Testosterone

# Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis

Changes in levels of the stress-sensitive hormone cortisol from morning to evening are referred to as diurnal cortisol slopes. Flatter diurnal cortisol slopes have been proposed as a mediator between chronic psychosocial stress and poor mental and physical health outcomes in past theory and research. Surprisingly, neither a systematic nor a meta-analytic review of associations between diurnal cortisol slopes and health has been conducted to date, despite extensive literature on the topic. The current systematic review and meta-analysis examined associations between diurnal cortisol slopes and physical and mental health outcomes. Analyses were based on 179 associations from 80 studies for the time period up to January 31, 2015. Results indicated a significant association between flatter diurnal cortisol slopes and poorer health across all studies (average effect size, r=0.147). Further, flatter diurnal cortisol slopes were associated with poorer health in 10 out of 12 subtypes of emotional and physical health outcomes examined. Among these subtypes, the effect size was largest for immune/inflammation outcomes (r=0.288). Potential moderators of the associations between diurnal cortisol slopes and health outcomes were examined, including type of slope measure and study quality indices. The possible roles of flatter slopes as either a marker or a mechanism for disease etiology are discussed. We argue that flatter diurnal cortisol slopes may both reflect and contribute to stress-related dysregulation of central and peripheral circadian mechanisms, with corresponding downstream effects on multiple aspects of biology, behavior, and health.

#### https://pubmed.ncbi.nlm.nih.gov/28578301/

# Salivary cortisol and cortisone in the clinical setting

Purpose of review: A resurgence of interest in salivary biomarkers has generated evidence for their value in assessing adrenal function. The advantages of salivary measurements include only free hormone is detected, samples can be collected during normal daily routines and stress-induced cortisol release is less likely to occur than during venepuncture. We review the use of salivary biomarkers to diagnose and monitor patients for conditions of cortisol excess and deficiency and discuss the value of measuring salivary cortisone versus salivary cortisol.   
  
 Recent findings: Developments in laboratory techniques have enabled the measurement of salivary hormones with a high level of sensitivity and specificity. In states of altered cortisol binding, salivary biomarkers are more accurate measures of adrenal reserve than serum cortisol. Salivary cortisone is a superior marker of serum cortisol compared with salivary cortisol, specifically when serum cortisol is low and during hydrocortisone therapy when contamination of saliva may result in misleading salivary cortisol concentrations.   
  
 Summary: Salivary cortisol and cortisone can be used to assess cortisol excess, deficiency and hydrocortisone replacement, with salivary cortisone having the advantage of detection when serum cortisol levels are low and there is no interference from oral hydrocortisone.

#### https://pubmed.ncbi.nlm.nih.gov/28375882/

# Cardiovascular Disease and Hair Cortisol: a Novel Biomarker of Chronic Stress

Purpose of review: This review focuses on the concentration of cortisol in human hair as a biomarker of chronic stress in cardiovascular disease (CVD). We outline the cardiovascular consequences of cortisol excess and provide a comprehensive overview of recent studies investigating the relationship of hair cortisol with CVD. In addition, clinical implications and limitations of the evidence are discussed, together with directions for future research.   
  
 Recent findings: Hair cortisol may be a reliable biomarker of chronic stress since it provides quantification of total cortisol secreted into hair over several weeks. A growing body of evidence suggests that elevated hair cortisol levels are associated with both the incidence of CVD and poorer recovery and treatment outcomes. Moreover, increased hair cortisol concentration has been linked with established cardiometabolic risk factors for CVD including high blood pressure, diabetes, and adiposity. Hair cortisol is a promising biomarker of chronic cortisol excess which may contribute to both the pathogenesis and prognosis of CVD. However, the current evidence relies on small-scale cross-sectional studies. Further research adopting longitudinal designs across larger samples of CVD patients and healthy participants is required to inform the development of novel evidence-based interventions.

#### https://pubmed.ncbi.nlm.nih.gov/31471749/

# Trends in Analysis of Cortisol and Its Derivatives

Determination of concentration of cortisol in various biological fluids can provide extensive information about a person's health. Historically, cortisol and its derivatives were (and still are) determined using immunoaffinity-based methods such as colorimetric ELISA assay, chemiluminescent immunoassay, fluorescence assays, radioimmunoassay, electrochemiluminescence immunoassay, immunochromatographic test, or sensors and immunosensors. Recently, mass spectrometry (MS)-based methods started to be used in determination of cortisol and its derivatives. These MS methods are net superior to immunoaffinity-based assays, but are not easily applicable and are also time-consuming and price prohibitive. Furthermore the standard MS instruments used are triple quadrupole instruments. Here we review the literature on the MS and non-MS based methods for determination of cortisol and its derivatives and also explore the use of a less used quadrupole-time of flight instrument in determination of these compounds.

#### https://pubmed.ncbi.nlm.nih.gov/31347077/

# Cortisol and finfish welfare

Previous reviews of stress, and the stress hormone cortisol, in fish have focussed on physiology, due to interest in impacts on aquaculture production. Here, we discuss cortisol in relation to fish welfare. Cortisol is a readily measured component of the primary (neuroendocrine) stress response and is relevant to fish welfare as it affects physiological and brain functions and modifies behaviour. However, we argue that cortisol has little value if welfare is viewed purely from a functional (or behavioural) perspective-the cortisol response itself is a natural, adaptive response and is not predictive of coping as downstream impacts on function and behaviour are dose-, time- and context-dependent and not predictable. Nevertheless, we argue that welfare should be considered in terms of mental health and feelings, and that stress in relation to welfare should be viewed as psychological, rather than physiological. We contend that cortisol can be used (with caution) as a tractable indicator of how fish perceive (and feel about) their environment, psychological stress and feelings in fish. Cortisol responses are directly triggered by the brain and fish studies do indicate cortisol responses to psychological stressors, i.e., those with no direct physicochemical action. We discuss the practicalities of using cortisol to ask the fish themselves how they feel about husbandry practices and the culture environment. Single time point measurements of cortisol are of little value in assessing the stress level of fish as studies need to account for diurnal and seasonal variations, and environmental and genetic factors. Areas in need of greater clarity for the use of cortisol as an indicator of fish feelings are the separation of (physiological) stress from (psychological) distress, the separation of chronic stress from acclimation, and the interactions between feelings, cortisol, mood and behaviour.

#### https://pubmed.ncbi.nlm.nih.gov/22113503/

# Mini-review of hair cortisol concentration for evaluation of Cushing syndrome

Introduction: The diagnosis of endogenous Cushing syndrome is often challenging and requires multiple repeated blood, urine, and saliva tests to detect elevated cortisol levels. Hair cortisol concentration has been described as a marker of long-term exposure to systemic cortisol in patients with Cushing syndrome. Like hemoglobin A1c is used to detect serum glucose exposure over months, segmental hair cortisol can help identify patients with milder forms of and/or periodic or cyclical Cushing syndrome, which may reduce time and costs associated with collection of urine, salivary, and serum cortisol.   
  
 Areas covered: Success of hair cortisol in detection of Cushing syndrome will be discussed in context of current literature, including differences between total or segmental hair cortisol in accurately determining timeline of cortisol exposure. Optimal methods of hair collection, storage, processing, and analysis and efforts toward standardization will be a major focus.   
  
 Expert commentary: Recent evidence suggests increased sensitivity and specificity of hair cortisol in detecting Cushing syndrome. Future guidelines should consider this test as a routine part of the repertoire of screening tests for Cushing syndrome. Possible confounders to explain discrepant results in the literature will be discussed.

#### https://pubmed.ncbi.nlm.nih.gov/30234410/

# Messengers of stress: Towards a cortisol sociology

In 2008, Timmermans and Haas called for a 'sociology of disease' to develop and challenge the sociology of health and illness. A sociology of disease, they argued, would take seriously the biological and physiological processes of disease in theorising health and illness. Building on two decades of Science and Technology Studies and feminist work on biological actors such as hormones and genes, we propose a 'cortisol sociology' to push further at this argument. As a 'messenger of stress', cortisol is key to understanding human and non-human health as a biosocial phenomenon. We argue that sociologists should engage with cortisol through critical yet open-minded reading of the relevant science and critical triangulation studies, and by tracking cortisol's movements from science into public worlds of biosensing and self-monitoring.

