the city of Gothenburg, and social media. Individuals interested in participating sent an e-mail to the study coordinator, who sent a screening form that included questions regarding psychological health and medication, and a screening for heart disease with the Physical Activity Readiness Questionnaire (PAR-Q) (58). They reported their current level of physical activity with the Saltin-Grimby Physical Activity Level Scale (SGPALS)(59), a four-graded single-item request: "Mark the alternative that best describes your physical activity level in the last year." The alternatives were as follows: 1) Mostly sedentary, sometimes walking, light gardening or comparable activities, 2) Light physical activity at least two hours per week, such as walking or bicycling to work, dancing, ordinary gardening or comparable activities, 3) More strenuous activity at least two hours per week, like playing tennis, swimming, running, gymnastics, bicycling, dancing, playing football or indoor hockey, heavy gardening or comparable activities, 4) Regular hard exercise several times per week for at least five hours, with a high physical effort.

Individuals reporting level 1 were defined as untrained and were invited to a physical screening at the ISM. The physical screening included assessments of weight and height, blood tests (HbA1c, glucose, insulin) and ECG. Individuals with diverging levels of glucose, HbA1c or blood pressure, abnormal resting ECG, anaemia, under- or overweight, medication with beta blockers, psychopharmacological drugs or asthma medicine, or inability to exercise at a relatively high intensity were excluded due to the exclusion criteria. Individuals with an abnormal ECG were further examined by a cardiologist before inclusion or exclusion in the study.

Oxygen uptake test

At both baseline and follow-up, the participants went through a bicycle ergometer test to assess their peak oxygen uptake, peak heart rate and time-to-exhaustion (TTE). The protocol was adapted to this specific group of untrained, healthy adults in the form of a ramp test (45). The test leader was the same person (the author) for almost all tests at both baseline and follow-up.

The participants warmed up for five minutes on the bicycle ergometer (Monark 828 E, Monark Exercise AB, Vansbro, Sweden). The relatively short time was set due to the risk of fatigue even at a low resistance. The cadence was set to 70 revolutions per minute, since a higher speed can be difficult to keep for a person unaccustomed to ergometer cycling, and a lower speed increases the risk of early fatigue in the legs. The initial load was 87.5 watt (W) for women and 105 W for men, increasing by 17.5 W (0.25 kilo pounds) every minute until exhaustion. The participants were verbally encouraged by the test leader during the test, with increasing frequency at the end of the test. Previous studies have shown that individuals, especially untrained individuals, can increase their performance when verbal encouragement is given (60). The test ended when the participant reached a plateau and/ or a decrease in oxygen uptake, had a respiratory exchange ratio above 1.1, hyperventilated and could not keep the required cadence on the bicycle, or chose to stop for other reasons. Oxygen uptake was measured as mL/kg/min with the Jaeger Oxycon Pro metabolic chart (Carefusion, Hoechberg, Germany) in a mixing chamber mode. The device was calibrated before each measurement according to the manufacturer's manual. HR was monitored with a pulse sensor (Polar 300 RS, Polar, Finland).

Trier Social Stress Test

One week after the VO_2 peak test, the participants performed a psychosocial stress test. The test used was the Trier Social Stress Test (TSST), which has been shown to strongly activate both autonomic and neuro hormonal stress responses during and after the test (39). It has been widely used in previous studies in this research area and is well established as a reliable and valid test (12, 61). The TSST is based on two parts: 1) a free speech and 2) an arithmetic task, both parts in the presence of a committee consisting of two men and one woman. The participant enters the test room and is given information about the procedures and is instructed to give a five-minute presentation of him- or herself in a fictitious job interview for his or her dream job. The participant is told that the test will be recorded both by video- and audiotape, and that the members of the committee are specialists in studying behaviour. The participant leaves the room for a preparation period of five minutes. Thereafter the participant re-enters the test room and starts the first part of the test- the free speech. The members of the committee give no form of encouragement during

the speech. If there is still time when the speech is over, the chairman of the committee encourages the participant to continue. If the participant has no more to say, it will be quiet in the room for the rest of the time. In the second part of the test, the participant is given a task to count down from 1637 in steps of 13. If the participant fails to give the right number, he or she must start from the beginning. This part lasts for five minutes. After the test the participant leaves the room.

No debriefing was held after the baseline TSST since almost the same test was performed at follow-up. There was a small change in the instructions given the second time, in that participants would instead apply for a job they had dreamed about as a child. After the follow-up TSST, the participants received a short debriefing and were informed that nothing from the test had been recorded and that the members of the committee were not experts in behaviour.

Randomization

After completing the psychosocial stress test, the participants were randomized to the intervention or control group by picking a sealed envelope. The randomization rate was 50 % to the intervention group and 50 % to the control group. Due to higher numbers of drop-outs than expected in the intervention group, the rate was changed to 70 % to the intervention group and 30 % to the control group during the last year of inclusion.

Outcomes

The main outcomes of the RCT were ACTH and cortisol response to acute psychosocial stress. In this thesis, DHEA, DHEA-S, blood pressure and heart rate were also assessed. Paper II included responses to physical stress as well.

Assessments

ACTH, Cortisol, DHEA, DHEA-S

Identical protocols for collection of blood samples of ACTH and cortisol were used for both the physical and the psychosocial stress tests with samples drawn 10 minutes before the test (-10), directly before the test (-0), directly after the test (+0), and thereafter 10, 20, 40 and 60 minutes after the test was finished.

DHEA and DHEA-S samples were drawn at -10, +0, 10, 20 and 60 minutes post-test. A total of 220 mL of blood were taken at each test session.

Plasma samples, collected in EDTA tubes, were used to assess ACTH, DHEA and DHEA-S. To separate plasma, the tubes were cold spun at 3500 revolutions per minute for 15 minutes and stored in micro tubes at -80 º C until analysed. Cortisol was assessed in serum and collected in Serum Sep Cloth Activator tubes. To separate serum, the tubes were spun at 20 º C for 10 minutes at 3500 revolutions per minute and stored at 6 º C until analysis the day after the test. Plasma concentrations of ACTH were assessed by immunoradiometric assay (limit of detection, 0.4 pmol/L) (CIS bio International, Gif-sur-Yvette Cedex, France). Serum concentrations of cortisol were assessed by electro chemiluminescence immunoassay (limit of detection, 0.5 nmol/L) (Roche Diagnostics GmbH, Mannheim, Germany). Serum concentrations of DHEA were determined using a Liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (limit of quantitation 175 pmol/L), and serum concentrations of DHEA-S were assessed by radioimmunoassay techniques (RIA) (limit of detection 0.14 μmol /L, Diagnostic Products Corporation, Los Angeles, CA, USA).

Blood pressure and heart rate

The participants wore an automatic blood pressure cuff (Welch Allyn, ABPM 6100, USA) from 10 minutes before the tests started to 60 minutes after the tests were finished. The device assessed systolic and diastolic blood pressure (SBP and DBP, respectively) and heart rate (HR) every five minutes at the TSST. At the VO_2 peak test the device assessed every 10 minutes, but it was turned off during the test and started again directly after the test was finished.

Perceived stress

Immediately after the psychosocial stress test, the participants rated their perceived stress according to an adapted version of the Borg CR 10 scale of Perceived Stressfulness (62). It is a 13-grade category scale, ranging from "nothing at all" to "maximal", modified to fit the rating of stressfulness during the psychosocial stress test.

Exercise training intervention

The week after the psychosocial stress test, participants randomized to the intervention group were instructed to start regular aerobic exercise during the intervention period. The goal was to reach a frequency of three times per week with a duration of 45-60 minutes at each session. The goal of intensity was to reach an average heart rate of at least 75 % of peak heart rate, measured at the peak oxygen uptake test, and sustain it during at least 80 % of the session. To measure the duration and intensity of exercise, the participants wore a pulse sensor (Garmin 210) at each session. Data was transferred from the sensor to a web-based training log (www.funbeat.se). In the training log, the participant manually recorded the type of activity performed. The data was registered to be further analysed in terms of frequency, duration, intensity and type of activity. For untrained individuals, an increase in exercise level from no exercise training at all to three times per week is challenging. Therefore, the participants were encouraged to increase their activity level gradually, starting at 30 minutes two times per week to reach the final level after 6-8 weeks.

Participants were free to choose the type of aerobic exercise they would do, as long as they reached the intended level of intensity. During the intervention, the participants received free access to a commercial fitness establishment (Nordic Wellness) with several facilities in the Gothenburg area. The participants were instructed to avoid resistance training, since it is thought to affect the hormonal systems differently than aerobic exercise (49).

To support the participants in their lifestyle change, they were offered four sessions with a coach, trained in motivational interviewing. The sessions were guided by Self-Determination Theory, which provides guidelines for the interviewer supporting participants as they increase their level of exercise (63). The coach had access to the training log and referred to it during the sessions.

Control group

Participants allocated to the control group were instructed to maintain their current level of exercise, that is, to not increase or decrease their degree of physical activity. After follow-up measures were taken, they were encouraged to start to exercise. They were called to a motivational group meeting and received one-year access to the same fitness establishment as the intervention group.

Ethics

The original study was registered at clinicaltrials.gov, ID NCT02051127, and designed according to the Consolidated Standards of Reporting Trials (CONSORT) Statement (64). All participants gave written informed consent before entering the study and were informed that they could withdraw their participation at any time. The study was conducted according to the 1964 Declaration of Helsinki and approved by the Regional Ethical Board, Gothenburg, Sweden, Dnr 917-12, and supported by funding from the Swedish Research Council for Health, Working and Welfare.

Data handling

Pre-test values in papers I-III were calculated as the mean value of the -10- and -0-minute values. In paper IV the -10-minute value was defined as the pre-test value. For all variables, peak value was the highest value measured during or after the stress test. The lowest value after the peak was also identified.

In papers II, III, and IV, reactivity values are presented, calculated by subtracting the pre-test value from the peak value. Percental change was calculated by dividing the absolute change from pre-test to peak by the peak value. Similarly, recovery values were calculated by subtracting the lowest value from the peak value, and percental change was calculated by dividing the difference by the peak value.

In paper IV, ratios for cortisol and DHEA and cortisol and DHEA-S were calculated by dividing the cortisol value by the value for DHEA and DHEA-S at pre-test and peak (65).

The area under the response curve with respect to increase (AUC_i) was calculated in accordance with Fekedulegn et al. (66). AUC_i is a suitable method to analyse total arousal over a limited time period and may simplify analysis of multiple assessments. It provides information on both changes over time and overall intensity of the response (66).

The rating of perceived stress during the TSST was dichotomized into two groups representing low stress and high stress, respectively. Ratings from 0 to 4 (“not at all” to “somewhat strong”) were considered low perceived stress, and 5-10+ (“strong” to “maximal”) were considered high perceived stress.

Statistics

A power analysis for the RCT was done before the study was started. The sample size calculation for the main outcome measure, cortisol, showed that 39 subjects in each group were needed to enable a detection of an effect size of Cohen's $f = 0.25$, with power ≥ 0.80 and $\alpha = 0.05$. It was anticipated that a number of subjects could drop out or withdraw their participation, which resulted in a goal to include at least 50 participants in each group.

Several statistical methods were used in the four papers included in this thesis (see table 2). First, to check whether the variables were normally distributed, Kolmogorov-Smirnov tests were used. In papers I, II and IV, group differences at baseline were analysed with an independent samples t-test. For categorical data, $\chi 2$ tests were used.

A mixed between-within subjects analysis of variance (ANOVA) method was used in papers II and III. It combines a repeated-measure design with a between-subjects design in the same analysis and also presents possible interaction effects (67).

In paper II, AUC_i for ACTH and cortisol as well as reactivity and recovery in SBP, DBP and HR were analysed with mixed between-within subjects ANOVA for both physical and psychosocial stress. Correlations were analysed with Pearson correlation coefficient analysis for normally distributed data, or Spearman's rank order correlation coefficient for data that was not normally distributed.

Paper III compared pre-test, peak and recovery values from baseline to follow-up with mixed between-within subjects ANOVA. Correlations were analysed for amount of training and response to the stress test using Pearson correlations analyses. Finally, recovery values were analysed with mixed between-within subjects ANOVA.

In paper IV, independent samples t-tests were used for pre-test values. Pearson correlation analyses were used to evaluate associations between variables, and paired samples t-tests were used to analyse physiological responses to acute psychosocial stress.

Table 3.

Statistical methods used in each paper.

	Independent samples t-test	**Paired samples t-test**	**Chi-square test**	**Mixed between-within subjects ANOVA**	**Pearson correlation coefficient /Spearman's rank order correlation coefficient**	**Kolmogorov-Smirnov test**
Paper I	x		x			
Paper II	x		x	x	x	x
Paper III				x	x	x
Paper IV	x	x	x		x	x

Statistical methods used in each paper.

ANOVA: analyses of variance

Results

Since all included papers are based on the same study, general results are presented first. Specific results for each paper are presented below.

Participants

A total of 416 individuals responded to the advertisement recruiting participants for the study. Of these, 170 fulfilled the inclusion criteria and were invited to the physical screening. Twenty-four individuals were excluded due to the exclusion criteria, and another 22 declined participation. Five participants did not complete the baseline measurements and were therefore excluded. The final number of participants at baseline was 119 (see study flow diagram, figure 3). Of these, 89 participants (75 %) worked full time, 21 (18 %) worked 50 to 90 % of full time and 8 participants (7 %) were studying. The number of participants included during spring (February to May) was 56 (47 %). In autumn (August to November), 63 participants (53 %) were included. Alcohol was used by 93 % of the participants; of these, 54 % reported a frequency of 2-4 times per month. Tobacco was used by 19 participants (16 %); four were smokers and 14 used snuff, and one participant used both cigarettes and snuff. Nearly three-quarters (n = 86, 72 %) of the participants reported an educational level of at least three years of post-graduate education. A majority (n = 97, 82 %) of the included participants were living in a relationship.

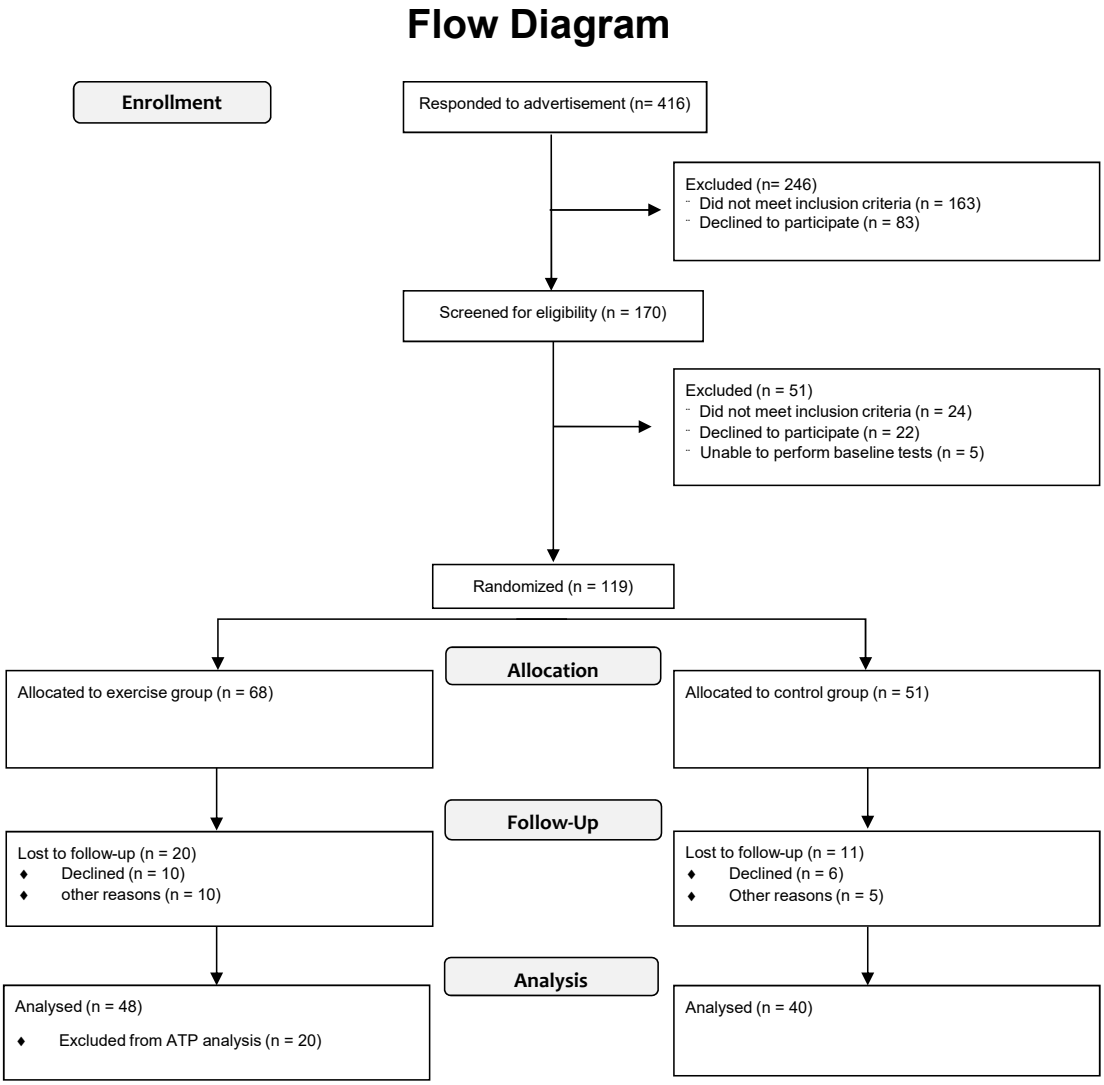
Activity level was self-reported as being "mostly sedentary" (equal to 1 in the SGPALS) in 89 % of the included participants. The remaining 11 % reported level 2 (light physical activity). The reason for including individuals reporting level 2 was an initial difficulty in the recruitment of participants. However, there were no significant differences in aerobic capacity between participants reporting level 1 or 2 in SGPALS ($t = -1.281$, $p = 0.203$).

Baseline values of aerobic capacity differed between sex and age groups. For both women and men, the aerobic capacity was shown to be higher than expected given their reported level of physical activity. Instead of VO_2 peak values corresponding to levels for untrained individuals, mean values for each age group showed values representing normal, or higher than normal, levels in the general population.

At follow-up, 31 participants had dropped out (20 individuals in the IG and 11 in the CG) for different reasons (unwillingness to go through retesting (n = 17), injuries (n = 4), changed working conditions (n = 3), starting anti-depressant medication (n = 4), pregnancy (n = 2) and randomization to the CG but started to exercise (n = 1)). See flowchart in figure 4. No significant difference was seen between the drop-out rate of participants included in spring and those included in autumn; 23 % of the spring participants dropped out, and 28 % of the autumn participants dropped out ($p = 0.506$). The drop-out analysis of demographic data showed no significant differences in the group of participants that did not return for the follow-up compared to the group that completed the study.

Figure 4.

Flow diagram over the randomized control trial



Paper I

This paper includes the study protocol used for the RCT ASTI. It also presents some baseline results to highlight methodological issues regarding the performance of an intervention study.

At baseline, the HPA-axis response to the TSST showed a mean increase of 214 % in ACTH and 94 % in cortisol, but large intra-individual differences were seen. The main hypothesis for the RCT was that individuals performing regular exercise training for six months would show an attenuated physiological response compared to participants in the control group. The prerequisite for such a change was that a positive response (increase) in the outcome measures from pre-test to peak would occur at baseline. However, for 13 participants, negative responses (decreases) were observed for ACTH or cortisol, and one participant responded negatively in both ACTH and cortisol. Thus, it would not be possible to detect attenuated responses to acute stress in these individuals.

The intended target group for the study was untrained individuals with low aerobic capacity. Although the majority of the included participants reported themselves as untrained at screening, baseline levels of aerobic capacity were comparable to average levels in the general population. Thus, several individuals included in the RCT were not as sedentary as expected.

Paper II

Paper II presents cross-sectional analyses of the correlations between the physiological response to acute physical and psychosocial stress in women and men.

The time point for reaching peak values of ACTH and cortisol differed between the physical and the psychosocial stress tests. At the physical test, 56 % reached their peak ACTH immediately after the test. For cortisol, 56 % of the participants reached their peak after 20 minutes. At the psychosocial test, 97 % of the participants reached their peak ACTH level during or immediately after the test, and 65 % of participants peaked in cortisol 10 minutes post-test. SBP, DBP and HR all peaked during or immediately after the tests.

Significant main effects for ACTH AUC_i were seen for test and sex (see response curves in figure 5). That is, for both women and men, AUC_i was significantly lower at the psychosocial stress test than at the physical stress test,

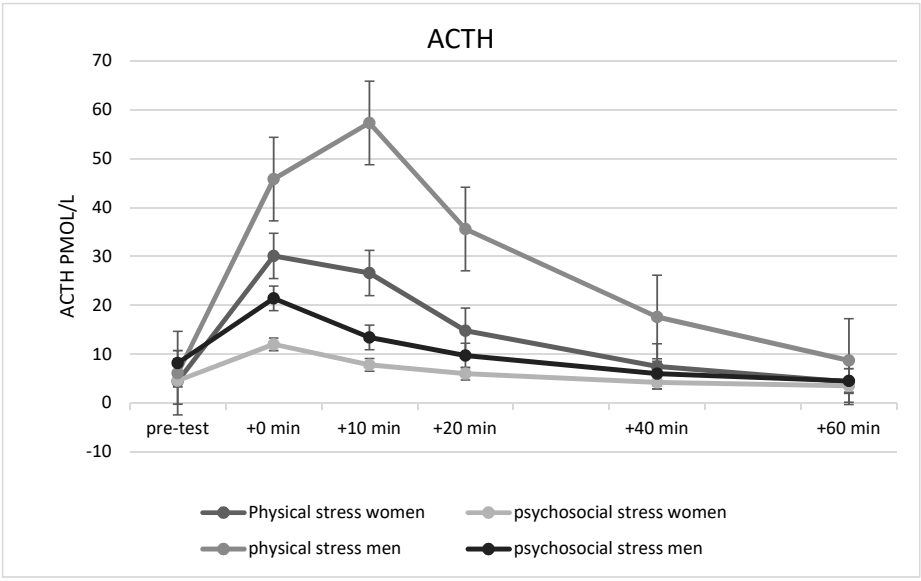
with men showing greater responses than women at both tests. Cortisol AUC_i did not differ between the tests, but significant main effects were seen for sex, showing greater response curves in men compared to women at both tests. There were also positive correlations between AUC_i at the physical and psychosocial stress tests for both ACTH and cortisol.

