

## **Stress and Health: A Review of Psychobiological Processes**

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## ABSTRACT

The cumulative science linking stress to negative health outcomes is vast. Stress can affect health directly, through autonomic and neuroendocrine responses, but also indirectly, through changes in health behaviors. In this review, we present a brief overview of: i) why we should be interested in stress in the context of health, ii) the stress response and allostatic load, iii) some of the key biological mechanisms through which stress impacts health such as by influencing hypothalamic-pituitary-adrenal axis regulation and cortisol dynamics, the autonomic nervous system, and gene expression, and iv) evidence of the clinical relevance of stress, exemplified through the risk of infectious diseases. The studies reviewed in this article confirm that stress impacts on multiple biological systems. Future work ought to consider further the importance of early life adversity and continue to explore how each of these biological systems interacts in the context of stress and health processes.

**Keywords:** allostatic load, cortisol, autonomic nervous system, genomics, HPA axis

## INTRODUCTION

On the 18<sup>th</sup> of May 1936, Hans Selye published a 595 word letter in *Nature* entitled “A Syndrome produced by Diverse Nocuous Agents” (Selye, 1936). This landmark ‘Letter to the Editor’ described what would later become known as the General Adaptation Syndrome, the subject of an early *Annual Review of Medicine* paper (Selye, 1951) as well as leading to an influential “sketch” by Selye (1950), whereby he argued that “Anything that causes stress endangers life, unless it is met by adequate adaptive responses; conversely, anything that endangers life causes stress and adaptive responses. Adaptability and resistance to stress are fundamental prerequisites for life, and every vital organ and function participates in them” (p. 1383). In the intervening 70 years, Selye’s early work has triggered a gargantuan scientific effort aimed at understanding adaptability, resistance and ultimately the pathways through which stress influences health, disease and longevity.

This review is not intended to be all encompassing or to provide a comprehensive overview of the enormous scientific literature investigating how large or small, acute or chronic, historical or recent, laboratory-based or naturalistic stressful events lead to ill-health, disease and reduced life expectancy. Instead we aim to present a brief overview of: i) the “why” i.e., why we should be interested in stress in the context of health, ii) the “how” i.e., review some of the key mechanisms through which stress impacts health (e.g., hypothalamic-pituitary-adrenal axis activity, autonomic nervous system and gene expression, and iii) the “does it matter?” i.e., is there evidence linking stress with clinically meaningful changes in our health. Finally, we consider an important area of research which looks at the health consequences of previous stressful experiences in the form of early life adversity. Along the way, we will highlight

exciting new developments, unanswered questions and point to promising future directions for research.

### **Why should we be interested in stress?**

Stress is now part of our everyday vernacular and central to the human condition. Scientific interest in stress dates back to the First World War (and beyond), when soldiers were found to exhibit “shellshock”, an extreme reaction to the trauma of battle that was subsequently acknowledged to be a manifestation of post-traumatic stress disorder (Lazarus, 1999). The increase in media coverage over many decades has corresponded with an exponential growth in research and public awareness of stress and its effects. In many countries around the world, it is acknowledged as a leading cause of long-term sickness, accounting for millions of working days lost (e.g., American Psychological Association, 2019; UK Health & Safety Executive, 2019). Stress is the focus of bestselling books, front covers of *Time* magazine and the subject of novels, plays and movies. We are interested in stress because it is everywhere. It impacts everyone and pervades all aspects of our lives. Moreover, it is now well established that stress can affect health directly, through autonomic and neuroendocrine responses (the subject of the current review), but also indirectly, through changes to health behaviours (e.g., O'Connor et al., 2008; Hill et al., 2018). In the latter case, stress may indirectly contribute to obesity, cardiovascular disease and cancer risk to the extent that it produces deleterious changes in diet and/or helps maintain unhealthy eating behaviors such as high fat intake, or low fiber or fruit/vegetable intake.

Nevertheless, the usefulness of the concept of stress has recently been called into question. Jerome Kagan (2016) argued that the overly permissive use of classifying any event as a stressor just because it leads to biological or behavioral change limits its utility. Instead, he

argues that the concept of stress should only be applied to events that ultimately pose a serious threat to an organism's wellbeing. Leading theorists and stress researchers have challenged this view. One group has argued that the concept of stress is useful as long as it is understood in biological terms within a broader framework of allostasis and allostatic load, adaptation to positive and negative life experiences and resultant health behaviors (McEwen & McEwen, 2016). Another group, Cohen, Gianaros and Manuck (2016) have presented a persuasive case that stress has served as a valuable heuristic, that has allowed researchers to integrate different traditions in the study of stress – epidemiological, psychological and biological – into a stage model of stress and disease. In an earlier article, Segerstrom and O'Connor (2012) have argued that the concept of stress has a long and productive history, but it also has its detractors who point out the imprecise and simplistic use of the term. For example, stress can be located in the environment, in appraisal or in response (e.g., emotions or physiology), therefore, careful conceptualisation and assessment is needed in order to differentiate among these locales, as well as to reveal interactions among them. Indeed, these issues are echoed by Slavich (2019) and his notion of “stressnology” – the problematic and primitive approach to studying the effects of life stress exposure on human health – and the call for better measurement and use of state of the art instruments. Notwithstanding these issues, we contend that the cumulative science linking stress to negative health outcomes is robust. Indeed, the fact that these relationships are evident, even in the face of concerns regarding imprecision in the conceptualization and measurement of stress, attest to the importance of stress for health.

## **Stress and health: the basics**

In order to survive, the human body is required to continually adapt to the changing internal and external environment. At its most basic level this is known as homeostasis, whereby the human body tightly regulates its internal physiological states (e.g., body temperature, oxygen supply etc.) in order to keep us alive. In order to maintain homeostasis, our body releases hormones (e.g., cortisol, adrenaline, & noradrenaline) and switches on the autonomic and central nervous system to allow us to adapt and respond to day to day activities (some of which may be stressful, others may not). The release of these so-called physiological “mediators”, cortisol, adrenaline, noradrenaline and changes in immune and metabolic parameters (known as allostasis, Sterling & Eyer, 1988) is protective and adaptive as long as they switch on and switch off in a balanced way when an environmental challenge or stressors are no longer present. However, when this fails to happen, and is maintained overtime, this may be damaging for our health and wellbeing.

McEwen (1998) proposed the concept of “allostatic load” to refer to the wear and tear that the body experiences due to repeated and long-term exposure to stress. Moreover, he also suggested that allostatic load was characterised by the inefficient switching on and turning off of what he called “stress mediators”, as well as in some cases, the mediators failing to mount an adequate response when required (e.g., the body releases too little or too much cortisol when faced with an acutely stressful encounter). More broadly, McEwen (1998) proposed that the long-term impact of exposure to stress affects the body at cardiovascular, metabolic, neural, behavioural and cellular levels and will increase risk of developing disease because the bodily systems stop working effectively (see McEwen & Seeman, 1999). Most recently, McEwen (2018) has discussed the concept of allostatic *overload*, that describes the harmful effects of

stress on our biological systems when a *host* of stress mediators are released to help us adapt but lead to damage as a result of excessive, prolonged and repeated overuse and dysregulation. At its core, allostatic overload reinforces the notion that stress impacts on multiple biological systems and that each of these systems interact with each other in order to adapt and respond to changing environmental demands that are perceived as stressful.