#### https://pubmed.ncbi.nlm.nih.gov/34056738/

# Regulation of Cortisol in Patients Undergoing Total Joint Arthoplasty

Osteoarthritis is a condition in which joint cartilage and bone degenerate progressively over time. Total joint arthroplasty is a definitive treatment. Cortisol is a hormone that is associated with pain and inflammation. This study aims to investigate the cortisol levels in patients undergoing total joint arthroplasty. Plasma samples were collected from 71 total joint arthroplasty (TJA) patients at baseline (pre-surgery), 24 hours post-operation, and 5 days post-operation. Cortisol levels were measured in each sample using a commercially available ELISA kit. All results were compiled as group means ± SD. The plasma cortisol level at baseline were 218.5 ± 12 ng/mL. The 24-hour post-surgical samples showed a marked increase in cortisol levels 240.7 ± 15 ng/mL. The blood samples drawn at the 5th day after surgery showed a downward trend (74 ± 12 ng/mL). At 5 days post-operation, cortisol levels were significantly lower than at baseline or 24 hours post-operation. These results point to the fact that prior to surgery, the patient's emotional stress contributes to increased serum cortisol levels. The higher level of cortisol persists at 24 hours post-operation due to inflammation from the procedure. This data also suggests that at 5 days post-operation, the inflammatory response from the surgery and emotional stress subside, resulting in a near normalization of the cortisol levels. Cortisol is a hormone that plays a major role in the body's response to surgery. The relevance between cortisol and different points in the surgical timeline has the potential to prognosticate and improve recovery measures.

#### https://pubmed.ncbi.nlm.nih.gov/34000837/

# Cortisol metabolism in critical illness: implications for clinical care

Purpose of review: Critical illness is uniformly characterized by elevated plasma cortisol concentrations, traditionally attributed exclusively to increased cortisol production driven by an activated hypothalamic pituitary adrenal axis. However, as plasma adrenocorticotropic hormone (ACTH) concentrations are often not elevated or even low during critical illness, alternative mechanisms must contribute.   
  
 Recent findings: Recent investigations revealed that plasma clearance of cortisol is markedly reduced during critical illness, explained by suppressed expression and activity of the main cortisol metabolizing enzymes in liver and kidney. Furthermore, unlike previously inferred, cortisol production rate in critically ill patients was only moderately increased to less than double that of matched healthy subjects. In the face of low-plasma ACTH concentrations, these data suggest that other factors drive hypercortisolism during critical illness, which may suppress ACTH by feedback inhibition. These new insights add to the limitations of the current diagnostic tools to identify patients at risk of failing adrenal function during critical illness. They also urge to investigate the impact of lower hydrocortisone doses than those hitherto used.   
  
 Summary: Recent novel insights reshape the current understanding of the hormonal stress response to critical illness and further underline the need for more studies to unravel the pathophysiology of adrenal (dys)functioning during critical illness.

#### https://pubmed.ncbi.nlm.nih.gov/24722172/

# Clinical applications of cortisol measurements in hair

Cortisol measurements in blood, saliva and urine are frequently used to examine the hypothalamus-pituitary-adrenal (HPA) axis in clinical practice and in research. However, cortisol levels are subject to variations due to acute stress, the diurnal rhythm and pulsatile secretion. Cortisol measurements in body fluids are not always a reflection of long-term cortisol exposure. The analysis of cortisol in scalp hair is a relatively novel method to measure cumulative cortisol exposure over months up to years. Over the past years, hair cortisol concentrations (HCC) have been examined in association with a large number of somatic and mental health conditions. HCC can be used to evaluate disturbances of the HPA axis, including Cushing's syndrome, and to evaluate hydrocortisone treatment. Using HCC, retrospective timelines of cortisol exposure can be created which can be of value in diagnosing cyclic hypercortisolism. HCC have also been shown to increase with psychological stressors, including major life events, as well as physical stressors, such as endurance exercise and shift work. Initial studies show that HCC may be increased in depression, but decreased in general anxiety disorder. In posttraumatic stress disorder, changes in HCC seem to be dependent on the type of traumatic experience and the time since traumatization. Increased hair cortisol is consistently linked to obesity, metabolic syndrome and cardiovascular disease. Potentially, HCC could form a future marker for cardiovascular risk stratification, as well as serve as a treatment target.

#### https://pubmed.ncbi.nlm.nih.gov/25924811/

# Cortisol in mood disorders

Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis has been well-described in mood disorders. Hypercortisolaemia, which has been attributed to a breakdown in glucocorticoid-receptor-mediated negative feedback mechanisms within the HPA axis, may be central to the pathogenesis of both the depressive symptoms and the cognitive deficits, which characterise severe mood disorders. Strategies to normalise glucocorticoid receptor (GR) function, and thus restore HPA functional integrity, have been the focus of recent research. Preliminary preclinical and clinical studies report encouraging results which suggest that lowering circulating cortisol levels, by up-regulating GRs, may have therapeutic efficacy in terms of improvements in depressive symptoms and cognitive functioning.

#### https://pubmed.ncbi.nlm.nih.gov/16019585/

# Obesity and cortisol status

The fact, that obesity is a prominent feature of hypercortisolism (Cushing's syndrome) has stimulated investigation on the possible existence of the reverse relationship, namely that hypercortisolism is a feature of obesity. We have reviewed half a century of literature on this question, and have found out the following: (1) Hypercortisolism can exist in two forms: systemic hypercortisolism, in which there is an overall bodily excess of cortisol, and tissue, or intracellular, hypercortisolism, in which there is increased intracellular concentration of cortisol without an overall bodily excess. (2) There are two parameters of systemic hypercortisolism: CPR and plasma cortisol concentration. Proper evaluation of the first parameter requires correction for the active metabolic mass, which is best performed by expressing CPR per gram of urinary creatinine. The second parameter can be confounded by the marked moment-to-moment fluctuations in plasma cortisol concentrations due to cortisol's episodic secretion. Proper evaluation requires measuring the 24-hour mean concentration. Of these two parameters of systemic cortisol status, the plasma concentration is the more critical and accurate. (3) Corrected CPR is normal in obese individuals, and 24-hour mean plasma cortisol concentrations are slightly but definitely subnormal. This combination of findings indicates diminished stimulability of the hypothalamic-pituitary-adrenal (HPA) axis, which normally regulates bodily cortisol status. This deduction is supported by empirical studies on HPA reactivity. (4) Tissue hypercortisolism, due to increased intracellular activity of 11beta-HSD-1, which catalyzes reduction of cortisone to cortisol, has been reported in obese mice and humans. The findings of various studies are not consistent, and whether the enzymatic overactivity is a cause or a result of obesity is still unclear.

#### https://pubmed.ncbi.nlm.nih.gov/15952076/

# Recent advances in cortisol sensing technologies for point-of-care application

Everyday lifestyle related issues are the main cause of psychological stress, which contributes to health disparities experienced by individuals. Prolonged exposure to stress leads to the activation of signaling pathways from the brain that leads to release of cortisol from the adrenal cortex. Various biomarkers have been affected by psychological stress, but cortisol "a steroid hormone" is known as a potential biomarker for its estimation. Cortisol can also be used as a target analyte marker to determine the effect of exposure such as organophosphates on central nervous system, which alters the endocrine system, leading to imbalance in cortisol secretion. Cortisol secretion of individuals depends on day-night cycle and field environment hence its detection at point-of-care (POC) is deemed essential to provide personalized healthcare. Chromatographic techniques have been traditionally used to detect cortisol. The issues relating to assay formation, system complexity, and multistep extraction/purification limits its application in the field. In order to overcome these issues and to make portable and effective miniaturized platform, various immunoassays sensing strategies are being explored. However, electrochemical immunosensing of cortisol is considered as a recent advancement towards POC application. Highly sensitive, label-free and selective cortisol immunosensor based on microelectrodes are being integrated with the microfluidic system for automated diurnal cortisol monitoring useful for personalized healthcare. Although the reported sensing devices for cortisol detection may have a great scope to improve portability, electronic designing, performance of the integrated sensor, data safety and lifetime for point-of-care applications, This review is an attempt to describe the various cortisol sensing platforms and their potential to be integrated into a wearable system for online and continuous monitoring of cortisol rhythm at POC as a function of one's environment.