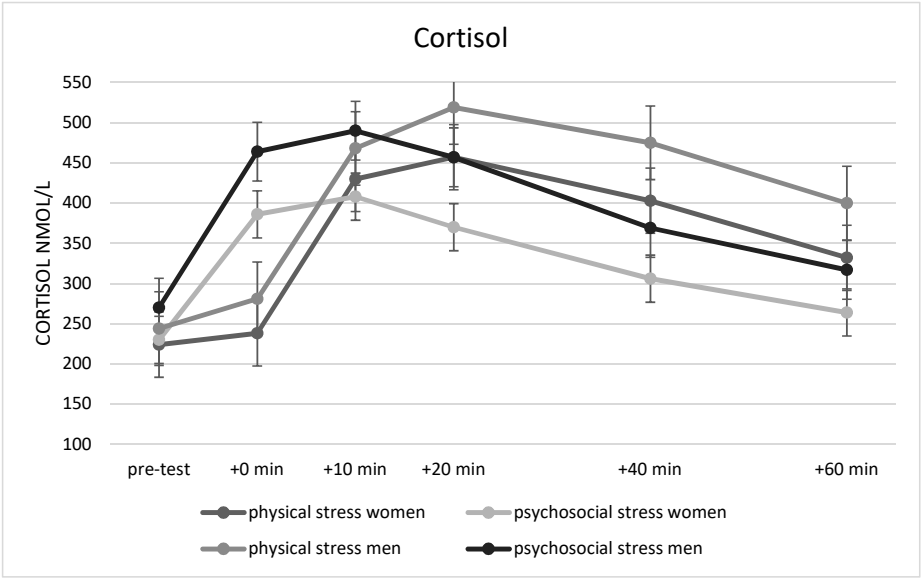
In the analyses of percental reactivity, autonomic variables showed significant main effects for test, with lower reactivity at the psychosocial stress test compared to the physical stress test for HR, and higher reactivity for SBP and DBP. Sex differences were seen in SBP, with women showing greater reactivity than men at the psychosocial stress test.

In the analyses of relationships between physiological response and perceived stress at the psychosocial stress test, no correlations were seen for any of the variables, regardless of whether high or low stress had been reported.

Figure 5.

Response curves for women and men at the physical and the psychosocial stress tests.





Paper III

The results from paper III present the main results from the RCT, on the effect of exercise training on physiological responses to acute psychosocial stress.

Compliance with the protocol varied considerably among participants in the intervention group. The lowest acceptable level was set to 26 exercise training sessions during the intervention period, which excluded 22 participants in the adherence-to-protocol analyses. Among the remaining participants, the mean number of sessions was 45 out of a possible 78.

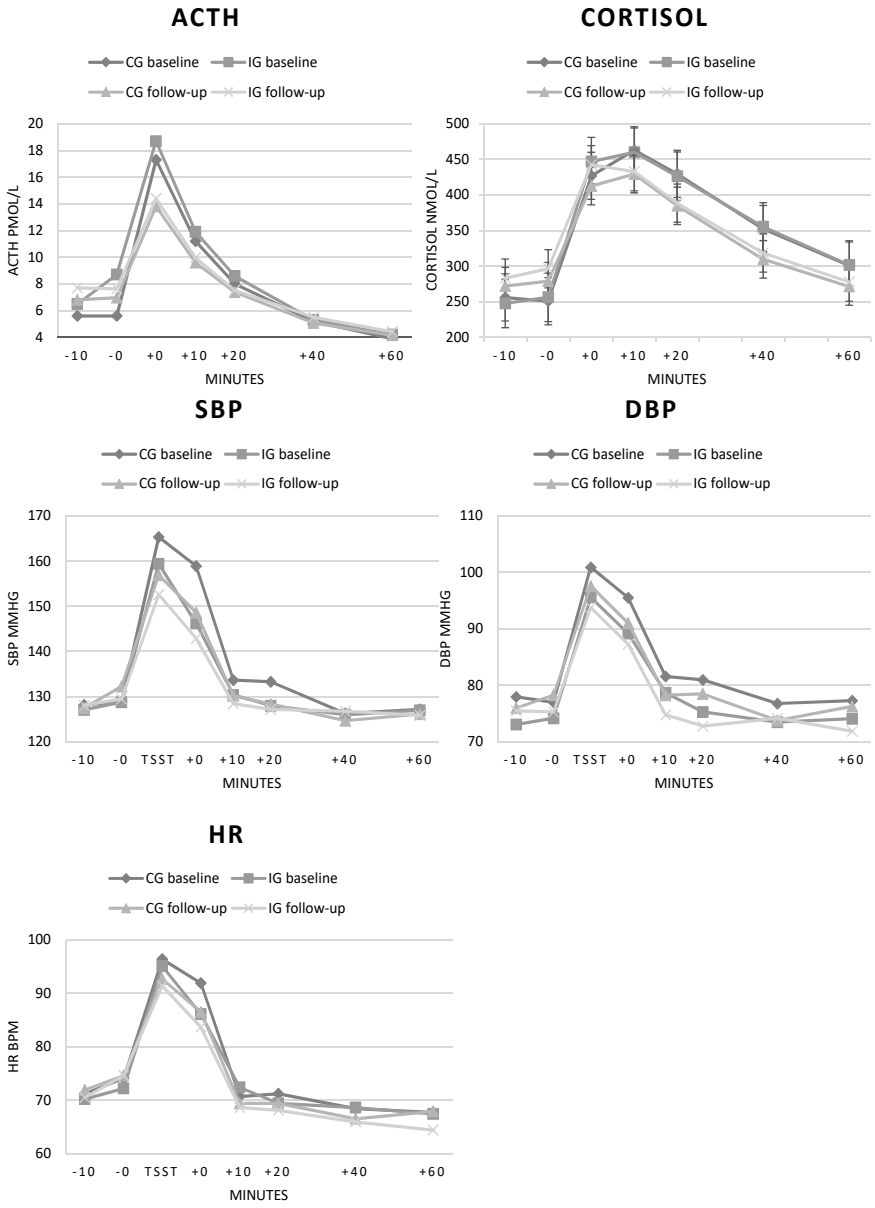
The mean level of aerobic capacity increased significantly in the intervention group (9.4 %) from baseline to follow-up. The increase did not change after exclusion of non-compliers. The mean time-to-exhaustion increased by 11 %, and when excluding non-compliers, the mean change was 9.5 %. Participants in the control group decreased their mean aerobic capacity and mean time-to-exhaustion (-3 % and -0.7 % respectively).

Both the intervention and the control group showed attenuated physiological responses to the stress test at follow-up, indicating habituations to the test or the test situation (see response curves in figure 6). ACTH and cortisol AUC_i showed decreased values for both groups, and the mixed between-within subjects ANOVA resulted in significant effects for time, but no group differences were seen at follow-up. For autonomic responses, no differences could be detected between the groups at follow-up.

There were no correlations between number of training sessions during the intervention and physiological response to the psychosocial stress test.

Figure 6.

Response curves for ACTH, cortisol, systolic and diastolic blood pressure and heart rate for the Trier Social Stress Test at baseline and the six-month follow-up



ACTH: adrenocorticotropic hormone, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate

Paper IV

In paper IV, the main focus was on DHEA and DHEA-S response to acute psychosocial stress and the potential relationship to aerobic capacity among women and men. Also, the catabolic/anabolic balance was analysed between cortisol and DHEA and DHEA-S, and the effect of age in the response to acute psychosocial stress.

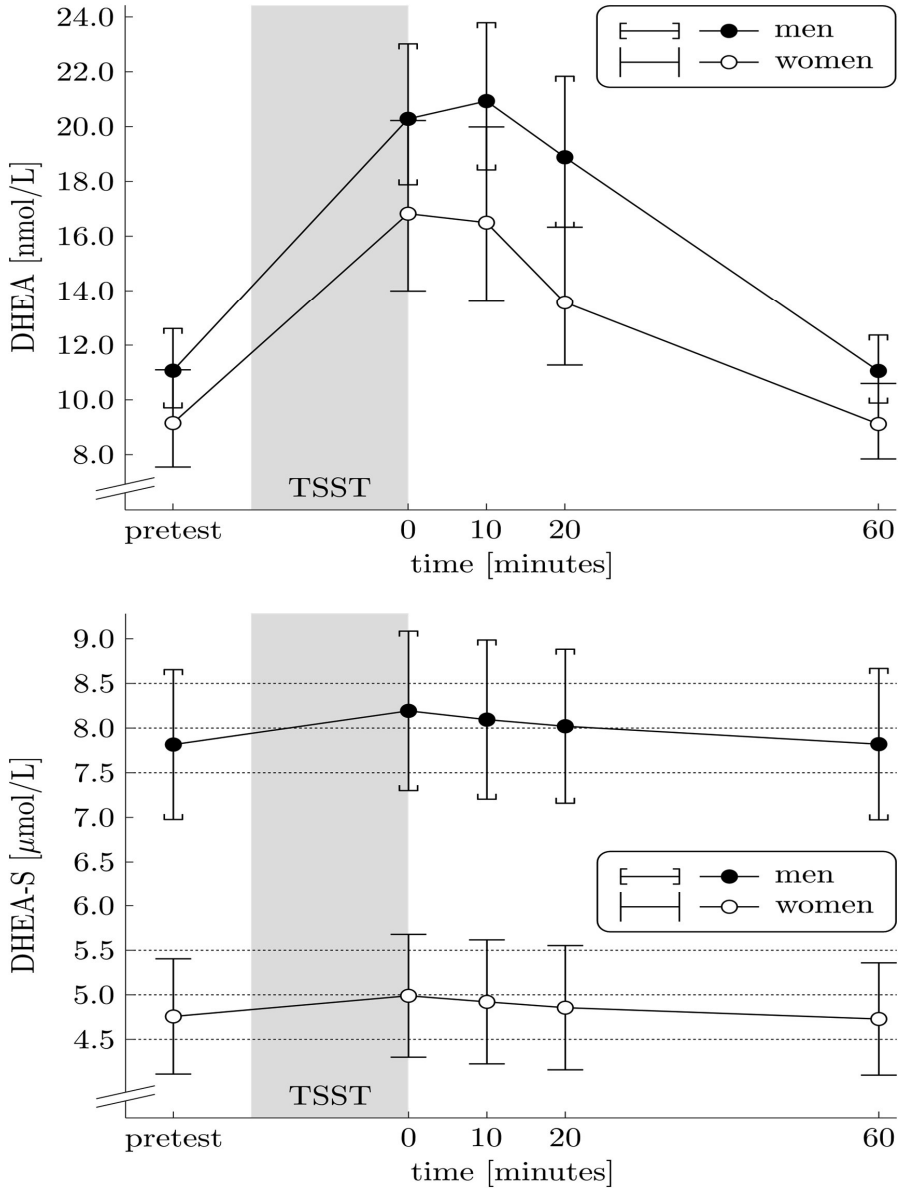
Both DHEA, DHEA-S and the cortisol/DHEA ratio increased significantly following the psychosocial stress test, with DHEA increasing on average 117 % for women and 120 % for men (see response curves in figure 7). Four individuals responded either negatively or not all in DHEA. The mean increase in DHEA-S was 10 % for women and 8 % for men. Negative responses were seen in DHEA-S for seven individuals, and six participants showed neither a positive nor a negative response to the stress test. The only variable that did not increase in response to the stress test was the cortisol/DHEA-S ratio.

Pre-test levels of DHEA and DHEA-S did not show any correlation to level of aerobic capacity. Nor did the magnitude in response of DHEA, DHEA-S, cortisol/DHEA ratio and cortisol/DHEA-S ratio to acute psychosocial stress show any significant correlations to aerobic capacity.

The response in DHEA was negatively correlated with age, but significant correlations were seen for DHEA-S, cortisol/DHEA ratio and cortisol/DHEA-S ratio and age.

Figure 7.

Response curves of DHEA and DHEA-S at the psychosocial stress test



DHEA: dehydroepiandrosterone, DHEA-S: Dehydroepiandrosterone sulphate, TSST: Trier Social Stress Test

Additional analyses

No correlations were seen between aerobic capacity and HPA-axis responses to the psychosocial stress test (ACTH: $t = 0.04$, $p = 0.682$, cortisol: $t = -0.13$, $p = 0.184$). For autonomic variables, a negative correlation was found for HR ($t = -0.21$, $p = 0.037$), but no correlations were seen for blood pressure (SBP: $p = -0.07$, $p = 0.502$, DBP: $t = 0.18$, $p = 0.067$)

Discussion

This thesis presents results from an RCT evaluating effects of aerobic capacity and exercise training on responses to acute physical and psychosocial stress. The main findings were that the six-month exercise training intervention increased time-to-exhaustion and aerobic capacity, but no effect was found on the physiological response to acute psychosocial stress. Hormonal variables (ACTH, cortisol, DHEA and DHEA-S) as well as autonomic variables (systolic and diastolic blood pressure and heart rate) increased following both acute physical and psychosocial stress, showing that the physiological systems did react to the stressful situations. However, the correlations between the physiological responses to physical and psychosocial stress were weak. Unfortunately, methodological issues hampered the interpretation of results. These and other findings will be discussed below.

Cross-sectional findings

Three of the papers included in this thesis presented cross-sectional data (papers I, II and IV). Data from baseline assessments was used to study physiological responses to acute stress and to analyse relationships and also to examine methodological issues that arose in this study.

Physiological responses to acute stress

Acute physical and psychosocial stress resulted in significantly increased mean values from pre-test to peak in both HPA-axis, DHEA, DHEA-S and ANS variables. This was expected, given that the participants were healthy and that the physiological systems, which are meant to react to acute stress, operate satisfactorily (68). The reactivity in ACTH, cortisol and heart rate was greater at the physical stress test, whereas reactivity in systolic and diastolic blood pressure was higher at the psychosocial stress test, which was also expected. The differences may partly be due to the fact that the acute psychosocial stress test entails less muscular activity than the physical stress test and thus requires a lower grade of metabolic actions and puts a higher demand on the heart for circulation of blood (69). However, the peak values for ACTH at the

psychosocial stress test might be incorrect. It was found that the true peak probably occurred during the test, when no samples were taken. Cortisol peaks with a 10-15 minute delay in relation to ACTH (70), and the post-test cortisol values indicated that peak in ACTH was plausibly reached before the first post-test sample. Because no blood samples were taken during the test, we do not know when the peak occurred and consequently not the actual magnitude of the peak value.

An interesting finding was that several individuals showed no or even negative responses to the psychosocial stress test in ACTH, cortisol, DHEA and/or DHEA-S. One plausible explanation is that these individuals were stressed already when they arrived at the lab. Only a short rest was applied before the test started. If the stress systems were activated before the test, there was no time to recover from that stressor before the TSST. However, the negative responses were also seen for ACTH and cortisol at the physical stress test, where the participants had at least one hour of rest before the test started. Another explanation could be that just the expectation of the tests as something unknown or unpleasant was enough to cause a stress reaction and start a process in the stress systems. In both cases, pre-test values would be heightened, and no or only small changes in the outcome measures would be detectable. However, an absence of cortisol response in some individuals has also been found in previous studies, showing 20-30 % non-responders in salivary cortisol, to the TSST (71). An earlier study found that cortisol non-responders were more likely to be smokers and/or females (72), but no such connections were seen in our study. Concerning DHEA and DHEA-S, not many studies can be found presenting data on responses to acute psychosocial stress, and only one shows that not all participants responded with an increase; in a study of young males, 30 % of the participants showed some variations in DHEA level after psychosocial stress, but there was no clear increase (73). Individual variations might be one explanation, but these variations may be caused by numerous underlying factors. The HPA-axis has been thoroughly studied primarily in terms of different aspects of responses to acute stress. Results from earlier studies have shown that experiences from childhood may impact the response to stress later in life (74). Also, an individual who has had a negative experience in a job interview will likely respond differently to a stress test that includes an interview-like situation compared to one who has had a good experience (19). Another study showed that one night of sleep deprivation leads to elevated pre-test cortisol levels and blunted cortisol reactivity in

response to a TSST (75). These are factors that are not easy to control for and that might affect results markedly.

A positive correlation was seen between AUC_i at the physical and psychosocial stress tests for cortisol. That is, individuals showing a strong cortisol response to the physical stress test also responded strongly to the psychosocial stress test, although the time point for reaching peak differed between the tests. This might indicate that in a healthy individual with well-functioning stress systems, the body reacts similarly independent of the origin of the stressor. It also indicates that the large inter-individual differences in hormonal response pattern are not necessarily problematic, but just point towards individual variances. For autonomic responses, no correlations were seen in reactivity between physical and psychosocial stress. It might depend on the differences in the system's response times, with the HPA-axis reacting within minutes while the ANS responds in a few seconds.

Perceived stress

No correlations were seen between perceived stress and the physiological response to acute psychosocial stress. The mental aspect of the experience thus does not seem to be related to the actual response, which is in line with a recent study by Ali et al. (76). They induced a pharmacological suppression of physiological responses in healthy women and men before a psychosocial stress test. Despite the inhibited stress systems, the participants in the intervention and the control groups experienced the stress test as equally stressful.

Campbell and Ehlert reported in a review that only one-fourth of the included studies found associations between the physiological and emotional responses to the TSST (61). Many factors are involved and affect each system, influencing the outcomes and the results. As examples they mention aspects of assessment, where both timing of assessments and the tools used to assess might affect the outcome measure. Another important factor is the psychological part, affecting emotional regulation as well as motivational engagement with the test situation. Finally, they also mention the physiological aspects of the response, taking into account the individual characteristics of the stress systems.

Associations between aerobic capacity, DHEA and DHEA-S

In paper IV, correlations between aerobic capacity and pre-test levels of DHEA and DHEA-S, as well as reactivity of these hormones to acute psychosocial stress, were studied. The analysis did not show any correlations with neither baseline levels nor reactivity in DHEA or DHEA-S to the psychosocial stress test. It can be argued that participants included in the study reported themselves as untrained at screening and that the range of aerobic capacity would be too small. It turned out, however, that levels of aerobic capacity were higher than expected, with mean values corresponding to normal levels in the general population. The span ranged from 20.4 to 45.1 mL/kg/min for women and from 24.0 to 56.6 mL/kg/min for men, showing an acceptable range for analyses of correlation, although a larger range would have been preferable. Only two previous studies have been found that examine the relation between aerobic capacity and basal levels of DHEA and DHEA-S (77, 78). One of those studied premenopausal women (range in VO_2 peak: 23.8-50.1, mean 39.5) (78), while the other studied postmenopausal women (range in VO_2 peak: 33.3-56.4, mean 47 mL/kg/min) (77). Neither of the studies found any correlation between DHEA and aerobic capacity, although a greater range in VO_2 peak was observed compared to our study. The hypothesis in paper IV was that individuals with a higher aerobic capacity would also show higher pre-test levels and higher production capacity of DHEA and DHEA-S in response to acute psychosocial stress. Both are considered anabolic hormones and have been proposed to have a protective role in the body (79). Since aerobic capacity and exercise training are associated with overall health and well-being (1), it would seem reasonable to suggest that there could be a connection to the health-promoting hormones DHEA and DHEA-S.

Longitudinal findings

One of the four papers included in this thesis comprised both baseline and follow-up data, presenting the results from the exercise training intervention. Due to the number of drop-outs in the intervention group, the results must be carefully interpreted but may still give some useful information.

Effects of exercise training

Paper III presented the main results from the RCT, that is, the analyses of the effects of six months of regular exercise training on physiological responses to acute psychosocial stress. Compliance in the intervention group was lower than expected, yet the aerobic capacity and time-to-exhaustion increased from baseline to follow-up, showing effects of the intervention despite a relatively large number of non-compliers (compliance will be discussed in more detail in the Methodological considerations-section).

Participants in the control group showed lower values for aerobic capacity at follow-up compared to baseline. This might be a result of reduced motivation to perform to exhaustion at the second VO_2 peak test. However, time-to-exhaustion did not change, indicating that oxygen uptake was lower, despite similar duration of the test.

Both the intervention and the control group showed reduced HPA-axis responses to the psychosocial stress test at follow-up compared to baseline, and no significant differences were seen between the groups. An adaptation seems to have occurred for both groups, which makes it difficult to interpret the results from the intervention. Previous research has found that when at least four months pass between the psychosocial stress tests, the risk of habituation to the test is small (80). Obviously, this did not seem to be true in our study. The participants were not informed that the same test would be repeated. Pre-test levels of ACTH and cortisol were higher at follow-up, indicating higher stress before the test started, maybe as a result of not knowing what to expect. However, when they realized that the follow-up test was almost the same as the one they had performed the first time, most participants responded with a lower reactivity. A blunted reactivity to the TSST was observed also in the aforementioned RCT by Klaperski et al (57), although the decrease was not as large as in our study. This points at the difficulties of repeating a stressor, and the importance of novelty when eliciting stress in laboratory settings.

Cross-stressor adaptation hypothesis

It was not possible to evaluate data from the longitudinal analyses in paper III, on the effects of the exercise training intervention, due to the assumed adaptations to the psychosocial stress test. Thus, since there are methodological limitations, the hypothesis can neither be confirmed, nor be ruled out. In fact, in paper II an association was observed between cortisol AUC_i at the physical

and psychosocial stress tests. It was shown that the response followed the same pattern, even though the physiological answer was not as strong at the psychosocial stress test as at the physical stress test. However, this association is based on cross-sectional data, which cannot be used to prove any reason to the association.

The role of aerobic capacity was also analysed, both in paper IV and in additional analyses. No correlations were seen between level of aerobic capacity and HPA-axis response. Moreover, the plausible effects of the anabolic hormones DHEA and DHEA-S did not contribute to any explanation for the hypothesis.

On the other hand, it could be observed that the adaptation to the acute psychosocial stress test resulted in attenuated responses, indicating less pressure on the responding systems. Both groups showed reduced responses to the TSST at follow-up, maybe depending on a more effective reaction, saving redundant expenses for the body. In healthy women and men, this is probably an adequate response, showing that the systems operate appropriately.

Methodological considerations

Conducting an RCT is complicated and requires extensive efforts. There are many pitfalls along the road, which are not always easy to take into account in advance. Despite rigorous planning, unexpected events often occur during a study.

One of the inclusion criteria in the ASTI study was based on decisions to include a working population of both women and men. Because the study entailed assessments of hormones, an age range of 20 to 50 years was set to diminish the risk that female participants had entered menopause. We also wanted to study a healthy population, and thus individuals with chronic diseases such as diabetes or cardiovascular disease were not included. The exclusion criteria were set to ensure that the primary the outcome measure would be correctly interpreted and due to prerequisites for the performance of a peak oxygen uptake test and an exercise training intervention. For example, individuals taking beta-blockers, psychopharmacological drugs, glucocorticoids or asthma medicine were excluded due to plausible effects on the HPA-axis- and ANS outcome measures.