### **The stress response**

Broadly speaking, two systems are activated when we experience stress. The first and easiest to activate is the sympathetic adrenal medullary (SAM) system. The second is the hypothalamic-pituitary-adrenal (HPA) axis. When an individual is suddenly under threat or frightened, the brain (the amygdala, then the hypothalamus) instantly activates the autonomic nervous system (ANS) to send a message to the adrenal glands to trigger the release of noradrenaline that in turn activates the internal organs. This is the basic ANS sympathetic response to threat. However, at the same time, the adrenal medulla releases adrenaline which is rapidly transported through the bloodstream in order to further prepare the body for its response. This system is known as the SAM system response. Within seconds adrenaline and noradrenaline have the entire body on alert, the so called 'fight or flight' response. As a result breathing quickens, the heart beats more rapidly and powerfully, the eyes dilate to allow more light in, and the activity of the digestive system decreases to permit more blood to go to the muscles. This effect is both rapid and intense.

In addition to the SAM response, when an individual experiences an unpleasant event in their environment that they perceive as stressful, the hypothalamus releases a peptide hormone called corticotrophin releasing factor (CRF). Once released, CRF is transported in the blood



supply to the pituitary gland where it stimulates the release of adrenocorticotrophic hormone (ACTH). Subsequently, ACTH travels through the circulatory system to the adrenal cortex where it stimulates production of the glucocorticoid cortisol - the so-called stress hormone. One of the central functions of cortisol is to increase access to energy stores, increase protein and fat mobilization, and decrease inflammation. Therefore, when an individual experiences stress, the release of cortisol triggers excess energy stored in the muscle and liver as glycogen to be liberated and broken down into glucose ready for utilization by the muscles and brain. However, it is important to bear in mind that cortisol is a complex hormone and it has multiple roles beyond the stress response (McEwen, 2019). As you will see later, cortisol plays key roles in regulating circadian rhythm by influencing genomic and nongenomic cellular and molecular mechanisms.

## **KEY BIOLOGICAL MECHANISMS THROUGH WHICH STRESS IMPACTS HEALTH**

Since Selye's ground-breaking work, researchers have attempted to investigate the effects of repeated and long-term stress exposure on physical health outcomes (as well as on mental health outcomes) and we consider some of this evidence later. But there has also been considerable interest in the key biological mechanisms that mediate the stress-health relationship. For example, what are the causal pathways that link stress to health outcomes such as an increased risk of disease onset, faster disease progression or reduced longevity? Which important biological processes does stress impact on before it affects health outcomes? How does stress influence the expression of genes that might impact on health? As we indicated earlier, the current review cannot possibly summarise all of the accumulated evidence. Instead, we focus on three important areas that have been influential in improving our understanding of how stress

influences health. The first deals with research that has investigated the effects of stress on the regulation of the HPA axis and the dynamics of cortisol. The second relates to work examining the influence of stress on the autonomic nervous system, particularly, blood pressure and heart rate variability and the third is concerned with exciting recent developments in social genomics showing that gene expression can be influenced by environmental factors such as stress.

### **Effects of stress on HPA axis regulation and cortisol dynamics**

Cortisol is the primary effector hormone of the HPA axis stress response system. Similar to other aspects of the endocrine system, the HPA axis is regulated by a negative feedback system, whereby the hypothalamus and the pituitary gland have receptors that detect changes in cortisol levels. For example, cortisol secretion will be inhibited when circulating levels rise or it will be stimulated when levels fall. However, if the HPA axis is repeatedly activated, this will trigger increased cortisol output, thereby exposing bodily tissues to excessive concentrations of the hormone (McEwen, 1998; McEwen, 2000; Lovallo, 2016; Miller et al., 2007). Over time, such repetitive activation may lead to tissue damage and contribute to future ill health by placing excessive pressure on various bodily systems including the HPA axis (i.e., allostatic load and overload; McEwen, 1998).

### **Cortisol responses to stress and future health risk**

A considerable body of research has explored whether individuals who exhibit exaggerated cortisol responses to stress are at increased risk of future ill-health (Bunea, Szentagotai & Miu, 2017; Dickerson & Kemeny, 2004; Lovallo, 2016; Zorn et al., 2017). This work has been heavily influenced by what is known as the “reactivity hypothesis” (first applied

to examining cardiovascular reactivity to stress (Olbrist, 1981) and discussed later), that emphasizes that individuals who exhibit the largest increases in blood pressure or heart rate in response to acute stressors will be at greatest risk of future ill-health. In the context of cortisol reactivity, a number of important studies have found evidence that increased cortisol reactivity to stress is associated with negative health outcomes (e.g., al’Absi & Wittmers, 2003; Hamer, O’Donnell, Lahiri & Steptoe, 2010; Hamer, Endrighi, Venuraju, Lahiri & Steptoe, 2012; Hamer & Steptoe, 2012). For example, al’Absi and Wittmers (2003) found evidence of enhanced HPA activity in response to an acute stressor was (cross-sectionally) associated with risk of hypertension. Similarly, Hamer and colleagues (2010), in another cross-sectional investigation, found heightened reactivity to a stressor was associated with coronary artery calcification (a marker of sub-clinical coronary atherosclerosis). In a three year prospective study from the Whitehall II cohort, Hamer and Steptoe (2012) found a 59% increase in the odds of incident hypertension per standard deviation change in cortisol responsivity to a stressor. In a separate analysis of the same cohort, this group showed that heightened cortisol reactivity to stress was also associated with progression of coronary artery calcification 3 years later (Hamer et al., 2012). Interestingly, these authors noted considerable variation in the cortisol stress responses with only 40% of participants exhibiting at least 1 mmol/liter increase. What about the other 60%? In an exciting development relating to cellular aging, Steptoe et al. (2017) recently found that healthy men and women who were “cortisol responders” to acute stressors had shorter telomeres 3 years later compared to those who were “non-responders”. These authors argued that cortisol responsivity may mediate, in part, the relationship between psychological stress and cellular aging.

Alongside the “heightened cortisol reactivity” work, research has emerged to suggest that

smaller increases or blunted cortisol responses to stress may also be indicative of current ill-health or future health risks (Lovallo, 2016). Early evidence to suggest that lower cortisol responses to stress are not necessarily protective came from a study in patients who were alcohol dependent and polysubstance-abusers. Lovallo et al. (2000) found that control patients exhibited the expected cortisol increase following a speech stress test, whereas, patients who were diagnosed as alcohol dependent or alcohol and stimulant dependent did not exhibit a significant cortisol increase. These findings indicated that hyporesponsiveness (also known as a blunted response) may also be a marker of dysregulation of HPA functioning.

Surprisingly, over the past 20 years, the health effects of low cortisol and/or blunted cortisol reactivity to stress has received less attention. That said, findings from the Dutch Famine Birth Cohort Study have been very influential, not just for understanding the cortisol reactivity hypothesis, but also the cardiovascular reactivity hypothesis (as will be outlined in a later section). This cohort study is a large population based investigation of people who were born in Amsterdam between 1943 and 1947, with a subsample of participants who completed an extensive stress protocol between 2002-2004 (Roseboom, de Rooij, & Painter, 2006). In terms of cortisol reactivity to stress, findings from this study showed that *lower* cortisol stress reactivity was associated with obesity and the risk of becoming obese and with symptoms of depression and anxiety (see de Rooij, 2013). Numerous other recent studies have also been published that show that low or blunted cortisol reactivity to stress is associated with high levels of chronic stress, and increased risk of negative physical and mental health outcomes (e.g., Lovallo et al., 2019; O'Connor et al., 2017; Padden, Concialdi-McGlynn, & Lydon, 2019; Zorn et al. 2017). For example, Padden and colleagues (2019) reported that blunted cortisol reactivity was the dominant pattern of physiological reactivity that emerged from studies of caregivers of

individuals with autism spectrum disorder. In another study, O'Connor et al. (2017) found that individuals who had previously made a suicide attempt exhibited low levels of cortisol in response to an acute stressor compared to control participants. Moreover, the results of a meta-analysis in the area of early-life adversity found evidence of a robust association between early-life adversity and a blunted cortisol response to social stress (Bunea, Szentágotai-Táatar, & Miu, 2017).