#### https://pubmed.ncbi.nlm.nih.gov/24212052/

# Cortisol is the predominant glucocorticoid in the giant paedomorphic hellbender salamander (Cryptobranchus alleganiensis)

Corticosterone is widely regarded to be the predominant glucocorticoid produced in amphibians. However, we recently described unusually low baseline and stress-induced corticosterone profiles in eastern hellbenders (Cryptobranchus alleganiensis alleganiensis), a giant, fully aquatic salamander. Here, we hypothesized that hellbenders might also produce cortisol, the predominant glucocorticoid used by fishes and non-rodent mammals. To test our hypothesis, we collected plasma samples in two field experiments and analyzed them using multiple analytical techniques to determine how plasma concentrations of cortisol and corticosterone co-varied after 1) physical restraint and 2) injection with adrenocorticotropic hormone (ACTH), the pituitary hormone responsible for triggering the release of glucocorticoids from amphibian interrenal glands. Using liquid chromatography-mass spectrometry, we found that baseline and restraint-induced plasma concentrations of cortisol were more than five times those of corticosterone. We then demonstrated that plasma concentrations of both glucocorticoids increased in response to ACTH in a dose-dependent manner, but cortisol concentrations were consistently higher (up to 10-fold) than corticosterone. Cortisol and corticosterone concentrations were not correlated with one another at basal or induced conditions. The extremely low plasma concentrations of corticosterone in hellbenders suggests that corticosterone could simply be a byproduct of cortisol production, and raises questions as to whether corticosterone has any distinct physiological function in hellbenders. Our results indicate that hellbenders produce cortisol as their predominant glucocorticoid, supporting a small and inconclusive body of literature indicating that some other amphibians may produce appreciable quantities of cortisol. We hypothesize that the use of cortisol by hellbenders could be an adaptation to their fully aquatic life history due to cortisol's ability to fulfill both mineralocorticoid and glucocorticoid functions, similar to its functions in fishes. Given the large number of amphibian species that are fully aquatic or have aquatic life stages, we suggest that the broadly held assumption that corticosterone is the predominant glucocorticoid in all amphibians requires further scrutiny. Ultimately, multi-species tests of this assumption will reveal the ecological factors that influenced the evolution of endocrine adaptations among amphibian lineages, and may provide insight into convergent evolution of endocrine traits in paedomorphic species.

#### https://pubmed.ncbi.nlm.nih.gov/31491375/

# Modulatory mechanisms of cortisol effects on emotional learning and memory: novel perspectives

It has long been known that cortisol affects learning and memory processes. Despite a wealth of research dedicated to cortisol effects on learning and memory, the strength or even directionality of the effects often vary. A number of the factors that alter cortisol's effects on learning and memory are well-known. For instance, effects of cortisol can be modulated by emotional arousal and the memory phase under study. Despite great advances in understanding factors that explain variability in cortisol's effects, additional modulators of cortisol effects on memory exist that are less widely acknowledged in current basic experimental research. The goal of the current review is to disseminate knowledge regarding less well-known modulators of cortisol effects on learning and memory. Since several models for the etiology of anxiety, such as post-traumatic stress disorder (PTSD), incorporate stress and the concomitant release of cortisol as important vulnerability factors, enhanced understanding of mechanisms by which cortisol exerts beneficial as opposed to detrimental effects on memory is very important. Further elucidation of the factors that modulate (or alter) cortisol's effects on memory will allow reconciliation of seemingly inconsistent findings in the basic and clinical literatures. The present review is based on a symposium as part of the 42nd International Society of Psychoneuroendocrinology Conference, New York, USA, that highlighted some of those modulators and their underlying mechanisms.

#### https://pubmed.ncbi.nlm.nih.gov/23845515/

# Cortisol's effects on human mental functioning

Popularization of the dexamethasone suppression test has focused attention on the relation between cortisol metabolism and mood and behavior. This article considers the biochemistry, physiology, and pharmacology of cortisol and cortisol-like substances. In addition, the effects of external stresses on cortisol metabolism and circadian rhythmicity of secretory patterns are reviewed. Finally, managing exogenous cortisol excess in a clinical setting is discussed.

#### https://pubmed.ncbi.nlm.nih.gov/7042773/

# Cortisol, high cortisol diseases and anti-cortisol therapy

Elevated cortisol is found in many diseases, including infectious, aging-related, depression and depression-associated conditions; even in some with no known origin, and no known therapy. While it was initially thought that 'high cortisol' is the result of these diseases, there is mounting evidence to the contrary, namely, that high cortisol actually plays a major role in inducing them, opening the possibility that anti-cortisol drugs might represent a new beneficial therapy. Evidence is here presented, showing that the use of anti-cortisol drugs has already induced beneficial results in conditions ranging from AIDS to depression. A main reason for not realizing the major role played by cortisol is due to a defective interpretation of cortisol results. If cortisol is within normal range of 0800 h or 1700 h, it has been considered normal, without realizing that swings, sometimes at immunosuppressive levels, might occur during its 24 h circadian rhythm. We suggest that a first step toward unveiling the role of cortisol in diseases would be to develop a standardized cortisol circadian rhythm chart that would show normal levels at any time during a 24 h period, enabling a more accurate comparison with cortisol values obtained under pathological conditions.

#### https://pubmed.ncbi.nlm.nih.gov/9264141/

# Cortisol Circadian Rhythm and Insulin Resistance in Muscle: Effect of Dosing and Timing of Hydrocortisone Exposure on Insulin Sensitivity in Synchronized Muscle Cells

Introduction/aim: Circadian clock disruption is emerging as a risk factor for metabolic disorders, and particularly, alterations in clock genes circadian expression have been shown to influence insulin sensitivity. Recently, the reciprocal interplay between the circadian clock machinery and hypothal-amus-pituitary-adrenal axis has been largely demonstrated: the circadian clock may control the physiological circadian endogenous glucocorticoid (GC) secretion and action; GCs, in turn, are potent regulators of the circadian clock and their inappropriate replacement has been associated with metabolic impairment. The aim of the current study was to investigate in vitro the interaction between the timing-of-the-day exposure to different hydrocortisone (HC) concentrations and muscle insulin sensitivity.   
  
 Methods: Serum-shock synchronized mouse skeletal muscle C2C12 cells were exposed to different HC concentrations resembling the circulating daily physiological cortisol profile (standard cortisol profile) and the circulating daily cortisol profile that reached in adrenal insufficient (AI) patients treated with once-daily modified-release HC (flat cortisol profile) and treated with thrice-daily conventional immediate-release HC (steep cortisol profile). The 24 h spontaneous oscillation of the clock genes in synchronized C2C12 cells was used to align the timing for in vitro HC exposure (Bmal1 acrophase, midphase, and bathyphase) with the reference times of cortisol peaks in AI patients treated with IR-HC (8 a.m., 1 p.m., and 6 p.m.). A panel of 84 insulin sensitivity-related genes and intracellular insulin signaling proteins were analyzed by RT-qPCR and Western blot, respectively.   
  
 Results: The steep profile, characterized by a higher HC exposure during Bmal1bathyphase, produced significant downregulation in 21 insulin sensitivity-related genes including Insr, Irs1, Irs2, Pi3kca, and Adipor2, compared to the flat and standard profile. Reduced intracellular IRS1 Tyr608, AKT Ser473, AMPK Thr172, and ACC Ser79 phosphorylations were also observed.   
  
 Conclusions: The current study demonstrated that late-in-the-day cortisol exposure modulates insulin sensitivity-related gene expression and intracellular insulin signaling in skeletal muscle cells.

#### https://pubmed.ncbi.nlm.nih.gov/33130679/

# A systematic review and meta-analysis of salivary cortisol measurement in domestic canines

Salivary cortisol is widely used as an indicator of stress and welfare in canine research. However, much remains unclear about the basic features of this hormone marker in domestic dogs. This systematic review and meta-analysis aimed to determine a reference range for cortisol concentration in the saliva of dogs and examine how canine characteristics, environmental effects and experimental considerations relate to salivary cortisol concentrations. A systematic review of literature databases and conference proceedings from 1992 to 2012 identified 61 peer-reviewed studies using domestic dog salivary cortisol. Researchers were contacted via email, and 31 raw data sets representing a total of 5,153 samples from 1,205 dogs were shared. Meta-analysis provided a cortisol concentration range of 0 to 33.79 μg/dL (mean 0.45 μg/dL, SEM 0.13). Significant effects (P < 0.05) were found for sex and neuter status, age, regular living environment, time in environment before testing, testing environment, owner presence during testing, and collection media. Significant effects were not found for dog breed, body weight, dog type, coat color, assay type, exercise, eating, or use of salivary stimulant. Care should be taken when using cortisol studies for dogs at a group or population level as there is a large amount of intraindividual and interindividual variability and external variables could influence salivary cortisol concentration. This analysis highlights the importance of carefully controlling experimental design to compare samples within and between individual dogs, as well as establishing and using best practices for saliva collection. Caution should be exercised in comparing different studies, as the results could be the reflection of a plethora of factors.

