Etiology and Pathophysiology

The physical activity, stress and metabolic syndrome triangle: a guide to unfamiliar territory for the obesity researcher

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Summary

Research aimed at deciphering the aetiology of obesity and the metabolic syndrome remains focused on two behavioural factors, namely diet and physical activity, even though epidemiologic research suggests that these two cornerstones of treatment and prevention account for only a small-to-moderate portion of the variance in these phenotypes. In recent years, this observation has prompted the intensified investigation of the pathogenic potential of factors that extend beyond the traditional concept of energy imbalance and examine the putative causes of this imbalance. Psychosocial stress has emerged as one such factor, raising the need for researchers to be informed about this expansive and complex literature. The purpose of this review is twofold (i) To introduce obesity researchers to fundamental concepts and historically important theoretical developments in the stress field and (ii) To outline the dyadic and triadic interactions between stress, physical activity and the metabolic syndrome. Although the expansion of the research focus to multiple, diverse and interacting putative causal agents will certainly increase the complexity of the research enterprise, this step seems essential for the comprehension and effective response to the continuing rise in the prevalence of obesity and the metabolic syndrome.

Keywords: Cortisol, catecholamines, exercise, emotion.

Introduction

Conventionally, diet and physical activity are considered the two cornerstones in the prevention and treatment of obesity, even though epidemiologic research suggests that diet and physical activity leave a considerable amount of the variance unexplained. As the prevalence of obesity and the metabolic syndrome continue to rise (1), researchers increasingly speculate that other genetic, epigenetic and environmental factors may augment the traditional concept of energy imbalance in the aetiology and pathophysiology of obesity and the metabolic syndrome (2–7).

One hypothesis implicates perturbations in the function of the hypothalamic-pituitary-adrenal (HPA) and sympathetic adrenomedullary (SAM) axes. This hypothesis draws upon the linkage between the physiology of the stress response, specifically elevated cortisol and catecholamine levels, and components of the metabolic syndrome (8). Several authors have examined the independent relationships between stress and components of the metabolic syndrome for both adults (9) and children (10,11). The dyadic relationships between physical activity and the components of the metabolic syndrome; physical activity and stress; and stress and the metabolic syndrome have been addressed in the literature. However, the triadic system of interactions between physical activity, stress and components of the metabolic syndrome has received limited attention (12,13).

This emerging multifactorial view of obesity and the metabolic syndrome presents exciting new avenues for exploration but also presents challenges for obesity researchers who are now called to become proficient in new, unfamiliar and complex subjects and literatures. The purpose of this review is to provide an overview of the literature linking physical activity, psychosocial stress and the metabolic syndrome. It begins with a section on the definition and scope of stress and continues with sections devoted to the dyadic and triadic relationships between these variables. It is assumed that most readers are already familiar with basic information on physical activity and the metabolic syndrome.

Stress

Definition and scope

Contemporary scientific interest on the impact of stress on health stems from a half-page publication by Hans Selye (14) in the journal *Nature* on 4 July 1936, entitled 'A syndrome produced by diverse nocuous agents'. In it, Selye outlined a so-called 'general adaptation syndrome', which manifests itself when an organism is exposed to damaging stimuli as diverse as cold, injury, transcision of the spinal cord, excessive exercise or intoxication. The syndrome, according to Selye's description, progresses in three stages, including an initial alarm reaction, a stage of resistance, and, if the damage continues, exhaustion and death. In the process, there is characteristic enlargement of the adrenal glands, involution of the thymus and lymph nodes, and ulceration of the stomach. Although the term 'stress' did not appear in that first publication, Selye is responsible for assigning to it the meaning it now has in the biomedical literature. The exact definition evolved over a period of decades. For example, 'we may define stress as the state manifested by a specific syndrome which consists of all the nonspecifically induced changes within a biologic system' (15) or, later (and more famously), 'stress is the nonspecific response of the body to any demand made upon it' (16).

These definitions illustrate the central importance in Selye's conceptualization of stress of the notion of non-specificity. Selye insisted that there are striking similarities in the way that the body responds and adapts to diverse challenges from within or outside, regardless of the exact nature of these challenges. Prompted by the notion of non-specificity, much of Selye's work on stress was devoted to the search for the so-called 'first mediator', an elusive substance that he believed was the single common signal for the initiation of the stress response to various stimuli. Importantly, the first mediator was sought strictly among the body's chemicals: 'The nature of the alarm-signals, which are sent out by various tissues in the body, is perhaps one of the most fundamental questions with which present-

day stress-research is confronted' (15). Several substances suspected to be the 'first mediator(s)' were examined and eliminated as candidates (e.g. adrenaline, noradrenaline, acetylcholine, histamine). It was only shortly before the end of his life that Selye gave serious consideration to the role of psychological factors:

> Stressors, it should be noted, are not exclusively physical in nature. Emotions, e.g. love, hate, joy, anger, challenge, and fear, as well as thoughts, also call forth the changes characteristic of the stress syndrome. In fact, psychological arousal is one of the most frequent activators (17).

Although extensive references to psychological factors did not start appearing until the late stages of his life, it is also important to point out that Selye's first pertinent observation came rather early, albeit as an incidental side note: 'even mere emotional stress, for instance, that caused by immobilizing an animal on a board (taking great care to avoid any physical injury), proved to be a suitable routine procedure for the production of a severe alarm reaction' (18).

This observation became the starting point for critics of Selye's concept of stress from the field of psychology. Richard Lazarus (19) focused on the fact that the magnitude of human stress responses is typically not proportional to the degree of objective danger. Thus, he rejected the idea of stress as a passive response and instead proposed that the key in the stress process is the subjective appraisal of threat. This appraisal is a cognitive inferential process about the meaning of the stimulus and its implications for the well-being and the goals of the individual, influenced jointly by the individual's psychological make-up (e.g. knowledge and beliefs) on the one hand and the situation on the other. This concept gradually matured into one of the most influential cognitive theories of stress and emotion (19,20).

Non-specificity or multihormonal patterning?