Taken together, the evidence is converging to suggest that heightened *and* blunted cortisol responses to acute stressors are associated with increased future health risk. To this end, Carroll and colleagues (2017) have put forward a model of blunted stress reactivity that attempts to integrate the evidence linking exaggerated and blunted stress responses into a single unifying framework. They argue that the health damaging effects of heightened reactivity to stress are well established especially in relation to cardiovascular pathology, however, understanding the effects of low or blunted reactivity remains in its infancy. Nevertheless, current theorizing suggests that there is a non-linear, inverted U relationship, such that high and low levels of cortisol are likely to be deleterious. Similar relationships have been demonstrated for other hormones and important aspects of behavior (cf., O'Connor et al., 2001).

### **Stress, cortisol awakening response and health outcomes**

The diurnal pattern of cortisol production is characterized by two distinct components: the peak levels after awakening (i.e., the cortisol awakening response [CAR]) and the diminishing levels throughout the rest of the day (i.e., the diurnal cortisol slope; Adam et al., 2017; Clow, Hucklebridge, Stalder, Evans & Thorn, 2010; Fries et al., 2009; O'Connor et al., 2009; Pruessner et al., 1997). As outlined earlier, cortisol plays an important regulatory function

for many of the body's basic biological systems (e.g., metabolic, immune, inflammatory processes) and disruption of its diurnal rhythm is likely to affect the functioning of these systems that may have consequences for health over time (Lupien, McEwen, Gunnar, & Heim, 2009; Sapolsky, Romero, & Munck, 2000). A relatively large amount of research has explored the links between diurnal cortisol levels across the day and health outcomes (Adam et al., 2017). We briefly review this literature in the next section, but first we consider the relationship between stress and the CAR.

The CAR, the steep rise in cortisol which occurs in the first 30 to 45 minutes after waking, has been a popular topic of recent research, though its function and regulation are not yet fully understood. There is evidence that it is under different regulatory control to cortisol secretory activity across the rest of the day (Schmidt-Reinwald et al., 1999, Clow et al., 2010). Moreover, it has been theorized that the function of the CAR is to prepare the individual for the demands of the upcoming day (Powell & Schlotz, 2012). The CAR has been linked with stress and a range of health outcomes, though, the pattern of results has been mixed (e.g., Adam et al., 2010; Chida & Steptoe, 2009; Clow et al., 2010; Gartland et al., 2014; Steptoe & Serwinski, 2016; O'Connor et al., 2013). In terms of psychological stress, a number of studies have found links between stress and increases in the CAR (e.g., De Vugt et al., 2005; Wust et al., 2000). Conversely, other evidence has shown that chronic stress may disrupt HPA axis regulation and lead to a blunted CAR (e.g., Thorn et al., 2006; Mortensen et al., 2019; O'Connor et al., 2009; 2013, Steptoe & Serwinski, 2016). Furthermore, in terms of health outcomes, a comprehensive meta-analysis, conducted by Chida and Steptoe (2009), confirmed similar findings and reported that different psychosocial factors are associated with both enhanced and reduced cortisol awakening responses. In particular, they found that the CAR was positively associated with job

stress and general life stress, but negatively associated with fatigue, burnout, exhaustion and post-traumatic stress syndrome. More recently, Boggero et al. (2017), using a combination of meta-analysis and P-curve analysis, also found divergent findings with depression being linked to higher CAR and posttraumatic stress being linked to lower CAR.

It is likely that methodological issues will have contributed to these mixed findings (see expert consensus guidelines, Stalder et al., 2016). Measurement of the CAR is particularly sensitive to protocol violations (e.g., getting out of bed before first sample is taken, not providing samples at the correct time). Therefore, future research needs to continue to take steps to minimize issues such as participant non-adherence which is likely to reduce the ‘noise’ in these findings (e.g., using electronic containers to collect cortisol samples that record the time at which they were opened). In addition, future studies investigating CAR ought to increase the number of measurement days in order to improve the reliability of the CAR measures (Segerstrom et al., 2014).

In terms of the relationship between stress and the CAR, Steptoe and Serwinski (2016) have argued that higher CAR may be observed under conditions that require individuals to actively cope with the demands of the upcoming day, whereas, lower CAR may be observed under severely stressful conditions that cannot be dealt with by active behavioural responses. Alternatively, it is our view, that the mixed findings may also be explained in terms of allostatic load and overload. For example, it is possible that moderate to high CAR during periods of increased demand and challenge may reflect the ‘normal’ adaptive response to a stressful environment (allostatic load). However, in the context of fatigue, posttraumatic stress disorder and burnout, the lower CAR may reflect dysregulation of the HPA following exposure to more severe chronic stress over a long period consistent with allostatic overload or so-called toxic

stress (McEwen, 2016). Indeed this view is consistent with recent meta-analysis evidence in the context of suicide (O'Connor et al., 2016) and more generally with another review linking chronic stress and the HPA axis (Miller, Chen & Zhou, 2007).

In sum, it is clear the CAR is an important index of HPA axis activity and it provides valuable insights into the relationship between psychological factors, HPA axis function, health and wellbeing. Similar to cortisol reactivity to stress, existing evidence suggests that low and high CAR may be associated with health risk. Future research ought to establish the precise regulatory function of the CAR incorporating longitudinal designs and repeated assessments.

### **Stress, the diurnal cortisol slope and health outcomes**

The variation in cortisol levels across the day is large with a nadir being reached at bedtime. The decline in cortisol secretion throughout the day following the waking peak is known as the diurnal cortisol slope. Like the CAR, the diurnal cortisol slope has been the focus of a great deal of research attention and it has been argued that disruption of cortisol's circadian rhythm may impact on a large range of central and peripheral biological systems that contribute to negative physical and mental health outcomes over time (Adam et al., 2017; Lupien et al., 2009). A substantial number of studies have found that there is an association between a flatter cortisol slope and adverse outcomes such as depression, cardiovascular disease, inflammation, fatigue, obesity and suicide attempt (Matthews et al., 2006; Nater et al. 2008; O'Connor et al., 2020; Schrepf et al., 2014; Ruttle et al., 2013). However, there are also studies that have failed to find associations between the diurnal cortisol slope or that have yielded inconsistent or contrary findings (e.g., Vedhara et al., 2006; Turner-Cobb, Rixon, & Jessop, 2011).



Despite the burgeoning amount of research in this area, the first systematic review and meta-analysis was only published in 2017. Adam and colleagues (2017) synthesized 179 associations from 80 studies and found consistent evidence to show that flatter cortisol slopes were associated with poorer health outcomes in 10 out of 12 subtypes of emotional and physical health (i.e., cancer, depression, externalizing, fatigue, inflammation/immune, internalizing, obesity/BMI/Adipose, other mental health, other physical health). Moreover, they also reported that the largest effect size was for immune/inflammation outcomes. These findings are important because they confirm that a flatter diurnal cortisol slope is associated with a broad range of health outcomes. The authors argue that these results suggest that there may be a general, shared mechanism that is common to multiple disease states (Adam et al., 2017). They go on to suggest that these findings provide convincing support for a direct causal pathway such that flattened diurnal cortisol rhythms precede and influence dysregulation in multiple downstream biological and behavioral systems that subsequently impact on the development of negative health outcomes.