#### https://pubmed.ncbi.nlm.nih.gov/27315597/

# Role of cortisol in patients at risk for psychosis mental state and psychopathological correlates: A systematic review

During recent decades, much evidence has been accumulated concerning the neuroendocrine basis of schizophrenia. Recently, research has focused on stress hormones, with cortisol being the most widely researched, during the prodromal phase of psychosis. Thus, the present study aims to systematically review the evidence concerning the role of cortisol in patients at risk for psychosis mental state and its associations with psychopathological correlates. We systematically reviewed the published reports referring to both 'at clinical risk for psychosis' and 'at genetic risk for psychosis' mental state. Sixteen studies were identified. A trend towards increased cortisol levels in saliva emerged. Findings concerning cortisol levels in the blood were minimal and less consistent. The longitudinal studies, though with divergent results, hinted towards upregulation of cortisol secretion prior to psychotic conversion. Regarding cortisol's reactivity, evaluated through neuroendocrine, psychosocial and naturalistic stressors, the findings were minimal and divergent. The hypothesized relation of psychotic symptomatology with cortisol in subjects at risk for psychosis was not confirmed by the majority of the studies. On the contrary, the anxiety parameter and stress-intolerance index were both positively associated with cortisol. In conclusion, the published reports related to the evaluation of cortisol levels/function at prodrome are hitherto minimal. Although the evidence favors cortisol's participation in the pathophysiology of psychosis, the exact cause-effect sequence and the intertwining of cortisol with psychopathology are still unclear.

#### https://pubmed.ncbi.nlm.nih.gov/25430397/

# Cortisol elevation post-hatch affects behavioural performance in zebrafish larvae

Maternal cortisol is essential for cortisol stress axis development and de novo production of this steroid commences only after hatch in zebrafish (Danio rerio). However, very little is known about the effect of elevated cortisol levels, during the critical period of stress axis activation, on larval performance. We tested the hypothesis that elevated cortisol levels post-hatch affect behavioural performance and this is mediated by glucocorticoid receptor (GR) activation in zebrafish larvae. The behavioural response included measuring larval activity in response to alternating light and dark cycles, as well as thigmotaxis. Zebrafish larvae at 3days post-fertilization were exposed to waterborne cortisol for 24h to mimic a steroid response to an early-life stressor exposure. Also, larvae were exposed to waterborne RU-486 (a GR antagonist) either in the presence or absence of cortisol to confirm GR activation. Co-treatment with RU-486 completely abolished the upregulation of cortisol-induced 11β-hydroxysteroid dehydrogenase type 2 transcript abundance, confirming GR signalling. Cortisol-exposed larvae displayed increased locomotor activity irrespective of light condition, but showed no changes in thigmotaxis. This cortisol-mediated behavioural response was not affected by co-treatment with RU-486. Cortisol exposure also did not modify the transcript abundances of GR and mineralocorticoid receptor (MR) in zebrafish larvae. Altogether, cortisol stress axis activation post-hatch increases locomotor activity in zebrafish larvae. Our results suggest that GR signalling may not be involved in this behavioural response, leading to the proposal that cortisol action via MR signalling may influence locomotor activity in zebrafish larvae.

#### https://pubmed.ncbi.nlm.nih.gov/28713045/

# Cortisol urinary metabolites in dogs with hypercortisolism, congestive heart failure, and healthy dogs: pilot investigation

Nonadrenal diseases (NAD), including congestive heart failure (CHF), can affect the conversion of cortisone to cortisol favoring the production of cortisol's urinary downstream metabolites 5α/5β-tetrahydrocortisol (THF) relative to tetrahydrocortisone (THE). We hypothesized that healthy dogs would have lower urinary levels of cortisol, cortisone, THF, and THE than dogs with hypercortisolism (HC) or CHF, and the latter would have higher urinary levels of THF and lower THE than dogs with HC. Four, 9, and 8 dogs with HC, CHF, and normal health, respectively, were included in a pilot prospective cross-sectional study. A single morning voided urine sample was analyzed for urinary cortisol metabolites by liquid chromatography-mass spectrometry. The percentages of conjugated urinary metabolites were significantly higher in dogs with CHF than in healthy dogs (p = 0.001), and not different in HC dogs (p = 0.07). Log-transformed urine cortisol metabolites-to-creatinine ratios in healthy dogs were significantly lower than the 2 other groups (p < 0.001). The urinary free THE:THF ratio was significantly higher (p < 0.001) than the urinary total and conjugated THE:THF ratios. Health status did not affect the total, conjugated, and free THE:THF ratios (p = 0.61). Additional studies are needed to investigate differences in cortisol metabolites between dogs with HC and NAD to accurately discriminate between the groups.

#### https://pubmed.ncbi.nlm.nih.gov/31924129/

# Late-night salivary cortisol measurement in the diagnosis of Cushing's syndrome

Making a definite diagnosis of Cushing's syndrome is a challenging problem. Unsuspected Cushing's syndrome occurs in 2-3% of patients with poorly controlled diabetes, 0.5-1% with hypertension, 6-9% with incidental adrenal masses, and 11% with unexplained osteoporosis and vertebral fractures. The increasing recognition of this syndrome highlights the need for a simple, sensitive, and specific diagnostic test. Patients with Cushing's syndrome consistently do not reach a normal nadir of cortisol secretion at night. The measurement of late-night salivary cortisol levels might, therefore, provide a new diagnostic approach for this disorder. Salivary cortisol concentrations reflect those of active free cortisol in plasma and saliva samples can easily be obtained in a nonstressful environment (e.g. at home). Late-night salivary cortisol measurement yields excellent overall diagnostic accuracy for Cushing's syndrome, with a sensitivity of 92-100% and a specificity of 93-100%. Several factors can, however, make interpretation of results difficult; these factors include disturbed sleep-wake cycles, contamination of samples (particularly by topical corticosteroids), and illnesses known to cause physiologic activation of the pituitary-adrenal axis. In this Review, we discuss the methods and value of measuring salivary cortisol for the diagnosis of Cushing's syndrome, and put forward some recommendations to maximize accuracy of results.

#### https://pubmed.ncbi.nlm.nih.gov/18446140/

# Cortisol and somatization

Somatization symptoms are frequently associated with depression, anxiety, and feelings of distress. These features interact with the activity of the HPA-axis. Therefore we investigated relationships between somatization symptoms and cortisol. Seventy-seven participants were classified into three groups: somatization syndrome (at least eight physical symptoms from the DSM-IV somatization disorder list), somatization syndrome combined with major depression, and healthy controls. The following data were collected: salivary cortisol at three time points (morning, afternoon, evening), nighttime urinary cortisol, serum cortisol after the dexamethasone suppression test (DST), and psychological variables such as depression, anxiety, somatization, and hypochondriasis. Salivary cortisol showed typical diurnal variations. However, the groups did not differ on any of the cortisol variables. A possible explanation may be counteracting effects of somatization and depression. Exploratory correlational analyses revealed that associations between cortisol and psychopathological variables were time-dependent. DST results correlated with psychological aspects of somatization, but not with the number of somatoform symptoms per se.

#### https://pubmed.ncbi.nlm.nih.gov/10876062/

# Cortisol's purpose

It is proposed that cortisol's primary purpose is to mobilize the body's defenses against water-losing intestinal diseases and corticosterone's against serum diseases. They do this by inversely controlling those immune cells, enzymes, and hormones, etc. that affect survival during infection. These glucocorticosteroids affect fight-or-flight mobilization as an adjunct made possible because most processes that enhance immunity have a reverse effect on fight-or-flight.

#### https://pubmed.ncbi.nlm.nih.gov/9824832/

# Cortisol extraction through human skin by reverse iontophoresis

Continuous monitoring of cortisol at the surface of the skin would advance the diagnosis and treatment of cortisol-related diseases, or of elevated cortisol levels related to stress in otherwise healthy populations. Reliable and accurate detection of cortisol at the skin surface remains a limiting factor in real-time monitoring of cortisol. To address this limitation, cortisol extraction through excised human skin by reverse iontophoresis was studied in vitro in side-by-side diffusion cells using a radiolabeled probe. The skin was subjected to four direct current regimens (0, 28, 56, 113μAcm-2) with the anode in the donor chamber and the cumulative cortisol concentrations recorded in the receiver chamber. The 56 and 113μAcm-2 regimens significantly increased transport of 3H-cortisol through the skin, and current density correlated directly with transcutaneous transport of 3H-cortisol. The threshold of detection of electroosmotic versus passive diffusion of cortisol through the skin was between 28 and 56μAcm-2. The results of this study are significant in examining how lipophilic analytes found in the bloodstream respond to reverse iontophoresis across the skin. In addition, a device integration technique is presented which illustrates how continuous cortisol extraction and sensing could potentially be achieved in a conventional wearable format.