John Mason (21–24) focused his critique of Selye's view of stress on the notion of a chemical 'first mediator' and the fundamental tenet of non-specificity. On the nature of the first mediator, Mason agreed with Lazarus in assigning a central role to psychological processes. In his words, the first mediator 'may simply be the psychological apparatus involved in emotional or arousal reactions to threatening or unpleasant factors in the life situation as a whole' (21). On the concept of non-specificity, Mason was a pioneer in broadening the scope of investigations beyond morphological changes in organs and tissues and beyond focusing on a single hormone or a single endocrine system. Instead, he systematically recorded changes across multiple endocrine systems in response to multiple challenges, including those of psychological nature. His conclusion was that, contrary to Selye's strong insistence on non-specificity, there was evidence of patterning and specificity: 'The picture emerg-

ing so far from our study of multihormonal patterns, in fact, is one suggesting that such patterns are organized in a rather specific or selective manner, depending upon the particular stimulus under study, and probably in relation to the complex interdependencies in hormonal actions at the metabolic level' (23).

The stress axes: specificity revisited

A tremendous amount of information has emerged on the endocrine, immune and central nervous system responses to stress and their interdependencies. Two endocrine systems continue to be regarded as the primary components of the stress response. One system extends from the parvocellular division of the paraventricular nucleus of the hypothalamus, via the portal circulation, to the anterior lobe of the pituitary gland and, finally, to the zona fasciculata of the adrenal cortex. This system is commonly referred to as the hypothalamic-pituitary-adrenocortical (HPA) axis. The three nodes in this axis produce, respectively, corticotropin releasing hormone, adrenocorticotropic hormone and cortisol. The other system extends from various brainstem and limbic nuclei (caudal raphe, ventromedial and rostral ventrolateral medulla, the ventrolateral pontine tegmentum and the hypothalamic paraventricular nucleus) via the splanchnic sympathetic ganglion to the chromaffin cells of the adrenal medulla. This system is commonly referred to as the SAM axis. Its end products are the catecholamines adrenaline and noradrenaline. Additional details on the physiological function and regulation of these systems or their interactions with other endocrine and immune systems are beyond the scope of this review. This information is readily available in physiology textbooks and recent reviews (e.g. Bohus et al. (25); Charmandari et al. (26); Chrousos (27)).

Here, we focus on the current status of the specificity debate and, in particular, the relationship between emotional states and the activation of the HPA and SAM axes. These issues, despite their fundamental importance, are not frequently addressed in the literature and, as a result, it may be difficult for a newcomer to the stress field to fully grasp their implications.

Supporting Mason's earlier findings, contemporary research continues to provide evidence refuting the notion of non-specificity. It appears that each stressor and, more specifically, each stressor at each level of intensity or severity, has a distinct and replicable 'signature' in the patterning of not only hormone levels but also the activity of brain regulatory centres (28,29). What is perhaps less well understood is the 'signature' of different psychosocial stressors or emotional states. Specifically, the question of whether particular types of stressful situations or emotions are linked to particular patterns of neuroendocrine responses remains open for investigation.

Let us begin with what has been, for over a century, the dominant model for conceptualizing the similarities and differences that characterize the subjective states that fall within the domain of affect, including moods and emotions. This model, known as the affect circumplex (30,31), posits that the global affective space can be defined by two orthogonal and bipolar dimensions; one represents affective valence (pleasure vs. displeasure) and the other represents the degree of activation (low vs. high). Different affective states are considered combinations of various degrees of the basic elements of valence and activation, such that they can be arranged in circular fashion in the two-dimensional space defined by these dimensions (see Fig. 1). States that are experientially similar (e.g. happy, glad) are close together on this circle, states that are antithetical (e.g. happy, sad) are 180° apart, and states that are unrelated to each other (e.g. tense, excited) are separated by 90° angles. The dimensions of valence and activation are believed to be the fundamental building blocks of affective life and emerge with remarkable consistency across different types of dimensional analysis (factor or scaling analyses), different types of stimuli (words, facial expressions of emotion) and different cultures (32,33).

This dimensional conceptualization of affect is remarkably consistent with an organizing framework that has been proposed for the specificity of endocrine responses to stress. This framework was proposed independently by two researchers as the culmination of long and prolific careers. One was Marianne Frankenhaeuser, whose work focused on human occupational health psychology, and the other was James Henry, whose work with animals focused on adaptation to stress and the mechanisms of cardiovascular disease (CVD). Their models postulate that the HPA axis and cortisol seem to be sensitive to differences along the affective valence dimension (pleasure vs. displeasure), whereas the SAM axis is primarily sensitive to differences along the activation dimension. According to Frankenhaeuser (34), 'epinephrine is a general (non-specific) indicator of mental arousal, increasing regardless of whether the affect is positive or negative'. In contrast, 'cortisol generally increases in negative affective states only'. Henry's model was summarized as follows: 'One system [HPA] responds with distress and with euphoria in situations associated, respectively, with loss of control and with success; the other [SAM], which is activated by situations demanding effort, decreases its response when relaxation predominates' (35). Frankenhaeuser (34,36) further noted that the cortisol response should be expected to be stronger when displeasure is combined with low activation (as in exhaustion or boredom) than when displeasure is combined with high activation (as in fear or tension). Frankenhaeuser offered the examples of depressed patients, prisoners awaiting trial, or people who lost jobs for the former and people under pressure to produce in low-control, coercive jobs for the latter. On