Adam et al. (2017) finish their review by introducing a new concept called “stress-related circadian dysregulation (SCiD) (p. 37)” and argue that the existing research showing that flatter diurnal cortisol slopes are associated with modifications of circadian biology is a sign of SCiD. They also suggest that future research on stress and health should focus on identifying the psychosocial origins of the early signs of stress-induced circadian dysregulations as it is likely these changes across multiple biological systems may lead to major mental and physical health problems in the future. Moreover, they argue that multiple co-regulatory systems are involved in the development of SCiD and that interventions should target multiple levels of the system (e.g., psychological, behavioural and biological) and ultimately aim to correct expected circadian

*rhythms* rather than correcting *levels* per se. This represents a promising area for future investigation.

### **Stress and hair cortisol**

An exciting recent advance in the area of stress and health research is the assessment of cortisol in hair. Hair cortisol provides an alternative biomarker of HPA activation, free from many of the limitations of other existing biological measures (saliva, urine & blood). Following the discovery of glucocorticoids in hair in 2004 (Lau et al., 2004), researchers have been exploring the reliability and validity of hair cortisol measurement. A one centimeter hair segment (closest to the scalp) provides a measure of average cortisol secretion over the past month, whereas, a three centimeter hair segment provides a measure of cortisol secretion over the past three months. Recent reviews have found that hair cortisol was a reliable indicator of chronic stress and positively associated with body mass index, waist-to-hip ratio, pregnancy in women undergoing in vitro fertilisation and cardiometabolic risk factors for cardiovascular disease (CVD) such as high blood pressure, diabetes, and adiposity (e.g., Lob & Steptoe, 2019; Massey et al., 2016; Stalder et al., 2017; Wright, Hickman, Laudenslager, 2015). Future research ought to incorporate hair cortisol measures in their study designs and include multiple assessments, ideally in longitudinal studies.

### **Effects of stress on ANS regulation and dynamics**

The evidence for the role of the ANS in stress and health is overwhelming and extensive. The sympathetic nervous system (SNS), associated with energy mobilization and the “fight or flight” response, and the parasympathetic nervous system (PNS), associated with vegetative and

restorative functions and “rest and digest”, represent the two major branches of the ANS. Under conditions of health, these systems are normally in dynamic balance with the PNS dominating. However, as outlined earlier, under conditions of stress an imbalance can occur in which fight or flight responses are chronically activated leading to excessive wear and tear on physiological systems (allostatic load). One mechanism that links the ANS to blood pressure (BP) is the baroreflex. Pressure sensitive receptors in the carotid and aortic arches sense increases and decreases in BP and transmit those signals to the brain to produce reflex adjustments in BP via regulation of sympathetic and parasympathetic outflow to maintain blood flow to vital organs such as the brain and heart (Benarroch, 2008). Thus, ANS activity as indexed by myocardial contractility, peripheral vascular resistance, heart rate (HR), and heart rate variability (HRV) work in tandem to regulate BP via the baroreflex. Importantly, there is emerging evidence for an important role of the baroreflex in long term BP regulation (Thrasher, 2006).

Autonomic imbalance, in which SNS tone is high and PNS tone is low, is associated with a wide range of disorders and diseases, both mental and physical including internalizing disorders, externalizing disorders, and psychotic disorders, as well as cardiometabolic diseases such as hypertension, coronary heart disease and diabetes (Beuachaine & Thayer, 2015; Thayer, Yamamoto, & Brosschot, 2010). Of particular relevance to the current review, one of the leading proponents of the autonomic imbalance concept, the cardiologist Stevo Julius, noted that one of the major causes of this autonomic imbalance is the chronic activation of the defense/vigilance response (Julius, 1995). From a psychological perspective this defense/vigilance response is associated with perseverative cognition (e.g., worry, rumination, and angry brooding) and a recent meta-analysis links such perseverative cognition to endocrine, cardiovascular, and autonomic activities such as increased cortisol, blood pressure (BP), and heart rate (HR) and

decreased vagally-mediated heart rate variability (HRV) (Ottaviani, Thayer, Verkuil, Lonigro, Medea, Couyoumdjian, & Brosschot, 2015) as well as other meta-analyses linking it to poorer health behaviors (Clancy et al., 2016; 2020). As noted above both increased and decreased or blunted responses have been associated with increased risk. Numerous models of stress that have tried to explain these relationships. One of the early models was the recurrent activation model or the so-called “reactivity hypothesis” (Krantz & Manuck, 1984). In this model repeated activation of stress systems would lead to poor health outcomes. However, evidence for the generalizability of these increased responses to laboratory tasks to real life stress responses was found to be limited (Lovallo, 2016) thus suggesting other mechanisms for how stress can influence physiological responses. Another early approach that has been largely overlooked was the “prevailing state” model (Manuck & Krantz, 1984). In this model, the large laboratory responses generalized to large generally elevated response levels (i.e., prevailing state) in real-life. More recently, as mentioned earlier, models suggesting that blunted responses may be associated with increased risk have been proposed (Carroll, Ginty, Whittaker, Lovallo, & de Rooij, 2017). One way in which these various models can be reconciled is the generalized unsafety theory of stress (GUTS) model (Brosschot, Verkuil, & Thayer, 2016 a,b; 2018). This model proposes that the fight or flight response is in fact the default response that is more or less always “on” unless “turned off” by safety. This actually comports well with the autonomic imbalance model of Julius and its association with the defense/vigilance response. As stated by Julius (1995) large magnitude responses of physiological systems to threat (reactivity) is adaptive, from an evolutionary perspective, and may have been “selected for” in our ancestors. However, when these responses are prolonged, by anticipatory activation or delayed recovery, they can lead to chronic ANS imbalance (prevailing state). Excessive activation of these systems can lead to their

overuse and dysregulation (blunted responses or allostatic overload). Importantly, Julius notes that in contemporary life, it is necessary to “dampen” this default defense response to reduce the deleterious effects of this previously adaptive rapid and strong defense reaction (Julius, 1995). Increasingly, research is suggesting that this is done by recognition of safety and that failures to recognize safety signals, rather than perceptions of threat, may be associated with poor mental and physical health (Craske et al, 2012; Mayne et al, 2017; Brosschot et al 2016 a,b, 2018). Needless to say, much more work is needed to further validate these intriguing ideas. However, in the next sections, we will provide some of the empirical support for the association of the ANS particularly BP and HRV to stress and health.

### **Effects of stress on BP, heart rate, heart rate variability, and their dynamics**

Numerous studies and meta-analyses have linked BP responses to mental stress to poor health outcomes. Whereas this literature is quite extensive we will briefly summarize just a few of the more recent reviews and meta-analyses before highlighting some of the primary studies. Gasperin and colleagues (2009) reported a meta-analysis of cohort studies on the effect of psychological stress on BP reactivity and recovery. They identified six eligible cohort studies representing over thirty-four thousand participants. Greater BP responses to psychological stress (greater reactivity as well as higher recovery levels) were associated with a 21% greater risk of elevated BP eleven years later relative to those with smaller BP responses. They suggest that management of psychological stress may be an important component of hypertension management. Landesbergis and colleagues (2013) examined the association between job strain and ambulatory BP. They reported the results of a meta-analysis of twenty-two cross-sectional studies and showed that a single exposure to job strain was associated with higher ambulatory

systolic (SBP) and diastolic (DBP) BP. Specifically, they showed that job strain was associated with 3.43 mmHg higher SBP and 2.07 mmHg higher DBP during working hours, 2.55 mmHg higher SBP and 1.90 mmHg higher DBP at home, and 3.67 mmHg higher SBP and 2.06 mmHg higher DBP during sleep. This latter finding is particularly relevant as sleep should represent a period of relative safety and a lack of BP dipping at night is associated with end organ damage such as left ventricular hypertrophy, myocardial infarction, and stroke (Cuspidi, Giudici, Negri, & Sala, 2010).