Several critical methodological issues need to be highlighted. First, in this study, we used the SGPALS questionnaire to identify individuals with low

aerobic capacity. The self-assessed response alternative 1 corresponds to a sedentary life-style, and an assumption that the individual is untrained. However, the results from the VO_2 peak test showed levels of aerobic capacity that were higher than expected, corresponding to normal levels in the general population (81). Generally, self-reported physical activity levels tend to be overestimated compared to true levels (82, 83). Here, the opposite effect was probably seen. Since the invitation was directed towards untrained individuals who wanted to start to exercise regularly, respondents might have considered it more beneficial to report lower levels of physical activity. There were therefore fewer "couch potatoes" included than desired. There are reasons to believe that the most inactive individuals would not respond to an advertisement for an exercise training intervention study, and more precisely targeted information is required to reach that group.

There is evidence that health benefits are greatest when the activity level is increased from "sedentary" to "moderately active" (84). Thus, it would have been preferable to perform the VO_2 peak test on individuals before participation to ensure that only those with low aerobic capacity were included. However, this would have demanded more resources. In addition, the VO_2 peak test was used as a physical stress test, and a large battery of physiological assessments were made in connection to the test. For ethical reasons, it would not be possible to conduct the test on individuals who had not already been included and had given their written informed consent.

Second, at both baseline and follow-up, a large number of tests and assessments were performed. For every test or assessment there were risks of errors that could potentially affect the test results. Each test was associated with specific difficulties that had to be handled separately. The VO_2 peak test included several critical moments, one of which was the performance of the test protocol. If unaccustomed to the efforts of a physical test performed to exhaustion, the strain and eventual pain might be perceived as frightening, and the participant may end the test before a true peak in aerobic capacity has been reached. However, in this study values of oxygen uptake, respiratory exchange ratio and breathing frequency were controlled during the test, and the test was terminated only after reaching certain criteria (a plateau and/ or decrease in oxygen uptake, a respiratory exchange ratio above 1.1, hyperventilation and an inability to maintain the required cadence on the bicycle).

Another critical part of the VO_2 peak testing was the equipment measuring oxygen uptake. The mask used to collect the expired gases during the test had

to be very tightly fitted because a leak would have given false values of gas exchange. Also, the expired gases had to be assessed correctly, and all technical equipment had to work satisfactorily. Results from two of the tests in our study could not be used because of technical issues with the equipment.

At both the physical and the psychosocial stress tests, blood samples were collected at seven time points. For some individuals, the blood supply was not sufficient at all time points. Despite the inserted venous catheter, which in most cases facilitated the sampling, and the well experienced personnel taking the samples, it resulted in some missing data. For blood pressure and heart rate monitoring, an automatic blood pressure cuff was used, assessing continuously before, during and after the tests. However, the device was turned off during the physical test, given the technical problems with assessment during the test. Also, immediately after the test, the device was not giving accurate outcomes, resulting in many missing +0 values for autonomic responses.

After randomization, the intervention took place. The intended level of exercise training was based on frequency, time and the intensity needed to plausibly affect the physiological systems (85). Considering the relatively untrained population included in this study, the exercise level was set rather high. Although theoretically motivated to start regular exercise training, most of the participants who were randomized to intervention group found the practical implementation challenging. The compliance was lower than expected, resulting in a decreased limit for what was counted as compliance. From the initial level of three times per week, 45-60 minutes per session, we decided to approve participants who exercised for at least two sessions per week, at least 45 minutes per session, in at least half of the intervention period. This decision limited the number of drop-outs but also weakened the results from the adherence to protocol analyses.

The weak compliance illustrates the efforts required to bring about behavioural changes. Although participants were well aware of the positive effects of exercise training and were instructed on how to proceed, it was difficult for them to start and maintain the new life-style. They were encouraged to increase the activity level stepwise in order to adapt both physically and mentally, starting at two times per week with a 30-minute duration. However, three times per week was a tough goal for many participants. Despite having contact with a coach to discuss obstacles connected to exercise training, the participants struggled with compliance. Unfortunately, the coaching personnel changed several times during the implementation of the study, interrupting the

continuity of the coaching. Additionally, to objectively measure frequency, duration and heart rate during the exercise training sessions, participants wore a pulse watch. As it turned out, there were some unexpected problems with handling the watches, which resulted in some missing data from the exercise interventions. In the control group, no problems with compliance were seen. Only one individual reported disrupted participation due to unwillingness to be a part of the control group.

The next critical point was associated with the follow-up assessments. It seems that among participants in the control group, the motivation to go through somewhat unpleasant testing, without having performed any activity to improve the results, was low. The compensation (one-year free access to a gym) was perhaps not sufficiently attractive. A second follow-up for the control group, to measure physiological improvements after increased exercise training, might have been more tempting for participants in this group.

Ethical considerations

All participation in the study was voluntary, and the participants were informed of their right to withdraw their participation at any time without stating a reason. However, some aspects need to be discussed in an ethical perspective.

It is primarily the two stress tests that need to be highlighted. The physical stress test, for example, was demanding and not only physically. For the included individuals, who were not accustomed to maximal testing and who, in addition, were required to wear an uncomfortable respiratory mask, it was common to experience the situation as unpleasant. Also, pushing the body to maximal effort is related to pain and discomfort when legs hurt and the breathing frequency is high, even for a well-trained athlete. Another ethical aspect is the exposure of participants to acute psychosocial stress. As part of the test, the participants were met with no form of response from the committee, which some of the participants experienced as unpleasant. Normally, participants are debriefed and informed about the false set-ups directly after the test. Since a similar test was to be used at follow-up, however, it was not possible to debrief the participants at baseline.

One important consideration of ethical aspects when conducting an exercise intervention study including a non-exercising control group, is the appropriateness of instructing untrained individuals, who were motivated to

start exercise, to refrain from increasing their level of physical activity. However, taking into account the non-training period preceding inclusion in the study, which was several years for many of the participants, six months is not a very long time to delay the start of exercise training. After the follow-up, all participants in the control group were offered a motivational group meeting and received 12 months of access to a fitness establishment.

Implications for future research

Based on lessons learned from performing the RCT, several thoughts about future research emerge. One of the most important aspects concerns the need for greater control of the intervention, starting with the inclusion of supervised exercise training sessions. It will require considerable resources, but maybe it is worth the cost to potentially be able to secure more complete and reliable data. It is also important to include the intended target group, which requires more extensive testing before inclusion. However, ethical questions must be taken into consideration that could potentially prohibit such procedures. The type of psychosocial stress test must be carefully considered to avoid the risk of adaptations.

This research field has no shortage of studies. On the contrary, many researchers have tried to explore the various possible perspectives, yet no consensus has been reached. The great variability in study designs and methods is a problem. The field is in need of clear guidelines to control for differences and facilitate comparisons. For example, intervention studies should use equal methods to evaluate effects of the intervention, and similar protocols for assessments of outcome measures. On the other side, individual variances are not easy to adjust for even in well-designed studies. Additionally, in every-day life variations are even larger, and clear results from laboratory testing might not be generalizable to real life. Maybe it is time to ask whether it is meaningful to measure specific hormones in different situations without controlling for all aspects. The next question would be: what are the benefits from a strictly regulated and standardized study that is not anchored in reality? Other aspects may be more interesting, for example, the experience of stress, or finding the individuals who are at risk of developing long-term stress in the future. Also, more focus should be on health-promoting aspects such as the anabolic hormones, and on finding beneficial keys to health rather than continuing to focus on factors that are deleterious to us.

Conclusions

Exercise training is important for overall health and wellbeing. High levels of aerobic capacity are associated with a lower risk of several diseases, including stress-related diseases. This thesis has studied the cross-stressor adaptation hypothesis, which presents a theory of one possible mechanism behind the positive effects of exercise training in stress-related illness. Unfortunately, methodological shortcomings obstructed analyses of the effect of the exercise training intervention on physiological responses to acute psychosocial stress. However, cross-sectional analyses of the correlations between aerobic capacity and hormonal responses to acute stress found no associations and thus could not confirm the theory. Neither did the subjective perception of stress at the psychosocial stress test correlate with the actual physiological response.

A more unexpected finding from the included papers was the extent of inter-individual differences seen in response to acute stress. Many factors seem to affect the reaction, making it difficult to control for all of them. The hormonal system is highly complex. We know it is essential for survival and that daily life without a well-functioning system would be challenging. In healthy individuals, HPA-axis and ANS seem to react adequately, independent of level of aerobic capacity. However, methodological limitations require careful interpretation of the included studies.

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Exercise training and physiological responses to acute stress: study protocol and methodological considerations of a randomised controlled trial

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ABSTRACT

Background This paper describes the protocol and methodological prerequisites for a randomised controlled exercise intervention. Selected baseline data from the study are also presented, demonstrating some methodological challenges related to exercise intervention trials. The aim of the trial was to study the effects of exercise training on physiological responses to acute psychosocial stress in untrained individuals.

Methods Individuals with a low level of physical activity were invited to participate in an exercise intervention lasting for 6 months. A total of 119 participants were included and went through a peak oxygen uptake test and a psychosocial stress test at baseline. Adrenocorticotropic hormone (ACTH) and cortisol were measured in connection to the stress test to identify the physiological response.

Results Almost 90% of the participants reported themselves as untrained, but results from the objectively measured oxygen uptake did not seem to correspond to the reported sedentary lifestyle. The primary outcome measures at baseline varied between individuals. The mean change from pre-test to peak value was 214% for ACTH and 94% for cortisol. Of these, 13 individuals did not respond in ACTH and/or and cortisol.

Discussion Supposedly untrained individuals seeking participation in an exercise intervention might not be as untrained as they report, a methodological consideration of importance when evaluating the effects of training. Another important consideration is related to the primary outcome measure, which should be measurable and possible to affect. Absence of reaction at baseline means that changes can only be detected as an increased reaction.

What are the new findings?

- The target population of an exercise intervention might be difficult to reach particularly regarding the inclusion criteria stating that the participants should be untrained.
- The individual variability regarding the physiological response to acute stress is large. Some individuals actually do not show any response, which will challenge the interpretations of a randomised controlled trial with the aim of studying physiological response to acute stress.

How might it impact on clinical practice?

- When planning a randomised controlled exercise intervention trial, fitness levels should be objectively measured.
- The primary outcome measure should be measurable and possibility of detecting changes over time should be present.

BACKGROUND

Exercise training has been shown to reduce the risk of several lifestyle-related diseases and to improve mood, well-being and physical performance.[1–4] The preventive effects of exercise training regarding depression and other mental health conditions are also well documented.[5 6] Thus, many symptoms related to psychosocial stress can be prevented with exercise training, and exercise has been suggested as an important general buffer for stress.[7 8]

Knowledge of the mechanisms behind the plausible stress-buffering effects of exercise is, however, still limited. The most widely studied possible physiological mechanism is the so-called cross-stressor adaptation hypothesis described by Sothmann *et al* in 1996.[9] The acute physiological response to exercise and psychological stress share the similarities of a potent increase in hypothalamic–pituitary–adrenocortical (HPA) responses.[10–12] Exercise training leads to adaptations with regard to hormonal responses during acute exercise in trained individuals.[13] The theory of cross-stressor adaptation proposes that similar adaptations are also seen in trained individuals during acute psychosocial stress.[9] The adaptations are suggested to occur partly on brain level, by regulations of neuroendocrine

functions, and partly on end-organ level, by feedback modifications and adaptations in the organs.

Previous research with regard to the cross-stressor adaptation hypothesis is, however, not consistent. The majority of existing studies in this field are of cross-sectional design. As far as we know, only one randomised controlled trial (RCT) has been conducted by Klaperski *et al*,[14] which is not surprising given the many methodological challenges related to conducting an RCT. For example, the response in the primary outcome measure must be measurable and changeable in all individuals included in the study. Another prerequisite often applied for exercise interventions is an inclusion criterion that assume the individual to be physically inactive at baseline. This might result in challenges connected to the inclusion of the intended population. However, the advantages of an RCT are several compared with a cross-sectional study, and the results from a well-performed RCT is usually more solid than from cross-sectional studies. In the RCT by Klaperski *et al*,[14] the 12-week exercise training intervention resulted in significantly decreased responses to the laboratory stressor, compared with the control group, confirming the cross-stressor adaptation hypothesis as valid.

The main aim of this paper is to present an RCT protocol and discuss two important methodological issues related to the conduction of an RCT, by presenting selected baseline results from the trial *Acute Stress and Exercise Training Intervention* (NCT02051127). The study is designed to investigate the effects of exercise training on the neuroendocrine (HPA -axis) responses to acute laboratory psychosocial stress in untrained individuals. The hypothesis is that the intervention will lead to blunted HPA-axis responses to the stress test.

METHODS/DESIGN

A 6-month exercise training intervention study was performed at the Institute of Stress Medicine (ISM) in Gothenburg, Sweden. The study was a two-armed RCT with equal allocation of participants to an intervention or a control group. All participants went through oxygen uptake tests and psychosocial stress tests at both baseline and follow-up. The inclusion of participants was running from 2013 to 2016. Information about the study was distributed by advertisement in two major newspapers in the district around Gothenburg in western Sweden, and through noticeboards and social media.

Study population and screening

Participants were initially screened using an emailed computer-based screening questionnaire, which the participants filled out and returned to ISM. Individuals fulfilling the inclusion criteria (see box 1) were booked for a physical screening at the ISM. This included blood tests, 12-lead resting ECG and collection of anthropometric data. Individuals who were not excluded due to any of the exclusion criteria (see box 1) were booked for baseline measurements, including a peak oxygen uptake (VO_2 peak) test and a psychosocial stress test (see below for description of baseline measures). After enrolment (see figure 1), 119 participants (58 women and 61 men) completed the baseline tests.

Box 1 Inclusion and exclusion criteria for the randomised controlled trial

Inclusion criteria
- Age 20–50years, essentially healthy (does not have diabetes, cardiovascular disease or mental illness).
- No exercise training within the last year and a self-rated level of physical activity equal to one in the Saltin Grimby Physical Activity Level Scale (for details, see Rödjer *et al*[29]).
- Working or studying at least 50%.

Exclusion criteria
- Glucose level of≥7mmol/L and HbA1c≥48mmol/L.
- Diverge resting ECG.
- Blood pressure>140/90mm Hg.
- Anaemia (Hb<120g/L for women, <130g/L for men).
- BMI<18.5or>35kg/m^2.
- Medication with beta-blockers, psychopharmacological drugs, glucocorticoids or asthma medicine.
- Unable to exercise at a relatively high intensity.

Study procedures

The baseline measurements were conducted in two sessions with 1 week in between, and all tests were performed between 13:00 and 15:00. The first session included a VO_2 peak test, cognitive testing and filling out questionnaires covering demographic data. The second test session included the Trier Social Stress Test (TSST) followed by the randomisation procedures, which was done with sealed envelopes and a 50/50% distribution between the groups. After 6months, follow-up measures were conducted. The procedures were exactly the same as those used when taking baseline measurements.

Peak oxygen uptake test

The VO_2 peak test was performed at the Centre for Health and Performance at the University of Gothenburg. To avoid any effects of food intake on the day of testing, all participants were served a standardised meal (around 500 kcal) containing controlled amounts of fat, protein and carbohydrates (20, 15 and 65 g, respectively) at least 2 hours before the test. After participants warmed up on the bicycle ergometer (Monark 828 E; Monark Exercise AB, Vansbro, Sweden), resistance was gradually increased, starting at 87.5 W for women and 105 W for men, increasing by 17.5 W every minute until exhaustion. Oxygen uptake was measured with the Jaeger Oxycon Pro metabolic chart (Carefusion, Hoechberg, Germany) in a mixing chamber mode, and heart rate was monitored with a pulse sensor (Polar 300 RS; Polar, Finland).

Trier Social Stress Test

The TSST is a validated and reliable test that has been shown to affect neurohormonal stress responses.[15] The

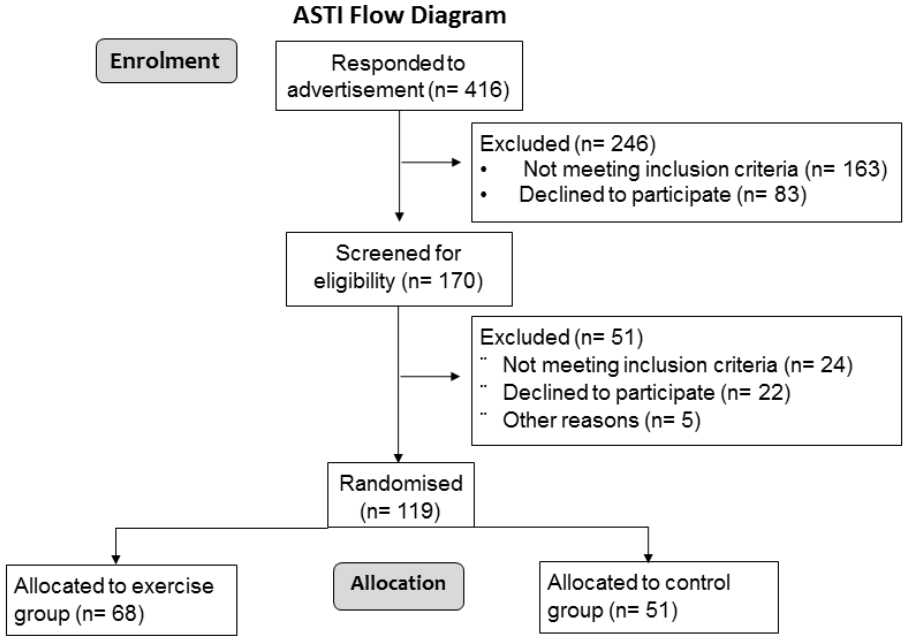

Figure 1 Flow diagram of study enrolment and intervention allocation. ATSI, Acute Stress and exercise Training Intervention.

test is based on two parts: a 5min free speech and an arithmetic task, both parts being performed in the presence of a three-person committee. The participants are falsely informed that the test is recorded to evaluate their behaviour and performance. Before participants arrived at the institute, they ingested a meal identical to that served before the physical stress test, approximately 2hours before the test. No debriefing was held after the baseline TSST since the test was repeated at the follow-up. However, after the follow-up TSST, the participants received information on the test and a short debriefing.

Exercise intervention

Participants randomised to the intervention group (IG) will be asked to start out exercise training for 6months. They will be instructed to reach an exercise level of three times per week, 45–60min during each time, reaching an average heart rate of at least 75% of peak heart rate (measured at the VO_2 peak test) 80% of the work out time. The participants will also be offered 1year of free access to a commercial fitness centre with facilities located in several places in and around the city of Gothenburg. Intensity and duration of the exercise will be monitored using a pulse watch (Garmin 210), and the data will be transferred and registered in an internet-based training log (www.funbeat.se). The log will be checked by the coach, and feedback will be offered throughout the training period. The participants will be asked to perform aerobic training of their choice, and to help them achieve the goal of regular exercise, four sessions of Motivational Interviewing will be offered to each participant. The sessions will be led by a trained coach, and the dialogue is guided by Self-determination Theory,[16] which provides guidelines for the interviewer in the support of participants to increase their level of exercise.

Participants randomised to the control group will be instructed to continue their current level of physical activity between baseline measures and follow-up. After that, they will be encouraged to start exercising. They are offered a motivational group meeting and will receive access to the same fitness centre as the IG after the follow-up.

Outcome measures and variables

Primary outcome measures

Neuroendocrine reactions to acute psychosocial stress before and after a 6-month exercise training intervention are the main outcome measures. Adrenocorticotropic hormone (ACTH) and cortisol responses represent HPA-axis reaction.

Measurement of HPA-axis response

A total of seven samples of plasma ACTH and serum cortisol were collected during each test session. Before the tests, the participants were provided with a peripheral venous catheter in an antecubital vein (BD Venflon Pro, Becton Dickinson Infusion Therapy). To separate plasma, the tubes were cold spun at 3500 rpm for 15min and stored at −80°C until analysed. To separate serum, the tubes were spun at 20°C for 10min at 3500 rpm and stored at 6°C until analysis the day after the test. Plasma concentrations of ACTH were measured by immunoradiometric assay (limit of detection, 0.4pmol/L) (CIS bio International, Gif-sur-Yvette Cedex, France). Serum concentrations of cortisol were measured by electrochemiluminescence immunoassay (limit of detection, 0.5nmol/L) (Roche Diagnostics GmbH, Mannheim, Germany).

Secondary outcome measures

Blood pressure and heart rate before, during and after TSST were measured using an automatic blood pressure cuff (Welch Allyn, ABPM 6100), acquiring data every 5min. Current level of perceived stress during the TSST was rated with Borg CR 10 Scale of Perceived Stressfulness (13 grades from 'not at all' to 'absolute maximum'). The cognitive test performed was the CNS Vital Signs,[17] a computerised test battery comprising seven different tests widely used in previous research studying neurocognitive function.[18–20] Symptoms of anxiety and depression were evaluated with the *Hospital Anxiety and Depression Scale*.[21] The *Shirom Melamed Burnout Questionnaire* was used to assess levels of burnout,[22] and the *Patient Health Questionnaire* assessed the occurrence of somatic symptoms.[23 24] To evaluate individual strategies for coping with stress, the *Coping Inventory for Stressful Situations* questionnaire was used,[25 26] and the 14-item questionnaire *Perceived Stress Scale* was used to evaluate the participants' perceived life stress during the last month.[27]

Statistics

All randomised participants will be included in initial analyses according to the intention-to-treat procedure. Additional analyses will follow, in accordance with adherence-to-protocol (ATP) procedure where participants with a low compliance will be excluded. The continuous baseline variables age, Body Mass Index, VO_2 peak and time-to-exhaustion analyses are presented as means and SD. Group differences at baseline were analysed using independent samples t-tests. ACTH was not normally distributed, but logarithmic transformation enabled the use of a parametric analysis. The categorical variable sex was analysed for group differences using a χ^2 test.

The magnitude of response in ACTH and cortisol was calculated by subtracting the pre-test value from the peak value. The per cent change was calculated by dividing the response value with the pre-test value.

A sample size calculation for the main outcome measure cortisol showed that 39 subjects in each group were needed to be able to detect an effect size Cohen's f=0.25, with power≥0.80and α=0.05 (G*power 3.1). Taking into account that a number of drop-outs would occur, the goal was to include 50 subjects in each group.

RESULTS

Physiological reactions to acute psychosocial stress

Basic characteristics of the included participants are shown in table 1. Mean ACTH and cortisol levels at all seven time points are presented in figure 2. The mean response in ACTH from pre-test to peak value was a 214% increase (range −42% to 1860%). For cortisol, the mean response was a 94% increase, ranging from −20% to 293%. A decrease was seen in 13 individuals for either ACTH or cortisol, and one individual showed decreased values in both hormones.