Russell's Circumplex Model
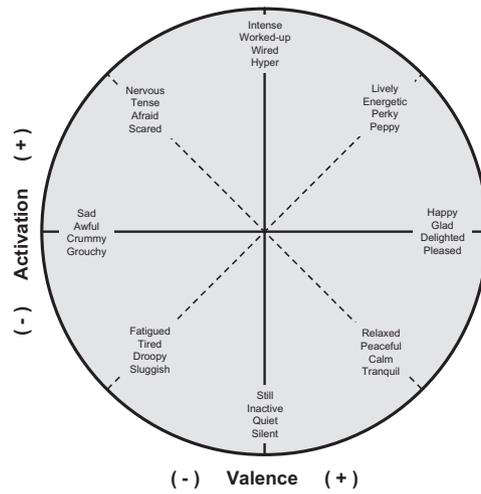
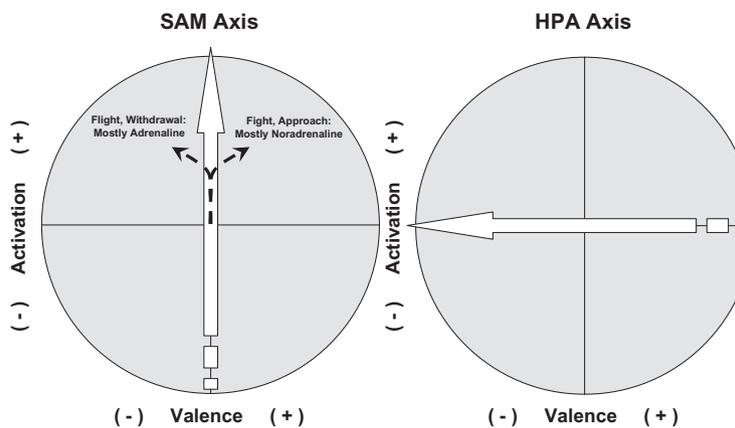## Frankenhaeuser's Specificity Model
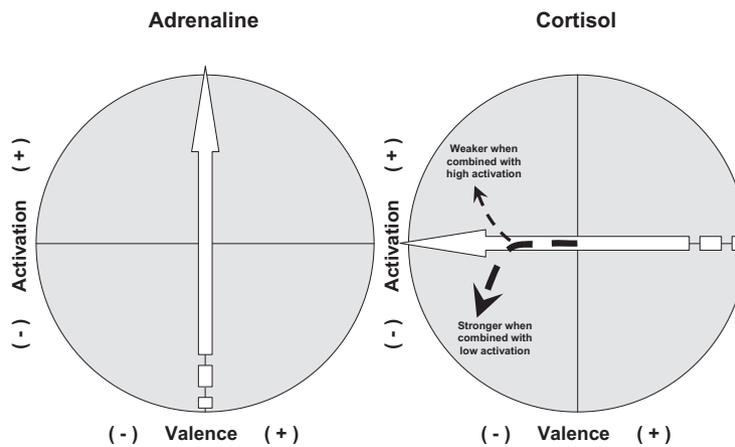
Henry's Specificity Model

Figure 1 Illustration of the compatibility between the circumplex model of affect proposed by Russell and the models of neuroendocrine response specificity proposed by Frankenhaeuser (based on research with humans) and Henry (based on research with animals). HPA, hypothalamic-pituitary-adrenocortical; SAM, sympethetic adrenomedullary.

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the other hand, although Frankenhaeuser (36) noted that 'the pattern of [epinephrine] and [norepinephrine] secretion from the adrenal medulla tends to be rather similar, irrespective of the quality or nature of the emotional experience', Henry (37,38) maintained that adrenaline is primarily associated with fear, whereas noradrenaline is primarily associated with anger. Today, the model proposed by Frankenhaeuser and Henry is commonly used as the conceptual basis for investigations focusing on HPA and SAM responses to psychosocial stressors (39).

For researchers interested in studying the dynamics of the HPA and SAM axes in response to psychosocial stressors, this conceptual framework has important implications. If the primary target of investigation is the HPA response, the experimental situation should involve negative affect. Typically, this is accomplished with tasks that allow little or no chance for the participants to successfully meet the given performance goal and combine such elements as social evaluation, loss of control and a sense of helplessness (40,41). Furthermore, given the relatively slow response of the HPA axis, these tasks are also fairly long and protracted.

A standard protocol commonly used for the investigation of the HPA response is the Trier Social Stress Test (42). This protocol involves standing in front of a microphone, a three-member panel, a video camera and a tape recorder and delivering a 5-min speech as a job applicant. After a preparation period, the speech is delivered but, upon finishing, the participant is told 'You still have some time left. Please continue!' After this, participants are instructed to subtract the number 13 from 1022 as quickly and accurately as possible, only to be told to restart with each mistake. In different samples, this protocol has been found to induce a twofold to fourfold increase in salivary cortisol levels.

On the other hand, if the primary target of investigation is the SAM response, the experimental situation should mainly involve high levels of activation and effort (ideally, uncontaminated by physical effort). Such tasks should be as engaging and engrossing as possible, challenging but also offering a reasonable chance of success (so that they do not elicit a consistently positive or a consistently negative outcome) (43). For additional methodological and technical considerations (e.g. diurnal patterns, timing of assessment protocols, analysis techniques), readers are referred to other recent tutorials (44–47).

Linking psychosocial stress to pathophysiology

Identifying the toxic element

Another important issue pertains to models linking psychological stress to pathophysiology. Such models are important for the applied researcher because they can identify the aspect of the psychobiological response that is potentially the most relevant to the pathology of interest and therefore essentially dictate what aspect of the response one should examine. The traditional approach has been to consider only the amplitude of the stress response (e.g. the elevation of heart rate or hormone levels). The assumption underlying this approach, referred to as the 'hyper-reactivity model', is based on the belief that it is the magnitude of the stress response that is the 'toxic element' or the aspect of the response most closely associated with stress-related pathologies. This assumption entails that, if one wishes to investigate the relationship between stress and a pathological condition (such as CVD or the metabolic syndrome), one should try to relate a measure of the magnitude of the stress response (e.g. beats min^{-1} of heart rate, mmHg of blood pressure or nmol L^{-1} of cortisol) with an index of the pathology of interest (e.g. coronary calcification score, body mass index or waist circumference). A corollary is that the effectiveness of interventions designed to reduce the toxic sequella of stress (e.g. exercise or relaxation techniques) should be judged by whether they can attenuate the magnitude of the stress response.