Similarly, numerous studies have shown an association between ANS imbalance as indexed by high HR and low vagally-mediated HRV and poor health outcomes. Some of this work has been summarized in reviews by one of us (Thayer & Lane, 2007; Thayer, Yamamoto, & Brosschot, 2010) and will not be detailed here. With respect to the role of stress, two systematic reviews have examined the effect of work stress on HRV. Jarczok and colleagues (2013) systematically reviewed the association between work stress and HRV and found nineteen studies representing over 8000 employees from 10 countries published between 1976 and 2008. They reported that adverse work conditions were generally associated with decreased HRV. A recent update of this analysis examined 18 studies published between 2013 and 2019 representing over 29,000 participants and reported that adverse work conditions again were generally associated with decreased HRV (Jarczok, Jarczok, & Thayer, 2020). Given that a recent large study reported that low levels of vagally-mediated HRV were associated with elevated risk in the clinical range (odds ratios ranging from 1.5 to 3.5) for a wide range of biomarkers these reviews of work stress suggest that such stress may have important implications for risk for a wide range of cardiometabolic and inflammatory diseases (Jarczok, Koenig, Wittling, Fischer, & Thayer, 2019).

Kivimaki and Steptoe (2018) provide a comprehensive review on the role of stress in the development and progression of cardiovascular disease. They show that pooling data from several large studies into “mega-studies” has led to increased understanding of the role of psychological stress in cardiovascular disease (CVD). For example, they reviewed studies on the aetiology of CVD in the general population and report hazard ratios ranging from 1.13 to 2.07 for psychological stressors as indexed by work stress and childhood stress being associated with CVD, coronary heart disease, and stroke. They conclude however that the evidence for scalable interventions to reduce such risk is scarce. These reviews provide strong evidence that psychological stress can have deleterious effects on health via the ANS. We next examine some primary studies that have investigated the effects of stress on ANS dynamics including delayed recovery especially during the night-time.

One area of emerging research is on circadian variation of ANS activity and its association with psychological stress. As alluded to above, night-time or sleep should represent a period of restoration, relative safety, and associated relative decreases in SNS and increases in PNS activity. It has long been reported that elevated HR and BP at night is associated with increased mortality. For example, it has been reported that relative to persons with a 10% or greater decrease in SBP or HR at night, those that had no SBP decrease but an HR decrease had a hazard ratio for mortality of 1.39, those that had a SBP decrease but no HR decrease had a hazard ratio of 1.46, and those that had neither a HR or SBP decrease had a hazard ratio of 1.9 (Ben-Dov, Kark, Ben-Ishay, Mekler, Ben-Aric, & Bursztyn, 2007). Both acute and chronic stress have been associated with a blunted HRV increase at night. In a study of healthy young adults it was reported that the acute stress of an impending public speech was associated with a blunted night time increase in HRV the night before the speech (Hall et al 2004). Work stress has also

been associated with a blunted HRV increase at night particularly in older workers (Loerbroks et al, 2010). Psychological factors have been associated with night time BP as well. Numerous studies have reported associations between stress, job strain, hostility, perceived discrimination as well as social integration and social support and BP dipping with the deleterious psychological factors being associated with less BP dipping and the salubrious psychological factors being associated with greater BP dipping (e.g., Fallo et al, 2002; Fan, Blumenthal, Hinderliter, & Sherwood, 2013; Tomfohr, Cooper, Mills, Nelesen, & Dimsdale, 2010). For example, a systematic review on the association between social support and BP dipping reported that greater functional social support was associated with a moderate to large effect on BP dipping (Fortmann & Gallo, 2013). These effects of stress on HRV and BP may be associated via the baroreflex. For example, one study found that lower HRV was associated with blunted BP dipping in patients with resistant hypertension (Salles, Ribeiro, Guimaraes, Muxfeldt, & Cardoso, 2014). Another study reported that low HRV predicted those that would develop a non-dipping BP pattern two years later (Dauphinot et al., 2010). Future studies are needed to more fully explicate the associations between psychological factors such as stress and circadian variations in ANS activity.

Models of the effects of stress on ANS function suggest that both large and small responses may be associated with poorer health outcomes. Ultimately, prolonged stress responses are needed to produce deleterious health effects and data collected during periods of rest or sleep may be particularly informative. Integrative models such as GUTS may help to reconcile these seemingly contradictory findings.



## **The role of social genomics in elucidating the relationship between stress and health**

Technological and scientific developments in our understanding of the human genome are now providing fascinating insights into the molecular mechanisms by which stress influences health. Specifically, the recognition that gene expression (the process by which genes are switched on or become ‘active’) can be influenced by the environment, combined with the development of powerful methods which permit the simultaneous mapping of the entire human genome (Cole, 2019) have allowed investigators to explore whether and how external factors like stress regulate the activity of our genes, and, therefore, influence health.

This exploration started just over a decade ago with a small study which focused not on stress, but its co-conspirator social isolation (Cole et al., 2007). Drawing on decades of research showing that socially isolated individuals have an increased risk of disease and mortality, the group examined whether patterns of gene expression differed in a systematic way between individuals reporting high versus low levels of subjective loneliness (based on responses to the UCLA Loneliness scale) over a 3 year period. They observed that the immune cells of chronically lonely individuals were characterised by an upregulation or increased expression of proinflammatory genes, and the downregulation of genes associated with antiviral resistance and antibody production. Put another way, the genes associated with increasing the risk or exacerbation of inflammation-related conditions were more likely to be switched on, and those associated with protecting us from viral illness were more likely to be switched off. These findings, for the first time, provided a molecular explanation for the increased risk of disease observed in individuals with low levels of social support. It was not long before chronic stress was among a host of different adverse experiences found to be associated with this distinctive

pattern of gene expression (Cole et al., 2007; Miller et al., 2014), that has gone on to be known as the conserved transcriptional response to adversity (CTRA).

### **Stress results not in the down-regulation, but the dysregulation of immunity**

Taken together, work on how varying indices of adversity influence the human genome has precipitated an important paradigm shift in our understanding of how stress effects health. In particular, it challenges the once dominant view that stress results in ill-health because it gives rise to widespread suppression of the immune system. On the contrary, it is now clear that chronic stress can precipitate changes in gene expression associated with both the upregulation and down-regulation of the immune system (Cole, 2013). This in turn, helps to explain the once seemingly anomalous observation that stress can be associated with diseases involving increased activity of the immune system (i.e., inflammation-related diseases such as heart disease and autoimmune conditions), as well as diseases associated with immune suppression (i.e., impaired responses to viral infections and vaccinations).