#### https://pubmed.ncbi.nlm.nih.gov/28081473/

# Suppressing the Morning Cortisol Rise After Memory Reactivation at 4 A.M. enhances Episodic Memory Reconsolidation in Humans

Evidence from animal and human research shows that established memories can undergo changes after reactivation through a process called reconsolidation. Alterations of the level of the stress hormone cortisol may provide a way to manipulate reconsolidation in humans. Here, in a double-blind, within-subject design, we reactivated a 3-d-old memory at 3:55 A.M. in sixteen men and four women, immediately followed by oral administration of metyrapone versus placebo, to examine whether metyrapone-induced suppression of the morning cortisol rise may influence reconsolidation processes during and after early morning sleep. Crucially, reactivation followed by cortisol suppression versus placebo resulted in enhanced memory for the reactivated episode tested 4 d after reactivation. This enhancement after cortisol suppression was specific for the reactivated episode versus a non-reactivated episode. These findings suggest that when reactivation of memories is immediately followed by suppression of cortisol levels during early morning sleep in humans, reconsolidation processes change in a way that leads to the strengthening of episodic memory traces.SIGNIFICANCE STATEMENT How can we change formed memories? Modulation of established memories has been long debated in cognitive neuroscience and remains a crucial question to address for basic and clinical research. Stress-hormone cortisol and sleep are strong candidates for changing consolidated memories. In this double-blind, placebo-controlled, within-subject pharmacological study, we investigate the role of cortisol on the modulation of reconsolidation of episodic memories in humans. Blocking cortisol synthesis (3 g metyrapone) during early morning sleep boosts memory for a reactivated but not for a non-reactivated story. This finding contributes to our understanding of the modulatory role of cortisol and its circadian variability on reconsolidation, and moreover can critically inform clinical interventions for the case of memory dysfunctions, and trauma and stress-related disorders.

#### https://pubmed.ncbi.nlm.nih.gov/34266897/

# Minireview: Stress-related psychiatric disorders with low cortisol levels: a metabolic hypothesis

Several stress-associated neuropsychiatric disorders, notably posttraumatic stress disorder and chronic pain and fatigue syndromes, paradoxically exhibit somewhat low plasma levels of the stress hormone cortisol. The effects appear greatest in those initially traumatized in early life, implying a degree of developmental programming, perhaps of both lower cortisol and vulnerability to psychopathology. In these conditions, lowered cortisol is not due to any adrenal or pituitary insufficiency. Instead, two processes appear involved. First, there is increased target cell sensitivity to glucocorticoid action, notably negative feedback upon the hypothalamic-pituitary-adrenal (stress) axis. Altered density of the glucocorticoid receptor is inferred, squaring with much preclinical data showing early life challenges can permanently program glucocorticoid receptors in a tissue-specific manner. These effects involve epigenetic mechanisms. Second, early life trauma/starvation induces long-lasting lowering of glucocorticoid catabolism, specifically by 5α-reductase type 1 (predominantly a liver enzyme) and 11β-hydroxysteroid dehydrogenase type 2 (in kidney), an effect also seen in model systems. These changes reflect a plausible early-life adaptation to increase the persistence of active cortisol in liver (to maximize fuel output) and kidney (to increase salt retention) without elevation of circulating levels, thus avoiding their deleterious effects on brain and muscle. Modestly lowered circulating cortisol and increased vulnerability to stress-associated disorders may be the outcome. This notion implies a vulnerable early-life phenotype may be discernable and indicates potential therapy by modest glucocorticoid replacement. Indeed, early clinical trials with cortisol have shown a modicum of promise.

#### https://pubmed.ncbi.nlm.nih.gov/21971152/

# Midnight salivary cortisol for the diagnosis of Cushing's syndrome in a Chinese population

Introduction: Cushing's syndrome is defined as chronic excess free cortisol in circulation. According to recent studies, midnight salivary cortisol is an accurate and non-stress method for screening and diagnosing Cushing's syndrome. However, there is limited data on midnight salivary cortisol for diagnosing Cushing's syndrome in the Chinese population.   
  
 Methods: Among 61 suspected Chinese patients, 48 patients were confirmed to have Cushing's syndrome. We evaluated the midnight salivary cortisol, midnight serum cortisol and 24-hour urine free cortisol excretion for diagnosis. Midnight salivary cortisol was collected from 21 healthy volunteers for control purposes.   
  
 Results: In the patient group, mean urine free cortisol excretion and midnight salivary cortisol levels were 296.50 ± 47.99 µg/day and 10.18 ± 1.29 ng/mL, respectively. Among the control group and normal participants, mean midnight salivary cortisol level was 0.53 ± 0.13 ng/mL and 0.50 ± 0.12 ng/mL, respectively. The cut-off value for midnight salivary cortisol was 1.7 ng/mL for diagnosing Cushing's syndrome, with a sensitivity of 98% and specificity of 100%. The diagnostic performance of midnight salivary cortisol (area under the curve [AUC] = 0.99) was superior to that of urine free cortisol (AUC = 0.89).   
  
 Conclusion: Our study confirmed the good diagnostic performance of midnight salivary cortisol for diagnosing Cushing's syndrome in a Chinese population. Correlation between midnight salivary cortisol and either urine free cortisol or midnight serum cortisol was good. Midnight salivary cortisol is a convenient and precise tool for diagnosing Cushing's syndrome and can be the screening test of choice for Chinese populations.

#### https://pubmed.ncbi.nlm.nih.gov/30488082/

# Elevated fingernail cortisol levels in major depressive episodes

Background: The extent to which cortisol levels are elevated in major depressive episodes (MDE), and hence could act as a biomarker of illness, remains unclear. Although patient characteristics may explain some of this variation - for example elevated cortisol being more often found in patients with severe, psychotic or melancholic depression - problems with the methods used to measure cortisol may also have contributed to the inconsistent findings. Fingernails are a novel sample that can be used to assess aggregate cortisol concentrations over a 15-day period, and may provide a more accurate reflection of longer term cortisol level changes in MDE and help clarify this issue. This methodology has not yet been utilised in MDE.   
  
 Methods: Cortisol levels reflecting a period of 15days were measured using fingernails in a group of 26 subjects experiencing a major depressive episode (MDE) and in an age and gender matched group of 45 healthy controls.   
  
 Results: Depressed subjects showed significantly higher mean cortisol levels measured in fingernails when compared with control subjects. Higher levels of cortisol were associated with higher depression severity scores, a diagnosis of non-reactive depression, and more prominent melancholic symptoms. Conversely, fatigue was negatively correlated with cortisol levels.   
  
 Conclusion: There is elevated cortisol in MDE when assessed using an aggregate measure over two weeks.Alterations in fingernail cortisol correlate with key clinical symptoms and subtypes of depression.

#### https://pubmed.ncbi.nlm.nih.gov/29153629/

# Heritability of cortisol levels: review and simultaneous analysis of twin studies

Cortisol has a pivotal role in physical and mental health, but relatively few studies have paid attention to individual differences in cortisol levels and the etiology of these differences, in particular their possible genetic basis. In this article we review the existing literature on the heritability of cortisol levels. Most of the studies, which have been carried out in genetically informative samples, lack methodological consistency with regard to frequency and timing of sample collection. The circadian rhythm in cortisol levels was often not taken into account. A power analysis shows that none of these studies used adequate sample sizes to distinguish genetic from shared environmental influences as a cause for familial aggregation. Results of a simultaneous analysis of 5 comparable twin studies suggest a heritability of 62%. Hence, we conclude that, to understand the contribution of genetic and (shared) environmental influences to variation in basal cortisol levels, future studies should be designed more rigorously with strict collection and sampling protocols, sufficient sample size and repeated measures across multiple days.

#### https://pubmed.ncbi.nlm.nih.gov/12510008/

# The potential role of cortisol as a biomarker of physiological interdependence in romantic couples: A systematic review

Significant evidence supports the link between relationships and health including the potential for interpartner regulation of intrapersonal physical and mental homeostasis. Physiological interdependence is proposed as a term to summarize the adaptive process in which partners demonstrate physiological contagion that evolves with repetition to create a new homeostatic state regulating individual physiological functioning. Through a systematic review consistent with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P), the present study reviewed the literature examining the interdependent role of diurnal cortisol with romantic couples. The literature search yielded thirteen articles that included statistical modeling testing interdependence between partners in a couple and at the individual level. Five themes emerged from the literature including cortisol synchrony, cortisol and health, cortisol and emotions, cortisol and internal relationship factors, and cortisol and factors external to the romantic relationship. Findings suggest a potential for romantic partners to regulate one another's emotional and physiological states, but this process may not be present in both partners. More research is needed to substantiate a regulatory role as the current literature supports correlations.