If one considers the totality of the stress response, it is apparent that the amplitude of the response is only one way to define it and, in many cases, it might not be the most meaningful descriptor. The impact on the body could be determined by several other criteria. Dys-regulation comes in many forms. McEwen (48) has used the concept of allostatic load, the wear and tear of the body that occurs as a result of repeated cycles of adapting to internal and external demands, to illustrate what these other forms might be. According to McEwen, the normal course of events in the process of 'allostasis' (i.e. adapting to changing demands) consists of an appropriately sized stress response of the SAM and HPA axes to help us deal with the demand, immediately followed by a rapid deactivation and return to baseline. This is what 'normally happens when the danger is past, the infection is contained, the living environment is improved, or the speech has been given' (48). However, there are at least four other scenarios, each of which can exacerbate the allostatic load. These include (i) Repeated activations with excessive frequency; (ii) Failure to habituate (i.e. show a gradually attenuating response to a familiar stressor); (iii) Delayed and slow recovery and return to baseline and (iv) Failure of a system to respond, resulting in compensatory or unregulated activation of other systems (for an application of the allostatic perspective to the pathophysiology of the metabolic syndrome, see van Dijk and Buwalda) (49). Chrousos and Gold (50) have focused on the 'chronicity' and 'excessiveness' of the stress response as its most pathogenic elements, essentially relaying a similar message:

Generally, the stress response is meant to be acute or at least of a limited duration. The time-limited nature of

this process renders its accompanying anti-anabolic, catabolic, and immunosuppressive effects temporarily beneficial and of no adverse consequences. *Chronicity* and *excessiveness* of stress system activation, on the other hand, would lead to the syndromal state that Selye described in 1936 (50).

In other words, besides how large a stress response is, it is also important to consider (i) How frequently it occurs; (ii) How long it lasts once it occurs and (iii) How quickly the body returns to baseline (also see the emerging literature on the 'perseverative cognition' hypothesis) (51–53).

One issue of paramount importance not mentioned so far but anticipated by the previous discussion on the (non-) specificity of the stress response pertains to the patterning of the response (54). Given what is known about the effects of catecholamines and cortisol on metabolic processes, would a SAM-dominant or an HPA-dominant response entail equal risk? This is unlikely. For researchers interested in obesity and the metabolic syndrome, it should be noted that the HPA axis appears to be involved in food intake and fat deposition more directly and in more ways than the SAM axis (55–58) and is receiving closer attention in applied research linking endocrine function to energy balance and metabolism (59). Researchers are urged to consider not only the magnitude of the stress response but also other aspects that may have pathogenic potential, including the number or frequency of responses per day, the ability to habituate to familiar stressors, the duration of stressful episodes, the rate of return to baseline and the patterning of neuroendocrine responses (also see Linden *et al.* (60); Schwartz *et al.* (61)).

Stress, obesity and the metabolic syndrome: possible mechanisms

Hypercortisolaemia has frequently been associated with adiposity, particularly visceral adiposity (62–64). Visceral fat accumulation can be viewed as a pathological adaptation to stress (65) as it is particularly sensitive to cortisol, perhaps because of the high density and apparent sensitivity of glucocorticoid receptors in this region. 11β-hydroxysteroid dehydrogenase type 1 (11HSD1) has emerged as a potential vector in the aetiological relationship between stress and obesity (66,67). 11HSD1 appears central in the conversion of the inactive cortisone to the active cortisol (68) and is predominantly expressed in metabolically highly active tissues, including the liver, adipose tissue, lung and areas of the central nervous system (69). In obesity, 11HSD1 activity appears to be magnified at adipocytes and depressed at the liver (66), which can create a state of hypercortisolaemia in the viscera.

Hypercortisolaemia also creates favourable conditions for increased lipoprotein lipase (LPL) and hormone-sensitive lipase activity, the chief enzymes involved in the conversion of triglycerides to free fatty acids in the circulation and intracellularly respectively. LPL is responsible for increasing the amount of triglycerides at the adipocyte (70) and, as insulin resistance often manifests concurrently with visceral adiposity, the increased circulating insulin exerts anti-lipolytic effects and subsequent decreased lipid mobilization (70). Likewise, cortisol appears to have a stimulatory effect on LPL activity when insulin is present (71). It is thought that chronic hypersecretion of cortisol may lead to impaired feedback and resistance, which mimics insulin resistance. Hormone-sensitive lipase imparts its most deleterious effect in the development of atherosclerotic plaque. Atherogenesis involves the uptake of lipoproteins by macrophages, which in turn leads to cellular accumulation of cholesterol and formation of foam cells or fatty streaks (72). This process may be exacerbated in persons with a dys-regulated or hyperactive stress response given that glucocorticoids stimulate the esterification of sterols in smooth muscle (73).

Complementary to the dys-regulation of the HPA axis, the SAM axis also plays a role in the pathogenesis of metabolic syndrome, particularly with regard to visceral obesity. Obese individuals with a dys-regulated HPA axis also have increased SAM activity, suggesting that stress severe enough to promote visceral obesity may intensify SAM activity (74). Additionally, visceral obesity is associated with a greater basal SAM activity compared with peripheral obesity or subcutaneous abdominal obesity (63). The presence of hypertension within the metabolic syndrome symptomatology seems to further intensify sympathetic reactivity. In persons with metabolic syndrome whose classification included hypertension, SAM activity was found to be greater than in non-hypertensives (75). This could in part be as a result of the decreased baroreflex sensitivity that is associated with visceral obesity (76). Because the HPA axis and locus coeruleus appear to be perturbed in obesity and insulin resistance (77–81), it has been hypothesized that these attributes of the metabolic syndrome are driven by exacerbated stress reactivity (82) and possibly mediate a causal relationship between psychosocial variables and CVD (83).