The discovery and characterization of the CTRA has had other notable implications for our understanding of the relationship between stress and health. One of these pertains to the debate regarding the utility of the term ‘stress’ and whether it should only be employed in contexts where a serious threat to well-being is likely (Kagan, 2016). Pursuant to Kagan’s criticism, the literature on stress and gene expression has also ‘fallen into the trap’ of conceptualizing stress in a variety of ways, most commonly through objective measures of adversity as well as subjective experiences (Cole, Hawkley, Arevalo, & Cacioppo, 2011; Miller et al., 2008). Although both conceptualizations have been shown to be associated with the CTRA pattern, Cole observes that activation of this pattern is often more strongly associated with

subjective experiences of adversity, than objective indices (Cole, 2013). Does this suggest that our focus should be only on indices that capture the subjective experience of stress? Perhaps. But as objective indices of stressor exposure can also be associated with genomic changes (and because some forms of “stress” manifest outside conscious awareness (Mehl, Raison, Pace, Arevalo, & Cole, 2017), it would seem preferable that we continue our permissive conceptualization of stress. However, rather than adopt a singular perspective (e.g., measure stress in terms of stressors or subjective responses), that we accommodate both in studies with sufficient power that we may be able to delineate the individual and combined consequences of the existence of a challenge, and psychological responses to that challenge, on human health (Miller & Chen, 2006).

### **Enhancing our understanding of the role played by cortisol**

A further area in which social genomics has helped our understanding of the stress-illness relationship concerns the role played by the HPA axis as a mediator. As discussed earlier, the activation of this axis, and the subsequent release of glucocorticoids, is an incontrovertible consequence of stress. Indeed, the immunomodulatory properties of cortisol has played a large part in sustaining the view that stress leads to ill-health due to widespread suppression of the immune system. However, the contradiction at the heart of this hypothesis is that if cortisol results in ill-health because it suppresses the immune system, then why does it not also protect us from conditions which arise or are exacerbated by increased immune system activity (i.e., inflammation-related and autoimmune diseases: Miller, Cohen, & Ritchey, 2002; Raison & Miller, 2003)? This led to the evolution of the glucocorticoid resistance hypothesis (Miller et al., 2002) which proposes that, although the HPA axis continues to produce cortisol in response to

chronic stress, the persistence of inflammation in the presence of cortisol occurs because glucocorticoid receptors on immune cells become desensitized over time. In other words, the immune cells become blunted to the signal to switch off, resulting in a mild, but persistent low level of inflammation. Both human and animal studies have provided support for this hypothesis (Miller et al., 2008; Cohen et al., 2012). But the combination of genome-wide expression analysis with bioinformatics have allowed us to understand the nature of this ‘blunting’ in more detail, with the evidence pointing towards chronic exposure to cortisol resulting in both the reduced expression of anti-inflammatory genes, as well an increased activity of the transcription factors promoting inflammation (Cole, 2013).

### **Interventions and gene expression: a promising area of enquiry**

We must acknowledge, however, that much of the evidence reviewed here between indices of adversity, such as stress, and patterns of gene expression is correlational. This of course raises two questions. First, are these relationships causal and, if so, in what direction i.e., does stress alter gene expression, or do these patterns of gene expression give rise to stress? Second are observed effects amenable to change? Results from early trials show great promise. A range of interventions often deployed in the context of stress, such as yoga, mindfulness and CBT have shown evidence of post-intervention alterations in gene expression (Antoni et al., 2012; Black et al., 2013; Bower et al., 2014; Creswell et al., 2012). These interventions have ranged from 8-12 weeks in duration and have been conducted with healthy individuals and people with disease. Their findings clearly illustrate significant changes to the CTRA profile post-intervention, consistent with a reduction in pro-inflammatory gene expression (Antoni et al., 2012; Bower et al., 2014; Creswell et al., 2012) and, to a lesser degree, an upregulation of

antiviral immunity (Black et al., 2013). Studies in animal models have also confirmed that stress and social adversity can causally increase inflammatory gene expression and decrease antiviral gene expression (Cole et al., 2015; Snyder-Mackler et al., 2016).

So our current understanding of how stress influences health has benefited immeasurably from social genomics. It has allowed us to move away from the simplistic view that stress only results in immune suppression, and explain the paradox of stress being able to simultaneously have an effect on disease processes that thrive during periods of immune activity, as well as those that require immune suppression. It has also facilitated a more sophisticated understanding of the role of the HPA axis as a mediator of the stress-health relationship. While the research on interventions, has served to consolidate the view that, not only can stress alter our well-being, but that psychological interventions can attenuate these deleterious effects. Questions abound regarding the potency of the intervention effects and whether they could result in clinically relevant improvements in health. Similarly, it remains unclear which factors determine whether individuals exposed to stress will succumb to diseases associated with an upregulation of genes associated with inflammation, or those associated with a down-regulation of viral immunity. But there seems little doubt that social genomics will continue to contribute to this discourse.

### **CLINICAL RELEVANCE OF STRESS: THE CASE OF INFECTIOUS DISEASES**

The preceding section has hopefully left the reader in little doubt that psychological stress has physiological repercussions which have implications for the functioning of the immune system. However, the criticism levelled at much of this work has been ‘does it matter?’ In other words, are these physiological changes clinically relevant; can they increase the risk of disease,

the progression of co-existing conditions or indeed influence mortality. Here we look at some of the evidence pertaining to disease risk, with a specific focus on infectious diseases.

### **The obstacles inherent in examining the clinical relevance of stress**

Attempts to understand if stress increases the likelihood of new illnesses has had to contend with three main challenges. The first is knowing when someone will experience stress and is of course common to all research in this field. Here the challenge is that one of the hallmarks of a stressful experience is its unpredictability ('when will it happen'; 'how bad will it be'; 'how long will it last' etc.). Thus on the face of it, any attempt to control or predict the experience of stress could diminish its ecological validity and the potency of its effects. But psychologists are of course adept at innovative study designs and experimental manipulation, and have developed a portfolio of approaches to ensure the presence of stress. Most commonly this has involved experimentally controlling stressor exposure (e.g., Trier Social Stress Test: Kirschbaum, Pirke, & Hellhammer, 1993); taking advantage of predictable stressful experiences (e.g., examinations: Glaser et al., 1992) or focusing on populations experiencing known chronic stressors (e.g., caregiving: Vedhara, Cox, et al., 1999).

The second challenge pertains to controlling exposure to a pathogen (any biological agent capable of producing illness). To determine if stress can give rise to illness, you clearly need your participants to be exposed both to stress and a pathogen to which they are vulnerable. This is because the experience of stress on its own is unlikely to give rise to disease within the confines of most study designs (notable exceptions being epidemiological cohorts which benefit from longitudinal follow-ups extending over many decades (Marmot & Brunner, 2005).

The third challenge is selecting an outcome measure representing health, which can be regarded as a clinically relevant. Initially the field was dominated by studies examining the effects of stress on experimental, or in vitro, tests of immunity. Although this literature was influential in establishing the veracity of the effects of stress on the body, for several reasons it did not allow us to determine its clinical relevance i.e., the consequences for health. First, these experimental tests rely on taking samples (e.g., blood, saliva) and then measuring aspects of immunity within the sample. Thus, the assessment of the immune system is conducted outside of the body. Second, they typically focus on single aspects of the immune system such as the number of immune cells or levels of activity in response to pathogens. However, this does not reflect the ways in which the immune system protects against disease, which usually involves the coordinated activity of multiple cells, proteins and chemicals that work together synergistically to eradicate or contain pathogens to which we are susceptible. Third, the pathogens are often synthetic i.e., substances unlikely to give rise to disease in humans. While these tests of immunity permit greater experimental control, they clearly differ considerably from the normal functioning of the immune system (Vedhara, Fox, & Wang, 1999). Thus, it soon became clear that experimental tests of immunity alone would not allow us to determine the clinical relevance of stress, and other psychosocial influences, for health.