Self-reported physical activity level and oxygen uptake

Self-reported levels of physical activity among the responders to the screening questionnaire and among participants finally included in the study are shown in table 2. The mean baseline VO_2 peak values for different age groups among included participants are shown in table 3.

Table 1 Basic characteristics of the participants at baseline

	Control group			Intervention group		
	n	Mean	SD	n	Mean	SD
Age (years)	52	40	7.8	67	38	7.2
sex (n ♀/ ♂)	52	33/34		67	25/27	
BMI (kg/m)	52	25.3	4.2	67	24.8	3.3
VO_{22} peak (mL kg^{-1} min^{-1})	48	32.9	6.01	61	34.2	7.1
TTE (min:sec)	52	7:22	2:23	67	7:39	2:19

BMI, Body Mass Index; TTE, time to exhaustion;♂, men;♀, women.

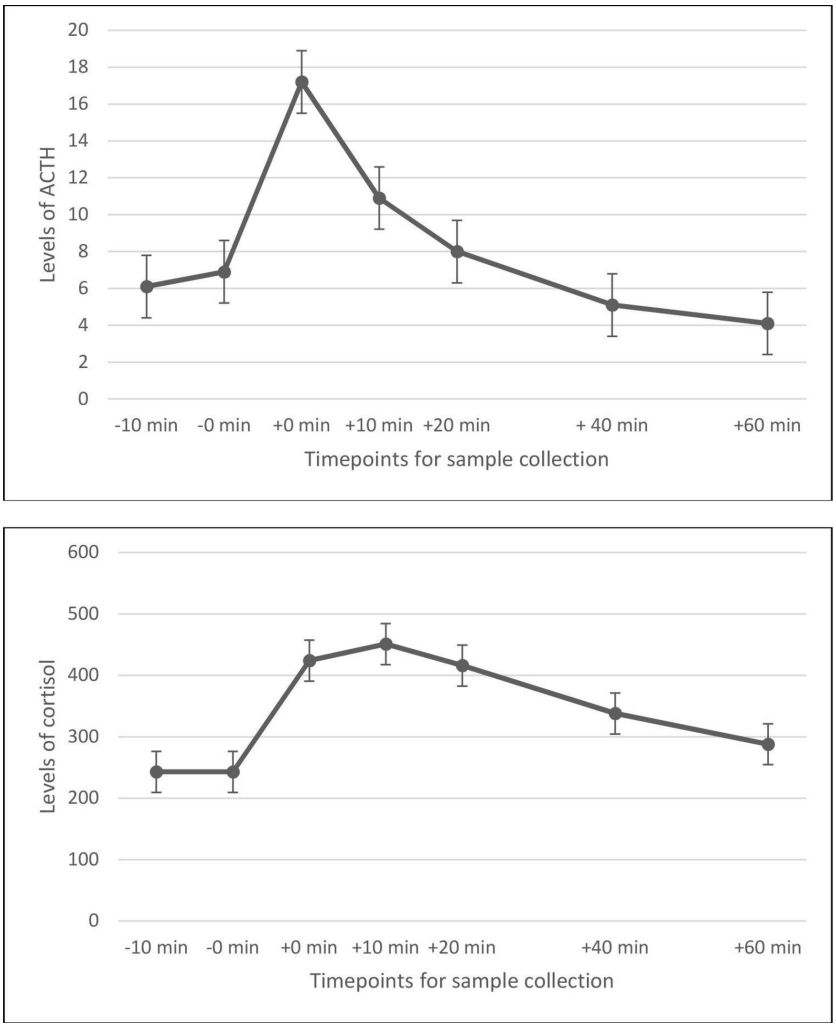

Figure 2 Response of adrenocorticotropic hormone (ACTH) and cortisol to the psychosocial stress test.

DISCUSSION

Protocol

Here, we present the protocol of an exercise intervention with the aim of investigating the effects of exercise training on neuroendocrine and autonomic responses to acute laboratory psychosocial stress in untrained individuals.

Table 2 Reported levels of physical activity at screening and among included participants

Responders	n	S n (%)	LPA n (%)	MVPA n (%)
Answered the screening questionnaire	234	189(76.5 %)	47(20 %)	8(3.5 %)
Included in the study	119	106(89 %)	13(11 %)	

LPA, light physical activity; MVPA, moderate to vigorous physical activity; S, mostly sedentary.

Table 3 Peak oxygen uptake values for different age group

	$VO_2$2 peak (mL kg^{-1} min^{-1})			
Age group	n	♀ (SD)	n	♂ (SD)
20–29	11	36.0(8.7)	5	37.3(6.1)
30–39	19	30.5(8.5)	25	38.5(7.5)
40–50	28	29.4(4.7)	31	34.9(5.5)

♂, men; ♀, women.

The results of the study will add to the knowledge of the mechanisms behind the plausible stress-buffering effects of exercise,which is still limited. The 'cross-stressor adaptation hypothesis' will be tested in an RCT design.[9] The theory of cross-stressor adaptation suggests that adaptation will be seen regarding the response of the HPA axis and the autonomic nervous system during acute psychosocial stress following exercise training. Since previous research is not consistent and most studies in the field are of cross-sectional design, this trial will hopefully add valuable knowledge to the field.

Baseline results

Conducting an RCT entails a number of methodological challenges. The most prominent is the presence of a valid and stable primary outcome measure. In this paper, we present baseline results of the HPA-axis response to acute laboratory stress, showing that the reaction varies considerably between individuals. An increase in ACTH and cortisol was seen for the majority of the individuals, but the variation was large. In fact, decreased levels were seen in ACTH and/or cortisol in response to acute stress in 13 individuals. The reasons for this result may be several. The most plausible is that the individuals were already affected by stress when they arrived at the laboratory. In these cases, the peak in stress hormones was probably reached before the test started, resulting in a decrease in the levels at the stress test. Another explanation is that the stress stimulus was too weak to cause a physiological response in some subjects, even though the instrument is validated and normally shows a clear reaction in most individuals.[28] These varying physiological responses to acute stress among the participants constitute methodological challenge. A precondition for all intervention studies is that the primary outcome measure is present and that plausible changes after the intervention are measurable. Since the hypothesis of this study is that a decreased reaction of ACTH and/or cortisol would be seen following the exercise training intervention, this will not be possible to detect in individuals not showing a reaction to the stress test at baseline. As far as we know, this issue is rarely raised, and the large individual variation in the reaction pattern between individuals could partly explain the large variation seen in different previously published studies. This so-called floor effect of an outcome measure is often considered when analysing questionnaires but is less commonly considered in studies of biological reactions. An important methodological consideration is whether these individuals should be removed from ATP analyses.

Who seek participation to the study?

Further methodological considerations are related to the participants who seek participation in a randomised controlled intervention trial. Several inclusion and exclusion criteria were set, some of which were easy to assess with objective measures whereas other criteria relied on self-reports from the participants.[29] In the advertisement for the study, we called for individuals who were untrained and had not been regularly physically active during the last year. Nevertheless, 20% of the respondents to the screening questionnaire reported light physical activity at least 4hours per week, and another 3.5% reported exercise training at least 2 to 3hours per week. In the final study population, the individuals reporting regular exercise training were excluded, but due to difficulties in recruiting participants, 11% of the sample reported a light physical activity level in the Saltin Grimby Physical Activity Level Scale. Still, the majority (89 %) of the final sample reported themselves as sedentary at screening. This, however, does not seem to be reflected by their oxygen uptake. Compared with reference values for VO_2 peak in the general population,[30] male participants in our study showed an average oxygen uptake, and women showed an oxygen uptake in the upper regions of reference values. Neither men nor women included in the study could thus be defined as 'untrained'. These results indicate that we have not reached the intended target group for the study. Importantly, there is a hereditary component of aerobic fitness (VO_2 peak) showing that aerobic fitness and physical activity level do not always correspond.[31] Apparently, we reached individuals reporting a sedentary lifestyle but with an oxygen uptake corresponding to a higher activity level.

Limitations

Some potential limitations are identified. One of them is related to the stress test. When repeating the test, there is risk for habituation to the test situation. However, previous research has shown that when at least 4months pass between the tests, the risk of habituation is small.[32] Another potential limitation is related to the exercise intervention. The participants are supposed to exercise on their own, three times per week. Here, the motivation to start out exercise might be an obstacle, but by offering individual motivational dialogues, the initial difficulties hopefully will be facilitated. Also, due to practical reasons, the possibility to blind is restricted, which might be seen as a limitation.

CONCLUSION

Here, we present an RCT protocol and discuss some important methodological issues regarding conducting an intervention trial. One challenge is to reach the target population, in this study untrained individuals. However, supposedly untrained individuals seeking participation in an exercise intervention might not be as untrained as they report themselves to be. Another important methodological consideration is to ensure that the outcome measures of the study are valid and stable over time. Individual physiological reactions to acute stress vary considerably, and some individuals do not react at all to acute stress. The variability regarding the physiological measures are rarely discussed, and in this case the primary outcome measure of the trial can only be affected in one direction (increase) in several of the participants. We conclude

that outcome measures of RCTs need to be thoroughly evaluated before the onset of the intervention to ensure a true outcome of the intervention.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the Regional Ethical Review Board, Gothenburg, Sweden, conducted according to the 1964 Declaration of Helsinki, number 917-12, and registered as a randomised controlled trial at ClinicalTrials.gov (ID no. NCT0251127).

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II

Physiological responses to acute physical and psychosocial stress in healthy women and men

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Background

To manage stress in daily life, we are provided with several stress physiological systems that respond to environmental and social changes. The two most studied are the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS). Acute stress exposure can be defined as both psychosocial and physical. It has been suggested that there might be a connection between these types of stress, but previous research has shown diverging results. Therefore, the aim of this study was to study patterns of response to physical and psychosocial stress, and whether they were correlated or not. We also wanted to study whether the physiological response to acute psychosocial stress was associated to the perception of stress.

Methods

In this cross-sectional study, healthy women and men (n = 119) went through a peak oxygen uptake test (physical stress) and the Trier Social Stress Test (psychosocial stress). In connection to both tests HPA-axis and ANS responses were assessed. Area under the curve with respect to increase (AUC_i), pre-test-, peak- and lowest values after the tests were identified and compared. Perceived stress was reported directly after the psychosocial stress test, using a modified version of the Borg CR 10 scale of perceived exertion.

Results

For cortisol AUC_i a correlation was seen between the physical and psychosocial stress tests. No correlations between the tests were seen for reactivity or recovery for ANS variables. Other main findings were that the physiological peak reaction to stress varied between individuals. Furthermore, no associations were found between perceived stress and physiological responses.

Conclusions

The physiological reactions to acute stress are heterogenous in several different aspects. A general relationship between acute physical and psychosocial stress reactions were not seen and the peak responses to stress occurred at different time points for different individuals. Additionally, no correlations were found between perceived stress and physiological responses to acute psychosocial stress. The lack of correlation between physical and psychosocial stress and the individual variation of the stress responses is an important knowledge for future research studying acute stress reactions.

Introduction

The acute stress reaction is the living organism's natural response to challenges. Mobilization of adequate responses to an acute stressor and timely cessation of the stress response is critical for survival. The acute stress response has been suggested to play a role in the development of both cardiovascular and metabolic diseases (1).

In the so-called cross-stressor adaptation hypothesis (2), a preventive perspective of the plausible connection between heightened physiological stress reactivity and disease can be found. The theory is built upon the view of stress responses as general, and that attenuated physiological adaptations to an exercise stressor will be seen also in response to psychosocial stress. An early review concluded that aerobically fit individuals exhibited a lower grade of autonomic stress responses, such as heart rate and blood pressure, and subjective experience of the task compared to unfit individuals (3). However, the discrepancy between different studies within the field is large and agreement has not yet been reached whether the cross-stressor adaptation hypothesis applies to autonomic reactions (4-6). The relationship between HPA axis response and exercise training in connection to acute psychosocial stress is not as thoroughly studied as the autonomic reactions, and no firm conclusion can be drawn regarding whether exercise training and/or higher aerobic capacity is related to attenuated HPA axis response to acute psychosocial stress (7-10).

Studying acute physiological stress responses in humans is faced with several methodological challenges that could explain the discrepancy between studies within this field. An interesting aspect when studying the cross-stressor adaptation hypothesis is whether a correlation exists between the physiological reactions to physical and psychosocial stress, i.e. do the same individuals who respond with high reactivity during psychosocial stress also respond with high reactivity during physical stress? As far as we know, only one previous study has explored this, studying young males performing a Wingate test and a psychosocial stress test, and the authors could not confirm such correlations (11).

Further methodological aspects related to the plausible variation of acute stress responses are warranted. Thus, even though the acute stress response is universal regarding which hormones are affected, the inter-individual variations are large, and several authors have discussed the variation

between individuals regarding different aspects of the human stress reaction (12, 13). It is well known that stress appraisal and emotional regulation can differ considerably as well as response threshold and time to peak when measured during acute psychosocial stress (14, 15). We have recently shown that not all individuals do react physiologically to psychosocial stress and thus plausible attenuation in stress responses cannot be measured in these individuals (16). Furthermore, when plausible changes in reactivity to acute stress, including attenuation, is studied one must ensure that the reactivity has been caught within the timeframe of the study. An additional perspective of studying stress reactions is the possibility of using the perception of stress as an indirect measure of the stress reaction. Previous research regarding associations between physiological responses and psychological appraisal during acute psychosocial stress has shown inconsistent results. Some earlier studies have reported findings of correlations (17-19), while other studies have found no such relations (20, 21). A review studying the correlations between the perceived stress experience and physiological stress responses found associations only in 25 % of the included studies (14).

Within the frame of an exercise intervention study, a number of individuals underwent both acute physical (exercise performed to exhaustion) and acute psychosocial stress tests (the Trier Social Stress Test). This created an opportunity to compare the different stress reactions. Thus, the primary aim of this study was to compare the acute physiological and psychological stress reaction in healthy women and men in terms of HPA-axis response and autonomic reactions. The secondary aim was to study the relationships between physiological responses and perceived emotional stress during an acute psychosocial stress test.

Methods

The cross-sectional data presented in this study originates from baseline measures of a randomized controlled trial (RCT) implemented at the Institute of Stress Medicine in Gothenburg, Sweden, during the years 2013 to 2016. All participants went through a physical stress test and a psychosocial stress test, and similar assessments of physiological responses were performed for both tests. Detailed descriptions of the RCT has been published earlier (16).

Participants

An invitation to the study was published in two major newspapers distributed in the Gothenburg area. Interested individuals were sent a screening questionnaire containing questions of age, health, work and physical activity level. Individuals fulfilling the inclusion criteria were invited to a physical screening, checking for exclusion criteria (for inclusion- and exclusion criteria, see table 1). The number of responders to the advertisement was 416, of these, 170 individuals were invited to a physical screening at the ISM. Twenty-two individuals declined participation, and 24 individuals were excluded after the screening. Five individuals were excluded after the initial tests due to incomplete measures, resulting in the final population of 119 participants. Before entering the study, the participants gave their written informed consent to participation, and were informed of their right to withdraw their participation at any time. The study was performed in accordance with the 1964 Declaration of Helsinki, and was approved by the Regional Ethical Board, Gothenburg, Sweden, registration number 917-12.

Physical stress test

To evaluate physiological responses to acute physical stress, the participants went through a peak oxygen uptake (VO_2 peak) test on a bicycle ergometer (Monark 828 E; Monark Exercise AB, Vansbro, Sweden). The test was performed at the Center for Health and performance at the University of Gothenburg. At arrival to the test lab, the participants ingested a standardized meal containing controlled amounts of fat, carbohydrates and protein, approximately two hours before the test was scheduled to start. The participants followed a test protocol including a five-minute warm-up on the bicycle with a 50-watt (W) resistance and a cadence of 70 rates per minute (rpm). For women, the initial resistance of the test was 87.5 W, while men started at 105 W. The resistance increased by 17.5 W every minute until exhaustion. The criteria for a fulfilled VO_2 peak test was a VO_2 leveling off, hyper ventilation, a Respiratory Exchange Ratio >1.1 and/ or inability to keep the required cadence. To measure the oxygen uptake the Jaeger Oxycon Pro metabolic chart (Carefusion, Hoechberg, Germany) was used in a mixing chamber mode. Heart rate was measured with a pulse sensor (Polar 300 RS, Polar, Finland).

Psychosocial stress test

The psychosocial stress test was performed one week after the physical stress test. The test used was the Trier Social Stress Test (TSST)(22), which is commonly used when studying physiological responses to acute psychosocial stress (23). Approximately two hours before arrival to the lab the participants ingested an identical meal as was served before the physical stress test. When arriving at the lab the participants had a short rest. The test was performed individually, starting with instructions in front of a three-member committee in a test-room. The participants were instructed to present themselves as if applying for their dream job. They got five minutes to prepare for the speech in another room, and then re-entered the test room. The presentation for the job lasted for five minutes. It was followed by an arithmetic part, where the participants were asked to count down from 1687 in steps of 13 for five minutes. If the participant failed, he or she had to restart the counting. After the test the participants left the room and rested for one hour.

Assessment of HPA-axis response

HPA-axis responses to acute physical and psychosocial stress were assessed as plasma ACTH and total serum cortisol. The participants were provided with a peripheral venous catheter in an antecubital vein (BD Venflon Pro, Becton Dickison Infusion Therapy). Samples were taken at seven occasions; approximately ten minutes before start (-10), directly before start (-0), immediately after the test (+0) and further 10, 20, 40 and 60 minutes after the test to enable analysis of the hormonal peak and recovery. To separate plasma, the tubes were cold spun at 3500 rpm for 15 min and stored at −80°C until analyzed. To separate serum, the tubes were spun at 20°C for 10 min at 3500 rpm and stored at 6°C until analysis the day after the test. Plasma concentrations of ACTH were measured by immunoradiometric assay (limit of detection, 0.4pmol/L) (CIS bio International, Gif-sur-Yvette Cedex, France). Serum concentrations of cortisol were measured by electro- chemiluminescence immunoassay (limit of detection, 0.5nmol/L) (Roche Diagnostics GmbH, Mannheim, Germany).

Assessment of autonomic response

Autonomic responses (systolic and diastolic blood pressure (SBP and DBP, respectively)) and heart rate (HR) were recorded by using an automatic blood pressure cuff (Welch Allyn, ABPM 6100, USA). The devise was measuring every ten minutes during the physical stress test and every five minutes during the psychosocial stress test, from 10 minutes before the test started to 60 minutes after the test was completed. At the physical test the device was shut off during the test due to technical difficulties with measurements during strenuous physical work.

Perceived stress

Perceived stress at the psychosocial stress test was evaluated immediately after the test using an adapted version of the Borg CR 10 Scale of Perceived Exertion (24). This version, named Borg CR 10 scale of Perceived Stressfulness, includes 13 grades from "not at all" to "absolute maximum". Perceived stress data was dichotomized into one group scoring 0-4 (not perceiving the stress to be significant) and one group scoring 5-10+ (perceiving the situation to be either strongly stressful, very strong or maximum).

Data handling

Pre-test values were calculated as the mean value of the -10- and -0-minute value. Peak value was the highest value after the test and the lowest value was the lowest identified value after the peak. Percental *reactivity* was calculated by subtracting the pre-test value from the peak value and divide the difference by the pre-test value. Percental *recovery* was calculated by subtracting the lowest value from the peak value and divide the difference by the peak value. Area under the response curve with respect to increase (AUC_i) (25) was calculated for ACTH and cortisol from pre-test to 60 minutes after the test.

Statistics

Background characteristics and potential group differences were analyzed with independent samples t-tests. For non-parametric demographical data (educational level and tobacco use), Chi square tests

were used. Correlations between time points for peak value at the physical and psychosocial stress tests for ACTH and cortisol and time point for lowest value for SBP, DBP and HR were analyzed using Spearman's rank order correlation.

Cortisol AUC_i at the physical and psychosocial stress tests were also analysed with a Pearson correlation analysis. ACTH AUC_i was not normally distributed; therefore, the non-parametric Spearman's rank order correlation was used. A mixed between-within subjects ANOVA was used to analyse reactivity to and recovery from acute physical and psychosocial stress. Further, correlations between reactivity as well as recovery were analysed using Pearson's correlation analysis. The reactivity variable for ACTH was not normally distributed and thus Spearman's rank order correlation was used.

Students t-test was used to analyse the physiological reactivity between the "high stress" and "low stress" group according to perceived emotional stress.

Results

Demographic descriptions of the participants are presented in table 2.

Physiological reactions to acute physical and psychosocial stress

An increase was seen in HR, SBP and DBP during or directly after the physical and psychosocial stress tests in both women and men (figure 1 and table 3). The autonomic responses differed somewhat between sexes. Thus, the SBP reactivity showed significant main effects of sex, with women showing greater SBP responses than men. Interaction effects were seen where women had a smaller difference in reactivity in SBP between the tests compared to men. For HR, men had a greater response than women to the physical stress test, but smaller during the psychosocial stress test. Sex differences regarding recovery was seen for both SBP and DBP, with women showing a greater percental decrease than men.

When analyzing AUC_i for ACTH and cortisol in response to the different test situations, the mixed between-within subjects ANOVA for ACTH AUC_i showed significant main effects of test ($F = 74.5$, $p < 0.001$, partial eta squared = 0.413). For cortisol AUC_i, significant main effects were seen for sex (F

= 21.7, p < 0.001, partial eta squared = 0.171), with men having higher values at both tests. No effects were seen of test (F = 0.0, p = 0.995) or interaction between test and sex (F = 0.701, p = 0.404). Response curves for ACTH and cortisol are shown in figure 2.

Relationships between physiological responses to physical and psychosocial stress

No correlations were seen for peak time point between the exercise stress test and the TSST for neither ACTH nor cortisol (r = -0.08, p = 0.422 and r = 0.10, p = 0.287, respectively). Neither were there any correlations between time point for reaching lowest value after the tests between the physical and psychosocial stress tests for SBP, DBP and HR (r = 0.037, p = 0.688, r = -0.044, p = 0.632 and r = 0.067, p = 0.488, respectively). However, when measuring AUC_i, significant correlation between the physical and psychosocial stress tests were seen for both ACTH and cortisol (r = 0.550, p < 0.000 and r = 0.619, p < 0.001, respectively). For reactivity, a positive correlation was seen in women for ACTH (r = 0.334, p = 0.012) and in men for cortisol (r = 0.342, p = 0.009). No correlations were seen for reactivity between the tests for any of the autonomic variables. For recovery, positive correlations were seen in women for ACTH (r = 0.441, p = 0.001) and SBP (r = 0.408, p = 0.010). For men, a positive correlation was seen for DBP (0.420, p = 0.006).

Physiological responses to acute psychosocial stress are not related to perceived emotional stress

Perceived stress data was dichotomized into “low-stress” (n= 77 (65%) and “high stress (n=41 (35%). No differences in percental increase for either hormonal nor autonomic reactivity were seen between these two groups (data not shown).