Evidence linking dys-regulations in both the HPA and the SAM axes to obesity and the metabolic syndrome is accumulating (84–88). Perhaps the most striking feature of this emerging literature is the diversity of the ways in which 'stress' has been operationalized. This reflects the continuing absence of a guiding overarching theoretical framework and a multiplicity of perspectives about the aspect of stress that carries the greatest pathogenic potential and should therefore be the focal variable. Thus, some studies focus on acute reactivity (with cardiovascular autonomic measures, catecholamines or cortisol being used as stress indices), some studies focus on chronic life stress, and some focus on baseline levels and diurnal patterns (mainly of cortisol).

Excellent reviews have been published on the relationship between stress and general health (89–91). In the following sections, we examine studies linking stress reactivity and chronic stress to obesity and the metabolic syndrome.

Acute stress

Stress reactivity studies have examined the relationship between the stress response (its amplitude and duration) and the risk factors of the metabolic syndrome. The most convincing evidence emerges when examining cardiovascular and endocrine reactivity in conjunction with abdominal obesity (Table 1). In laboratory stress-induction paradigms, adiposity is consistently associated with exaggerated heart rate and blood pressure responses (92–95), possibly driven by increased cardiac output and total peripheral resistance (96,97). Exaggerated catecholamine (94) and glucocorticoid (98–102) responses have also been found to be associated with central adiposity. Furthermore, abdominal adiposity appears related to slower cardiovascular (97,103) and endocrine (99) recovery. As noted earlier, slow recovery following exposure to stress may suggest increased allostatic load or burnout (103,104) and may increase risk independently of the magnitude of the stress response.

Chronic stress

Chronic psychosocial stress and associated long-term dysregulation of neuroendocrine stress responses were initially investigated by examining the relationship of the socioeconomic gradient with all-cause and CVD mortality (105–109). Recent investigations have further examined this relationship along with the influence of persistently negative emotions. The links between chronic stress and obesity or the metabolic syndrome seem particularly evident in the context of occupational stress (110–114).

The Whitehall II study, a follow-up of the initial Whitehall study of the 1960s that linked differences along the social gradient with morbidity and mortality, has been crucial in elucidating the relationship between occupational stress and CVD (115). The Whitehall II included baseline assessments of cardiovascular health and psychological well-being on 10 308 non-industrial civil servants from 20 departments in central London. Clinical screenings and questionnaire assessments have been conducted every five years. Additional questionnaire data have been collected in-between clinical screenings. There have since been seven follow-up periods, with the final assessment including 67% of the original cohort (116). The main findings from this study are shown in Table 2 and demonstrate a relationship between high job strain and effort–reward imbalance and health (117–130). Additionally, a recent follow-up demonstrated a dose–response association between exposure to work-related stress and the odds of metabolic syndrome occurrence (131). Even after excluding participants who were obese at baseline (assuming that obesity is a proxy indicator for metabolic syndrome), the association between exposure to work stress and metabolic syndrome remained (131).

Other prospective cohort studies (Table 2) have shown similar results among diverse populations (132–139). Moreover, stress-related variables have long been suspected to increase the risk of CVD (132) and all-cause mortality (132,133). Although establishing a causal relationship remains an ongoing challenge, the evidence linking chronic exposure to stress with poor metabolic health is growing.

Physical activity, exercise and stress

The rationale for employing physical activity as an intervention to buffer the harmful effects of stress is based on the fact that a bout of exercise (structured and purposeful physical activity) itself can be a stressor and, as such, it can engage most of the same biological pathways as psychosocial stress (i.e. SAM, HPA, cardiovascular system). Sothmann *et al.* (140) conducted an extensive review in the mid-1990s and concluded that a bout of exercise that is designed to elicit an improvement in aerobic fitness typically elicits a stress response as well. Thus, the working assumption is that exercise can produce beneficial adaptations in the stress pathways while avoiding harmful effects on health. In turn, these exercise-induced adaptations are expected to also manifest themselves as responses to psychosocial stressors that are modified in a way that entails reduced potential for harm. This rationale is referred to in the literature as the 'cross-stressor adaptation hypothesis' (140,141).

Until now, the majority of studies investigating this hypothesis have utilized measures of cardiorespiratory responses (e.g. heart rate, blood pressure) and laboratory stressors (e.g. mental arithmetic, Stroop word-colour conflict task, hand or foot cold pressor task). Most of these studies are also cross-sectional rather than experimental. Their results have been summarized in a series of recent meta-analyses, but the conclusions are not entirely consistent (142–144) (Table 3).

Narrative reviews that have focused on neuroendcrine responses to stress (SAM, HPA) do not report positive findings. Péronnet and Szabo concluded: 'Following an extensive review of the literature, we are unable to confirm that physical exercise training results in modification of sympathetic response to psychosocial stress' (145). Likewise, in a recent update on the status of the cross-stressor adaptation hypothesis, Sothmann remarked: 'The few studies conducted to date with humans suggest that, while exercise training for three to four months may increase key physiological measures of fitness, it generally has not induced changes in stress reactivity as indicated by neuroendocrine measures where a short-term psychosocial challenge is the precipitating factor' (141). Sothmann