The field was then revolutionized by two methodological innovations that occurred in close succession which addressed both the problem of pathogen exposure and identifying outcomes which could be considered acceptable indices of disease or vulnerability to disease, namely viral challenge and vaccine studies.

## **Viral challenge studies**

The viral challenge paradigm was pioneered by Sheldon Cohen and colleagues. This approach typically involves quarantining healthy volunteers for several days during which they are exposed to one or more respiratory viruses (using nasal drops) and then followed up for evidence of infection (determined through the presence of virus in nasal samples, or a significant increase in antibody levels) and, arguably most importantly, illness i.e., developing a clinical cold. In their early work illness was operationalized as the presence of infection and physician and self-report ratings (Cohen, Tyrrell, & Smith, 1991). More recently they have adopted the objective markers of nasal mucus production (determined by collecting and weighing used tissues) and the ability to clear mucus from the nose (determined by the time taken for participants to taste a saccharine solution administered into the nose; Cohen, Janicki-Deverts, Turner, & Doyle, 2015).

In their very first study (Cohen et al., 1991) the authors computed a stress index derived from scales measuring stressful life events, negative affect and perceived stress and examined the relationship between their stress index and the likelihood of both infection and illness. They reported a dose response relationship, such that increases in stress, increased the risk of developing a cold. Furthermore, these effects occurred across a range of different viruses.

This study provided clear evidence that psychological stress was associated with an increase in the risk of disease, specifically infectious disease, and that the effect was generalizable across a range of pathogens. Furthermore, by capturing both a measure of infection and illness, they were also able to establish that the relationship between stress and infection was much stronger than the relationship between stress and illness. This is perhaps unsurprising as



we would expect the immune system, in otherwise healthy individuals, to contain and eradicate most infections before they result in symptoms of disease.

Since this ground-breaking work, Cohen and colleagues have used this paradigm to help us elucidate further the connections between stress and the risk of disease. Indeed, of particular relevance to Kagan's criticism of the overuse of the term stress, the viral challenge studies have shown us that, in terms of the common cold at least, individuals at greatest risk of illness are those contending with chronic stressors (of 1 month or longer in duration) and where the sources of stress are interpersonal or employment related (Cohen et al., 1998). This increased risk associated with chronic stressors has also been supported by the unparalleled meta-analytical review of stress and immunity conducted by Segerstrom and Miller (Segerstrom & Miller, 2004) which synthesized evidence from over 300 empirical studies, conducted over a 30 year period, and concluded that there was clear evidence that chronic stressors result in widespread suppression of the immune system.

The viral challenge studies have also illuminated the pathways by which stress may alter our vulnerability to disease. Specifically, they find that while health behaviors such as sleep quality, physical activity and smoking are often associated with developing an illness, these behaviors appear to largely have direct effects i.e., they do not completely mediate the relationship between stress and illness onset (Cohen, 2005). They have also contributed to our understanding that the relationship between stress and health is both nuanced and multifaceted, involving a range of psychosocial factors able to exert both direct and indirect effects on health. For example, the relationship between stress, social support and vulnerability to the common cold appears to vary according to how support is defined. Measures of social integration (which capture the number of roles in which the respondent has social contacts) appear to enjoy a direct

relationship with disease vulnerability: such that individuals reporting greater social integration are less vulnerable to the common cold following exposure to two cold viruses: an effect not influenced by stress (Cohen, 2005; Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997).

Conversely, in a study looking at the effects of stress due to interpersonal tension, perceived social support and hugging on illness risk, revealed that, unlike social integration, perceived support did not have a direct effect on risk of illness. In contrast, there was evidence of a buffering effect: i.e., interpersonal tension was associated with an increased risk of illness in participants with low levels of social support, but unrelated to illness risk in people with high levels of perceived support. On the other hand, hugging had a direct and protective effect on illness risk, i.e., being hugged more often was associated with a reduced risk of infection), and also an indirect effect, moderating the effect of interpersonal tension on infection risk, such that increased interpersonal tension was associated with a greater risk of illness in people who received fewer hugs (Cohen et al., 2015). Of course, the recent Covid-19 outbreak highlights that the relationship between different definitions of stress and support are also likely to be affected by the nature of the infectious agent i.e., we can speculate that hugging would not be protective in the context of Covid-19.

Taken together, the evidence from viral challenge studies has done much to quash the skeptical view that stress is a modern day complaint with no lasting consequences for health. They have shown that stress is associated with an increased risk of illness in otherwise healthy individuals; and have highlighted the importance of precision in not only how we operationalize stress, but also the myriad of psychosocial factors related to stress. But these studies remain limited by their observational designs which require us to assume that stress is the reason some people develop illness and others don't. The causal nature of the relationship requires

experimental designs and it is here that the vaccine studies are beginning to provide tantalizing findings.

### **Vaccine studies**

Much like the viral challenge studies, vaccine studies have provided investigators with a means of controlling the nature, timing and virulence of the pathogen to which we expose our participants. Although, unlike the viral challenge studies, because vaccinations are not intended to result in illness, they are considered by many to be a more ethical alternative. Hot on the heels of the first viral challenge study (Cohen et al., 1991), Ron Glaser and colleagues reported their first vaccine challenge study (Glaser et al., 1992). In this work they examined the relationship between negative mood (related to examinations) and health in a cohort of healthy students. Their test of 'health' was to examine how well participants' immune systems responded to a series of Hepatitis B vaccinations. Vaccines contain live, attenuated, modified, or killed pathogens (or their toxins). When administered, vaccines stimulate an immune response, the nature of which depends on the type of pathogen administered. However, most often the cascade of immune activity following vaccination ends with the production of antibodies. Thus, Glaser et al. gave their participants all 3 of the Hepatitis B vaccines as part of a standard vaccine schedule. They administered each one on the third day of a three day exam period, and collected blood samples immediately prior to each vaccination to measure the antibody response to the vaccination. So, although the focus was still on measuring a single aspect of the immune system (i.e., antibody levels), this outcome conferred several advantages over experimental tests of immunity that had up to this point dominated the field. First, antibody levels are recognized to correlate well with protection from disease (Plotkin, 2010). Second, they represent the

culmination of an integrated immune response. Third, they capture a response that occurs within the person (rather than *in vitro*) and one which is precipitated following exposure to a natural, not synthetic, pathogen and, finally, the response is achieved without exposing individuals to the risk of disease. In so doing, Glaser et al. provided the scientific community with a test of health that offered a surrogate, but credible, measure of an individual's risk of disease.

Their results revealed that students who seroconverted after the first vaccination (i.e., produced an increase in antibody levels indicative of protection against the disease) were those who reported the lowest levels of anxiety and stress across the exam periods. This association between measures of mood and antibody responses to vaccination, has been replicated many times across a range of populations and vaccinations (Vedhara et al., 1999; Marsland et al., 2006). Indeed, successive reviews have attested to the presence of a clear and convincing relationship in support of stress being negatively associated with antibody responses: suggesting stress results in reduced vaccine effectiveness and, therefore, increases the risk of disease (Cohen, Miller, & Rabin, 2001; Pedersen, Zachariae, & Bovbjerg, 2009). The public health implications of these findings are profound given that vaccines are usually targeted at those at greatest risk of disease (e.g., the elderly), and suggest that vaccines may be least effective in those whom they most seek to protect.