#### https://pubmed.ncbi.nlm.nih.gov/32919209/

# Cortisol boosts risky decision-making behavior in men but not in women

Acute stress may escalate risky decision-making in men, while there is no such effect in women. Although first evidence links these gender-specific effects of stress to stress-induced changes in cortisol, whether elevated cortisol is indeed sufficient to boost risk-taking, whether a potential cortisol effect depends on simultaneous noradrenergic activation, and whether cortisol and noradrenergic activation exert distinct effects on risk-taking in men and women is unknown. In this experiment, we therefore set out to elucidate the impact of cortisol and noradrenergic stimulation on risky decision-making in men and women. In a fully-crossed, placebo-controlled, double-blind design, male and female participants received orally either a placebo, hydrocortisone, yohimbine, an alpha-2-adrenoceptor-antagonist leading to increased noradrenergic stimulation, or both drugs before completing the balloon analogue risk task, a validated measure of risk-taking. Overall, participants' choice was risk-sensitive as reflected in reduced responding in high- compared to moderate- and low-risk conditions. Cortisol, however, led to a striking increase in risk-taking in men, whereas it had no effect on risk-taking behavior in women. Yohimbine had no such effect and the gender-specific effect of cortisol was not modulated by yohimbine. Our data show that cortisol boosts risk-taking behavior in men but not in women. This differential effect of cortisol on risk-taking may drive gender differences in risky decision-making under stress.

#### https://pubmed.ncbi.nlm.nih.gov/28750292/

# Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge

Stress and stress-related health impairments are major problems in human life and elucidating the biological pathways linking stress and disease is of substantial importance. However, the identification of mechanisms underlying a dysregulation of major components of the stress response system is, particularly in humans, a very challenging task. Salivary cortisol responses to diverse acute challenge paradigms show large intra- and interindividual variability. In order to uncover mechanisms mediating stress-related disorders and to potentially develop new therapeutic strategies, an extensive phenotyping of HPA axis stress responses is essential. Such a research agenda depends on substantial knowledge of moderating and intervening variables that affect cortisol responses to different stressors and stimuli. The aim of this report is, therefore, to provide a comprehensive summary of important determinants of, in particular, human salivary cortisol responses to different kinds of laboratory stimuli including acute psychosocial stress as well as pharmacological provocation procedures. This overview demonstrates the role of age and gender, endogenous and exogenous sex steroid levels, pregnancy, lactation and breast-feeding, smoking, coffee and alcohol consumption as well as dietary energy supply in salivary cortisol responses to acute stress. Furthermore, it briefly summarizes current knowledge of the role of genetic factors and methodological issues in terms of habituation to repeated psychosocial stress exposures and time of testing as well as psychological factors, that have been shown to be associated with salivary cortisol responses like early life experiences, social factors, psychological interventions, personality as well as acute subjective-psychological stress responses and finally states of chronic stress and psychopathology.

#### https://pubmed.ncbi.nlm.nih.gov/19041187/

# Hair cortisol concentration in veal calves reared under two different welfare production labels

The hypothesis of this study was that veal calves reared under enhanced welfare standards undergo less stress than calves raised in a conventionally system that meets the minimal standards of the Swiss animal welfare legislation, and that this difference is reflected by differences in hair cortisol concentrations and the size, weight and total cortisol concentration of the adrenal glands. A total of 100 veal calves reared under two different animal welfare production labels were used; the labels differed with respect to stocking density and access to an outdoor area and pasture. The production labels included Quality Management and Naturafarm. Hair samples for cortisol measurement were collected from all calves and the adrenal glands were obtained at slaughter. The left adrenal gland was used for cortisol measurement and the right gland was used for histological and morphometric measurements. The median hair cortisol concentrations of the two production groups were 2.4 and 2.3 pg/mg hair, which did not differ significantly. Likewise, the median cortisol concentration of the adrenal cortex (1.7 and 1.6 μg/g), the total adrenal cortisol content (4.8 and 4.7 μg), the weights of the cortex (3.2 and 3.1 g) and medulla (1.7 and 1.7 g) and the thickness of the zona fasciculata (1430 and 1532 μm) did not differ significantly between groups. Thus, it appears that the calves of the two production labels did not suffer obvious stress. This finding notwithstanding, all veal calves deserve to be reared under optimised animal-appropriate welfare conditions.

#### https://pubmed.ncbi.nlm.nih.gov/30711850/

# Hair cortisol measurement in mitotane-treated adrenocortical cancer patients

The only approved drug for the treatment of adrenocortical cancer (ACC) is mitotane. Mitotane is adrenolytic and therefore, hydrocortisone replacement therapy is necessary. Since mitotane increases cortisol binding globulin (CBG) and induces CYP3A4 activity, high doses of hydrocortisone are thought to be required. Evaluation of hydrocortisone therapy in mitotane-treated patients has been difficult since there is no good marker to evaluate hydrocortisone therapy. Measurement of cortisol in scalp hair is a novel method that offers the opportunity to measure long-term cortisol levels. Our aim was to evaluate whether hair cortisol measurements could be useful in evaluating recent hydrocortisone treatment in mitotane-treated ACC patients. Hair cortisol levels were measured in 15 mitotane-treated ACC patients on hydrocortisone substitution and 96 healthy individuals. Cortisol levels were measured in 3 cm hair segments, corresponding to a period of 3 months. Hair cortisol levels were higher in ACC patients compared to healthy individuals (p<0.0001). Seven ACC patients (47%) had hair cortisol levels above the reference range. None of the patients had hair cortisol levels below normal. In contrast to hydrocortisone doses (β=0.03, p=0.93), hair cortisol levels were associated with BMI (β=0.53, p=0.042). There was no correlation between hair cortisol levels and hydrocortisone doses (β=0.41, p=0.13). Almost half of the ACC patients had high hair cortisol levels, suggesting long-term over-substitution of hydrocortisone in some of the patients, whereas none of the patients was under-substituted. Hair cortisol measurements might be useful in long-term monitoring hydrocortisone treatment in mitotane-treated ACC patients.

#### https://pubmed.ncbi.nlm.nih.gov/24627099/

# Design of Intermittent Control for Cortisol Secretion Under Time-Varying Demand and Holding Cost Constraints

Objective: We take the release of stress hormone cortisol as a part of an intermittent control feedback system in contrast to the existing continuous models. By modeling cortisol secretion as an impulsive system, we design an impulsive controller as opposed to a continuous controller for adjusting cortisol levels while maintaining the blood cortisol levels within bounds that satisfy circadian demand and cost constraints.   
  
 Methods: We develop an analytical approach along with an algorithm for identifying both the timing and amplitude of the control.   
  
 Results: The model and the algorithm are tested by two examples to illustrate that the proposed approach achieves impulsive control and that the obtained blood cortisol levels render the circadian rhythm and the ultradian rhythm consistent with the known physiology of cortisol secretion.   
  
 Conclusions: The approach successfully achieves the desired circadian impulsive control, which has great potential to be used in personalizing the medications in order to control the cortisol levels optimally.   
  
 Significance: This type of bioinspired intermittent controllers can be employed for designing noncontinuous controllers in treating Addisonian disease, which is caused by the adrenal deficiency.

#### https://pubmed.ncbi.nlm.nih.gov/31135341/

# Hormones in speed-dating: The role of testosterone and cortisol in attraction

There is evidence that testosterone and cortisol levels are related to the attraction of a romantic partner; testosterone levels relate to a wide range of sexual behaviors and cortisol is a crucial component in the response to stress. To investigate this, we conducted a speed-dating study among heterosexual singles. We measured salivary testosterone and cortisol changes in men and women (n = 79) when they participated in a romantic condition (meeting opposite-sex others, i.e., potential romantic partners), as well as a control condition (meeting same-sex others, i.e., potential friends). Over the course of the romantic speed-dating event, results showed that women's but not men's testosterone levels increased and cortisol levels decreased for both men and women. These findings indicate that men's testosterone and cortisol levels were elevated in anticipation of the event, whereas for women, this appears to only be the case for cortisol. Concerning the relationship between attraction and hormonal change, four important findings can be distinguished. First, men were more popular when they arrived at the romantic speed-dating event with elevated cortisol levels. Second, in both men and women, a larger change in cortisol levels during romantic speed-dating was related to more selectivity. Third, testosterone alone was unrelated to any romantic speed-dating outcome (selectivity or popularity). However, fourth, women who arrived at the romantic speed-dating event with higher testosterone levels were more selective when their anticipatory cortisol response was low. Overall, our findings suggest that changes in the hormone cortisol may be stronger associated with the attraction of a romantic partner than testosterone.