Time point for peak value following acute stress differs between individuals

Blood samples were collected before and immediately after the tests. When analyzing post-test values at the physical stress test, the highest value for ACTH was observed for 56% of the participants at the first post-test time point (+0-minute) and 10 minutes later for 42% of the participants. For cortisol, 56 % peaked at the 20-minute post-test time point (table 4). Lowest value occurred at the 60-minute time

point for ACTH and cortisol for all participants. For autonomic assessments at the physical stress test, the highest values were recorded at the +0-minute time point for all participants.

A majority of the participants (97%) showed the highest value for ACTH at the +0-minute time point at the acute psychosocial stress test (see table 4). For cortisol, this number was 24 %, and 65 % of the participants showed their highest value at the 10-minute time point. Since the peak in cortisol usually occurs 10-30 minutes after the peak in ACTH (26), these results might indicate that the peak in ACTH may have occurred before the +0-minute assessment.

As can be seen in table 5, the peak value for autonomic variables differed somewhat between individuals. Thus, most of the participants reached their peak value for blood pressure and heart rate 10-15 minutes into the psychosocial stress test, but one fourth peaked in heart rate immediately after finishing the test (table 5).

Discussion

The main results of this study are that a general relationship between acute physical and psychosocial stress reactions are not seen. While correlation regarding the magnitude of the HPA axis response to acute stress, measured as AUC_i, is seen, no correlation between the two test situations are seen for autonomic measures. Thus, those individuals reacting with high HPA axis responses during acute psychosocial stress are also those showing high responses during exercise stress whereas this is not the case for autonomic reactions. Also, the time point for peak values does not seem to correlate, indicating that individuals with an early peak reaction during the psychosocial test are not necessary those peaking early during the physical exercise stress test. This intra-individual variability could to certain extent explain the heterogenous results between studies exploring the cross-stressor adaptation hypothesis, particularly when measuring autonomic responses. However, the results including peak values for ACTH must be carefully interpreted, due to the risk of not having caught the true peak. The acute ACTH and cortisol responses were only measured pre- and post the test sessions since no blood samples could be taken during the stress tests. The peak value for cortisol is usually reached somewhere between 10-30 minutes after the peak in ACTH (26, 27). Thus, it can be concluded that the peak in ACTH at the psychosocial stress test for most of the participant must have been reached

during the first half of the 20 minutes long TSST, since the highest cortisol levels were measured between 0 to 10 minutes after cessation of the test. At the physical stress test, the ACTH peak most probably occurred after the test since the mean time for the exercise test was around 6-7 minutes, and the peak value for cortisol was reached 10-20 minutes post-test.

The delay in reaching peak value in cortisol after the physical stress test is an important finding. To ensure that the peak in cortisol following acute exercise stress in healthy individuals is captured, cortisol should be measured up to 60 minutes following the exercise stress. This is in accordance with the results of Hermann and co-workers, showing a peak in cortisol measured around 20-45 minutes post exercise (11). This methodological issue is of importance to discuss as many acute exercise interventions studying cortisol reactions take the samples solely immediately after the test (28). Even though the exercise sessions studied usually are of longer duration than the VO_2 peak test used in this study, it is reasonable to believe that all peaks in cortisol have not occurred during the short-term sampling times set in these studies. For autonomic responses, most of the participants reached their peak value 10-15 minutes into the acute psychosocial stress test. However, around one fourth reached their peak heart rate first after cessation of the test. Thus, to ensure that peak for autonomic responses are captured following acute psychosocial stress in healthy individuals, measurements should be continued some period after the test situation.

This current study confirms the view that perception of stress is not related to the physiological response. We also confirm that different individuals respond differently to acute stress including different time points of peak reaction. Thus, stress reactivity is a complex phenomenon involving cognitive, emotional, physiological, cultural and behavioural factors. Expecting that different individuals will respond with the same pattern at the same time point is thus not likely (12, 14). Kudielka and co-workers discussed the variability in acute cortisol responses including the role of age, genetic factors, gender, smoking and other plausible factors affecting the physiological stress responses (13).

There are several limitations that needs to be discussed. Firstly, and most importantly, the major limitation that blood samples were not taken during the stress tests. Thus, peak values occurring

during acute psychosocial stress could not be directly captured. However, for the exercise test, we can indirectly calculate the peak time point for ACTH since the peak cortisol responses for all participants occurred post exercise. At the psychosocial stress test, most of the peaks in ACTH and some of the peaks in cortisol might have occurred during the TSST. Since our results are similar to a previous study by Hermann et al. (Hermann 2018), showing a delayed peak in cortisol at a physical stress test compared to a psychosocial stress test, we feel confident that AUC_i data for cortisol is reliable, since highest value seemed to occur directly after the test and up to 30 minutes onwards. However, the AUC_i calculation for ACTH is less reliable since most of the peaks in ACTH probably occurred during the acute stress session. Due to technical problems, heart rate and blood pressure could not be measured during the exercise test session and this must be acknowledged as a limitation.

Measuring emotional perception of an acute stress situation is a methodological challenge and as far as we know, no valid measure is available. An adapted version of the Borg Rating of Perceived Exertion scale was used in this study (24), but this scale has not been validated for this context. To increase the likelihood of valid conclusion regarding perceived stress, data was dichotomized into two categories discriminating those reporting that they found the situation to strongly affect them and those who did not.

The strength of this study is the relatively large study population and comparatively long period of post-test samplings which is uncommon, at least when exercise stress is studied. Very few studies have been conducted where the same individuals have performed both psychosocial and physical stress tests. This offers a possibility of comparing reactions between the two different test situations.

One important practical application of these results is that no conclusion can be made from single measures. Furthermore, peak measures are difficult to use since peak seem to occur at different time points for different individuals, occurring both before, during and after cessation of the stress test, depending on the outcome variable. Peak measurers are usable for the autonomic responses occurring mostly during the acute stress whereas HPA axis responses should preferably be measured by using AUC_i. When including cortisol as an outcome measure, sample collection needs to be continued for at least 45-60 minutes post stress.

In conclusion, different individuals respond differently to acute stress and the physiological reaction is not related to the emotional perception of the situation. The lack of correlation, at least for the autonomic responses, between the psychosocial stress situation and the physical stress situation plausibly makes it difficult to capture the so-called cross-stressor adaptation effects. Generally, when studying acute physiological stress responses in humans it is important to acknowledge the intra-individual variations and the time-frames required to ensure that stress responses are captured in a healthy study population.

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Table 1. Inclusion- and exclusion criteria for the study

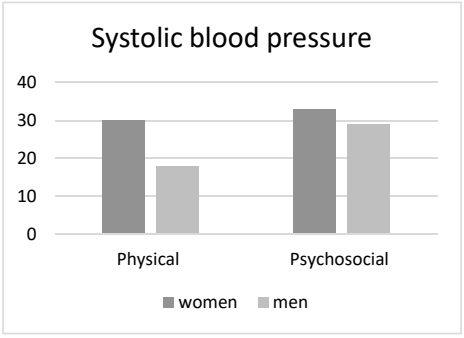
Inclusion criteria
• Age 20-50 years, essentially healthy (do not suffer from diabetes, cardiovascular disease or mental illness) • No regular physical exercise within the last year and a self-rated level of physical activity equal to 1 in the Saltin Grimby Physical Activity Level Scale (SGPLALS) (1- mostly sedentary, 2- light physical activity such as walking, gardening or bicycling to work at least two hours a week, 3- more intensive exercise such as doing aerobics, dancing, swimming, playing football or heavy gardening at least two hours per week, 4- high intensity exercise several times per week, at least five hours) (29, 30) • Working or studying at least 50 %.
Exclusion criteria
• Glucose level of ≥7 and HbA1c ≥48 mmol/l • Diverge resting ECG • Blood pressure >140/90 • Anemia (Hb <120 for women, <130 for men) • BMI <18.5 or >35 kg/m2 • Medication with beta-blockers, psychopharmacological drugs or asthma medicine • Unable to exercise at a relatively high intensity

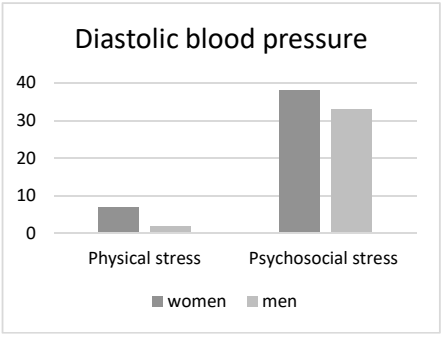
Table 2. Characteristics of participants included in the study.

	Women		Men	
		SD		SD
Age (range)	38 (21-50)	8.0	39 (23-50)	7.2
BMI	24.3	3.7	25.7	3.7
Post gradual education	91 %		84 %	
Tobacco user	3.4 %		30 %	
VO_2 peak (mL/kg/min)	30.5	5.5	36.4	6.5
TTE (min:sec)	6:08	1:34	8:52	2:11

SD: standard deviation, BMI: body mass index, VO_2 peak: peak oxygen uptake, TTE: time-to-exhaustion

Figure 1. Percental reactivity in autonomic variables to the physical and psychosocial stress test





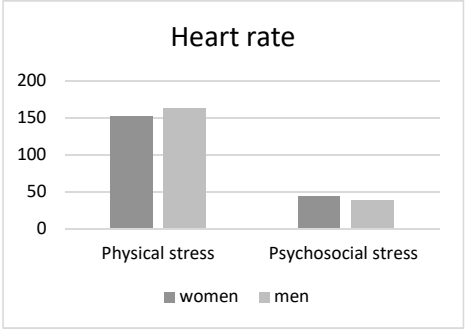
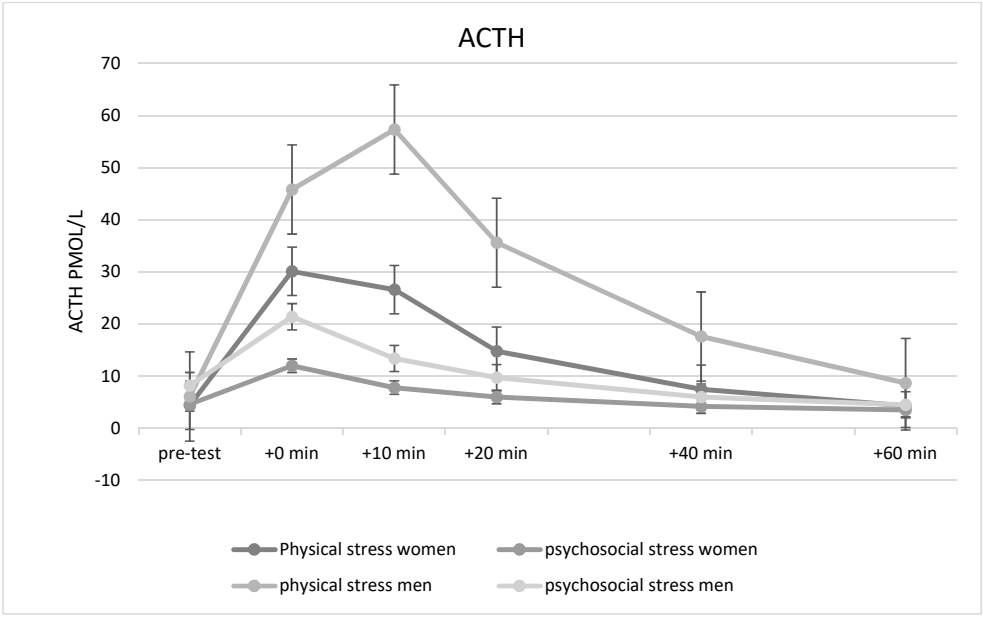


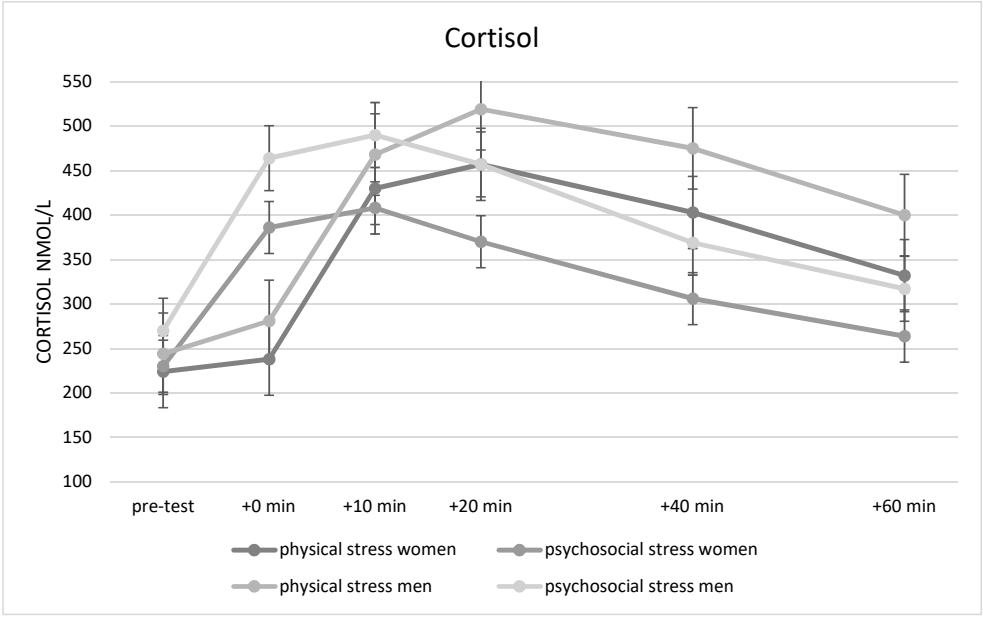
Table 3. The mixed between-within subject's ANOVA for the relationship between physical and psychosocial stress.

	Percental reactivity									
		test			sex			time*sex		
	n	F	p	eta squared	F	p	eta squared	F	p	eta squared
Cort (nmol/L)	116	26.6	**< 0.001**	0.19	0.1	0.767	0.00	0.0	0.958	0.00
SBP (mmHg)	77	12.4	**< 0.001**	0.14	8.7	**0.004**	0.10	4.1	**0.046**	0.05
DBP (mmHg)	77	197.1	**< 0.001**	0.72	3.9	0.052	0.05	0.0	0.912	0.00
HR (Bpm)	98	797.6	**< 0.001**	0.89	0.3	0.615	0.00	5.0	**0.028**	0.1
	Percental recovery									
		test			sex			time*sex		
	n	F	p	eta squared	F	p	eta squared	F	p	eta squared
Cort (nmol/L)	117	21.4	**< 0.001**	0.16	1.4	0.244	0.01	1.0	0.323	0.01
SBP (mmHg)	81	4.8	**0.031**	0.06	5.7	**0.019**	0.07	3.1	0.083	0.04
DBP (mmHg)	81	70.6	**< 0.001**	0.47	6.1	**0.015**	0.07	0.6	0.436	0.01
HR (Bpm)	105	292.7	**< 0.001**	0.74	1.8	0.181	0.02	1.2	0.278	0.01

Cort: cortisol, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate

Figure 2. Response curves for ACTH and cortisol at the physical and the psychosocial stress tests





ACTH: Adrenocorticotropic hormone

Table 4. Time point for reaching peak value in ACTH and cortisol following the physical and psychosocial stress tests

		Time point for peak value				
	n (%)	0 min	10 min	20 min	40 min	60 min
ACTH	VO_2 peak test	66 (56)	50 (42)	2 (2)		
	TSST	115 (97)	2 (2)	2 (2)		
Cortisol	VO_2 peak test	3 (3)	30 (25)	67 (56)	15 (13)	4 (3)
	TSST	29 (24)	77 (65)	9 (8)		1 (1)

ACTH: adrenocorticotropic hormone, VO_2 peak: Peak oxygen uptake, TSST: Trier Social Stress Test

Table 5. Time point for reaching peak value in autonomic variables during the psychosocial stress test, lasting for 20 minutes

	5 min	10 min	15 min	+0 min
SBP	5%	26%	53%	16%
DBP	5%	20%	43%	32%
HR	9%	28%	38%	25%

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate

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III

The effects of exercise training on HPA-axis reactivity and autonomic response to acute stress – a randomized controlled study

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Abstract

Exercise training is suggested to have a stress-buffering effect on physiological reactions to acute stress. The so-called ”cross-stressor adaptation hypothesis” is one of many theories behind the plausible effects, proposing that the attenuated physiological reaction seen in trained individuals in response to acute exercise is also seen during acute psychosocial stress. However, few randomized controlled trials (RCT) are available in this field. Therefore, the aim of the present trial was to study the effects of a six-month aerobic exercise intervention on the physiological response to acute laboratory stress. A two-armed RCT including untrained but healthy individuals aged 20-50 years was conducted. Assessments included a peak oxygen uptake test and a psychosocial stress test (the Trier Social Stress Test). A total of 88 participants went through both baseline and follow-up measures (48 in the intervention group and 40 in the control group) with an even distribution of women and men (20/28 in the intervention group and 18/22 in the control group, respectively). Outcome measures were adrenocorticotrophic hormone, cortisol, systolic- and diastolic blood pressure and heart rate responses to acute psychosocial stress. Oxygen uptake and time-to-exhaustion increased following the intervention, while a decrease was seen in the control group. The analyses showed attenuated responses to acute psychosocial stress for all variables in both groups at follow-up, with no differences between the groups. No correlation was seen between volume of exercise training and reactivity to the stress test. Despite the increased oxygen uptake in the intervention group, no differences were seen between the groups for any of the outcome variables at follow-up. Thus, in this study, the cross-stressor adaptation hypothesis could not be confirmed. Both groups showed decreased reactions indicating a habituation to the stress test.

Keywords: physical activity, longitudinal study, psychosocial stress

Introduction

Regular exercise training has been shown to play a great role for health, not only for somatic complaints, cardiovascular- and overall mortality, but also for mental well-being [1-4]. Also, exercise training has been proposed as a buffer for the detrimental effects of stress [5]. The mechanisms behind the possible stress-buffering effects of exercise and fitness are still not fully known but seem to be related to both physiological and psychological aspects. One of many plausible mechanisms is the so-called "cross-stressor adaptation hypothesis", described by Sothman et al. in 1996. The theory suggests that the attenuated physiological reaction seen in trained individuals in response to acute exercise is also valid in response to acute psychosocial stress [6]. However, previous research is not consistent regarding the effect of exercise training on physiological stress responses.

The central physiological stress response systems are the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system [7, 8]. When exposed to acute stress, the HPA axis is activated resulting in increased levels of the stress hormones adrenocorticotropic hormone (ACTH) and cortisol. A similar pattern is seen for the autonomic responses, where the onset of stress will increase heart rate and blood pressure. These responses are usually adequate and essential for the body to be able to overcome increased metabolic demands. In everyday life with recurring onsets of stress, the magnitude of the physiological response may play a role in health. Thus, if the stress reaction is frequently triggered without sufficient time to recover, it could result in elevated basal levels of stress hormones, blood pressure and heart rate with the risk of deteriorating health as a consequence [9-11].

An early review concluded that aerobically fit individuals exhibited a lower grade of autonomic stress response (e.g. heart rate, blood pressure or subjective experience of the task) compared to unfit individuals [12]. Later, van Doornen et al. [13] suggested that it is not possible to predict an individual's autonomic response to psychosocial stress by the level of fitness, partly because of the varying definitions of fitness, and partly because of the different mechanisms involved in physical and psychosocial stress. This was later confirmed by Jackson and Dishman [14], finding that when fitness was measured as VO_2 peak the effect was smaller than when self-reported levels of exercise were

used, which might depend on the genetic component in fitness [15]. In the same year Forcier et al. [16] published a paper showing that fitness was related to a less pronounced reaction of heart rate and systolic blood pressure in response to acute psychosocial stress. However, the definition of fitness was not specified and only a few of the longitudinal studies included in the analysis involved a control group. Thus, agreement has not yet been reached regarding whether the cross-stressor adaptation hypothesis applies to autonomic reactions.

The relationship between HPA axis response and exercise training in connection to acute psychosocial stress is not as thoroughly studied as the autonomic reactions. Moreover, available studies show different results, also regarding sex differences. Klaperski [17] found that trained young women (18-28 years) showed a less pronounced physiological response, measured as salivary cortisol, to an acute psychosocial stress test compared to untrained women. Likewise, Rimmele et al. [18] showed that male elite athletes showed a lower reaction for cortisol, blood pressure and heart rate compared to untrained men in response to acute psychosocial stress. This was recently confirmed by Gerber et al. [19], presenting similar results in young male and female students. Thus, participants reporting high self-reported perceived stress and low level of physical activity showed a more pronounced increase in cortisol in response to psychosocial stress test than participants reporting a low level of stress and high level of physical activity. No sex differences were seen in this study. In contrast, Childs and de Wit [20] did not support these results, showing no effect of regular exercise on saliva cortisol response to acute psychosocial stress. Furthermore, in this study men responded with a greater cortisol response to the stressor than women. In conformity with the results from Childs and de Wit, a recent cross-sectional study found no associations between cardiorespiratory fitness, cortisol, blood pressure and heart rate in women, in response to an acute psychosocial stress test [21].

Most of the above-mentioned studies are cross-sectional. Longitudinal studies are few, and only one randomized controlled trial (RCT) was found measuring HPA-axis response to acute psychosocial stress in relation to exercise. Klaperski et al. [22] examined the effect of exercise training on the HPA-axis reactivity in untrained individuals, compared to a control group. The group performing aerobic exercise showed a reduced reactivity to acute stress regarding levels of cortisol, heart rate and heart

rate variability compared to the control group. However, a reference group performing relaxation training also showed a reduced cortisol reaction compared to the control group, which does not allow firm conclusions whether the effects seen is solely due to exercise training. Thus, there is a need to further study the effects of exercise on physiological responses to acute stress.

Therefore, the primary aim of this RCT was to examine the effects of a six months aerobic exercise training intervention on HPA axis reactivity to acute psychosocial stress in untrained individuals. As the secondary aim we also studied the effects on autonomic responses. The hypothesis is that aerobic exercise training will result in attenuated HPA axis reactivity, assessed by ACTH and cortisol levels, and an attenuated autonomic response, assessed as blood pressure and heart rate, in response to acute psychosocial laboratory stress.

Methods

This study is a two-armed RCT, designed according to the Consolidated Standards of Reporting Trials (CONSORT) Statement [23], and registered at clinicaltrials.gov (ID NCT02051127). Selected parts of the original study protocol will be used in this paper. Baseline evaluations included a peak oxygen uptake test (VO_2 peak) and a psychosocial stress test (see descriptions below). After initial tests, the participants were randomized to either the control (CG)- or the intervention group (IG). The randomization was done by a nurse, using sealed envelopes and a 50/50 % distribution to the intervention- and control groups.