The vaccine literature has, however, also provided a growing body of work suggesting that some forms of stress (e.g., acute stress: Edwards et al., 2006), and factors that can be regarded as protective against stress (e.g., physical activity or positive mood: Ansorge & Schön, 1987; Edwards et al., 2007), may actually enhance the effectiveness of vaccines. Indeed we have also seen a corresponding increase in clinical trials in this area. These trials typically examine the effects of psychological interventions (aimed at reducing stress, or enhancing areas of

functioning that protect or buffer against stress), on how effective vaccines are in protecting against disease. A recent systematic review identified nine such trials (Vedhara et al., 2019) and reported that the majority ( $n=6/9$ ) showed some evidence of an improved antibody response following a psychological intervention. However, the review also noted significant methodological issues including: heterogeneity in intervention approaches (four broad categories of intervention across nine trials); that effects on antibody outcomes were not uniform (benefit across all antibody outcomes and all time points was only seen in a third of trials) and that many trials did not report on adherence to the interventions or effects on mediating mechanisms targeted by the interventions. Thus, in keeping with the infancy of the area, the authors remarked this was, at best, an early signal in support of psychological interventions having the potential to boost the effectiveness of vaccines in protecting against disease.

### **So does it matter?**

The viral challenge and vaccine studies have done much to demonstrate the clinical relevance of stress for health. In the context of infectious disease, at least, there is robust evidence that the experience of stress will increase your risk of illnesses such as the common cold and impair the ability of vaccines to protect the most vulnerable from diseases such as influenza. These paradigms have also been influential in illustrating that not all forms of stress are created equal (with strongest effects repeatedly associated with chronic experiences of stress); and that a focus on stress alone, will serve only to curtail our understanding of the exquisite interplay between our psychology and biology. But is all this limited to our understanding of the role of stress in our risk to infectious diseases? Perhaps not. As evidence emerges suggesting that diseases such as asthma and heart disease may have their origins in

infectious diseases (Cohen, 2005), then these findings may have consequences for our understanding of the role of stress in health more broadly.

## **THE IMPORTANCE OF EARLY LIFE ADVERSITY FOR STRESS AND HEALTH PROCESSES**

A final area that requires brief consideration relates to work on the exposure to early life adversity and stress and health processes. The majority of the current review has focused primarily on concurrent, chronic or acutely stressful experiences, however, we want to highlight and acknowledge the important research on the influence of past stressful experiences. Evidence is accumulating that there are serious health consequences of early life adversity (also known as adverse childhood experiences [ACEs]; Bellis et al., 2015; Danese & McEwen, 2012; Hughes et al., 2017; Waehrer et al., 2020). Individuals who have experienced early life adversity (e.g., experienced childhood trauma, domestic violence) have been found to have more physical and mental health problems in adulthood compared to individuals who have not experienced early life adversity (Bellis et al., 2015). Moreover, maltreated children and adults have been shown to have abnormally active nervous, endocrine and immune systems (Danese & McEwen, 2012) and are significantly more likely to develop disease (i.e., cancer, diabetes, stroke) and have a greater mortality rate compared to non-maltreated children and adults (Bellis et al., 2015). Recent findings have also found that early life adversity, measured as exposure to childhood trauma, is associated with increased vulnerability to suicide (Carr et al., 2013; O'Connor et al., 2018; 2020). In one study, O'Connor et al. (2020) found that approximately 80% of adults who had attempted to end their own life had experienced at least one moderate-to-severe childhood trauma.

Adverse childhood experiences have also been linked to altered dynamics of the HPA axis and to persistent sensitization of the stress response system (Carpenter et al., 2007, 2011; Gerritsen et al., 2010; Lovallo et al., 2013; 2019; O'Connor et al., 2016). Carpenter showed that higher levels of childhood trauma were linked with lower cortisol reactivity to a laboratory stressor (Carpenter et al., 2007; 2011). Another study found evidence that childhood maltreatment was associated with flattened morning cortisol levels in mid-adulthood (Power et al., 2012). Similar findings were also reported by Gerritsen et al. (2010), whereby early life events were associated with lower cortisol in the morning and a flatter slope across the day in a large sample of older persons. A recent meta-analysis found that childhood maltreatment was associated with low awakening cortisol in studies incorporating more rigorous designs (i.e., agency-referred samples; Bernard, Frost, Bennett, & Lindhiem, 2017). In the context of suicide risk, two recent studies found that higher levels of childhood trauma were associated with lower resting cortisol, blunted cortisol reactivity to stress and a lower cortisol levels in the morning in adulthood (O'Connor et al., 2018; 2020).

A promising model has been proposed linking early life adversity to stress reactivity and health risk. Lovallo (2016) has argued that adverse early life experiences cause modifications in frontolimbic brain function which may then lead directly to: 1) reduced stress reactivity, 2) altered cognition (characterised by a shift in focus to more short-term goals and impulsive response selection) and 3) unstable affect regulation. Lovallo (2016) has also suggested that these three negative consequences influence the development of a more impulsive behavioral style that may increase risk of addiction and the engagement in poor health behaviours. Persuasive evidence for aspects of Lovallo's model comes from the Oklahoma Family Health Patterns Project, a cohort study of healthy young adults with or without a family history of

alcoholism. Irrespective of family history, the authors showed that early life adversity was associated with reduced cortisol reactivity to an acute stressor in adulthood (Lovallo et al., 2013). Future research ought to utilise Lovallo's framework and examine further how precisely early life adversity influences HPA axis functioning and stress responsivity. Similarly, the data reported by Kivimaki and Steptoe (2018) suggesting that the effect of childhood stress was greater than the effect of stress during adulthood on the development of cardiovascular disease invites more research into the consequences of childhood adversity on adult health. Incorporating measures of adverse childhood experiences into studies of stress and health will continue to remain an important and fruitful avenue for research.

## CONCLUSIONS

The cumulative science linking stress to negative health outcomes is vast. Stress can affect health directly, through autonomic and neuroendocrine responses, but also indirectly, through changes in health behaviors. The studies reviewed in this article confirm that stress impacts on multiple biological systems and that each of these systems interact with each other in order to adapt and respond to changing environmental demands that are perceived as stressful. While the field has attracted much criticism for the heterogeneity in the way stress has been conceptualized and measured, this variability has also played an important role in enhancing our understanding of what types of stress affect health and in what ways. Moreover, we have clearly moved away from a simple model of stress in which it results in too much cortisol, reduced HRV, heightened blood pressure or impaired immunity to an understanding that these systems interact and become dysregulated in more nuanced ways. We are now seeing that stress can alter the production of stress mediators in ways that can increase and blunt, upregulate and downregulate, all of which are likely to have serious implications for health. Future work ought



to consider further the importance of early life adversity and continue to explore how each of these systems interacts in the context of stress and health research.

In 1950 Hans Selye wrote “It will take many years, indeed many generations, before the details of the general adaptation syndrome are satisfactorily elucidated. In fact, we shall never truly "understand" this phenomenon, since the complete comprehension of life is beyond the limits of the human mind” (p. 1383). Well, here we are many years and many generations forward, and although we may not truly understand the entire phenomenon of stress, permissive or otherwise, we have taken giant leaps forward. There are still more exciting times ahead.

### **Acknowledgements**

We would like to thank Steve Cole, Rory O’Connor and Ronan O’Carroll for providing feedback on an earlier draft of this article and to Sarah Wilding for assistance with some of the referencing.

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