Table 1 Summary of studies examining stress reactivity and recovery and obesity

References	Focus	Subjects	Design	Stressor(s)	Summary of findings
Barnes *et al.* (95)	Relation between WHR and haemodynamic function	95 normotensive adolescents (mean age 14.8 years) with family history of hypertension	Experimental	Postural change, 5-min video game, forehead cold	• After controlling for overall (BMI) and peripheral (triceps skin-fold) adiposity, the highest WHR tertile showed greater (i) SBP reactivity to postural change and video game and (ii) DBP reactivity to postural change and forehead cold than lowest tertile
Davis *et al.* (92)	Relationship between body fat distribution and haemodynamic stress	24 women (11 central obese, 13 peripheral obese)	Experimental	Speech task, cold pressor task	• Central obesity associated with greater increases in SBP and DBP • Peripheral obesity related to greater Q in response to behavioural stressor
Epel *et al.* (98)	Whether women with high WHR across BMIs consistently show heightened cortisol reactivity	59 women, premenopausal	Experimental	Mental arithmetic, visuospatial puzzle, speech task	• Women with high WHR found laboratory challenges more threatening • Lean women with high WHR lacked habituation to stressor and continued to secrete more cortisol on subsequent days when compared with lean women with low WHR • Central fat is related to greater psychological stress and cortisol reactivity
Gluck *et al.* (99)	WHR and cortisol responsivity in obese women with BED	22 obese women (11 BED, 11 non-BED)	Experimental	Cold pressor task	• Cortisol AUC and peak cortisol reactivity associated with WHR in BED (stressed) group
Goldbacher *et al.* (64)	Association between WC and cardiovascular stress reactivity	211 boys and girls, 14–16 years (50% female, 50% Black)	Experimental	Mental arithmetic, mirror image tracing, type A adolescent structured interview, cold pressor task	• Greater WC associated with greater SBP and DBP reactivity in boys only
Jern *et al.* (96)	Effects of degree of obesity and distribution of body fat on central and peripheral haemodynamics	29 normotensive, apparently healthy men 18–22 years	Experimental	Timed mental arithmetic	• Increased WHR is associated with lower Q and greater TPR, irrespective of BMI • Relationship between central adiposity and cardiovascular reactivity was only partially attributable to metabolic syndrome-related factors and remained significant after controlling for them
Ljung *et al.* (94)	Differences between generally and abdominally obese men in activity and regulation of HPA and SNS	50 men, 45–60 years (diabetes-free, BMI 25–33)	Experimental	Simulation with corticotrophin-releasing hormone, arithmetic stress test	• Men with higher WHR had higher diurnal ACTH but similar cortisol • Elevated pulse pressure and heart rate at baseline and post-stressor • Increased urinary excretion of catecholamine metabolites
Mårin *et al.* (100)	Relation between cortisol response and body fat distribution	87 obese women under the age of 45 years (mean age 41 years)	Correlational	Colour-word test, backward subtraction, cold pressor	• Significant positive correlations between serum cortisol during stress and abdominal sagittal diameter

Table 1 *Continued*

References	Focus	Subjects	Design	Stressor(s)	Summary of findings
Mujica-Parodi et al. (101)	Relation between body fat and cortisol response to real-life stress	Study 1: 56 men, 22 women, 18–50 years; Study 2: 14 men, 6 women, 18–48 years	Correlational	Study 1: first-time tandem skydive; Study 2: cognitive tests	• Body fat was significantly correlated with cortisol reactivity in both studies ($r = 0.33$, $r = 0.52$)
Moyer et al. (102)	Relation between WHR and cortisol response to laboratory stressors	41 women, 18–40 years	Experimental	Anagrams, puzzles, arithmetic, short speech	• Women with high WHR had higher cortisol at the end of the 60-min stress period and larger AUC
Rosmond et al. (62)	Relation between stress-related cortisol (assessed 7 times during random day) and body fat and distribution	284 men, all 51 years of age	Observational, correlational	Naturally occurring stress during the day, assessed by the question 'Did you feel any stress during this hour?'	• Significant positive correlation between stress-related cortisol and recumbent sagittal trunk diameter, fasting insulin and glucose, total cholesterol, LDL cholesterol, DBP
Steptoe et al. (103)	Psychobiological pathways mediating relationship between social inequalities and CVD risk	Whitehall II cohort (subset of 123 men and 105 women, 47–58 years)	Experimental with prospective follow-up	Colour-word interference task, mirror tracing	• Lower SES associated with delayed cardiovascular recovery (blood pressure and heart rate) after mental stress
Steptoe and Wardle (97)	Relationship between adiposity and cardiovascular stress reactivity and recovery	225 men and women, 47–59 years	Experimental with prospective follow-up	Colour-word interference task and mirror tracing	• Stress tasks elicited increased blood pressure because of increased cardiac activation and increased peripheral resistance • BMI and WHR cross-sectionally associated with post-stress recovery of SBP, DBP and a standardized Q
Waldstein et al. (93)	WC in relation to mental stress-induced blood pressure and heart rate response in older Black men and women	22 older Black (11 men, 11 postmenopausal women)	Experimental	Stroop colour-word test, speech task, mental arithmetic	• Positive association between central adiposity and stress-induced blood pressure and heart rate reactivity

ACTH, adrenocorticotropic hormone; AUC, area under the curve; BED, binge-eating disorder; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HPA, hypothalamic-pituitary-adrenal; LDL, low-density lipoprotein; Q, cardiac output; SBP, systolic blood pressure; DBP, diastolic blood pressure; SES, socioeconomic status; SNS, sympathetic nervous system; TPR, total peripheral resistance; WC, waist circumference; WHR, waist-to-hip ratio.

Table 2 Prospective cohort studies examining relationship between stress and health