#### https://pubmed.ncbi.nlm.nih.gov/31348926/

# Sources of biological and methodological variation in salivary cortisol and their impact on measurement among healthy adults: a review

Salivary cortisol is often used in occupational field studies when measuring stress reactions. For purposes of precision and accuracy in measurement, and interpretation of results, it is crucial to know the sources of variability that exert systematic influence on sampling. Variability can be both biological and methodological in origin, and failure to identify its sources may induce erroneous interpretations of Type I and Type II. This review aims to increase our knowledge and provide an overview of the biological and methodological variations of relevance for field measurements of salivary cortisol. It is concluded that: (i) time of sampling has to be carefully registered and included in the statistical analysis; (ii) samples have to be collected at the same time of year in longitudinal designs; (iii) food intake has to be avoided in at least the 2 h before sampling; (iv) vigorous exercise has to be avoided in at least the 2 h, preferably longer, before saliva is collected for measurement of cortisol; (v) variation in results obtained by different laboratory techniques emphasizes use of the same, or otherwise made comparable, laboratory techniques; (vi) concentration of cortisol is dependent on the material of the tampon; (vii) despite the absence of hard evidence, it is recommended that information be collected and results possibly statistically controlled for alcohol consumption, medication, such as oral contraceptives, and treatment for mental diseases; (viii) saliva samples can be stored at -20 degrees C for at least 1 year; (ix) cross-comparisons of absolute concentrations across studies might be difficult and therefore the establishment of reference intervals for the population studied and method used is recommended.

#### https://pubmed.ncbi.nlm.nih.gov/18609093/

# New reference intervals for cortisol, cortisol binding globulin and free cortisol index in women using ethinyl estradiol

Healthy women using contraceptives containing a low dose of an estrogen may have a higher serum concentration of cortisol (s-cortisol) and cortisol binding globulin (s-CBG) than the commonly used upper reference limits. There are no published reference intervals for s-cortisol, s-CBG, serum free cortisol index (s-FCI) or cortisol in saliva (sa-cortisol) for these women. The aim was to establish the above-mentioned reference intervals and document the differences in s-cortisol and s-CBG in one group of women using and another group not using ethinyl estradiol (EE). In this cross-sectional study, the reference limits presented were given as the 2.5 and 97.5 percentiles of the distribution of reference values in a population of 277 healthy volunteer women, aged 18-45 years. 157 women were not using any type of estrogen, while 120 women were using contraceptives containing a daily dose of 15-35 μg of EE. Serum and salivary cortisol, and serum CBG were measured using standard laboratory methods. S-FCI was calculated as s-cortisol/s-CBG. The reference intervals for s-cortisol in samples collected at 0800-1030 am in women using and not using EE contraception were: 284-994 nmol/L and 159-569 nmol/L respectively, and for s-CBG: 847-3366 nmol/L and 860-1940 nmol/L, respectively. For s-FCI and sa-cortisol, no clinically significant differences were found. Sa-cortisol may be the preferred measurand for evaluation of possible hypercortisolism in women using estrogens, since cortisol in saliva is not influenced by estrogen. If assessing morning s-cortisol and s-CBG in women using EE, we recommend using separate - and not the commonly used - reference intervals.

#### https://pubmed.ncbi.nlm.nih.gov/31161807/

# Scalp hair cortisol for diagnosis of Cushing's syndrome

Objective: Current first-line screening tests for Cushing's syndrome (CS) only measure time-point or short-term cortisol. Hair cortisol content (HCC) offers a non-invasive way to measure long-term cortisol exposure over several months of time. We aimed to evaluate HCC as a screening tool for CS.   
  
 Design: Case-control study in two academic referral centers for CS.   
  
 Methods: Between 2009 and 2016, we collected scalp hair from patients suspected of CS and healthy controls. HCC was measured using ELISA. HCC was available in 43 confirmed CS patients, 35 patients in whom the diagnosis CS was rejected during diagnostic work-up and follow-up (patient controls), and 174 healthy controls. Additionally, we created HCC timelines in two patients with ectopic CS.   
  
 Results: CS patients had higher HCC than patient controls and healthy controls (geometric mean 106.9 vs 12.7 and 8.4 pg/mg respectively, P < 0.001). At a cut-off of 31.1 pg/mg, HCC could differentiate between CS patients and healthy controls with a sensitivity of 93% and a specificity of 90%. With patient controls as a reference, specificity remained the same (91%). Within CS patients, HCC correlated significantly with urinary free cortisol (r = 0.691, P < 0.001). In two ectopic CS patients, HCC timelines indicated that cortisol was increased 3 and 6 months before CS became clinically apparent.   
  
 Conclusions: Analysis of cortisol in a single scalp hair sample offers diagnostic accuracy for CS similar to currently used first-line tests, and can be used to investigate cortisol exposure in CS patients months to years back in time, enabling the estimation of disease onset.

#### https://pubmed.ncbi.nlm.nih.gov/28289104/

# A Disposable Printed Liquid Gate Graphene Field Effect Transistor for a Salivary Cortisol Test

Circadian rhythm of salivary cortisol is of clinical significance, tracking salivary cortisol in domicile is welcomed by both doctor and patient, due to its merits of noninvasion, ease of sampling, and free-of-stress response. Here, we present a portable salivary cortisol test setup based on a liquid gate graphene field effect transistor (Lg-GFET) for the first time. In this work, the Lg-GFET was prepared by the printing technology and exploited as a sensitive material. In the procedures of device preparation, the modified liquid exfoliation method and direct-ink-write technology were utilized for synthesizing the graphene ink and printing Lg-GFETs; then, the as-prepared Lg-GFETs were decorated and functionalized by tetrakis(4-carboxyphenyl) porphyrin and the cortisol aptamer, successively. Their sensitivity, selectivity, and robustness are seriously examined. The test results indicate that the sensors have good linear sensitivities over a seven-log analyte concentration range (0.01 to 104 nM) and the anti-interference ability to distinguish from the substancess with similar chemical structures. Moreover, the conceptual application for tracking circadian rhythm was carried out successfully. Conclusively, the proposed flexible Lg-GFET-based salivary cortisol detection platform can satisfy the requirements of the salivary cortisol's assay for instant detection. Additionally, it also provides an alternative solution for developing similar household medical appliances.

#### https://pubmed.ncbi.nlm.nih.gov/34344148/

# Direct immune-detection of cortisol by chemiresistor graphene oxide sensor

In this study, a biosensor to detect a stress biomarker of cortisol using cortisol monoclonal antibody (c-Mab) covalently immobilized on reduced graphene oxide (rGO) channel as electrical sensing element was demonstrated. Highly specific immune-recognition between the c-Mab and the cortisol was identified and characterized on a basis of resistance change at the rGO channel based chemiresistor sensor achieving the limit of detection of 10pg/mL (27.6 pM). In addition, cortisol concentrations of real human salivary sample and buffer solution of rat adrenal gland acute slices, which could secret the cortisol induced by adrenocorticotropic hormone (ACTH), were directly measured by the chemiresistor corresponding to the specific sensing of the cortisol. The rGO chemiresistor could selectively measure the cortisol levels in spite of diverse neuroendocrine's existence. The potential perspective of this study can be a protocol of new cortisol sensor development, which will be applicable to point-of-care testing (POCT) targeted for salivary cortisol, in vitro psychobiological study on cortisol induction, and implantable sensor chip in the future.

#### https://pubmed.ncbi.nlm.nih.gov/28728007/

# Cortisol Predicts Performance During Competition: Preliminary Results of a Field Study with Elite Adolescent Taekwondo Athletes

Competitive taekwondo composes a high stress situation leading to an increase in the stress hormone cortisol. Little is known about cortisol's relation to outcome (winning vs. losing) and performance in taekwondo. Therefore, the aim of the study was to investigate cortisol relation to outcome, performance and whether cortisol can predict performance during a competition. Twenty taekwondo combatants (13 males; Mage = 15) provided four salivary samples (C1: 30 min prior, C2: during, C3: after, and C4: 30 min after competition) during an international competition. Total points made in the two rounds during their first fight were used as a performance indicator. Results show no difference in cortisol between winners and losers, before or after competition. However, a negative correlation between performance and C1 as well as C4 was detected. Unexpected, a positive correlation between cortisol during the competition (C2) and performance was identified. A stepwise multiple regression analyses showed that C2 predicted 25.5% of the performance variance. Even if the sample size is relatively small due to the field experimental setting, some conclusions can be drawn to motivate future research. Potentially, in taekwondo it seems advantageous for performance to have higher levels of stress as indicated by cortisol during a competition, whereas particularly before the competition, sport psychological interventions should be provided to combatants to reduce their psychophysiological stress level.