The IG performed aerobic exercise training for six months, while the CG maintained their current level of physical activity. Both groups then underwent the same tests as were conducted at baseline. The inclusion ran from spring 2013 to spring 2016, with the last follow-up performed in the autumn of 2016. Baseline measures and intervention periods were running all year to avoid seasonal effects. The method has previously been described in detail elsewhere [24].

Participants

Inclusion criteria were: age 20-50 years; essentially healthy (not suffering from any known somatic or psychiatric disease such as diabetes, heart disease or stress-related diseases) and working or studying at least 50 % of full time. In addition, the individuals should not have performed any regular exercise during the last year and rate themselves as being mostly sedentary, corresponding to level 1 in the Saltin Grimby Activity 4-Level Scale [25, 26]. Exclusion criteria were: glucose level ≥ 7 mmol/L; HbA1C ≥ 48 mmol/mol; diverging electrocardiography (ECG); blood pressure above 140/90 mmHg; anemia (Hb <120 g/L for women, <130 g/L for men); BMI less than 18.5 or above 35 kg/m^2; medication with beta blockers, psychopharmacological drugs or asthmatic medicine and inability to exercise at a relatively high intensity.

Information about the study was distributed by advertisement in two major newspapers in the district around Gothenburg in western Sweden, and through notice boards and social media. The number of responders to the advertisement for the study was 416. Of these, 170 individuals were eligible according to the inclusion criteria and were offered a physical screening to test for exclusion criteria, resulting in 24 individuals being excluded. A further 22 individuals declined participation or did not enter the study for other reasons (Fig 1*)*. A final number of 119 individuals went through the baseline tests. All participants gave written informed consent before entering the study and were informed that they could withdraw their participation at any time. The study was conducted according to the 1964 Declaration of Helsinki and approved by the Regional Ethical Board, Gothenburg, Sweden, Dnr 917-12.

Peak oxygen uptake test

To assess the aerobic capacity and heart rate of the participants, a VO_2 peak test was conducted at the Centre for Health and Performance, University of Gothenburg. The test was performed on a bicycle ergometer (Monark, 828 E, Monark Exercise AB, Vansbro, Sweden). The participants started the test by warming up for five minutes with a cadence of 70 revolutions per minute at a low resistance (50 W). The VO_2 peak test was a ramp test with increasing resistance and the same cadence as during

warm up. The women started at 87.5 W, increasing by 17.5 W every minute until exhaustion. The men started at 105 W, also increasing by 17.5 W until exhaustion (VO_2 levelling off or Respiratory Exchange Ratio >1.1 and inability to keep the cadence). A total work of 5-8 minutes was considered as optimal for reaching peak values. Peak oxygen uptake, expressed as mL/kg/min was measured with the Jaeger Oxycon Pro metabolic chart (Carefusion, Hoechberg, Germany) in the mixing chamber mode. The device was calibrated before each measurement according to the manufacturer's manual. During the test, the heart rate (beats per minute, bpm) was monitored and measured with a pulse sensor (Polar 300 RS, Polar, Finland).

Psychosocial stress test

One week after the oxygen uptake test, the Trier Social Stress Test (TSST) was performed at the Institute of Stress Medicine in Gothenburg between 1 p.m. and 3 p.m. The TSST is the most commonly used laboratory stress test developed to elicit a physiological reaction to acute psychosocial stress in a standardized setting [27]. The TSST has been shown to have good validity and reliability and is widely used in this research area [20, 28, 29]. Before arriving at the lab, the participants had ingested a standardized meal containing controlled amounts of fat, protein and carbohydrates, approximately two hours before the test. After a short rest, the participant entered the test room and was given instructions in front of a committee consisting of three members. A video camera and a microphone were installed, and they were falsely told that they were video- and audio taped for later analyses of their behavior and voice. After five minutes of preparation in another room, the participant re-entered the test room. The first part of the test was a five-minute free speech, where the participants were asked to apply for their dream job in front of the committee. The topic was slightly modified in the follow-up session, where the participant instead was asked to apply for a job they dreamed about as a child. The committee gave no form of response to the participant during the speech. The second part was an arithmetic task (serial subtraction), also five minutes long, and after the test the participant left the room. To study the recovery after the test, the participants rested for 60 minutes in a calm setting.

Exercise training intervention

One week after randomization, participants allocated to the IG were called for a group meeting where they received information about the intervention and were instructed to start regular aerobic exercise training. Aerobic exercise is the most studied form of exercise in this field and was chosen to enable comparisons with other studies. The duration of six months was set to enable a gradual increase of their level of activity and to have sufficient time to reach physiological changes. The goal was to reach an exercise level of three times per week, 45-60 minutes per session and with an average heart rate of at least 75 % of peak heart rate, measured at the VO_2 peak test. To monitor the intensity and duration of exercise, the participants used a heart rate monitor (Garmin Forerunner ® 210, USA), at every training session and transferred the data recorded directly to an internet-based training log (www.funbeat.se). The participants were free to choose what type of activity to perform, and if they wanted to exercise individually or together with others, as long as the goal for the average heart rate was fulfilled. The participants were asked to avoid performing resistance training during the intervention period, since resistance training might affect the outcome variables in a different way than aerobic exercise [30]. They were also offered four meetings with a trained coach to identify strengths and potential obstacles to getting through the intervention. The participants were given one-year free access to a commercial fitness establishment (Nordic Wellness) with several facilities in and around Gothenburg to further facilitate adherence to training.

Individuals in the CG were instructed to keep their activity level unchanged during the six-month intervention period and refrain from any exercise training. After the follow-up, they were encouraged to start exercising and received one-year free access to the same fitness establishment as the intervention group.

Outcome measurements

The primary outcome of the study was HPA-axis response to acute psychosocial stress, assessed as plasma ACTH and total serum cortisol response, before and after the intervention. The participants were provided with a peripheral venous catheter in an antecubital vein (BD Venflon Pro, Becton

Dickinson Infusion Therapy, USA), and a total of seven blood samples were drawn during each TSST. An initial sample was drawn 10 minutes before the test started (-10). The second was drawn immediately before the test (-0), and the third immediately after the test was finished (+0). Remaining samplings were made 10, 20, 40 and 60 minutes after the test in order to study the response and the recovery. Samples for serum were collected in EDTA tubes, and samples for plasma were collected in Serum Sep Cloth Activator tubes. To separate the plasma, tubes were cold spun at 3500 revolutions per minute for 15 minutes and stored at -80 º C until analyzed. To separate serum, tubes were spun at 20 º C for 10 minutes at 3500 revolutions per minute and stored at 4 º C until analyzed the day after the test. Plasma concentrations of ACTH were assessed by immunoradiometric assay (limit of detection, 0.4 pmol/L) (CIS bio International, Gif-sur-Yvette Cedex, France). Serum concentrations of cortisol were assessed by electro chemiluminescence immunoassay (limit of detection, 0.5 nmol/L) (Roche Diagnostics GmbH, Mannheim, Germany). To assess the secondary outcomes, autonomic reactions in terms of heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), an automatic blood pressure cuff (Welch Allyn, ABPM 6100, USA) was used. The device was assessing every five minutes from 10 minutes before the TSST to 60 minutes after the test.

Data handling

Pre-test values were the mean value of the -10 and -0 values taken before the test started, peak value was the highest value after the test (10 or 20 minutes for ACTH and cortisol and during or directly after for SBP, DBP and HR). For ACTH and cortisol, the lowest value was the last one (60 min) for all participants. For SBP, DBP and HR, that are more responsive, the lowest value occurred between 10 and 60 minutes after the test.

The *reactivity* was defined as percental change from baseline to peak value and was calculated by dividing the absolute change with the peak value. *Recovery* was defined as percental change from peak to lowest value and was calculated by dividing the absolute change with the peak value. Non-responders in HPA axis were defined as a zero- or negative response in ACTH and/or cortisol from pre-test to peak values.

Statistics

A sample size calculation for the main outcome measure cortisol showed that 39 subjects in each group were needed to be able to detect an effect size Cohen's f = .25, with power ≥ .80 and α = .05 (G*power 3.1). Expecting that several of drop-outs would occur, the goal was to include 50 subjects in each group.

To analyze group differences in the physiological response to TSST at baseline and follow up, mixed between-within subjects' analysis of variance (ANOVA) were used for ACTH, cortisol, SBP, DBP and HR at baseline and follow-up using all seven time points in the analysis.

To study the effects of the intervention, group differences and changes from baseline to follow-up for the three points pre-test, peak and lowest value after the test were analyzed with mixed between-within subjects' ANOVA.

In the third step, three summarizing measures were performed. To study the total output of ACTH and cortisol, area under the curve with respect to increase (AUC_i) [31] was calculated from pre-test to 60 minutes after the stress test . As a measure of reactivity to and recovery from the psychosocial stress test percental response from baseline to peak and percental recovery from peak to lowest value was used for all outcome measures. Mixed between-within subjects' ANOVA was performed to study differences from baseline to follow-up for these parameters.

We were also interested in whether the number of training sessions during the intervention correlated with the response in ACTH, cortisol, SBP, DBP and HR. For this, Pearson's Correlation analyses was used.

Since women and men were analyzed together, adjustments were made for sex in all analyses mentioned above. All participants included in the study who performed both baseline and follow-up measures were included in the initial analysis according to the Intention-to-treat (ITT) principle. The lowest accepted level of exercise was set to at least two times per week during at least half of the intervention period (a minimum of 26 sessions). In the first sub-analysis, only participants who had

reached the accepted level of training sessions were included, according to the Adherence-to-protocol (ATP) principle. In the second sub-analysis, participants defined as non-responders in ACTH and cortisol from pre-test to peak value at baseline were excluded.

All data were analyzed with IBM SPSS statistics version 22. For normally distributed data, values are presented as means and standard deviations (SD), with a significance level set to $p < 0.05$. For not normally distributed data, results are presented as geometric mean and anti-logged confidence intervals (CI).

Results

The number of individuals randomized to either the intervention or the control group was 119, with 68 participants randomized to the IG and 51 to the CG. Since the adherence to the intervention protocol was lower than expected in the IG, the distribution of randomization was changed to 70 % for the IG and 30 % for the CG during the last year of inclusion. The dropout rate was 20 individuals in the IG and 11 in the CG due to unwillingness to go through retesting (n = 16), injuries (n = 4), changed working conditions (n = 4), starting anti-depressant medication (n = 4), pregnancy (n = 2) and randomization to the CG but started to exercise (n = 1). In total, 88 participants (72 %) (48 in the IG and 40 in the CG) went through both baseline and follow-up measures (*see study flow diagram, figure 1*). There was an even distribution of women and men in both groups, with 18 women and 22 men in the CG and 20 women and 28 men in the IG. For baseline characteristics of the participants, see Table 1.

Table 1. Baseline characteristics of the participants.

	Control		Intervention	
		SD		SD
Sex	♀ 18/ ♂ 22		♀ 20/ ♂ 28	
Age (range)	41 (24-50)	7.8	38 (23-49)	6.7
BMI	24.7	3.9	25.0	3.1
Postgraduate education	85 %		92 %	
Tobacco user	20%		13%	
VO_2 peak (mL/kg/min)	33.4	6.2	34.8	6.8
TTE (min:sec)	7:19	02:32	7:58	02:23

BMI: Body Mass Index, VO_2 peak: peak oxygen uptake, TTE: Time-To-Exhaustion, SD: standard deviation

Adherence to protocol

The mean number of training sessions in the intervention group was 33 sessions per person (range 0 to 77) out of a possible maximum of 78 sessions during the intervention period. After exclusion of participants who performed fewer than 26 sessions, the mean number of sessions for the remaining participants was 45 (range 27 to 77). In the ATP analysis, 20 subjects in the IG who did not reach the intended level of physical exercise were excluded.

Oxygen uptake

In the age group 20-29 years, the mean oxygen uptake at baseline was 37.5 mL/kg/min for both women and men (n = 6 and n = 5, respectively). In the age groups 30-39 and 40-50 years, the mean values for women were 30.1 and 29.0 mL/kg/min, respectively (n = 11 and n = 21), and for men 37.7 and 36.3 mL/kg/min, respectively (n = 21 and n = 24). At follow-up, the VO_2 peak and TTE had increased significantly in the IG (9.4 % and 11.0 %, respectively) between baseline and the six-month follow-up (both measures $p < 0.001$). When including only participants following the intervention protocol, the increase in VO_2 peak was 9.4 %, and the increase in TTE was 9.5 %. At the same time, the CG decreased their VO_2 peak (-3.0 %, $p = 0.018$) and time-to-exhaustion (- 0.7 %, $p = 0.713$). A mixed between-within subjects' ANOVA for VO_2 peak confirmed the significant effects of time ($F [1, 81] = 12.33$, $p = 0.001$, eta squared 0.13). Also, the group differences ($F [1, 81] = 6.74$, $p = 0.011$, eta squared = 0.08) and interaction effects ($F [1, 81] = 41.81$, $p < 0.001$, eta squared = 0.34) were

confirmed. Likewise, TTE showed significant effects of time ($F [1, 86] = 20.71$, $p < 0.001$, eta squared 0.19), group ($F [1, 86] = 4.11$, $p = 0.046$, eta squared 0.05) and interaction ($F [1, 86] = 26.50$, $p < 0.001$, eta squared 0.24).

HPA axis response to acute psychosocial stress

The HPA-axis responses to the TSST are shown in Fig 2. At baseline TSST, four participants showed no ACTH response and additional four participants showed no cortisol response to acute stress.

Mean values for the seven time-points are presented for cortisol, while ACTH was not normally distributed and thus geometric means are displayed. At baseline, the mixed between-within subject's ANOVA for ACTH, including all seven time-points, showed a significant effect of time, and follow-up measures gave the same result (Table 2), confirming significant physiological reactions to acute stress. The exclusion of participants not following the protocol did not change the results. Also, for cortisol, baseline results showed a significant effect of time. At follow-up, the interaction effect was significant as well, with the intervention group having a greater response between time-point two and three compared to the control group. However, when excluding participants not following the protocol the interaction effect was no longer significant ($F [6, 56] = 1.88$, $p = 0.100$).

Table 2. Mixed between-within subjects' ANOVA for all seven time points at baseline- and follow-up TSST

	Baseline									
		time			group			time*group		
	n	F	p	eta squared	F	p	eta squared	F	p	eta squared
ACTH (pmol/L)*	82	4.94	< **0.001**	0.29	1.77	0.118	0.13	2.07	0.154	0.03
Cortisol (nmol/L)*	79	7.01	< **0.001**	0.37	0.04	0.850	0.00	1.25	0.291	0.10
SBP (mmHg)*	64	4.81	**0.001**	0.34	3.33	0.073	0.05	3.66	**0.004**	0.28
DBP (mmHg)*	66	4.91	< **0.001**	0.34	5.01	**0.029**	0.07	0.70	0.649	0.07
HR (Bpm)	66	17.20	< **0.001**	0.64	0.00	0.962	0.00	2.28	**0.048**	0.19
	Follow-up									
		time			group			time*group		
	n	F	p	eta squared	F	p	eta squared	F	p	eta squared
ACTH (pmol/L)*	86	6.64	< **0.001**	0.34	2.23	0.139	0.03	1.03	0.410	0.07
Cortisol (nmol/L)*	84	8.10	< **0.001**	0.39	0.20	0.655	0.00	2.25	**0.048**	0.15
SBP (mmHg)*	70	3.22	**0.008**	0.24	0.00	0.999	0.00	0.82	0.556	0.07
DBP (mmHg)*	69	5.27	< **0.001**	0.34	1.24	0.270	0.02	1.82	0.110	0.15
HR (Bpm)	70	19.84	< **0.001**	0.65	1.45	0.233	0.02	1.41	0.225	0.12

ACTH: adrenocorticotropic hormone, SBP: Systolic blood pressure, DBT: Diastolic blood pressure, HR: Heart rate, Bpm: Beats per minute *Adjusted for sex

Values and results from the mixed between-within subjects' ANOVA for the physiological reactivity to TSST are shown in table 3. Significant effects of time were seen for ACTH and cortisol, showing decreased responses at the follow-up TSST compared to the baseline TSST. No effects of group and no interaction effects were seen for neither ACTH nor cortisol. Mixed between-within subjects' ANOVA on recovery from the psychosocial stress test showed no significant differences between the groups for ACTH. For cortisol, there was a significant effect of time showing an increased recovery at follow-up compared to baseline.

Table 3. Values for percental reactivity to and recovery from the psychosocial stress test, along with results from the mixed between-within subjects' ANOVA for reactivity and recovery at baseline and follow-up

		Percental reactivity				**Mixed between-within subjects' ANOVA**								
		Control group		Intervention group		baseline to follow-up			group			time*group		
	n	baseline	follow-up	baseline	follow-up	F	p	eta squared	F	p	eta squared	F	p	eta squared
ACTH (pmol/L)	85	261 (159; 364)	108 (69; 147)	215 (157; 273)	100 (62; 139)	25.67	**< 0.001**	0.236	0.42	0.518	0.01	0.35	0.555	0.00
Cort (nmol/L)	81	96 (73; 119)	73 (53; 94)	94 (79; 109)	60 (51; 70)	17.76	**< 0.001**	0.18	0.64	0.426	0.01	0.60	0.442	0.01
SBP (mmHg)*	83	34 (29;39)	24 (21; 28)	29 (25; 34)	23 (19; 27)	0.85	0.360	0.01	2.68	0.106	0.03	1.00	0.321	0.01
DBP (mmHg)	83	26 (31; 40)	30 (26; 34)	36 (30; 43)	29 (25; 33)	7.61	**0.007**	0.09	0.00	0.964	0.00	0.12	0.727	0.00
HR (Bpm)*	78	44 (35; 53)	20 (12; 28)	40 (33; 47)	25 (18; 33)	0.04	0.846	0.00	0.08	0.778	0.00	2.15	0.147	0.03

		Percental recovery				**Mixed between-within subjects' ANOVA**								
		Control group		Intervention group		baseline to follow-up			group			time*group		
	n	baseline	follow-up	baseline	follow-up	F	p	eta squared	F	p	eta squared	F	p	eta squared
ACTH (pmol/L)*	87	68 (62; 74)	60 (53; 67)	70 (64; 75)	65 (61; 69)	0.94	0.334	0.01	1.17	0.282	0.01	1.03	0.313	0.01
Cort (nmol/L)	84	33 (29; 37)	38 (35; 41)	36 (33; 39)	39 (37; 41)	7.87	**0.006**	0.09	0.60	0.442	0.01	0.41	0.526	0.01
SBP (mmHg)*	85	29 (27; 31)	27 (24; 29)	27 (26; 29)	25 (22; 27)	0.55	0.459	0.01	2.59	0.112	0.03	0.00	0.99	0.00
DBP (mmHg)	85	31 (28; 33)	31 (28; 34)	31 (29; 34)	31 (29; 34)	0.28	0.596	0.00	0.18	0.674	0.00	0.13	0.717	0.00
HR (Bpm)*	84	30 (26; 35)	33 (29; 36)	36 (32; 40)	36 (33; 38)	0.35	0.557	0.00	3.12	0.081	0.04	1.68	0.199	0.02

*Adjusted for sex

ACTH: adrenocorticotropic hormone, SBP: Systolic blood pressure, DBT: Diastolic blood pressure, HR: Heart rate, Bpm: Beats per minute

Effects of exercise training on HPA-axis AUC_i

The change in ACTH AUC_i from baseline to follow-up was significant, showing decreased values for both groups at follow up (F [1, 80] = 10.76, p = 0.002, eta squared = 0.119). No significant group- or interaction effects were seen (F [1, 80] = 1.32, p = 0.255 and F [1, 80] = 0.51, p = 0.477, respectively). The same result was shown for cortisol AUC_i, with a significant effect of time (F [1, 75] = 41.57, p < 0.001, eta squared = 0.357) but no group- or interaction effects (F [1, 75] = 0.00, p = 0.992 and F [1, 75] = 0.16, p = 0.688, respectively).

Autonomic response to acute psychosocial stress

Response curves with mean values for the seven time-points for SBP, DBP and HR are shown in Fig 2 and the results from the mixed between-within subjects' ANOVA are displayed in Table 2. At baseline, results for SBP showed significant effects of time and interaction, with both groups showing reactions to the stress test, and the intervention group having a greater response than the control group. At follow-up, only time was significant, confirming a response to the stress test. For DBP, the baseline results showed significant effects of time and group, showing reactions to the stress test in both groups and the control group having higher values than the intervention group. At follow-up, only time was significant. For baseline HR, significant effects were seen of time and interaction, with both groups showing a response to the stress test, and the control group having a smaller recovery. The follow-up results did only show significant effects of time. Excluding participants not reaching the goal for exercise training did not change these results.

Values and results from the mixed between-within subjects' ANOVA for the physiological reactivity to TSST are shown in Table 3. Significant effects of time were seen for DBP, showing a decreased reactivity at follow-up compared to baseline, but not for SBP or HR. The analyses showed no effects of group and no interaction effects for any of the variables. For recovery from psychosocial stress, no significant differences were shown between the groups for SBP, and the same were seen for DBP and HR.

Effects of exercise training on pre-test-, peak- and lowest value

Mean values for the time-points pre-test, peak and lowest value are presented in Table 4. Variables marked with a * is presented as geometric means and its anti-logged 95 % CI. Results from the mixed between-within subjects' ANOVA for pre-test-, peak- and lowest values from baseline to follow-up are presented in Table 5. The pre-test values were significantly higher for cortisol and HR at the follow-up TSST compared to the baseline TSST. At the same time, peak values for SBP and DBP were lower at follow-up compared to baseline, with low effect sizes. For lowest value, HR showed significantly lower levels at follow-up compared to baseline, also with a low effect size. Excluding non-compliers did not change the result.