Study	Subjects	Stress measures	Summary of findings
Whitehall II (107,117–131)	British civil servants (men and women), 35–55 years, working in central London in 1985–1988	Work-related stress at baseline and regular follow-ups	• Effort–reward imbalance at work is associated with CVD and poor overall health • Dose–response association between exposure to work-related stress and the odds general and abdominal obesity • Dose–response association between exposure to work-related stress and the odds of metabolic syndrome occurrence • Effect of job strain on weight gain or loss is dependent on baseline BMI
The Pitt County Study (134)	Representative sample of Black people in eastern North Carolina, aged 25–59 years at baseline (1988)	Perceived Stress Scale assessed at baseline	• Higher perceived stress at baseline predicted a greater change in BMI over the 13-year follow-up in women but not in men
Health and Behaviour in Teenagers Study (HABITS) (135)	British youth (2346 boys and 1719 girls) attending school in central London, 11–12 years at baseline (1999)	Perceived Stress Scale assessed at baseline and annually for 5 years	• Waist circumference and BMI were greater in moderate- and high-stress groups compared with low-stress, across all 5 years • Perceived stress did not predict increases in waist circumference or BMI at any time point
Finnish Public Sector Cohort Study (136)	Finnish men and women who participated in the Finnish Public Sector Cohort Study	Work-related stress control vs. demand and effort vs. reward assessed at baseline	• High job demand and low job control as well as effort–reward imbalance are associated with a greater BMI
Healthy Women Study (137)	541 healthy premenopausal women who were screened annually for an average of 15 years	Self-report measures of depression, tension, anxiety, anger and perceived stress	• Depression, stressful life events, perceived stress, anger and tension were associated with the cumulative prevalence of the metabolic syndrome, even after controlling for age, education, hormone replacement and behavioural risk factors • 1 SD increase in depression was associated with 1.21–1.43-fold increase in risk of the metabolic syndrome during follow-up • One stressful life event over the past 6 months was associated with 1.49–2.12-fold increase in risk
Brain Resource International Database (138)	696 adults (51% women), 18–82 years, without history of neurological, medical or psychiatric disorders	Self-report of childhood abuse and trauma; subclinical depression, anxiety, stress	• The number of early life stressors (but not depression, anxiety or stress) was significantly but weakly associated with BMI ($r = 0.08$) • Overweight (17%) and obese (30%) men were more likely to report a history of being bullied or socially rejected compared with normal weight (9%) • Obese men (17%) were more likely to report history of emotional abuse than overweight (6%) and normal weight (2%) • No significant differences for women
Midlife in the United States Study (139)	633 men, 722 women, 25–74 years, who were followed up for an average of 9.2 years	Self-reported stress related to work, personal relationships, life constraints, finances	• Increased BMI during follow-up was related with financial stress (both men and women), work-related stress for men, job-related demands, perceived constraints in life, strain in relationships with family for women

BMI, body mass index; CVD, cardiovascular disease; SES, socioeconomic status.

added that 'it is theoretically reasonable to postulate that . . . a beneficial effect should be present, but the experimental approaches to date have offered limited confirming data in the human' (141).

Clearly, this line of research is still at an early stage. However, this is not really a function of the number of studies that have been conducted (which is substantial) but rather the result of the low methodological quality (with only a few of the studies being prospective randomized experimental trials) and conceptual sophistication.

A striking feature of the meta-analyses summarized in Table 3 is not the magnitude of the effects but rather the

Table 3 Summary of meta-analyses on the relationship between physical activity or cardiorespiratory fitness and stress reactivity

Meta-analysis	Focus	Studies	Summary of findings
Jackson and Dishman (142)	Cardiorespiratory fitness effects on cardiovascular or neuroendocrine reactivity	73 studies (409 effect sizes)	• Small but significant positive effect size ($d = 0.08$) showing that fitness was actually associated with a slight increase in the magnitude of stress reactivity to psychosocial stressors • Small negative effect size ($d = -0.27$) indicating that fitness was associated with a faster rate of recovery • Effects were smaller in experimental and quasi-experimental studies compared with cross-sectional or correlational studies • The effect from 19 randomized experimental studies comparing an exercise training group with a non-exercise control group was not statistically different from zero
Forcier _et al._ (143)	Cardiorespiratory fitness effects on cardiovascular reactivity and recovery	33 studies	• Fitness was associated with an average attenuation of heart rate reactivity of 1.84 beats min^{-1} and an average attenuation of systolic blood pressure reactivity of 3.69 mmHg. These figures indicate approximately a 15–25% attenuation of the stressor-induced reactivity • An average attenuation of diastolic blood pressure reactivity of 1.42 mmHg was not significantly different from zero • Fitness was associated with faster heart rate recovery by 1.24 beats min^{-1}, but not systolic or diastolic blood pressure recovery
Hamer _et al._ (144)	Blood pressure responses to a psychosocial stressor following an acute bout of aerobic exercise	15 studies	• Average effect size of .40 for diastolic and 0.38 for systolic blood pressure. These were the equivalents of 3.0 and 3.7 mmHg attenuation of the blood pressure response compared with controls • The effect sizes remained consistent when the stressful tasks were administered up to 30 min post-exercise • The authors speculated that exercise might produce benefits by placing individuals frequently within the post-exercise 'window' during which the attenuation of stress responses occurs

large variability between studies, which can probably be accounted for by differences in the design, the nature and intensity of the stressors, the selection of indices of reactivity and the timing of the assessment protocols. This variability highlights what is perhaps the largest problem in this field, namely the absence of a consistent hypothesis-generating conceptual framework. As stated by Sothmann, 'there has been limited effort to perform series of investigations to test even the most basic of theoretical paradigms' (141). Others have made similar observations.

Jackson and Dishman (142) focused on what has been highlighted in this review as a fundamental consideration, namely what should be considered the pathogenic element of the response and therefore how a beneficial effect of exercise should be judged. They noted the following: 'The implicit assumption in most of the studies we reviewed was that a reduction in reactivity is the favorable stress response. An alternative possibility is that response patterns of specific components of integrated stress responses, and especially their recovery after stress, might indicate a healthier response pattern' (142).

Other critics have focused on the basic premise of the cross-stressor adaptation hypothesis, namely that there is similarity in the cardiovascular and neuroendocrine responses to exercise and to psychosocial stress. van Doornen _et al._ (146) reviewed evidence showing that the similarities are 'only superficial'. They also strongly criticized the practice of focusing only on the amplitude of neuroendocrine responses, stating that (i) The levels of a hormone present only one part of the picture, the other being the up- or down-regulation of the receptors (number and affinity) and (ii) A complete description of the response necessitates the examination of the recovery phase. The point about the 'superficiality' of the similarities between responses to exercise and psychosocial stressors, in particular, has re-emerged in recent years as research on the central regulatory mechanisms of stress has become more in-depth. Specifically in reference to the systems regulating HPA activity, researchers have identified distinct systems responsive to 'systemic' or 'interoceptive' (i.e. homeostatic, physiological) vs. 'neurogenic' or 'exteroceptive' (i.e. emotional, psychological) stressors (147) and 'systemic' (i.e. homeostatic, requiring no cortical mediation) vs. 'processive' stressors (requiring cortical mediation and, presumably, interpretation) (148). The presence of distinct brain regulatory mechanisms presents a potential challenge for the cross-stressor adaptation hypothesis, suggesting that, at least within the central nervous system, adaptations to exercise may not directly transfer to responses to social stimuli.