#### https://pubmed.ncbi.nlm.nih.gov/30054758/

# Salivary cortisol day curves in Addison's disease in patients on hydrocortisone replacement

Using salivary cortisol (SC) measurements, cortisol exposure in Addison's disease patients on hydrocortisone replacement was determined and compared with healthy controls. Cortisol pharmacokinetics was assessed in 31 patients with Addison's disease on replacement hydrocortisone doses (median daily dose 20 mg; range 5-50 mg) and 30 healthy control subjects. Saliva samples (n=16) were collected between 08:00 and 00:00 h in 1 day, using a passive drool technique. Cortisol exposure was evaluated by noncompartmental approach. In the patients, cortisol exposure was significantly higher than in controls: median inter-quartile range (IQR) peak cortisol (C(max)) 174.5 (59.3-837.0) vs. 6.50 (4.7-19.3) nmol/l, p=0.0001; area under the curve (AUC) 390.1 (177.1-928.9) vs. 21.4 (14.6-28.4) minutes\*nmol/l, p=0.0001, trough cortisol level (C(min)) 0.49 (0.49-0.96) vs. 0.49 (0.49-0.49) nmol/l, p=0.02, occurring at 480.0 (0.1-660.0) vs. 405.0 (180.0-570.0) min, p=0.56. First peak cortisol was 174.5 (53.0-754.7) vs. 6.27 (3.90-8.47) nmol/l, p=0.0001 and second peak cortisol 18.90 (5.22-76.9) vs. 3.12 (1.76-4.79) nmol/l, p=0.0001. The time to first peak cortisol differed between the 2 groups, 30 (30-75) vs. 0.1 (0.1-30) minutes; p=0.0001. At doses studied, hydrocortisone replacement therapy results in cortisol pharmacokinetics being markedly different from endogenous cortisol profiles in healthy control subjects. Addison's disease patients had significantly higher SC levels compared to healthy control subjects.

#### https://pubmed.ncbi.nlm.nih.gov/22893258/

# Cortisol shifts financial risk preferences

Risk taking is central to human activity. Consequently, it lies at the focal point of behavioral sciences such as neuroscience, economics, and finance. Many influential models from these sciences assume that financial risk preferences form a stable trait. Is this assumption justified and, if not, what causes the appetite for risk to fluctuate? We have previously found that traders experience a sustained increase in the stress hormone cortisol when the amount of uncertainty, in the form of market volatility, increases. Here we ask whether these elevated cortisol levels shift risk preferences. Using a double-blind, placebo-controlled, cross-over protocol we raised cortisol levels in volunteers over 8 d to the same extent previously observed in traders. We then tested for the utility and probability weighting functions underlying their risk taking and found that participants became more risk-averse. We also observed that the weighting of probabilities became more distorted among men relative to women. These results suggest that risk preferences are highly dynamic. Specifically, the stress response calibrates risk taking to our circumstances, reducing it in times of prolonged uncertainty, such as a financial crisis. Physiology-induced shifts in risk preferences may thus be an underappreciated cause of market instability.

#### https://pubmed.ncbi.nlm.nih.gov/24550472/

# Saliva versus serum cortisol to identify subclinical hypercortisolism in adrenal incidentalomas: simplicity versus accuracy

Purpose: Subclinical hypercortisolism (SCH) leads to metabolic derangements and increased cardiovascular risk. Cortisol autonomy is defined by the overnight 1 mg dexamethasone suppression test (DST). Saliva cortisol is an easier, stress-free, and cost-effective alternative to serum cortisol. We compared 23 h and post-1 mg DST saliva with serum cortisol to identify SCH in adrenal incidentalomas (AI).   
  
 Methods: We analyzed 359 DST obtained retrospectively from 226 AI subjects (173F/53 M; 19-83 years) for saliva and serum cortisol. We used three post-DST serum cortisol cutoffs to uncover SCH: 1.8, 2.5, and 5.0 μg/dL. We determined post-DST and 23 h saliva cortisol cutoffs by ROC curve analysis and calculated their sensitivities (S) and specificities (E).   
  
 Results: The sensitive 1.8 μg/dL cutoff defined 137 SCH and 180 non-functioning adenomas (NFA): post-DST and 23 h saliva cortisol S/E were: 75.2%/74.4% and 59.5%/65.9%, respectively. Using the specific 5.0 μg/dL cortisol cutoff (22 SCH/295 NFA), post-DST and 23 h saliva cortisol S/E were 86.4%/83.4% and 66.7%/80.4%, respectively. Using the intermediate 2.5 μg/dL cutoff (89 SCH/228 NFA), post-DST and 23 h saliva cortisol S/E were 80.9%/68.9% and 65.5%/62.8%, respectively.   
  
 Conclusion: Saliva cortisol showed acceptable performance only with the 5.0 μg/dL cortisol cutoff, as in overt Cushing's syndrome. Lower cutoffs (1.8 and 2.5 μg/dL) that identify larger samples of patients with poor metabolic outcomes are less accurate for screening. These results may be attributed to pre-analytical factors and inherent patient conditions. Thus, saliva cortisol cannot replace serum cortisol to identify SCH among patients with AI for screening DST.

#### https://pubmed.ncbi.nlm.nih.gov/31456173/

# Basal cortisol levels and the relationship with clinical symptoms in multiple sclerosis: a systematic review

Multiple sclerosis (MS) is a demyelinating, progressive and neurodegenerative disease. A disturbance on the hypothalamic-pituitary-adrenal axis can be observed in patients with MS, showing altered cortisol levels. We aimed to identify basal cortisol levels and verify the relationship with clinical symptoms in patients with MS. A systematic search was conducted in the databases: Pubmed, Web of Science and SCOPUS. Both higher and lower cortisol levels were associated with MS. Higher cortisol levels were associated with depression and anxiety, while lower levels were associated with depression, fatigue and urinary dysfunction. Higher cortisol levels may be associated with the progression and severity of MS.

#### https://pubmed.ncbi.nlm.nih.gov/30365626/

# FECAL CORTISOL LEVELS IN SCIMITAR-HORNED ORYX, ORYX DAMMAH, REVEALS DIFFERENCES BETWEEN CAPTIVE ENVIRONMENTS

Due to the intensive management of the scimitar-horned oryx, Oryx dammah, involving both captivity and reintroductions, understanding the stress associated with environmental situations this endangered species might experience would be particularly helpful. Fecal cortisol levels were measured across seasons, between captive management programs, and among varying reproductive states in animals held at Fossil Rim Wildlife Center (FRWC) and Kansas City Zoo (KCZ). A total of 72 samples were collected from FRWC and 69 samples were collected from KCZ. The herd size and sex ratio changed for both locations in the middle of sampling due to translocations and birth. The herd sizes ranged from 25 to 28 individuals at FRWC and 22 to 24 individuals at KCZ. An ELISA was optimized and utilized to investigate fecal cortisol variances across seasons, captive management programs, and among varying reproductive states. Fecal cortisol levels ranged from 68.9 to 668.7 pg/g throughout this study, but key differences were found in response to reproductive status, environmental conditions, and social status. The highest level of fecal cortisol measured (668.7 pg/g) was in a pregnant female 9 days prior to parturition. During winter months, an increase in fecal cortisol levels occurred in both herds (FRWC 160.3 pg/g to 335.1 pg/g and KCZ 118.8 pg/g to 505.0 pg/g). In addition, when intact males were held together in an enclosure, the dominant males had lower fecal cortisol levels compared with submissive males during three of the four sampling periods. Understanding how these data relate to the physiologic stress response will require further study, but these results can be utilized to help establish expected fecal cortisol ranges in multiple environments and can aid current captive scimitar-horned oryx management programs, as well as future reintroduction efforts.

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# Basal cortisol's relation to testosterone changes may not be driven by social challenges

Multiple studies show a negative correlation between basal cortisol and testosterone changes in the presence of competition and social-evaluative stressors. These negative associations are proposed to be derived from psychological responses to competition and social-evaluative stress. However, we argue that the association between basal cortisol and testosterone change may instead be a statistical consequence of positively associated variables. In this paper, we present a mathematical rationale for this alternative explanation and examples from two studies that are consistent with this alternative explanation. Both studies show that the associations between basal cortisol and testosterone change have covariance patterns consistent with this alternative possibility. We conclude that the often-found positive association between basal cortisol and basal testosterone opens the door for alternative explanations of the basal cortisol-testosterone change association rooted in the patterns of associations between hormones measured over time. We also suggest future research directions and methods for testing alternative explanations.

#### https://pubmed.ncbi.nlm.nih.gov/28779629/