Table 4. Values for pre-test-, peak- and lowest value at the psychosocial stress test at baseline and follow-up

			Pre-test			
		Control group			Intervention group	
	n	baseline	follow-up	n	baseline	follow-up
ACTH*, pmol/L	40	4.6 (3.8; 5.6)	5.8 (4.8; 7.0)	45	6.1 (5.1; 7.2)	7.0 (6.2; 7.9)
Cortisol*, nmol/L	38	233 (204; 265)	254 (221; 293)	44	242 (224; 262)	277 (255; 305)
SBP, mmHg	40	129 (123; 134)	130 (124; 135)	46	128 (123; 133)	129 (125; 133)
DBP, mmHg	40	78 (74; 81)	77 (74; 81)	46	74 (70; 77)	75 (73; 78)
HR, bpm	38	73 (70; 76)	79 (76; 83)	44	71 (68; 74)	78 (76; 80)
			Peak			
		Control group			Intervention group	
	n	baseline	follow-up	n	baseline	follow-up
ACTH*, pmol/L	40	13.0 (10.2; 16.8)	10.6 (8.4; 13.5)	47	15.6 (13.0; 18.7)	12.6 (10.8; 14.7)
Cortisol, nmol/L	40	450 (406; 493)	439 (398; 480)	45	468 (436; 501)	456 (426; 486)
SBP, mmHg	39	171 (162; 180)	163 (156; 170)	46	164 (158; 171)	158 (151; 164)
DBP, mmHg	39	104 (100; 109)	101 (97; 105)	46	99 (95; 102)	97 (94; 100)
HR*, bpm	38	101 (95; 108)	94 (87; 99)	46	97 (92; 104)	95 (90; 99)
			Lowest value			
		Control group			Intervention group	
	n	baseline	follow-up	n	baseline	follow-up
ACTH*, pmol/L	40	3.5 (3.0; 4.0)	3.7 (3.2; 4.3)	47	3.9 (3.5; 4.4)	4.1 (3.6; 4.6)
Cortisol, nmol/L	40	301 (267; 334)	271 (241; 301)	45	302 (272; 331)	278 (256; 298)
SBP, mmHg	36	120 (115; 125)	118 (113; 123)	44	118 (115; 122)	118 (114; 122)
DBP, mmHg	36	72 (68; 75)	67 (65; 72)	44	68 (65; 70)	66 (64; 69)
HR, bpm	36	64 (61; 67)	63 (60; 65)	44	63 (60; 65)	61 (58; 63)

*geometric mean and anti-logged 95 % confidence intervals (CI)

ACTH: adrenocorticotropic hormone, SBP: Systolic blood pressure, DBT: Diastolic blood pressure,

HR: Heart rate, Bpm: Beats per minute

Table 5. Mixed between-within subjects' ANOVA for pre-test-, peak- and lowest value at baseline and follow-up

Pre-test										
		baseline to follow-up			group			time*group		
	n	F	p	eta squared	F	p	eta squared	F	p	eta squared
ACTH (pmol/L)*	85	1.63	0.205	0.02	4.51	**0.037**	0.05	0.19	0.668	0.00
Cort (nmol/L)*	82	4.27	**0.042**	0.05	0.58	0.447	0.01	0.32	0.575	0.00
SBP (mmHg)*	86	1.93	0.169	0.02	0.14	0.706	0.00	0.01	0.931	0.00
DBP (mmHg)*	86	2.49	0.119	0.03	2.66	0.107	0.03	0.89	0.349	0.01
HR (Bpm)	82	24.24	**< 0.001**	0.23	1.04	0.311	0.01	0.07	0.935	0.00
Peak										
		baseline to follow-up			group			time*group		
	n	F	p	eta squared	F	p	eta squared	F	p	eta squared
ACTH (pmol/L)*	87	0.46	0.500	0.01	2.08	0.153	0.02	0.00	0.953	0.00
Cort (nmol/L)*	85	2.33	0.131	0.03	0.35	0.558	0.00	0.00	0.983	0.00
SBP (mmHg)	85	15.55	**< 0.001**	0.16	2.06	0.155	0.02	0.74	0.393	0.01
DBP (mmHg)*	85	5.14	**0.026**	0.06	5.21	**0.025**	0.06	0.59	0.444	0.01
HR (Bpm)*	84	0.09	0.763	0.00	0.20	0.657	0.00	2.47	0.120	0.03
Lowest										
		baseline to follow-up			group			time*group		
	n	F	p	eta squared	F	p	eta squared	F	p	eta squared
ACTH (pmol/L)*	87	1.48	0.227	0.02	1.85	0.177	0.02	0.02	0.880	0.00
Cort (nmol/L)*	85	1.72	0.194	0.02	0.01	0.931	0.00	0.05	0.822	0.00
SBP (mmHg)*	88	0.44	0.507	0.01	0.15	0.704	0.00	0.44	0.509	0.01
DBP (mmHg)*	88	1.13	0.235	0.02	3.74	0.057	0.04	2.28	0.135	0.03
HR (Bpm)	88	5.44	**0.022**	0.06	0.71	0.403	0.01	0.13	0.720	0.00

*Adjusted for sex

Pre-test: mean value of the -10 and -0 minutes samples taken before the test started. Peak: highest value after the test (10 or 20 minutes for ACTH and cortisol and during or directly after for SBP, DBP and HR). Lowest value: last value (60 min) for ACTH and cortisol, the lowest value between 10 and 60 minutes for SBP, DBP and HR. ACTH: adrenocorticotrophic hormone, SBP: Systolic blood pressure, DBT: Diastolic blood pressure, HR: Heart rate, Bpm: Beats per minute

Correlations between number of training sessions and response to TSST

When analyzing correlations between the number of sessions performed during the intervention and the response to the stress test no correlation was seen for ACTH ($r = -0.12$, $p = 0.434$), cortisol ($r = -0.03$, $p = 0.861$), SBP ($r = -0.03$, $p = 0.869$), DBP ($r = -0.04$, $p = 0.818$) or HR ($r = -0.07$, $p = 0.659$).

Discussion

The main result of this study is that physiological reactions to acute psychosocial stress is not significantly affected in untrained individuals performing regular exercise training for six months, compared to a non-training control group. Thus, neither HPA-axis responses (ACTH and cortisol) nor autonomic responses (SBP, DBP and HR) to acute psychosocial stress showed any changes following the six-month exercise intervention. Accordingly, in this study we could not confirm the hypothesis that aerobic exercise training will result in attenuated HPA-axis reactivity and autonomic responses to acute psychosocial laboratory stress. The participants in the IG significantly improved their peak oxygen uptake and TTE at the same time as the CG showed a reduced VO_2 peak and TTE, confirming that aerobic training effects did occur following the intervention.

The results showed higher pre-test values for cortisol and HR at follow-up irrespective of the intervention, indicating higher stress levels at arrival that might be caused by experiences from the baseline test. On the other hand, reactivity values of ACTH, cortisol and DBP were lower at follow-up, maybe as a result of habituation to the situation when the participants discovered that the same test was repeated. Additionally, no correlations were found between number of training sessions and reactivity to the stress test, and no differences were seen between the groups for reactivity and recovery. Thus, the result of our study does not confirm the hypothesis that regular exercise training affects HPA-axis or autonomic response to acute laboratory stress. However, the great individual variances in physiological response to acute stress and the assumed adaptation to the stress test might have affected the interpretation of the results.

There are several possible reasons for different results in the present study compared to earlier studies. Previous studies are mainly cross-sectional, comparing highly fit individuals with untrained individuals. Some of these studies show a less pronounced physiological response for highly fit individuals [13, 18, 19, 32], while others do not [21, 33, 34]. In some cases, when studying opposites (trained/ untrained), a difference can be detected. However, in our study the change in oxygen uptake, although significant, was possibly not large enough to significantly affect the physiological responses. Maybe, the effect on the physiological stress response is only existent in highly trained individuals, which we did not study.

To the best of our knowledge, only two randomized controlled studies have been conducted measuring the physiological responses to acute psychosocial stress in relation to changes in fitness [22, 35]. Both studies showed an attenuated physiological reaction for participants allocated to exercise intervention compared to the non-exercising controls. In the study by Klaperski et al., the increase in activity level in the intervention group was comparable to our study. However, a comparison whether the increased exercise level affected fitness to the same extent as in our study is complicated due to the different methods used to measure fitness. Klaperski et al. related fitness to the participant's relative power at individual anaerobic threshold, whereas our study used a peak oxygen uptake test. In contrast to both the study by Klaperski and co-workers and our study, the study by von Haaren et al. used an academic examination period as a real life psychosocial stressor. The increase in VO_2 peak was comparable to our study, but the result differed in that the intervention group in the study by von Haaren et al. showed a reduced autonomic response to the stressor. However, the types of stressors used in the studies cannot be easily compared. While our study used a ten-minute laboratory, unpredictable stressor, von Haaren and co-workers used a two-day examination period, well known to the participants. Thus, despite the similar designs in all three studies, the results diverge.

Another factor to consider when comparing studies is the labelling of exercise levels and fitness. There are large discrepancies between studies in terms of what is considered "fit" and "unfit", both with respect to aerobic capacity and the level of exercise training. In some studies, the term "unfit" (or

"low fit") is used for individuals who do not perform any exercise [20, 32], while other studies use the same term for individuals who perform up to four hours of exercise per week [33, 34]. At the same time, the use of the term "fit" (or "high fit") has been used for individuals who exercise for at least one hour per week [20], which results in an overlap of several hours of exercise per week between the terms "unfit" and "fit".

Furthermore, the methods for determination of fitness differ between studies. Some studies use self-reported activity levels, while other studies use some kind of fitness test to evaluate the participant's aerobic capacity. The substantial differences regarding the measures and definitions of terms related to fitness may partly explain the inconsistence of existing studies.

In our study, the participants reported themselves as untrained at screening, but this was not reflected by their level of oxygen uptake, which falls into the normal range of aerobic capacity for both men and women according to Koch et al. [36]. This result indicates that we may not have reached our intended target group of untrained individuals in the present study. Generally, when studying the effects of exercise on different physiological health measures, the greatest difference is seen between individuals with low fitness compared to individuals with a little higher fitness [37]. This might not be the case for the outcome measures of this study. Thus, the exercise training effects in the intervention group might not have been large enough to yield the physiological effects hypothesized. A screening for oxygen uptake before inclusion would have been preferable instead of relying on self-reports of physical activity level.

Another important aspect related to detecting changes on a group level is the large individual variation in physiological responses to acute stress. Thus, a larger study population is perhaps needed to detect possible effects following an exercise intervention on the physiological systems.

In this trial, women and men were analyzed together. Since we had an even distribution of women and men in both groups and adjusted for sex in the analyses, this was considered appropriate. The results showed no differences for women and men, which is in line with previous findings of Gerber et al [19].

Strengths and limitations

The major strength of the present study is the RCT design and the relatively large study population. Including participants during the whole year diminished the seasonal effects. In addition, the consistency of personnel regarding the testing also contributed to an increased reliability of the results. Another strength is the measurement of VO_2 peak, which present the absolute value of oxygen uptake, instead of a calculated value from submaximal assessments or self-reported levels of physical activity.

We are also aware of some limitations that need to be discussed. Firstly, as mentioned above, many of the included participants might not have been as untrained as they reported. Secondly, almost half of the participants (20 out of 47) in the intervention group had difficulty reaching the lowest acceptable level of exercise training and were thus not included in the ATP analyses. Changing from a low level of physical activity to engage in exercise three times per week seems to be difficult. Sherwood and Jeffery [38] reviewed factors influencing an individual's capability to implement a physically active lifestyle. They enumerate the items identified as important and mention, for example, exercise self-efficacy, prior history of physical activity, social support, time and access. Despite the four coaching sessions aiming to support the participants in our study, several participants found it difficult to complete the intervention. Maybe a more intensive and prolonged protocol would have resulted in a larger effect in the outcomes, but that would have required a greater achievement from both participants and research staff, which was not considered feasible in this study. Since the majority of the participants did not follow the protocol, another approach to the intervention program would have been necessary, with some supervised sessions in order to maintain the participants' exercise level.

A third important factor to discuss is the type of stressor used in this study. Both groups showed decreased reactivity and/ or reduced peak levels in all variables except HR in response to the TSST at the second time of the test. This indicates a habituation to the test, although previous research has suggested that when at least four months have passed between the tests, the risk of habituation is small [39]. In fact, a small change was made in the task at the second test, but the modification was

obviously not enough for participants to experience the task as novel. The TSST may be relevant in cross-sectional studies, but in further longitudinal studies the use of TSST in its original setting needs to be taken into consideration when the follow-up time is as short as six months.

The phase of menstrual cycle was not recorded which must be seen as a limitation and might have affected our results. Lastly, it was not possible to blind the participants regarding which group they took part in, but the TSST committee was blinded and had no insight in terms of which group the participants belonged to.

Conclusions

Regular exercise training did not affect the physiological responses to acute stress when compared to untrained controls. Thus, we cannot confirm that the cross-stressor adaptation hypothesis is a plausible mechanism explaining the stress-buffering effect of exercise training. A large-scale RCT, minimizing existing limitations of available studies, would be needed to further explore whether the cross-stressor adaptation hypothesis is valid.

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Fig 1. Study flow diagram

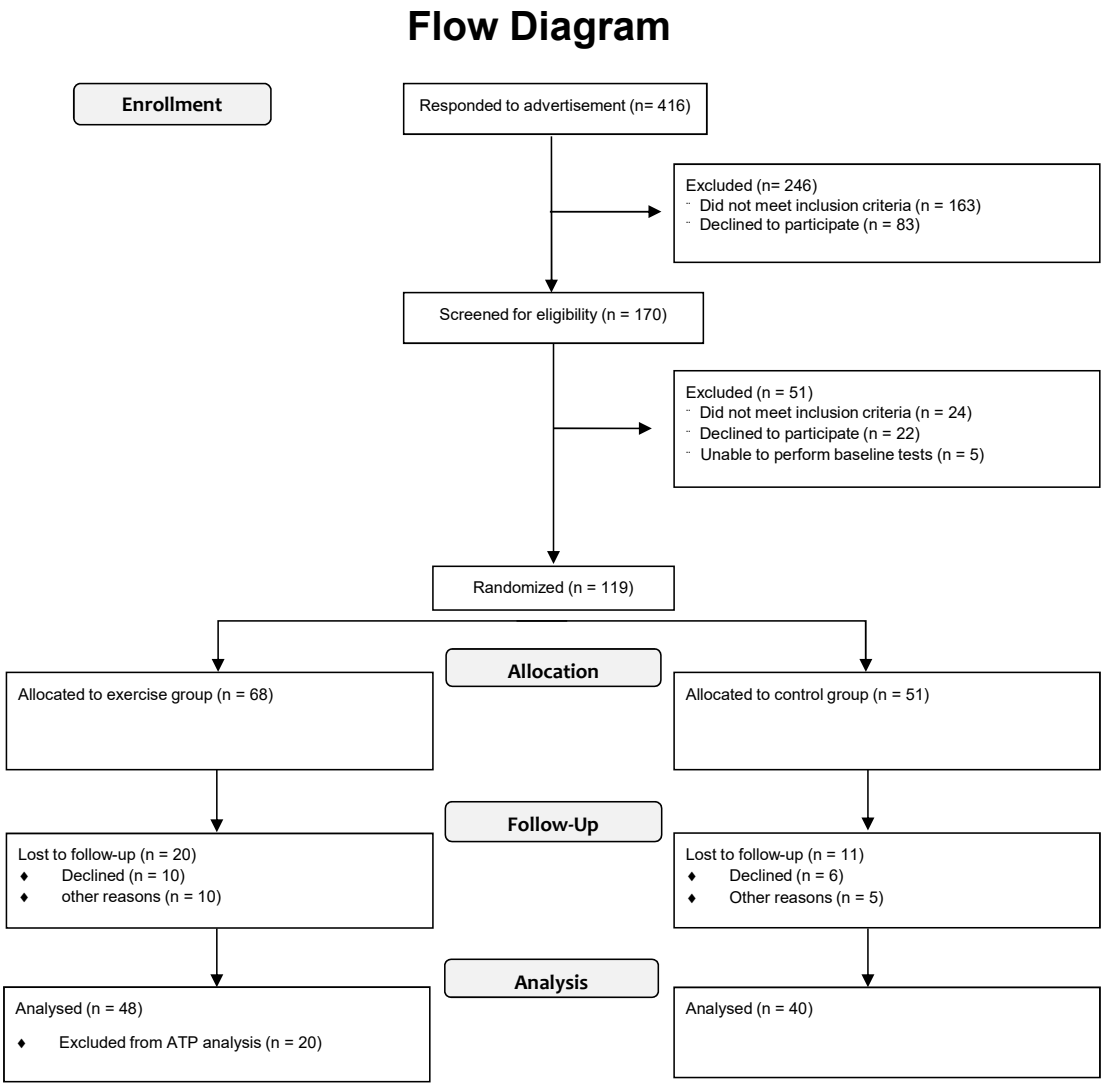
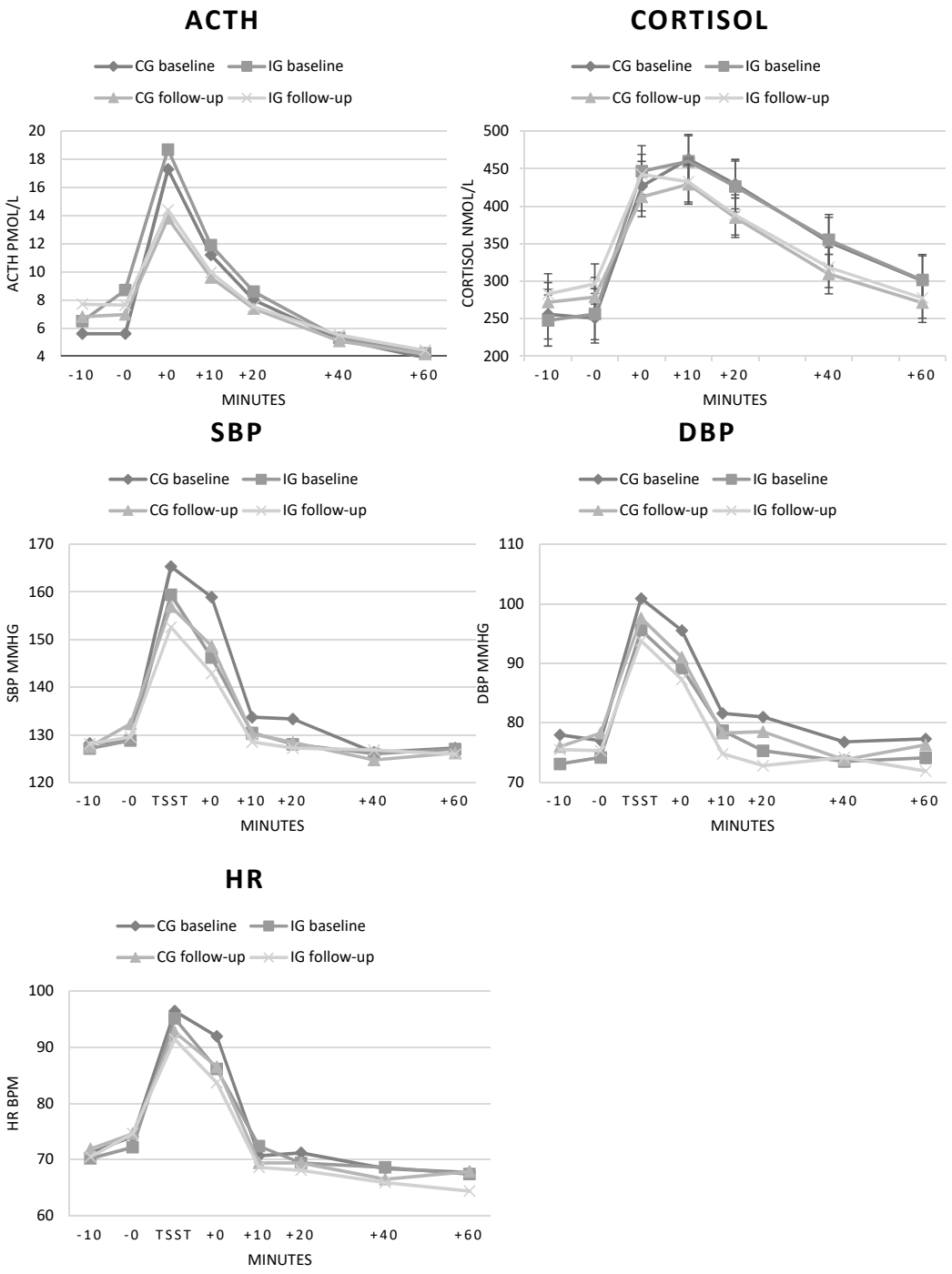


Fig 2. HPA-axis- and autonomic responses to the psychosocial stress test



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IV

DHEA and DHEA-S response to acute psychosocial stress and the relation to aerobic capacity in healthy women and men

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Abstract

Background

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) are two anabolic hormones, secreted from the adrenal cortex in response to adrenocorticotrophic hormone (ACTH). The aim of this study was to investigate the production capacity of DHEA and DHEA-S in response to acute psychosocial stress and its relation to aerobic capacity.

Methods

Eighty-one healthy but untrained individuals aged 20 to 50 years (34 women and 47 men) performed a psychosocial laboratory stress test and a peak oxygen uptake test. Levels of DHEA and DHEA-S were assessed before (pre-test), directly after and 10, 20 and 60 minutes after the stress test. Correlations between pre-test levels and magnitude of response in DHEA and DHEA-S and aerobic capacity was performed, as well as analyses of catabolic/anabolic balance.

Results

Both women and men responded to the stress test with a significant increase from pre-test to peak value in both DHEA, DHEA-S and cortisol/DHEA-S ratio, but not for cortisol/DHEA ratio. No correlations were found between pre-test levels or magnitude of response in DHEA and DHEA-S and aerobic capacity.

Conclusions

No correlations were found between aerobic capacity and pre-test levels of DHEA or DHEA-S, or between aerobic capacity and the production capacity of these hormones in response to acute psychosocial stress. A similar increase was seen in the catabolic hormone cortisol and the anabolic hormone DHEA in response to acute psychosocial stress, pointing at the plausible protective effect of DHEA in acute psychosocial stress.

Keywords

DHEA, DHEA-S, VO_2 peak, HPA-axis, physical activity

Background

Different physiological systems are activated in response to acute stress situations. One of the most frequently studied stress systems is the hypothalamic-pituitary-adrenal (HPA) axis (1), typically assessed as levels of adrenocorticotrophic hormone (ACTH) and cortisol. Increased levels of cortisol are important for the body to be able to meet the metabolic demands during acute stress (2, 3).

Other hormones not as frequently studied, but also released in the presence of ACTH in response to acute stress, are dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S)(4). DHEA and DHEA-S (abbreviated as DHEA/-S when mentioned together) are classified as anabolic hormones and are secreted in the deepest layer of the adrenal cortex. They are synthesized from cholesterol, converted to pregnenolone and thereafter further transformed to DHEA and DHEA-S (5). DHEA/-S peak in early adulthood and decrease thereafter with increasing age (6). The levels of DHEA fluctuate during the day, showing a diurnal rhythm. Because of a larger pool and slower clearance rate, DHEA-S is more stable over time, which result in smaller diurnal variations (5). DHEA/-S have been shown to have anti-oxidative, anti-inflammatory and anti-glucocorticoid effects (7, 8). Low levels of these hormones have been associated with medical conditions, including cardiovascular disease (9), and with increased risk for mortality (10).