Thus, it is clear that how the effectiveness of exercise is defined is crucial. Dienstbier (149) has proposed a radical

reconceptualization of the role of exercise and aerobic fitness in the study of stress. He suggested that 'physiological toughness' consists of a rapid and robust sympathetic nervous system and catecholamine 'pulse' that helps the individual cope effectively and efficiently with the challenge at hand, a low basal rate and a muted HPA axis response, and a quick return to baseline. The key feature of this model is that the magnitude of the SAM reactivity, which has been the cornerstone of the hyper-reactivity model and the focus of most research on the exercise–stress relationship, is considered adaptive rather than maladaptive and having relatively little pathogenic potential. Consistent with McEwen's (48) notion of allostatic load, what Dienstbier believes to have the greatest pathogenic potential is an inadequate initial response, a slow, protracted, or incomplete recovery, and the inability to habituate across multiple exposures to the same stressor. According to Dienstbier, an 'obvious avenue toward toughening is a program of aerobic exercise', (149) which, in his estimation, can bring about most of the adaptations considered critical in this model.

In summary, although the average effects are small and the results from individual studies are inconsistent, there is some evidence that exercise training and aerobic fitness can elicit a more favourable adaptive pattern of stress responses. It would be premature to interpret the current ambiguity as evidence that exercise and physical activity in general cannot provide an effective buffer against the harmful effects of stress. A balanced assessment of this literature suggests that it exhibits some signs of methodological and conceptual immaturity that characterize most emerging lines of research. Conceptually informed hypotheses and methods considering the totality of the stress response (i.e. not just its amplitude but also its frequency, duration, recovery and patterning) have the potential to shed light on the exercise–stress relationship in the following years.

Physical activity, stress and the metabolic syndrome

Chronic stress-related activation of the HPA axis creates a state of hypercortisolaemia, whereas physical activity exhibits an advantageous relationship with components of the metabolic syndrome and could help attenuate some of the negative impact of stress. Much like the exercise–stress literature, the research on the role of physical activity and/or exercise in the relationship between stress and the metabolic syndrome is still in its infancy. To our knowledge, only two studies have examined whether physical activity moderates the relationship between stress and obesity or other components of the metabolic syndrome (12,13). Both studies have focused on young people, aged 8–24 years.

Yin *et al.* (12) examined the relationship of personal and community stress and physical activity with adiposity in 303 individuals, aged 12 and 24 years. Importantly, both stress and physical activity were assessed by self-reports. Adiposity was assessed in three ways: waist circumference, sum of three skin-folds and body mass index. After controlling for age, race, gender, socioeconomic status and parental smoking, personal stress was associated with the body mass index but not with physical activity. Furthermore, the interaction of both personal and community stress with physical activity significantly predicted adiposity measures. However, it should be noted that these interaction terms accounted for only 2–3% of the variance in adiposity measures, with the total models accounting for no more than 15% and 22%.

Another study examined the role of physical activity in the relationship between stress and a metabolic risk composite score in a small sample ($n = 38$) of boys between the ages of 8 and 18 years (13). In this study, stress was assessed by a battery of self-reports related to the appraisal of the demands of daily life (i.e. perceived stress, anxiety, depression, self-esteem), as well as via variables known to influence the well-being of school-age youth (e.g. appearance-related teasing). In addition to adiposity, this study examined a metabolic risk score as a composite consisting of waist circumference, mean arterial pressure, glycosylated haemoglobin and high-density lipoprotein cholesterol. After dividing the sample into high and low physical activity groups via a median split (77 min of moderate-to-vigorous physical activity per day), the relationship between the various indicators of stress with the metabolic risk score were examined within each group. School- and sports-related self-esteem (negatively), as well as trait-anxiety (positively) were significantly associated with the metabolic risk score ($r = -0.64$, -0.53, 0.53, respectively) in the low physical activity group. Conversely, none of the stress variables were associated with the metabolic risk score in the high physical activity group (13).

These preliminary studies raise the possibility that physical activity may exert its beneficial effects not only by raising energy expenditure but also by buffering the relationship of psychosocial stress with obesity and the metabolic syndrome. However, these studies also underscore the lack of consensus in adopting an operational definition of stress. It seems reasonable to suggest that both physiological (e.g. blood pressure, cortisol) and psychosocial variables should be assessed in order to best represent and define 'stress' in future studies.

Summary and conclusions

The prevalence of obesity and the metabolic syndrome has risen to alarmingly high levels. Consequently, disentangling the causal pathways involved in the aetiology of these

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conditions and enhancing their prevention and treatment have become high-priority targets for the global public health community. As is the case with other diseases, the prevention and treatment of obesity and the metabolic syndrome depend on risk factor management. To this end, there is accumulating evidence that the traditional focus on energy imbalance (i.e. diet and physical activity) offers a narrow perspective by excluding factors that may play equally critical roles.

Interest in the role of stress in the aetiology of obesity and the metabolic syndrome is currently rising. However, as stress is an umbrella term used to describe the body's response to numerous physical, psychosocial and environmental challenges, operationalizing the concept in research studies is difficult. Nonetheless, a growing body of evidence linking stress, in diverse contexts, with adverse health effects suggests that stress should not be overlooked when designing prevention and treatment programmes. Likewise, there is some evidence suggesting that physical activity, besides its role in energy expenditure, may positively influence obesity and the metabolic syndrome through its influence on the relationship between stress and these conditions.

The aim of the present review was to provide a summary of the conceptual rationale and the extant empirical evidence on the interconnections between physical activity, stress and obesity/metabolic syndrome. In the process, we highlighted both the considerable untapped potential of this line of research and the persistent gaps in theory and methods. It is the hope of these authors that this review will stimulate further research on the role of multiple interrelated aetiological factors in obesity and the metabolic syndrome.

Conflict of Interest Statement

No conflict of interest was declared.

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