The suggested role of DHEA and DHEA-S in the acute stress response is to counteract the catabolic effects of cortisol (11). In fact, cortisol and DHEA/-S has many opposing properties. For example, while cortisol has immunosuppressive effects, DHEA/-S has been shown to be an important up-regulator of the immune system (12). To illustrate the relation and balance between the catabolic effect of cortisol and the anabolic processes induced by DHEA/-S, a ratio can be calculated (cortisol/DHEA ratio) (13). A high ratio indicates low anabolic balance where cortisol is the more dominant of the two hormones (13), which has been shown to be a risk factor for e.g. depression (14).

Previously, the magnitude of response of DHEA/-S during acute stress has been shown to be correlated to the HPA axis response (4). There is also evidence for DHEA-S production capacity being lower during acute psychosocial stress in individuals reporting prolonged stress compared to non-

stressed individuals (15). Furthermore, it is suggested that the DHEA-S production capacity during acute psychosocial stress negatively correlates with age (4).

Aerobic capacity is strongly associated with all-cause mortality (16) and could possibly contribute to the inter-individual differences seen in DHEA/-S response to acute psychosocial stress. The so-called "cross-stressor adaptation hypothesis" refers to a theory suggesting that regular exercise training, which acts as a physical stressor, will lead to physiological adaptations of the stress systems to non-exercise stressors as well (17). The hypothesis is mostly studied for responses in the autonomic nervous system (18) and the HPA axis (19). To our knowledge, no previous study has explored whether aerobic capacity, assessed as peak oxygen uptake (VO_2 peak), relates to production capacity of DHEA/-S and the cortisol/ DHEA/-S ratio in response to acute stress. Therefore, we wanted to study this new perspective of the cross-stressor adaptation hypothesis.

Thus, the main aims of this paper were to study 1) the possible correlation between aerobic capacity, pre-test levels of DHEA/-S and magnitude of DHEA/-S responses to acute psychosocial stress, 2) the catabolic/anabolic balance between cortisol and DHEA/-S and 3) whether age is affecting the response in DHEA/-S to acute psychosocial stress.

Methods

This is a cross-sectional study based on baseline data from a randomized controlled trial (RCT) conducted at the Institute of Stress Medicine (ISM) in Gothenburg, Sweden, from 2013 to 2016. Study procedures have previously been described in detail elsewhere (20).

Participants

Participants were recruited through advertisements in two major newspapers in the area of Gothenburg and through social media. Inclusion criteria were being 20 to 50 years of age, essentially healthy (self-reported), working or studying at least 50 % of full time and reporting themselves as untrained according to the Saltin-Grimby Physical Activity Level Scale (21). This scale is a single-item question with four response alternatives (see Rödjer et al (22)). The first level corresponds to a sedentary life-style, while levels 2-4 represents graded increases in activity level from light to strenuous exercise

training. Exclusion criteria were having high glucose level (≥ 7 mmol/L) or HbA1C (≥ 48 mmol/mol), abnormal electrocardiogram (ECG), high blood pressure ((> 140/90) or anaemia (Hb < 120 g/L for women and < 130 g/L for men) or high or low body mass index (< 18.5 or > 35 kg/m^2). Also, medication with beta -blockers, psychopharmacological drugs or asthma medication and inability to exercise at a relatively high intensity led to exclusion. Individuals who had an abnormal ECG were further examined by a cardiologist before inclusion/ exclusion.

The number of responders to the advertisement was 416, of which 170 individuals fulfilled the inclusion criteria and were invited to a physical screening at the ISM. Twenty-two individuals declined participation in the study, and 24 more individuals were excluded after screening due to exclusion criteria. Five individuals were excluded after the initial tests due to incomplete measures, resulting in 119 participants. Of these, 81 individuals had complete data on DHEA and DHEA-S and were included in the final analyses. A drop-out analysis revealed no differences in baseline characteristics in this group compared to the total sample of 119 individuals.

All participants gave written informed consent before entering the study and were informed that they could withdraw their participation at any time. The study was conducted according to the 1964 Declaration of Helsinki and approved by the Regional Ethical Board, Gothenburg, Sweden, Dnr 917-12.

Assessment of aerobic capacity

The participants went through a VO_2 peak test on a bicycle ergometer (Monark 820 E; Monark Exercise AB, Vansbro, Sweden) in order to measure their aerobic capacity and time-to-exhaustion (TTE). The test was performed at the Center for Health and Performance at Gothenburg University, Sweden. The protocol was designed as a ramp test, starting with a five-minute light warm-up and thereafter increased resistance every minute until exhaustion. Heart rate was recorded with a pulse sensor (Polar 300RS, Polar Finland), and oxygen uptake (mL/kg/min) was measured with the Jaeger Oxycon Pro metabolic chart (Carefusion, Hoechberg, Germany) in a mixing chamber mode.

Psychosocial stress test

To enable assessment of individual reactions to psychosocial stress, the Trier Social Stress Test was used (23). It has been previously shown to elicit significant physiological stress responses in both women and men (24). The participants were presented with a task in front of a committee consisting of three members. After a preparation period of five minutes in another room, the participants re-entered the test room. In the first part of the test, a fictitious job interview, the participants presented themselves for five minutes. The second part of the test was an arithmetic task, not presented beforehand. After the TSST the participants rested for 60 minutes. All tests were performed between 1 p.m. and 3 p.m.

Assessment of DHEA, DHEA-S and cortisol

DHEA and DHEA-S were assessed in plasma ten minutes prior to the stress test (pre-test), directly after the stress test (+0 minutes) and 10, 20 and 60 minutes after the test. Peak value was identified as the highest level of the +0, 10 or 20 minutes value, while the last sample (60 minutes) was defined as the recovery value. Cortisol was assessed in serum and samples were collected at the same intervals as for DHEA/-S. Plasma samples were collected in EDTA -tubes and were cold spun at 3500 revolutions per minute for 15 minutes and stored in micro tubes at -80 º C until analysed. Serum samples were collected in Serum Sep Cloth Activator tubes, which were spun at 20 º C for 10 minutes at 3500 revolutions per minute and stored at 4 º C until analysed the day after the test.

Serum concentrations of DHEA were determined using a Liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (limit of quantitation 175 pmol/L), and serum concentrations of DHEA-S were assessed by radioimmunoassay techniques (RIA) (limit of detection 0.14 µmol /L, Diagnostic Products Corporation, Los Angeles, CA, USA). Serum concentrations of cortisol were assessed by electro chemiluminescence immunoassay (limit of detection, 0.5 nmol/L) (Roche Diagnostics GmbH, Mannheim, Germany).

Statistics

Pre-test values are presented as means together with the 95 % confidence interval (CI). The pre-test values for cortisol/DHEA ratio and cortisol/DHEA-S ratio were calculated by dividing the value for cortisol by the value for DHEA and DHEA-S, respectively. DHEA and cortisol/DHEA ratio were not normally distributed according to the Kolmogorov-Smirnov test. Logarithmic transformations were therefore used to elicit a normal distribution and enable parametric analyses. Pre-test values for these variables are presented as the geometric mean and anti-logged CI (marked with a * in the tables). Independent samples t-tests were used to evaluate differences between women and men at pre-test, and log values were used for the variables not normally distributed. Sex differences in smoking and educational level were evaluated using a Chi square test.

To evaluate the associations between variables, Pearson correlation analyses were used. For data not normally distributed Spearman's Rank Order Correlation was used.

The physiological responses to acute stress were assessed with paired samples t-tests separately for women and men, using pre-test and peak values. Percental response was calculated by subtracting the pre-test value from the peak value and dividing the difference by the pre-test value. Participants not showing increased values of DHEA or DHEA-S in response to the stress test (decrease or no change) were classified as non-responders.

Results

Background characteristics

In total, 81 participants were included (34 women and 47 men) in the study. There were no differences between women and men in the background characteristics regarding age, BMI and educational level. The frequency of tobacco users was higher among men than among women (see table 1).

Pre-test values

Pre-test hormonal levels are shown in table 2. As expected, pre-test DHEA-S levels were higher in the male participants than in the females, while DHEA levels did not differ between sexes. The

cortisol/DHEA-S ratio was higher among women than among men, but the cortisol/DHEA ratio was the same for both sexes. Additionally, men showed higher values for cortisol, VO_2 peak (mean value for women: 30.5, CI 28.5; 32.5, and for men: 36.7, CI 35.0; 38.7, p = < 0.001) and time-to-exhaustion (mean value for women: 7:06, CI 5:35; 6:43, and for men: 9:00, CI 8:38; 9:55, p = < 0.001) at pre-test.

DHEA, DHEA-S, cortisol/DHEA- and cortisol/DHEA-S ratio response to psychosocial stress

Response curves of DHEA and DHEA-S are presented in figure 1. Mean values of DHEA and DHEA-S increased significantly from pre-test to peak value in both women and men. For participants showing a positive response (75/81 = 93 %) to the TSST, the mean increase in DHEA was 117 % for women (range 17 to 291 %) and 120 % for men (range 19 to 350 %). One woman and one man showed negative responses from pre-test to peak (-27 and -43 %, respectively), and one woman and one man did not show any changed levels of DHEA in response to the test. For DHEA-S, the mean increases for participants responding with an increase (69/81 = 85 %) was 10 % for women (range 2 to 25 %) and 8 % for men (range 1 to 16 %). Five women and two men showed negative responses from pre-test to peak values (range -4 to -1 % for the women and -3 % for the men), and four women and two men did not respond in DHEA-S at the psychosocial stress test. Results from the paired samples t-tests analysing the increase from pre-test to peak value are presented in table 4. The only variable that did not increase in response to the stress test was the cortisol/DHEA ratio.

DHEA, DHEA-S, cortisol/DHEA- and cortisol/DHEA-S ratio and aerobic capacity

No correlation was seen between aerobic capacity and pre-test levels of DHEA or DHEA-S, or between aerobic capacity and cortisol/DHEA ratio or cortisol/DHEA-S ratio at pre-test, for either women or men (see table 3).

DHEA and DHEA-S, cortisol/DHEA- and cortisol/DHEA-S ratio response and aerobic capacity

No correlations were seen between aerobic capacity and DHEA-, DHEA-S, cortisol/DHEA- and cortisol/DHEA-S ratio response to the TSST (see table 3).

DHEA, DHEA-S, cortisol/DHEA-, cortisol/DHEA-S ratio response to acute stress and age

Age was negatively correlated with response in DHEA ($r = -.23$, $p = 0.038$), while no correlation was seen for DHEA-S response and age ($r = -0.021$, $p = 0.85$). Neither the cortisol/DHEA response ratio nor the cortisol/DHEA-S response ratio was shown to be significantly correlated with age ($r = 0.221$, $p = 0.052$ and $r = 0.104$, $p = 0.364$, respectively).

Discussion

The main aim of this study was to evaluate a new perspective to the cross-stressor adaptation hypothesis by investigating the possible correlation between aerobic capacity and DHEA/-S production capacity during acute psychosocial stress, which has not been studied before. We also studied the catabolic/anabolic balance between cortisol and DHEA/-S, both in pre-test levels and in response to acute psychosocial stress. In addition, age was analysed in relation to DHEA/-S and catabolic/anabolic balance in response to acute stress. The main results were that no correlations were seen between aerobic capacity, measured as VO_2 peak, and DHEA/-S levels. Possibly, the range for the VO_2 peak values was too small (19.8 to 44.7 for women and 25.6 to 52.5 for men) but, according to previous research, this population showed oxygen uptake levels corresponding to reference values for the general population (25). Besides, two earlier studies on basal levels of DHEA/-S and aerobic capacity was found, showing a somewhat greater span in aerobic capacity, yet no correlations were seen (26, 27).

Neither pre-test levels, nor the magnitude of response in DHEA/-S to the stress test showed correlations to aerobic capacity. Based on the cross-stressor adaptation hypothesis, we assumed that individuals with higher aerobic capacity would show higher production capacity in the health-promoting hormones DHEA/-S in response to acute psychosocial stress. This would have been plausible, given that exercise training has been shown to prevent several public health diseases (28-30) and has beneficial effects on general health and well-being (31). However, the results of this study could not show such correlations. As far as we know, this is the first publication on the possible correlation between aerobic capacity and DHEA/-S production capacity during acute psychosocial laboratory stress. More studies are required to enable reliable conclusions about the possible correlation between aerobic capacity and DHEA/-S responses to acute stress.

DHEA, DHEA-S and cortisol/DHEA-S ratio increased significantly from pre-test to peak for both women and men. This increase is seen as an adequate response for the body to overcome a stressor. One variable that did not change in response to the stress test was the ratio between cortisol and DHEA, indicating that the magnitudes of the response in cortisol and DHEA were comparable. To our knowledge, no other study has reported similar data. In this group of healthy adults, it might be a relevant result. In a well-balanced response, both anabolic and catabolic processes are active, and the fact that the same increase is seen in DHEA as in cortisol may be an indication of the protective effects of DHEA.

In this study, large inter-individual variations were seen in the magnitude of response in DHEA/-S to the stress test. At the same time, some individuals showed no response at all, or even negative responses. The explanation for these differences in response is not fully known but might be explained by higher stress levels at arrival for some of the participants. If a stressful event was experienced before arriving, the stress hormones were probably still at high levels when the first sample was taken. In that case, the negative feedback from the previous stress reaction would lead to decreased levels at the time of the stress test, despite the introduction of a new stressor.

Associations between DHEA/-S, cortisol/DHEA- and cortisol/DHEA-S ratio responses and age

A negative correlation was seen between response in DHEA and age, but no other correlations were seen. Both DHEA and DHEA-S are age dependent, and the lack of correlation for age and response in DHEA-S, cortisol/DHEA ratio and cortisol/DHEA-S ratio is difficult to explain. One factor that might play a role is the pre-test values. As discussed above, some individuals might have experienced stress before arriving at the lab, resulting in higher pre-test levels, which could have affected the correlations.

Strengths and limitations

The major strength of this study is the number of women and men, increasing the validity of the results. Another strength is that aerobic capacity was objectively measured with a peak oxygen uptake test instead of self-reported activity levels or a submaximal test with estimated peak values.

We sought untrained individuals reporting a sedentary lifestyle. This could be seen as a limitation, potentially evaluating a smaller span of aerobic capacity. However, when testing the oxygen uptake of the participants, the values for VO_2 peak were higher than expected and equivalent to oxygen uptake values in the general population. Therefore, we considered it possible to use in this study.

Conclusions

The results from the present study shows that in this population of healthy women and men, no correlations were found between aerobic capacity and pre-test levels of DHEA/-S, or between aerobic capacity and the production capacity of these hormones in response to acute psychosocial stress. Women and men exhibited a similar increase in DHEA/-S in response to acute stress. Additionally, cortisol and DHEA showed an equal percental increase, indicating that hormonal responses are not limited to HPA -axis response, which is in line with previous studies.

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Table 1. Characteristics for participants included in the study

	Women	**Men**	p
Age (mean (SD))	39 (7.5)	39 (7.3)	0.847
BMI (kg/m^2) (mean (SD))	24.3 (3.3)	25.3 (3.6)	0.193
Tobacco user (n (%))	1 (3)	13 (28)	**0.004**
Post-graduate education (n (%))	32 (94)	39 (83)	0.133

BMI: Body Mass Index

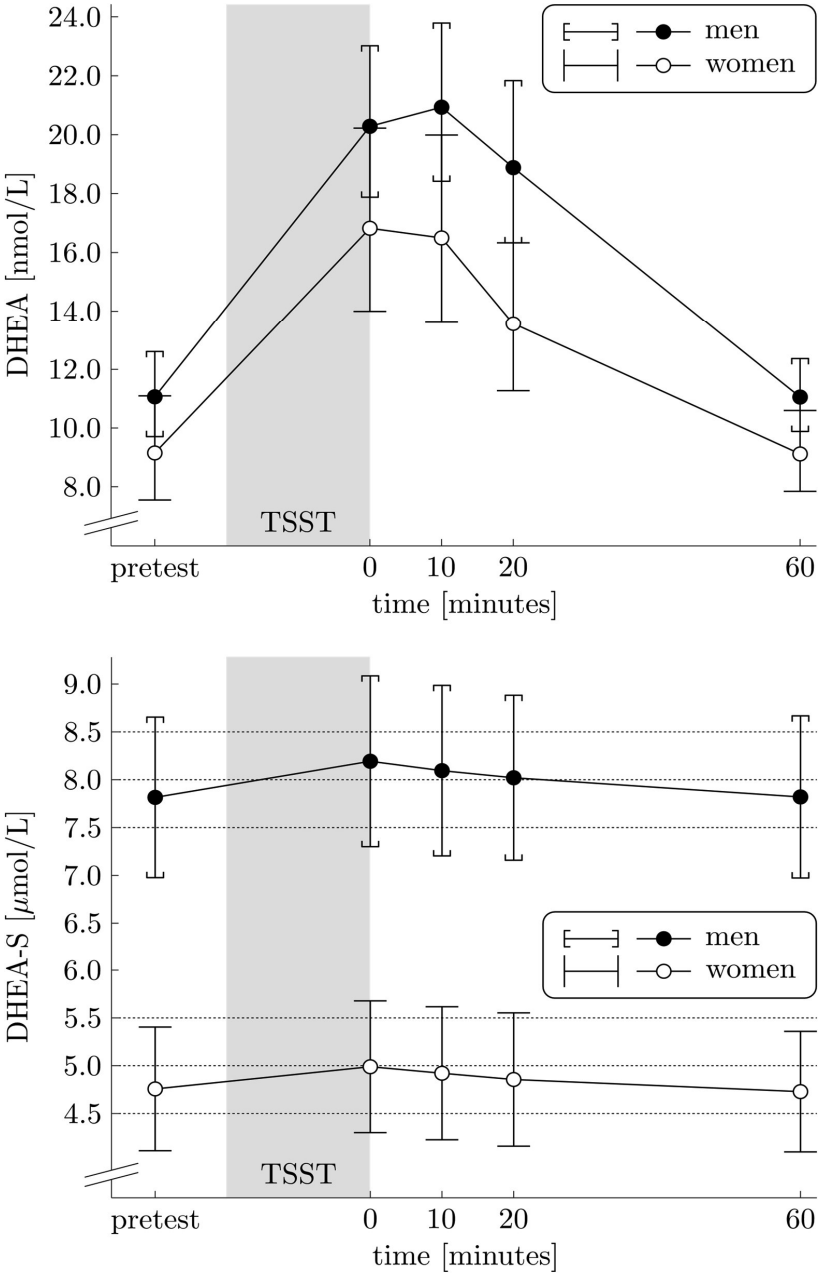
Table 2. Mean pre-test hormonal values for women and men measured 10 minutes before the acute psychosocial stress test

	Women mean (95 % CI)	**Men** mean (95 % CI)	p
DHEA (nmol/L) *	9.2 (7.6; 11.1)	11.1 (9.6; 12.5)	0.103
DHEA-S (µmol/dL)	4.8 (4.0; 5.3)	7.8 (6.9; 8.8)	**< 0.001**
Cortisol (nmol/L)	225.6 (195.3; 259.9)	272.9 (247.1; 308.1)	**0.029**
Ratio C; DHEA*	23.4 (19.7; 27.7)	23.5 (20.5; 26.8)	0.935
Ratio C; DHEA-S	48.0 (42.1; 73.2)	35.3 (32.9; 50.1)	**0.013**

**geometric mean (anti-logged 95 % CI)*

DHEA: dehydroepiandrosterone, DHEA-S: dehydroepiandrosterone sulfate, ACTH: adrenocorticotropic hormone, C: cortisol

Figure 1. Levels of DHEA and DHEA-S in response to acute psychosocial stress in women and men



DHEA: Dehydroepiandrosterone, DHEA-S: Dehydroepiandrosterone sulfate, TSST: Trier Social Stress Test

Table 3. Physiological response to the Trier Social Stress Test for women and men

	Pre-test	Peak	Difference	Paired samples t-test			
	Mean (95 % CI)	Mean (95 % CI)	Mean (95 % CI)	t	df	p value	effects size eta squared
Women							
DHEA (nmol/L) *	9.2 (7.5; 11.1)	17.6 (14.6; 21.2)	8.4 (7.4; 11.6)	-10.0	31	**<0.001**	0.76
DHEA-S (µmol/L)	4.8 (4.1; 5.4)	5.1 (4.4; 5.8)	0.3 (0.2; 0.4)	-5.7	33	**<0.001**	0.50
ratio C/ DHEA*	23.4 (19.7; 27.7)	21.7 (18.7; 25.3)	-1.7 (-4.6; 0.7)	1.5	31	0.155	0.06
ratio C/ DHEA-S	56.5 (41.3; 71.7)	92.0 (76.4; 107.5)	35.5 (25.4; 45.6)	-7.1	33	**<0.001**	0.61
Men							
DHEA (nmol/L) *	11.1 (9.7; 12.7)	22.1 (19.3; 25.2)	11 (9.5; 14.6)	-12.2	46	**<0.001**	0.76
DHEA-S (µmol/L)	7.8 (7.0; 8.7)	8.4 (7.5; 9.3)	0.6 (0.4; 0.7)	-9.0	46	**<0.001**	0.64
ratio C/ DHEA	23.5 (20.5; 28.8)	22.6 (19.7; 26.0)	-0.9 (-3.4; 2.4)	0.8	45	0.423	0.01
ratio C/ DHEA-S	41.5 (32.9; 50.1)	69.3 (59.5; 79.1)	27.8 (21.2; 34.4)	-8.5	45	**<0.001**	0.61

**geometric mean (anti-logged 95 % CI)*

DHEA: dehydroepiandrosterone, DHEA-S: dehydroepiandrosterone sulfate, C: cortisol, CI: confidence interval, df: degrees of freedom

Table 4. Correlations between aerobic capacity and pre-test levels of DHEA, DHEA-S, cortisol/ DHEA ratio and cortisol/ DHEA-S ratio, and between aerobic capacity and response of DHEA, DHEA-S, cortisol/ DHEA ratio and cortisol/ DHEA-S ratio to acute psychosocial stress

	Women		**Men**	
	r	p	r	p
Pre-test				
DHEA (nmol/L) *	-0.02	0.918	0.05	0.744
DHEA-S (µmol/dL)	0.08	0.662	0.19	0.228
ratio C/ DHEA	-0.09	0.628	-0.01	0.937
ratio C/ DHEA-S	-0.14	0.426	-0.15	0.338
Response				
DHEA (nmol/L) *	0.07	0.713	-0.10	0.541
DHEA-S (µmol/dL)	0.07	0.694	0.08	0.629
ratio C/ DHEA	0.02	0.935	0.10	0.539
ratio C/ DHEA-S	0.33	0.062	0.02	0.881

**Non-parametric analyses*

DHEA: dehydroepiandrosterone, DHEA-S: dehydroepiandrosterone sulfate, ACTH: adrenocorticotropic hormone, C: cortisol

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